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Age-related differences in functional and directed sensorimotor connectivity during tonic contraction of ankle muscles across childhood development and adolescence

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Abstract

In adults, oscillatory activity in the sensorimotor cortex is coherent with contralateral muscle activity at beta frequencies (15-35 Hz) during tonic contraction. This functional coupling reflects the involvement of the sensorimotor cortex, the corticospinal pathway, and likely also ascending sensory feedback in the task at hand. However, little is known about the development of task-related sensorimotor connectivity during childhood and adolescence. To address this, we recorded electroencephalography (EEG) from the vertex (Cz) and electromyography (EMG) from ankle muscles (proximal and distal anterior tibial, TA; soleus, SOL; gastrocnemius medialis, GM) in 33 participants aged 7-23 yr during tonic dorsi- and plantar flexion requiring precise maintenance of a submaximal torque level. Coherence was calculated for Cz-TA, Cz-SOL, TA-TA, and SOL-GM signal pairs. We found strong, positive associations between age and beta band coherence for Cz-TA, Cz-SOL, and TA-TA, suggesting that oscillatory corticomuscular connectivity is strengthened during childhood development and adolescence. Directionality analysis indicated that the primary interaction underlying this age-related increase was in the descending direction. In addition, performance during dorsi- and plantar flexion tasks was positively associated with age, indicating more precise control of the ankle joint in older participants. Performance during dorsi- and plantar flexion was also associated with beta band coherence, suggesting that participants with greater beta band coherence also exhibited greater precision. We propose that these results indicate an age-related increase in oscillatory corticospinal input to the ankle muscle motoneuron pools during childhood development and adolescence, with possible implications for maturation of precision force control. Within the theoretical framework of predictive coding, we suggest that our results may reflect an age-related increase in reliance on feedforward control as the developing nervous system becomes better at predicting the sensory consequences of movement. These findings may contribute to the development of novel intervention strategies targeting improved sensorimotor control in children and adolescents with central motor disorders.

1.0 Introduction

Human motor skills exhibit a protracted developmental maturation that continues through adolescence (Dayanidhi et al., 2013; Johansson and Cole, 1992; Petersen et al., 2010). During the same period, the sensorimotor system undergoes considerable modifications. In the corticospinal pathway, white matter density, volume, and fractional anisotropy have been shown to increase at least until late adolescence (Kumar et al., 2009; Paus et al., 1999). Age-related increases in cortical synaptic density during early childhood, followed by decreases during late childhood and adolescence, have also been demonstrated (Huttenlocher, 1990, 1979). Moreover, central ascending pathways also show prolonged maturational patterns evidenced in decreases in central conduction delay measured by somatosensory evoked potentials (Müller et al., 1994). These modifications all likely contribute to the fine-tuning of network connectivity patterns. Surprisingly, however, little is known about the normal development of task-related connectivity in functional sensorimotor networks.

Features of neural activity in functional networks can be distinguished by assessing the statistical coupling between electrophysiological signals in the frequency domain (Boonstra, 2013; Halliday et al., 1995). In adults, oscillatory activity in the sensorimotor cortex is coherent with contralateral muscle activity in the beta band (15-35 Hz) during tonic contractions (Conway et al., 1995; Halliday et al., 1998; Salenius et al., 1997; Ushiyama et al., 2011). This corticomuscular coherence reflects the functional oscillatory coupling between the cortex and muscle and thus provides a non-invasive means for investigating the cortical involvement in a given motor task. The corticospinal tract has been repeatedly implicated in mediating beta band corticomuscular coherence (Baker et al., 1999; Hansen and Nielsen, 2004; Mima et al., 2000; Salenius et al., 1997), suggesting that this coupling reflects the descent of oscillations from the motor cortex to the spinal cord by way of corticospinal projections.

However, increasing evidence suggests that corticomuscular coherence may not only reflect descending motor commands, but also ascending sensory feedback, forming an oscillatory sensorimotor loop (Lim et al., 2014; Riddle and Baker, 2005; Witham et al., 2011). It is possible to distinguish these components of coherence using directionality (or causality) analysis (Halliday et al., 2016; Witham et al., 2011) and thus to obtain information about the interplay between feedforward and feedback information flow during a given motor task. Though the precise functional significance of corticomuscular coherence is debated, a novel role for cortical beta band synchrony in predictive coding has recently been proposed (Palmer et al., 2016; Tan et al., 2016). The predictive coding theory advances the hypothesis that motor commands may be viewed as predictions of the sensory consequences of movement. Movements are thought to be optimized (e.g. during development) through a process in which error signals conveyed through sensory feedback are used to improve the precision of feedforward predictions, which gradually reduces reliance on sensory feedback as an error signal (Adams et al., 2013; Franklin and Wolpert, 2011). Recent work suggests that beta oscillations in the sensorimotor cortex (and by inference, beta band corticomuscular coherence) may specifically be related to the degree of certainty in feedforward predictions (Tan et al., 2016) and provides a relevant theoretical framework for exploring childhood development of functional and directed sensorimotor connectivity.

To date, only few studies have investigated age-related differences in corticomuscular coherence during childhood development, and most interest has been devoted to the control of upper extremities. Thus, in spite of their essential role in postural control and gait, the maturation of the cortical control of ankle muscle activity is not well understood. Although one study has demonstrated greater central common drive to an ankle dorsiflexor in older compared to younger children (Petersen et al., 2010), developmental changes in functional and directed connectivity between the cortex and ankle dorsi- and plantar flexors have yet to be investigated directly.

In this study, we explored age-related differences in corticomuscular coherence relating to the voluntary control of tonic ankle muscle contraction in children, adolescents, and adults. We also employed directionality analyses to investigate age-related differences in the strength of descending and ascending components of the functional connectivity reflected in coherence. Based on the recently suggested link between beta band oscillations in the sensorimotor cortex and certainty in feedforward prediction (Palmer et al., 2016; Tan et al., 2016), we hypothesized that the strength of the descending component of beta band corticomuscular coherence would exhibit age-related increases, indexing greater certainty in feedforward estimations.

2.0 Methods

2.1 Participants

Thirty-three healthy participants (age range 7-23 yr, 16 female) were recruited for this study by convenience sampling (see Table 1).

All participants were free from neurological disease. Written, informed consent was acquired from participants and their parents (for participants under the age of 18) based on verbal and written information they received about the experiment prior to participation. Procedures were approved by the ethics committee for the Capitol Region of Denmark (H-16021214) and adhered to Declaration of Helsinki standards.

2.2 Dorsi- and plantar flexion tasks

Participants performed 2 min of tonic dorsi- and plantar flexion requiring precise maintenance of a submaximal torque level as detailed previously (Spedden et al., 2018). In brief, participants were seated in a chair with their left foot fastened to a pedal containing a strain gauge force transducer. First, maximal voluntary contraction (MVC) for dorsiflexion was determined as the peak torque attained across three attempts. Participants were instructed to apply maximal torque for 1-2 s, and attempts were separated by 30 s rest. Verbal encouragement was given to promote maximal effort. Participants were then instructed to maintain a 10% MVC target torque level for 2 min. Participants were shown the target level as a horizontal line projected onto the wall in front of them and were asked to follow this line as precisely as possible with a trace indicating actual torque applied to the pedal. Subsequently, MVC and submaximal contraction procedures were repeated for plantar flexion.

