Developmental trends of theta–beta interelectrode power correlation during resting state in normal children

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Abstract

The possibility that power-to-power (theta–beta) frequency coupling increases during development was analyzed. Three minutes of spontaneous EEG in an open eyes condition were recorded in a sample of 160 subjects ranging from 6 to 26 years old. Theta (4–7 Hz) and beta band (15–20 Hz) power was calculated in a trial-by-trial basis. Inter-electrode power correlations (IPC) were computed in each subject as the correlation between the power of two frequency bands recorded in two electrodes. An increase in theta–beta IPC with age was obtained. IPCs were higher when theta was seeded in posterior regions than in anterior or central regions. Moreover, the significant correlations between each individual IPC and age were calculated, making it possible to draw IPC versus age correlation maps in order to capture the IPC development topography. An increase was found in significant correlations in the left hemisphere compared to the right hemisphere. There were no differences in the inter-hemispheric versus intra-hemispheric IPC maturation spatial patterns. An increase in power-to-power–frequency coupling in theta–beta occurs during development, suggesting an increase in functional connectivity with age. Frequency coupling between theta and beta rhythms would be one of the mechanisms facilitating integration of long distance functional networks during development.

Keywords Inter-electrode power correlation (IPC) · Power-to-power–frequency coupling · Normal child development · Spontaneous electroencephalogram · Age effect · Sex effect

Introduction

The study of brain rhythms, their interactions, and their relationship with behavior is a major topic in the field of neuroscience (Gross 2014). The techniques that make it possible to record brain rhythms are the electroencephalogram (EEG) and magnetoencephalogram (MEG) (Buzsáki 2006). The EEG is produced by local field potentials in the brain, generated by synchronously active local neural populations of sufficient size (Thatcher et al. 2008; Lopes da Silva 2013). This recording can be performed in the absence of any specific task, referred to as the continuous resting-state paradigm or spontaneous EEG. Resting-state studies can be used to identify functional or effective connectivity patterns in the brain (Gross 2014). Functional connectivity is defined as the statistical relationship or mutual information between two neuronal systems that exhibit functional integration (Friston et al. 2013). The number of different analytic approaches used to

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study functional connectivity in EEG resting-state paradigms is rising, along with interest in this field (Jirsa and Müller 2013; Diessen et al. 2015, Wilmer et al. 2010; Dasdemir et al. 2017). Examples of these approaches are power correlation, coherence, phase-lag index, synchronization index, phase locking value and different kinds of cross-frequency coupling analysis, among others.

In the present study, inter-electrode power correlation (IPC) is applied, defined here as the correlation between the Power Spectrum Density (PSD) of two frequency bands recorded in two electrodes, or one electrode and itself, on a trial by trial basis (a detailed description of IPC can be found in the “Methods” section). The IPC measure would be considered a basic indicator of functional connectivity in its simplest form: “temporal correlations between remote neurophysiological events” (Friston 1994). The PSD is computed by means of Fast Fourier Transform (FFT), which is a frequency analysis that allows short segments of the signal to be decomposed into a complex spectrum in the frequency domain for each analyzed segment (Gross 2014). The spectral power is a representation of the energy or power for each observed frequency. Given the large number of frequencies whose PSD in two electrodes can be correlated, in the present report we focus on the theta versus beta correlation because there is a co-maturation of the PSD in these two frequency bands during development (Rodríguez-Martínez et al. 2015). Theta–beta IPC values can be considered a form of power-to-power cross-frequency coupling (Jirsa and Müller 2013).

There are at least two methodological limitations of considering the interpretation of EEG correlational connectivity measures (Kida et al. 2016). On the one hand, the electric fields generated at one particular point in the cortex and spread by volume conduction can lead to a spurious correlation because two electrodes could be recording the power of a common electric field source. However, for the developmental problem of functional connectivity, if IPC values increase systematically with age (ages 6–26 years) across the whole scalp, it would be more parsimonious to admit that there is an increase in mutual influence between the brain areas than to assume a complicated rearrangement of sources across the scalp that would ultimately increase the IPC values with age. Additionally, if the increase of IPC with age between two electrodes would be due to the action of a unique source propagated by volume conduction to two different electrodes, the IPC should be greater in near than in far electrodes, given that the signals would be more similar in nearby electrodes than in long distance electrodes. Therefore, if IPC values show a trend to be higher in long distance than in nearby electrodes, as age increases, a genuine influence of age in inter-electrode connectivity, not contaminated by volume conduction of a single source, should be accepted.

On the other hand, EEG requires differential amplification or a common reference potential in order to record brain electric fields, and the reference could affect the connectivity measures. This problem is common in EEG recordings, but it can be mitigated if the reference is situated in relatively electrically inactive areas, as in the case of the linked mastoids in the present report. Therefore, if IPC would increase with age the co-variation of power between different electrodes would be interpreted as an increase of functional integration.

Developmental neuroscience is still in the early stages (Goldenberg and Galván 2015), given that extensive use of new non-invasive recording techniques is relatively recent, but some results related to EEG signals have consistently been found. One of the main descriptors of EEG development, as pointed out by various researchers (Clarke et al. 2001; Gmehlin et al. 2011; Rodríguez-Martínez et al. 2012, 2015), is the decrease in absolute Power Spectral Density (PSD) from delta to beta frequency bands with age, whereas there is a decrease in relative PSD of slow waves (delta and theta) and an increase in the relative PSD of faster oscillations (alpha and beta) with age. This observation has been related to synaptic pruning. Whitford et al. (2007) found that the PSD curvilinear decrease in slow waves during development parallels the decrease in grey matter in frontal and parietal lobes, measured by Magnetic Resonance Imaging (MRI). Clarke et al. (2001) added that this maturation occurs earlier in the midline than in the hemispheres, and Rodríguez-Martínez et al. (2012) posited that posterior regions mature earlier than anterior sites. Using MEG recordings, Gómez et al. (2016) proposed that the decrease in power with age cannot be entirely attributed to the increase in the electrical resistivity of the skull with age. These findings are coherent with the developmental trend of grey and white matter tissue (Schuz et al. 2002; Gogtay et al. 2004, Giedd et al. 2009). Another robust observation is the displacement of the alpha peak frequency to 10 Hz when it reaches its mature form (Gmehlin et al. 2011). The increase in frequency in brain oscillations would be a property not only of the alpha rhythm, but also of theta and beta rhythms (Rodríguez-Martínez et al. 2015). This increase in the frequency of oscillations with age in beta and theta has been demonstrated by topographical analysis, which showed similar maps at different frequencies for different ages of development (Rodríguez-Martínez et al. 2017).

Studies designed to unravel functional connectivity patterns from a developmental point of view are still scarce. Thatcher et al. (2008), measuring coherence and phase delays in the beta frequency band (13–25 Hz), observed that short range connections increased coherence with age, and that coherence mediated by long-range fasciculi decreased coherence as a function of age. This