2.3 Electrophysiological recordings

During dorsi- and plantar flexion tasks, electroencephalography (EEG) was recorded from above the leg area of the sensorimotor cortex using a cup electrode placed at the vertex (Cz) and a reference electrode placed 5 cm frontal to Cz. The vertex was determined as the intersection between the middle of the distance from nasion to inion and the middle of the distance between ears (tragus-tragus). Electromyography (EMG) was recorded from ankle muscles of the left leg following shaving and abrasion of the skin using pairs of surface electrodes (~2 cm interelectrode distance) placed over the proximal and distal ends of the anterior tibial muscle (TA), over the middle of soleus (SOL) and over the medial head of gastrocnemius (GM). The ground electrode was a lead plate covered with a damp cloth placed on the left elbow. EEG and EMG signals were amplified (EEG x 10,000, EMG x 1000) and filtered from 5 to 1000 Hz before being digitized at 2000 Hz (Micro 1401 and Spike 2, Cambridge Electronic Design, UK).

2.4 Data analysis

All data analysis was performed in MATLAB (Version R2016b, MathWorks, MA, USA) using custom scripts and Neurospec 2.11 software (Halliday, 2015). Prior to spectral analysis, signals were linearly de-trended and normalized to have common unit variance. EMG signals were also rectified to maximize information about motor unit potential timing (Halliday et al., 1995).

The correlation structure of EEG-EMG and EMG-EMG coupling during tonic dorsi- and plantar flexion was assessed using the framework presented by Halliday and colleagues (1995). EEG-EMG and EMG-EMG synchronization in the frequency domain was quantified using the coherence function. Coherence is a bounded correlational measure ranging from 0 to 1, describing the strength of linear association between two signals at a given frequency. EEG-EMG (corticomuscular) coherence describes the rhythmic synchronization of cortical and muscular activity, while EMG-EMG (intra- or intermuscular) coherence describes the strength of rhythmic common drive to two populations of motoneurons of the same muscle or synergists. EMG-EMG coherence was included as an indirect measure of common oscillatory corticospinal input (Farmer et al., 1993).

Coherence was calculated from finite Fourier transforms of disjoint signal segments (1024 samples 0.5 s, frequency resolution 1.95 Hz), which were then averaged to construct auto- and cross-spectral estimates. Individual analyses were based on 120 s of data.

Coherence is defined as the magnitude squared of the cross spectrum S_{xy} normalized by the product of the two auto spectra S_{xx} and S_{yy} for frequency *f:*

Thus, coherence reflects the consistency of amplitude ratios and phase relationships at each frequency across segments.

Coherence was calculated for the following signal pairs: Cz-TA (proximal end), Cz-SOL, TA-TA, and SOL-GM at each Fourier frequency. The beta band (15-35 Hz) was of particular interest due to its prominence during tonic contractions (Conway et al., 1995; Ushiyama et al., 2011). We additionally quantified coherence area in the beta band, as well as in the alpha (5-15 Hz) band, by summing coherence estimates at the frequencies comprising each band. We chose to present coherence results as areas (rather than e.g., peak coherence), because a total coherence estimate covering the frequencies of interest is feasibly the most physiologically relevant measure. It seems unlikely that the sensorimotor system uses just one frequency to communicate, while it is more plausible that a range of frequencies are involved.

We also calculated a ratio describing the 'peakiness' of the Cz auto spectra in the beta band to investigate whether age-related differences in coherence were related to the maturation of relative sensorimotor beta band power. This ratio was defined as the summed power in the Cz autospectra from 15-35 Hz relative to the summed power from 5-50 Hz.

Synchrony in the time domain was also assessed for EEG-EMG and EMG-EMG signal pairs using the cumulant density function, calculated from the inverse Fourier transform of the cross spectrum (Halliday et al., 1995). The cumulant density function is an unbounded correlational measure analogous to the cross-correlation function, where deviations from zero indicate a correlation between two signals q_{xy} at a given time lag u. Thus, this function assesses the delay and time span of dependency between two signals. For EMG-EMG cumulant densities, we calculated the duration of the central peak at 50% of peak maximum (Vaughan and Kirkwood, 1997), as it has been argued that short-term synchronization may reflect common corticospinal input to motor neuron pools (Datta et al., 1991; Farmer et al., 1993).

During either recording or analysis, several signals were identified as poor due to either technical problems or artifacts and were thus excluded from further analysis. Cz EEG signals from 5 participants recorded during dorsiflexion were rejected (ages 11, 12, 13, 14, and 16 yr) as well as from four of these five participants recorded during plantar flexion (11, 12, 13, and 14 yr). Two EMG signals were also identified as inadequate: EMG from the proximal end of TA in one participant (23 yr) and EMG from GM in one participant (19 yr).

EMG-EMG coherence results were visually inspected for indications of cross-talk, i.e., volume conduction causing artificially high coherence. As no results displayed high coherence over a broad range of frequencies, or extremely narrow zero-lag synchronization in cumulants (Hansen et al., 2005), no data was excluded from the analysis on this basis.

We also investigated contributions from descending and ascending activity to corticomuscular coherence by using a novel, non-parametric approach to decompose regular coherence into forward and reverse components (Halliday, 2015; Halliday et al., 2016). The advantage of this approach over typical parametric approaches based on auto-regressive (AR) models is that it is not limited by recently raised concerns regarding AR model validity (Halliday et al., 2016). In brief, this method uses a Minimum Mean Square Error (MMSE) pre-whitening filter prior to coherence analysis, which reduces coherence to the magnitude squared of the pre-whitened cross spectrum. An inverse Fourier transform of the pre-whitened cross spectrum is then used to obtain a correlational function in the time domain from which directionality is determined based on lags between the two signals. A Fourier transform is performed separately for positive lag values indicating EEG→EMG (descending) directionality and negative lag values indicating EMG→EEG (ascending) directionality to obtain factors used to decompose the original coherence to directional components (see Halliday, 2015 for further details). For the present analysis, we calculated directional estimates for the beta band by integrating descending and ascending directionality components over beta frequencies. Directionality components are also presented as percentages of the integrated total coherence in the beta band.

Performance on dorsi- and plantar flexion tasks was quantified as the root mean square (RMS) error describing the deviation of actual torque exerted from the target torque level for each data point. RMS error was normalized to MVC to account for observed age-related increases in maximal torque production.

2.5 Statistics

The statistical significance of individual coherence and cumulant density estimates was determined at the 5% significance level and is illustrated by the inclusion of 95% confidence interval limits in plots (see Halliday et al., 1995 for calculation).

We assessed the relationship between age and coherence statistically using Pearson correlations between age and coherence area for beta and alpha bands. Coherence areas were logarithmically transformed prior to statistical testing to normalize variance. Pearson correlations were also used to investigate associations between age and beta peakiness ratio; beta coherence area and beta peakiness ratio; and age and EMG-EMG cumulant density peak duration. Normal distributions were confirmed by visual inspection of histograms. As an exploratory analysis, we also investigated whether beta band coherence differed by gender using one-way ANOVA, with beta band coherence as the dependent variable and gender as the independent variable.

To investigate associations between age and directionality estimates; age and task performance (RMS error); and RMS error and coherence areas, we used Spearman rank correlations due to departures from normality evident in histograms (RMS error and directionality estimates).

For correlations where we tested coherence areas in multiple frequency bands, the significance level was adjusted using the Bonferroni correction to account for testing 4 correlations per task (i.e., two frequency bands each for EEG-EMG and EMG-EMG coherence), resulting in a threshold value of $p<0.013$ for these tests. For all other tests, a threshold of $p<0.05$ was used. For statistically significant correlations, 95 % (unadjusted) and, where applicable, 99 % (adjusted) confidence intervals (CI) for correlation coefficients are provided, and least squares lines with CIs are displayed in scatter plots.

3. Results

Table 1 presents a summary of participant characteristics.

[TABLE ONE AROUND HERE]

3.1 Results from single participants

Fig. 1 shows raw Cz EEG and TA EMG signals, auto spectra, cumulant density functions, and coherence spectra from a 7-, 14-, and 22-yr old participant during tonic dorsiflexion. Differences in Cz-TA (Fig. 1I) and TA-TA (Fig. 1J) coherence spectra between the three participants were evident; both spectra for the 7-yr old lacked clear features, whereas large and distinct peaks were visible centered around 20 Hz for the two older participants, with the 22-yr old exhibiting the greatest peaks. It should be noted that while the Cz-TA coherence spectra shown are representative for other participants with similar age in this sample, the amplitude of TA-TA coherence for the 22-yr old is remarkably high at ~0.7.

[FIGURE 1 AROUND HERE]

Fig. 2 shows individual results from plantar flexion for three other participants aged 9, 15, and 21 yr. These results generally exhibit patterns similar to those observed for dorsiflexion, though the coherence spectrum for SOL-GM also showed peaks at ~10 Hz, with peak coherence amplitude increasing with increasing age.

[FIGURE 2 AROUND HERE]

3.2 Coherence areas and cumulant density peak widths

To examine the relationship between coherence and age statistically, we assessed correlations between alpha and beta coherence areas for each coherence measure and age (Fig. 3). For Cz-TA (Fig. 3A-B), coherence area was positively correlated with age for the beta band ($r=0.759$, CI 0.532 to 0.884, $p<0.001$), but not for the alpha band ($r=0.367$, $p=0.060$). This was also the case for TA-TA (Fig. 3C-D), where a significant, positive correlation was detected only for beta frequencies (beta: $r=0.551$, CI 0.25 to 0.754, $p=0.001$; alpha: $r=0.104$, $p=0.570$). Using the adjusted significance level of $p<0.013$, the two beta band correlations remained significant (Cz-TA adjusted CI 0.451 to 0.905; TA-TA adjusted CI 0.157 to 0.793).

Cz-SOL coherence area (Fig. 3E-F) was positively correlated with age in both alpha (r=0.499, CI 0.162 to 0.732, p=0.006) and beta bands (r=0.637, CI 0.354 to 0.814, p<0.001), though no correlations were significant for SOL-GM coherence (Fig. 3G-H; alpha r=-0.321, p=0.084; beta r=0.164, p=0.386). Both alpha and beta band correlations for Cz-SOL remained significant when using the adjusted significance threshold (adjusted CI, alpha 0.0607 to 0.776; adjusted CI, beta 0.261 to 0.846).

An ANOVA was also performed to assess whether beta band coherence differed by gender. A significant effect of gender was detected, indicating that beta coherence was greater in females compared to males for Cz-TA ($F_{1,25}$=4.55, p=0.043), TA-TA ($F_{1,30}$= 5.18, p=0.030), and SOL-GM ($F_{1,28}$=9.24, p=0.005), though not for Cz-SOL (p=0.067).

We additionally quantified the width of EMG-EMG cumulant density peaks to examine whether the duration of synchronization was related to age. Cumulant density peak durations at 50% of peak maximum were not correlated with age for TA-TA (r=-0.287, p=0.111) or for SOL-GM (r=-0.042, p=0.825). Mean durations for TA-TA and SOL-GM were 12±2 ms and 10±5 ms (mean±sd), respectively.

3.3 Beta peakiness ratios

Ratios between summed power in the beta band and summed power from 5-50 Hz were calculated as a measure of relative beta power or spectral ‘peakiness’ at Cz with the aim of investigating whether age-related differences in corticomuscular beta band coherence were related to sensorimotor cortical beta oscillations.

These ratios were significantly correlated with age (Cz-TA p<0.001, CI 0.391 to 0.838, r=0.672; Cz-SOL p<0.001,CI 0.252 to 0.773, r=0.566), suggesting that relative beta power at Cz increases with increasing age. Beta peakiness ratios were also positively associated with beta band corticomuscular coherence (Cz-TA p=0.003, CI 0.220 to 0.772, r=0.554; Cz-SOL p<0.001, CI 0.342 to 0.809, r=0.629), suggesting a link between cortical beta oscillations and corticomuscular coherence.

3.4 Corticomuscular coherence directionality estimates

Fig. 4A shows the strength of interaction in descending and ascending directions for Cz-TA beta band coherence by age. Visual inspection of this data indicated that with increasing age, the strength of the interaction in the descending direction increased markedly, whereas age differences in the ascending component were less evident, though both components were positively correlated with age (descending: r_s=0.814, CI 0.628 to 0.912, p<0.001, ascending: r_s=0.563, CI 0.233 to 0.777, p=0.002). For Cz-SOL (Fig. 4B), an age-related increase in the strength of the descending component of beta coherence also appeared most prominent, with both components again exhibiting significant positive correlations with age (descending: r_s=0.647, CI 0.368 to 0.819, p<0.001, ascending: r_s=0.536, CI 0.212 to 0.755, p=0.003). For both Cz-TA and Cz-SOL, directionality components expressed as percentages of total beta band coherence (Fig. 4C-D) indicated that the percentage of interaction in the descending direction increased with age (Cz-TA: r_s=0.652, CI 0.361 to 0.827, p<0.001; Cz-SOL: r_s=0.517, CI 0.186 to 0.743, p=0.004), whereas the percentage of interaction in the ascending direction decreased with age.

3.5 Dorsi- and plantar flexion task performance

The relationship between task performance and age was investigated by assessing correlations between RMS error during dorsi- and plantar flexion and age (Fig. 5). For both tasks, a negative correlation was detected between age and RMS error (dorsiflexion: r_s=-0.480, CI -0.707 to -0.1637, p=0.005; plantar flexion: r_s=-0.519, CI -0.732 to -0.2138, p=0.002), indicating that older participants exhibited less error when attempting to precisely maintain the target torque level.

We also performed a partial correlation analysis to determine to what extent correlations between RMS error and age were influenced by beta band coherence. When controlling for shared variance due to beta band coherence area, correlations between RMS error and age became non-significant for both dorsi- (r_s=-0.121, p=0.565) and plantar flexion (r_s=-0.288. p=0.145), suggesting that the observed associations between performance and age were driven by beta band coherence.

3.6 Coherence and task performance

To examine whether coherence was directly related to task performance, correlations were calculated between alpha and beta coherence areas and RMS error. For Cz-TA and TA-TA correlations, an outlier with high dorsiflexion RMS error (~8 % MVC) was removed to avoid associations effected by this one data point.

A negative association between Cz-TA coherence RMS error during dorsiflexion was detected for alpha (r_s=-0.422, CI -0.696 to -0.042 , p=0.033) and beta (r_s=-0.573, CI -0.786 to -0.239, p=0.003) bands, though only the beta band correlation was significant at the adjusted threshold (adjusted CI -

0.830 to -0.115), indicating that participants with greater beta band coherence also exhibited less error. For TA-TA coherence, neither alpha nor beta areas were correlated with age (alpha, r_s=-0.076, p=0.683; beta, r_s=-0.256, p=0.164).

For Cz-SOL, alpha band coherence was not correlated with RMS error during plantar flexion (r_s=-0.369, p=0.054), but a significant, negative association was present for the beta band (r_s=-0.488, CI -0.728 to -0.140, p=0.009) which also exceeded the corrected significance level (adjusted CI -0.781 to -0.018). Correlations between RMS error and SOL-GM coherence for both alpha (r_s=0.067, p=0.729) and beta (r_s=-0.094 p=0.628) areas were non-significant.

4.0 Discussion

Our results show a robust association between increasing age and increasing beta band cortico- and intramuscular coherence during tonic ankle muscle contractions in participants aged 7-23 yr. This development was apparent in individual coherence spectra and was confirmed statistically by positive correlations between age and beta band coherence area for Cz-TA, Cz-SOL, and TA-TA. Directionality analysis revealed that this increase was predominantly in the descending direction for both Cz-TA and Cz-SOL. In addition, we detected associations between performance during dorsi- and plantar flexion tasks and age, suggesting that older participants exhibited more precise control of the ankle joint. Interestingly, these associations became non-significant when controlling for beta band coherence, suggesting that age-related differences in performance depended on beta coherence. This was also supported by the presence of associations between performance and Cz-TA and Cz-SOL coherence, indicating that participants with greater beta band coherence also demonstrated greater precision in force production. Together, these results suggest the occurrence of age-related changes in descending oscillatory activity from the sensorimotor cortex to the ankle muscles with possible implications for maturation of precision ankle joint control during childhood development and adolescence.

4.1 Age-related differences in beta band coherence and cumulant density functions

The corticomuscular coherence we detected in older participants is in agreement with prior work suggesting that the sensorimotor cortex contributes significantly to the control of activity in TA and SOL based on task-related functional and directed connectivity measures. In adults, Cz EEG has been shown to be coherent with TA and SOL activity at beta frequencies during tasks including tonic contraction, cyclical, bilateral movements, and walking (Jensen et al., 2019; Petersen et al., 2012; Ushiyama et al., 2017; Yoshida et al., 2017). Importantly, the directionality of information flow between brain regions and leg muscle activity has also recently been investigated during walking, and these results suggest that motor cortical areas are causally responsible for precise temporal control of TA activity during the swing phase (Artoni et al., 2017). Our results support and expand upon this previous work by suggesting that this descending cortical involvement in the control of ankle muscle activity progressively increases as a function of childhood development.

One prior study has demonstrated age-related increases in beta band intramuscular coherence during childhood development for the TA muscle during tonic contractions and walking (Petersen et al., 2010), in line with the present results. In addition, the TA-TA coherence amplitudes we detected were comparable to those previously presented for tonic contractions (Petersen et al., 2010). To the best of our knowledge, however, this is the first study to demonstrate age-related differences in corticomuscular coherence in leg muscles during childhood development and adolescence. Although we detected a clear age-related increase in beta band coherence for Cz-SOL, SOL-GM beta band coherence was not associated with age. The absence of a significant correlation with age for this measure may be simply due to relatively large variation hindering detection of associations, and/or age differences in other sources of common drive obscuring detection of the activity reflected in Cz-SOL coherence.

An additional interesting finding was that the relative power of beta oscillations at Cz (beta 'peakiness' ratio) was positively associated with both age and beta band corticomuscular coherence area. The presence of age-related differences in cortical beta oscillations is in broad agreement with previous work showing that the post-movement beta rebound response in the sensorimotor cortex (Gaetz et al., 2010; Trevarrow et al., 2019) and beta band event related desynchronization (Gaetz et al., 2010; Heinrichs-Graham et al., 2018) mature during childhood development. It has also been demonstrated that cortical beta band power is related to the strength of corticomuscular coherence in adults (Kristeva et al., 2007; Ushiyama et al., 2011), suggesting that the two measures are not likely independent. However, this relationship may not be entirely straightforward, seeing as administration of benzodiazepine has been shown to increase cortical beta power in the absence of corresponding increases in corticomuscular coherence (Baker and Baker, 2003). Regardless, our results link these prior findings by suggesting that the maturation of corticomuscular coherence may be related to the development of cortical beta band oscillations during childhood and adolescence.

In an exploratory analysis, we also detected significant effects of gender on beta band coherence area, indicating greater coherence in females than in males. As previous studies have suggested a lack of gender differences in beta band coherence in adults (Spedden et al., 2018; Ushiyama et al., 2010) the gender differences we detected may be indicative of different trajectories in corticospinal development for males and females. Though this does not appear to have been previously investigated in the context of corticomuscular coherence, studies using MRI approaches support the presence of gender differences in corticospinal maturation during childhood and adolescence (Herve et al., 2009; Pangelinan et al., 2016; Perrin et al., 2009).

The age-related differences we observed in cortico- and intramuscular beta band coherence were accompanied by differences in cumulant density functions. Inspection of individual plots indicated that EMG-EMG cumulant densities exhibited a central peak slightly displaced from zero lag, as well as greater peak amplitudes in older participants, indicating an increase in the strength of common synaptic drive to the two pools of neurons with increasing age.

We also found that the duration of EMG-EMG cumulant peaks was not associated with age, indicating that the type of synchronization does not change during childhood development. The time course for TA-TA and SOL-GM synchronization was generally consistent with short-term synchrony (Bremner et al., 1991; Datta et al., 1991) which has been suggested to result from input from collaterals of common last order neurons (Bremner et al., 1991; Sears and Stagg, 1976) likely of corticospinal origin (Datta et al., 1991; Farmer et al., 1993). In light of our observation that corticomuscular coherence exhibited age-related increases, the lack of an association between age and the duration of synchronization peaks indicates that it may specifically be the patterning, i.e., frequency content, of corticospinal input, that matures with age. Another possibility is that only the narrowest part of these peaks exclusively reflects direct corticospinal input, which has been argued based on measurements performed in the cat (Vaughan and Kirkwood, 1997), perhaps rendering detection of possible age differences in this specific source of synchrony less straightforward. However, the relevance of this argument for the present data is difficult to discern considering the large differences in the temporal precision of correlations that can be detected in invasive approaches in the cat compared to the use of surface EMG in humans.

Cumulant density functions for EEG-EMG couplings indicated the emergence of central peaks flanked by secondary peaks in parallel with the emergence of beta band coherence peaks, indicating rhythmic interactions between signal pairs. The amplitude of the central peaks also appeared to increase with age, indicating greater corticomuscular synchrony in older participants. We observed that the lags for the main peaks varied between participants and did only in some cases agree with corticospinal conduction times of ~30 ms for TA and SOL. This is likely a consequence of contributions from both ascending and descending pathways to corticomuscular coherence, as it has been demonstrated that the interpretation of these lags as representing conduction times is only useful in the case of a purely feedforward system (Cassidy and Brown, 2003; Witham et al., 2011).

4.2 Directionality components of beta band corticomuscular coherence

Our directionality analysis indicated that for both Cz-TA and Cz-SOL, the strength of beta band coherence in the descending direction increased with increasing age. For both signal pairs, the strength of the ascending component also increased significantly with age, but this appeared far less pronounced than the increase in the descending component. As these increases in absolute directional interactions for both ascending and descending components are likely linked to increases in total beta band coherence, we also investigated the age-related progression of the relative distribution of directionality components. With increasing age, the percentage of the beta band coherence reflecting descending directionality increased, while the percentage reflecting ascending directionality decreased. An age-related increase in the strength of the descending component of corticomuscular coherence likely reflects an increase in task-related oscillatory corticospinal activity, as has been suggested based on regular cortico-, intra-, and intermuscular coherence analysis (Farmer et al., 2007; James et al., 2008; Petersen et al., 2010), whereas the lower strength of the ascending interaction indicates that ascending sensory activity may play a less important role in the functional corticomuscular coupling during this task. In addition, the age-related decrease observed in the relative ascending component may suggest a reduction in the task-related reliance on sensory feedback with advancing age. This is consistent with studies demonstrating that sensory feedback in spinal circuits is reduced with increasing age during childhood and early adolescence with corresponding improvements in motor function (Hodapp et al., 2007; Willerslev-Olsen et al., 2014).

4.3 Functional significance of beta band coherence

In parallel with age-related increases in cortico- and intramuscular coherence, we detected age-related decreases in error in torque production during dorsi- and plantar flexion tasks. To further explore the basis of these age-related differences in task performance, we examined partial correlations between age and error while controlling for beta band corticomuscular coherence. Interestingly, associations between age and error became non-significant when accounting for common variance due to beta coherence areas, indicating that these age-performance associations in fact depended on beta band coherence. In support of this, error was also directly correlated with beta band corticomuscular coherence for both tasks, suggesting that participants with greater beta band coherence also exhibited lower error. These findings are in accordance with results from several prior studies demonstrating that beta band corticomuscular coherence is greater when high precision is required (Kristeva-Feige et al., 2002; Kristeva et al., 2007; Witte et al., 2007). Together, these findings suggest that beta band coherence may play a role in the control of precision in force production during steady state motor output. We did, however, only detect a significant association between beta band coherence and error for corticomuscular coherence, whereas associations for intra- and intermuscular coherence were not significant. This may be due to the more indirect nature of these measures, which entails that they may be less sensitive compared to corticomuscular coherence.

Though a precise mechanistic model for the functional role of beta band corticomuscular coherence is lacking, we suggest that the predictive coding hypothesis (Adams et al., 2013; Franklin and Wolpert, 2011) provides a useful framework for understanding our findings. The age-related increases we found in the strength of descending relative to ascending components, accompanied by age-related increases in force precision, could be interpreted to reflect the maturation of predictive control. If the development of motor control is viewed in terms of a gradual learning process involving the improvement of feedforward predictions by minimizing the difference between actual and predicted sensory consequences, our results may indicate the development of a robust internal model, entailing more stable motor output and reduced reliance on sensory feedback as an error signal. Further support for this interpretation is provided by recent work by Tan and colleagues (Tan et al., 2016) suggesting that beta oscillations in the sensorimotor cortex are associated with certainty in feedforward prediction of movement trajectory, advocating a specific role for beta oscillations in predictive coding (Palmer et al., 2016). Thus, an age-related increase in beta band corticomuscular coherence during childhood development and adolescence may suggest that with advancing age, confidence in internal feedforward estimations grows, which manifests behaviorally as greater precision in motor output. It should be noted, however, this link to predictive coding has to date only been drawn for beta oscillations in the sensorimotor cortex, so future studies should investigate whether this is also the case specifically for corticomuscular coherence.

4.4 Alpha band coherence

Alpha band coherence was also observed for TA-TA and SOL-GM upon visual inspection of individual plots, but the area of alpha band coherence for intramuscular measures was not significantly correlated with age. We did, however, find a significant positive association between age and alpha band coherence for Cz-SOL. Coherence in the alpha band is often present in intra- and intermuscular coherence, but is not typically prominent in corticomuscular coherence (Conway et al., 1995; Farmer et al., 1993; Salenius et al., 1997). Indeed, the corticomuscular coherence values we observed in this frequency band were very low. It has been suggested that this lower frequency coherence may be associated with physiological tremor (Raethjen et al., 2002), which occurs in the same frequency range, as well as that spinal circuits may act to reduce corticomuscular coherence at these frequencies to reduce physiological tremor (Williams and Baker, 2009). In this context, the basis for an age-related increase in alpha band corticomuscular coherence is not apparent, but the low coherence values in this frequency band warrant in any case a conservative interpretation.

4.5 Methodological considerations

We recorded EEG using a single electrode placed presumably above the sensorimotor cortex, i.e., at Cz. This entails that it was not possible to determine whether this was the optimal electrode position for detecting corticomuscular coherence in all participants. Nevertheless, we find the use of this electrode position well-justified based on results from a number of studies using EEG and MEG arrays demonstrating that beta band corticomuscular coherence is indeed maximal at Cz during contraction of leg and foot muscles (Gross et al., 2000; Jensen et al., 2019; Mima et al., 2000; Petersen et al., 2012; Salenius et al., 1997; Spedden et al., 2018; Yoshida et al., 2017). These robust findings indicate that individual differences in e.g. brain folding and head shape do not appear to have a substantial effect on the optimal electrode placement for detecting corticomuscular coherence.

Another limitation of using a single electrode is that we were not able to perform blind source separation to (1) identify and remove possible artifacts originating from eye blinks, saccades, and/or EMG activity; and (2) use source localization to perform coherence analysis using a sensorimotor cortex component rather than a single electrode. We did, however, take precautions to limit these artifacts by asking participants to relax face and neck muscles and minimize blinking during EEG recordings. In addition, one study has compared the use of a single electrode and sensorimotor cortical source to calculate corticomuscular coherence and found similar coherence magnitudes (Gwin and Ferris, 2012), supporting the validity of the present approach.

Moreover, it is possible that the presence of cross talk between EMG electrode pairs may have contributed to intra- and intermuscular coherence measures. We think this is unlikely, however, based on the absence of broadband coherence in individual spectra and the lack of very large and narrow cumulant peaks precisely at zero lag (Hansen et al., 2001). What is more, if this were an influencing factor, then we would expect to see greater coherence in young participants, where EMG electrode pairs were separated by shorter distances, but the youngest participants were on the contrary those who exhibited the lowest coherence magnitudes.

Finally, our results should be interpreted in light of the relatively small sample size of n=33. Thus, further studies with a larger sample are needed to confirm our findings.

5.0 Conclusion

Our results indicate that the functional oscillatory coupling between the sensorimotor cortex and ankle muscles during tonic contraction exhibits an age-related strengthening during childhood and adolescence. Analysis of the directionality of this coupling showed that the primary interaction underlying this age-related increase was in the descending direction, suggesting that these changes likely reflect an increase in task-related oscillatory corticospinal activity during development. In addition, the strength of the functional corticomuscular coupling was associated with precision in ankle joint control. In terms of the predictive coding hypothesis, we suggest that our results may be interpreted as reflecting an age-related increase in reliance on feedforward control as the maturing nervous system becomes better at predicting the sensory consequences of movement, with possible implications for precision force control.

These findings contribute to our knowledge of the developmental processes associated with the maturation of the corticospinal pathway to the leg muscles, as well as the role of oscillatory activity in precision force control during development. From a clinical perspective, these results may provide a precursor to the development of interventions targeting rehabilitation of motor function in children and adolescents with central motor disorders.

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Tables

	7-9 yr	**10-12 yr**	**13-15 yr**	**16-18 yr**	**19-23 yr**
N	6	6	7	6	8
Gender (M/F)	2/4	3/3	6/1	3/3	2/6
Height (cm)	133±5	160±16	175±8	173±10	172±4
Body mass (kg)	27.2±4.3	41.7±5.8	65.1±12.1	64.1±8.1	74.1±9.2
MVC DF torque (Nm)	39.0±12.3	60.0 ± 8.7	122.2 ± 44.1	84.6 ± 26.0	113.5 ± 25.3
MVC PF torque (Nm)	49.2 ± 17.4	74.5 ± 30.4	122.9 ± 34.7	108.5 ± 47.0	169.9 ± 52.8

Table 1: Participant characteristics. Descriptive statistics are presented as mean ± standard deviation except for gender. MVC, maximal voluntary contraction; DF, dorsiflexion; PF, plantar flexion.

Figure captions

Figure 1: **Individual data from three participants during dorsiflexion**. Raw Cz EEG (A), TA_{prox} (B) and TA_{dist} EMG (C); auto spectra for Cz (D), TA_{prox} (E), and TA_{dist} (F); cumulant density functions for Cz-TA (proximal end) (G) and TA-TA (H); and coherence spectra for Cz-TA (I) and TA-TA (J). Dashed horizontal lines on cumulant density and coherence plots indicate 95 % confidence interval limits. Shaded areas highlight the beta band (15-35 Hz). TA, anterior tibial muscle; TA_{prox}, proximal end; TA_{dist}, distal end.

Figure 2: **Individual data from three participants during plantar flexion**. Raw Cz EEG (A), SOL (B) and GM EMG (C); auto spectra for Cz (D), SOL (E), and GM (F); cumulant density functions for Cz-SOL (G) and SOL-GM (H); and coherence spectra for Cz-SOL (I) and SOL-GM (J). Dashed horizontal lines on cumulant density and coherence plots indicate 95 % confidence interval limits. Shaded areas highlight the beta band (15-35 Hz). SOL, soleus muscle; GM, medial head of gastrocnemius muscle.

Figure 3: Correlations between age and alpha and beta band coherence area. Logarithmic coherence areas for Cz-TA (A-B), TA-TA (C-D), Cz-SOL (E-F), SOL-GM (G-H) plotted by age. Correlation coefficients and p-values are for Pearson correlation. For statistically significant correlations, least squares lines and 95 % confidence intervals are shown. TA, anterior tibial muscle; SOL, soleus muscle; GM, medial head of gastrocnemius muscle.

Figure 4: Correlations between age and directionality components. Strength of beta band interactions in ascending and descending directions for Cz-TA (A) and Cz-SOL (B) plotted by age. Relative contributions from ascending and descending components to the total beta band coherence for Cz-TA (C) and Cz-SOL (D) plotted by age. Correlation coefficients and p-values are for Spearman rank correlation. For statistically significant correlations, least squares lines and 95 % confidence intervals are shown. TA, anterior tibial muscle; SOL, soleus muscle; GM, medial head of gastrocnemius muscle.

Figure 5: Correlations between RMS error and age. RMS error plotted by age for dorsiflexion (A) and plantar flexion (B). Correlation coefficients and p-values are for Spearman rank correlation. For statistically significant correlations, least squares lines and 95 % confidence intervals are shown. RMS, root mean square; MVC, maximal voluntary contraction.

Figure 1

[redacted]

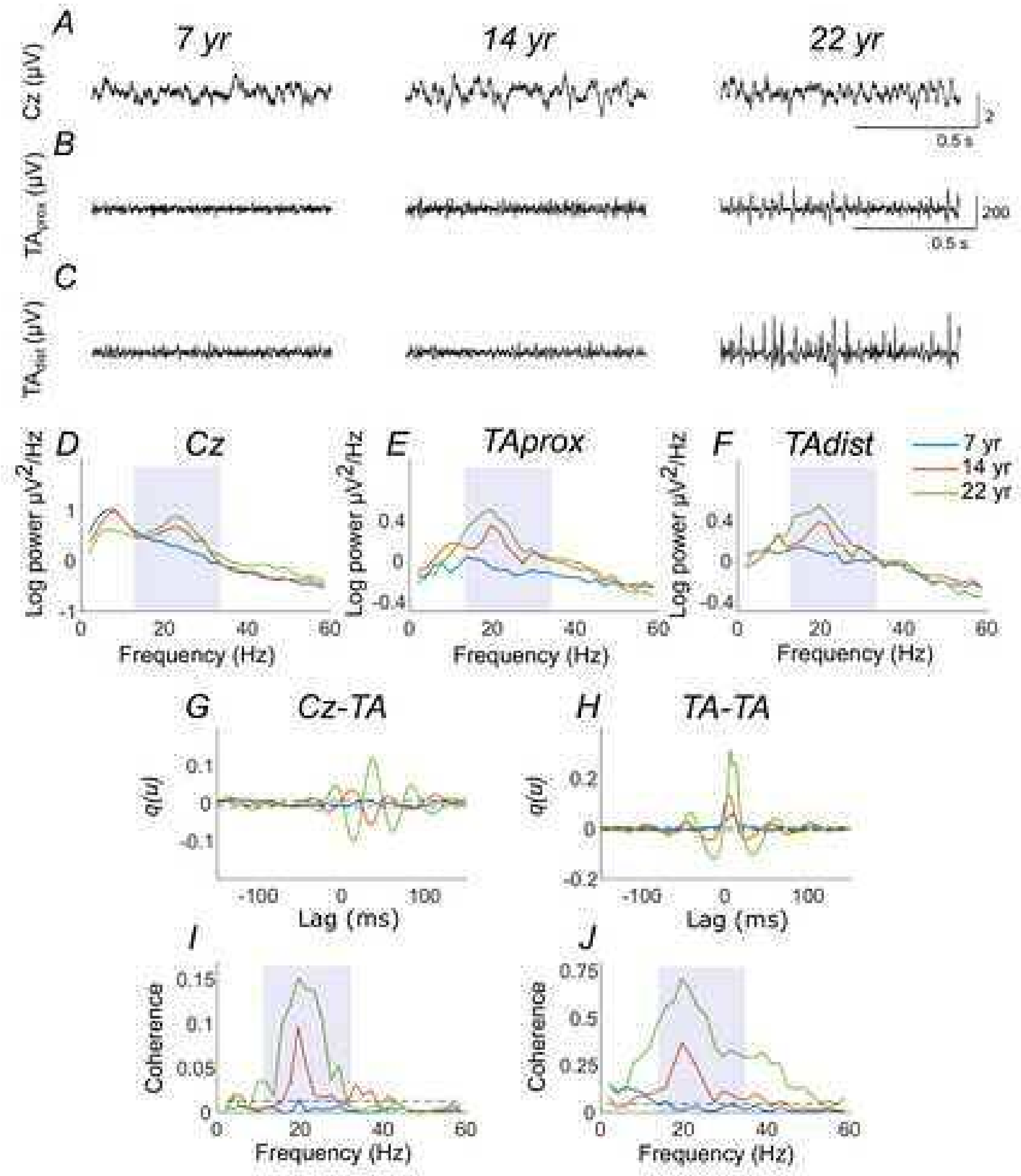

Figure 2

[redacted]

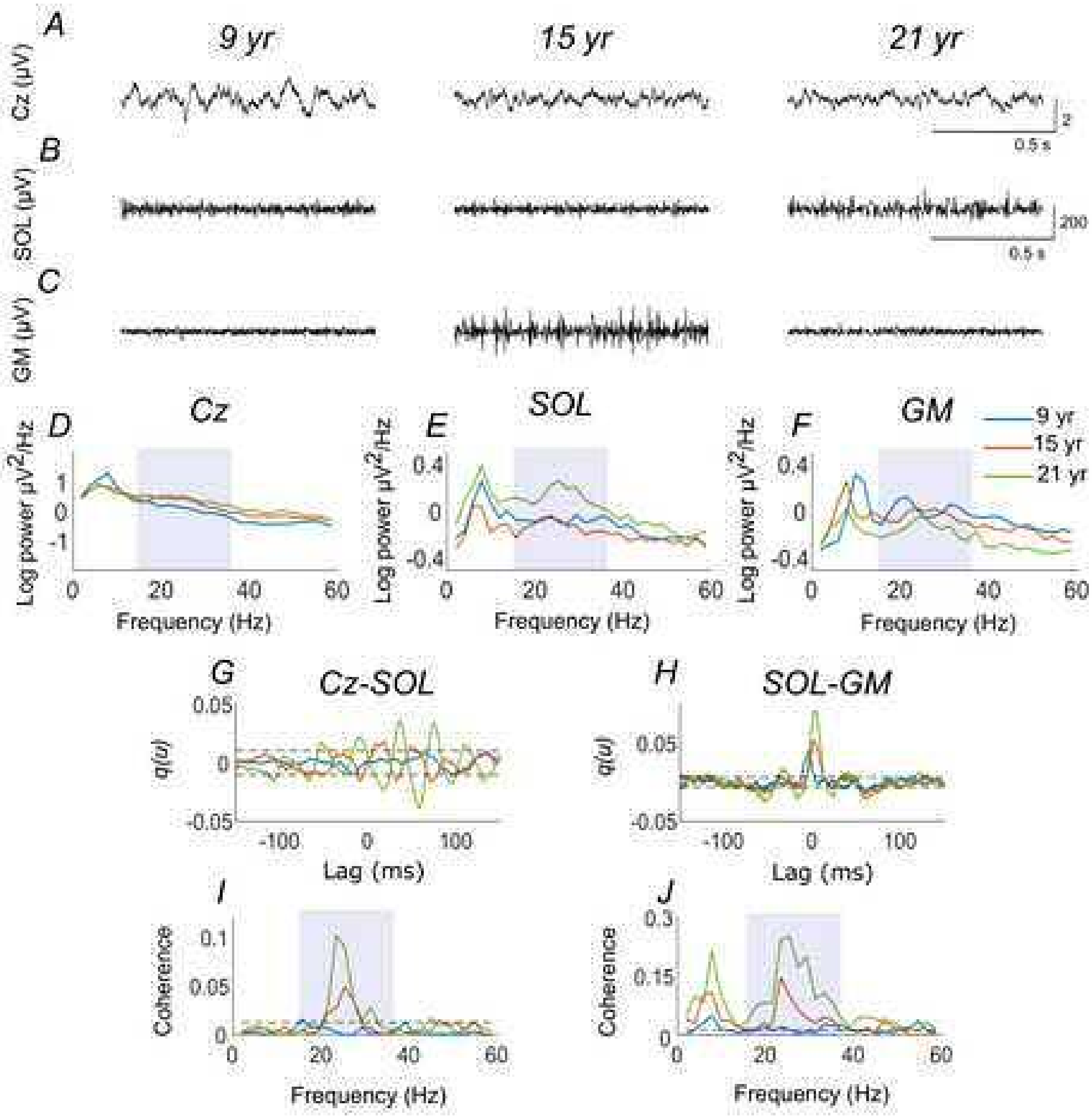

Figure 3

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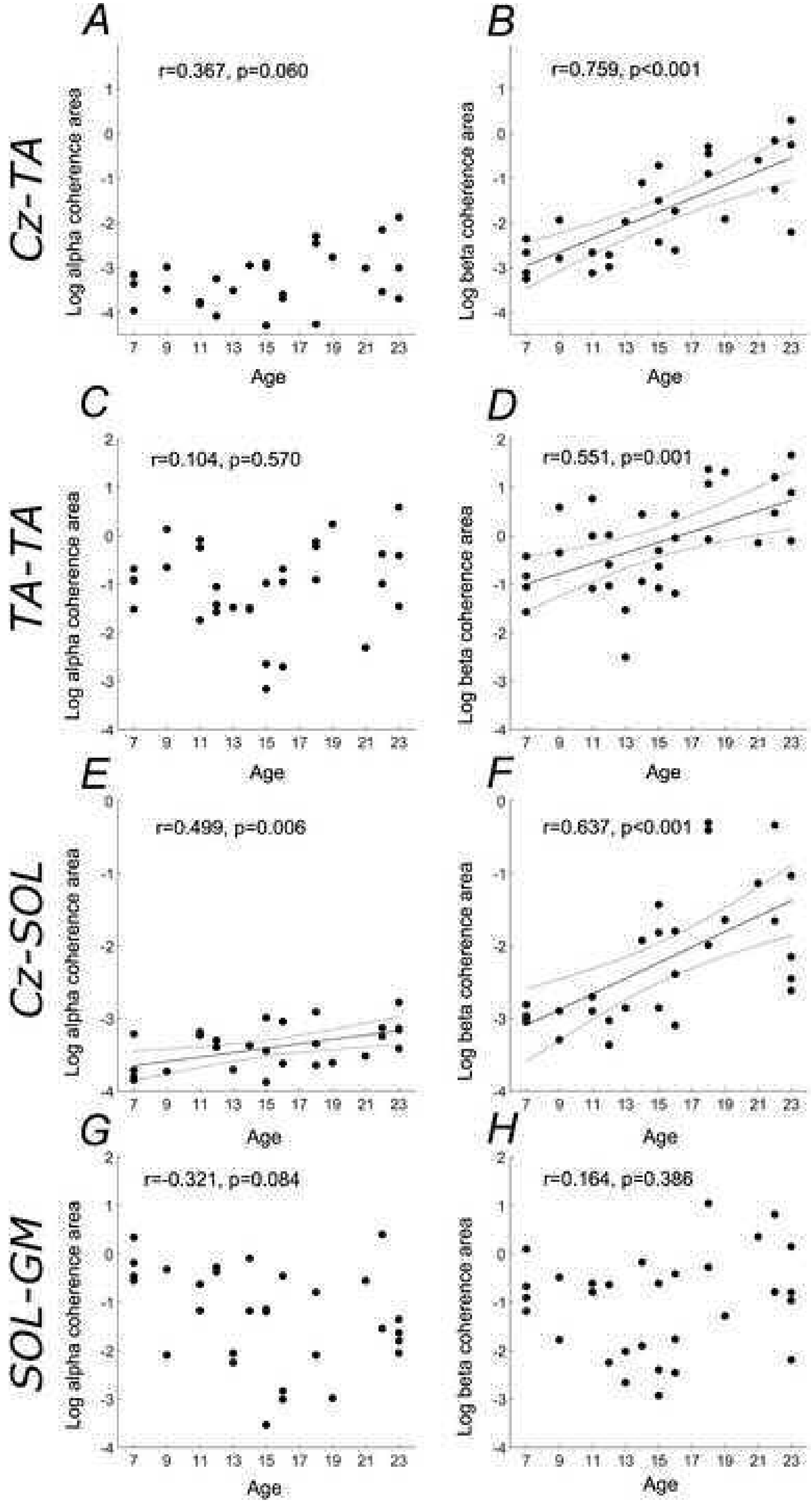

Figure 4

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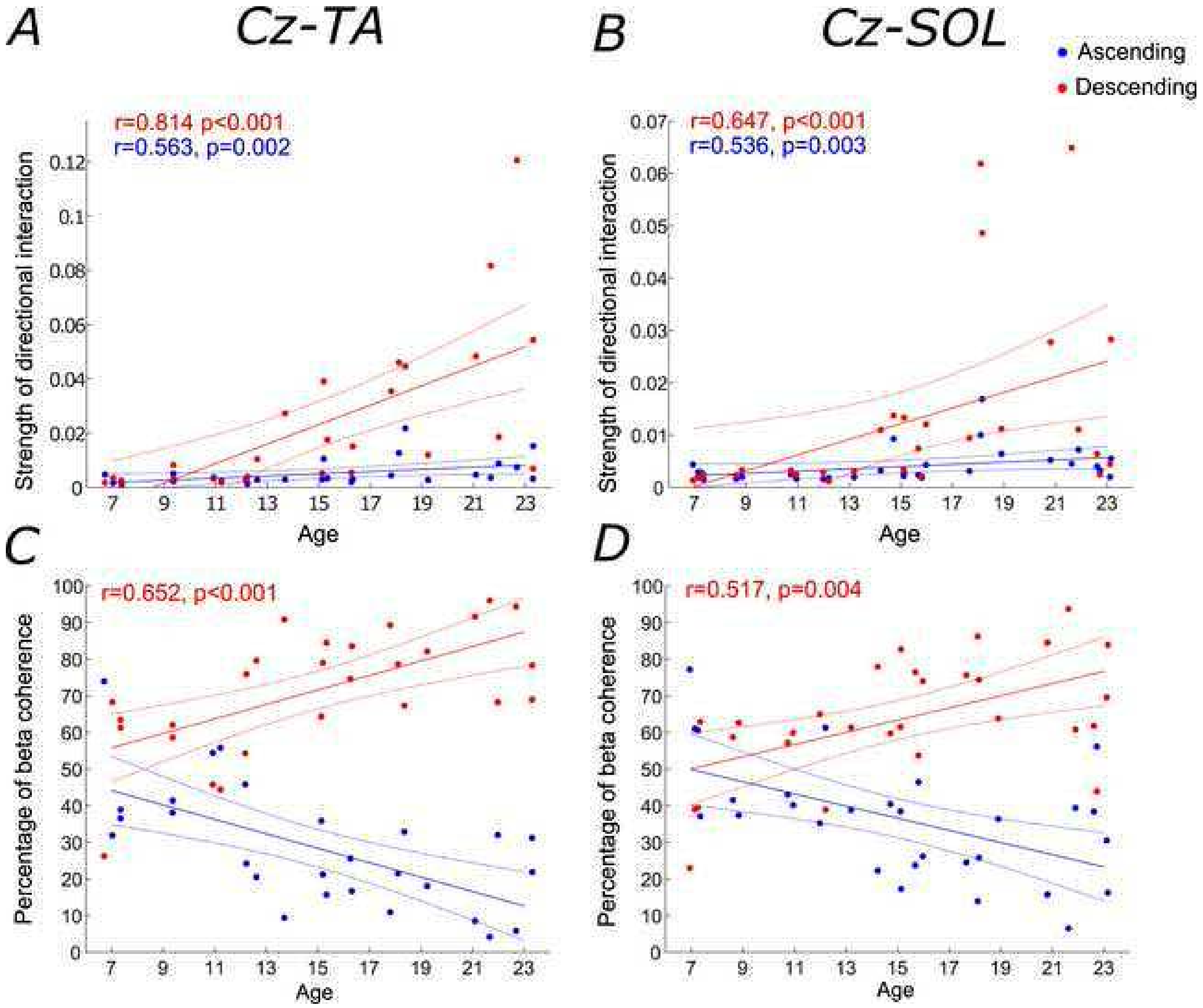
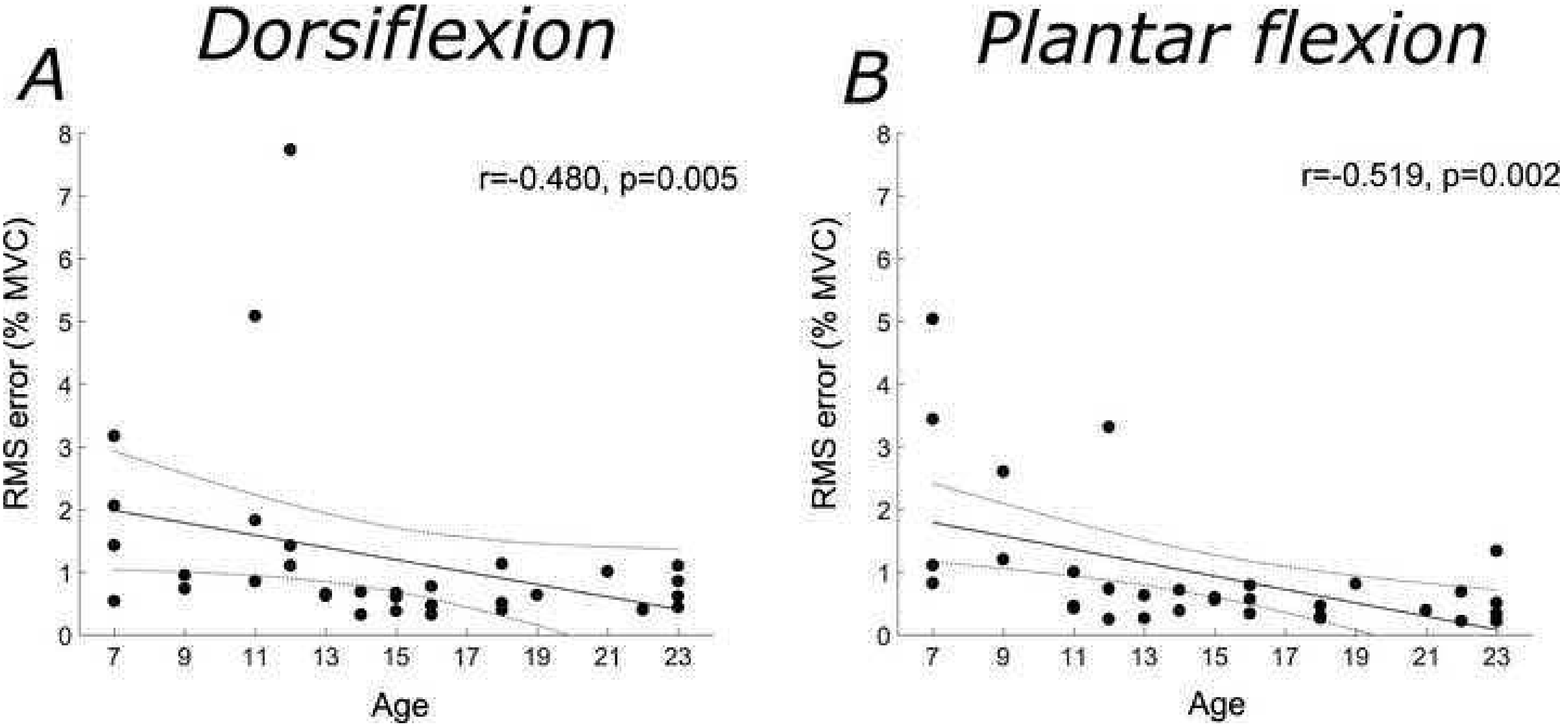


Figure 5

[redacted]



***Data and Code Availability Statement**

Data and code availability statement

Data files will be uploaded to the Zenodo database upon acceptance. The MATLAB code used for the primary analysis is available at www.neurospec.org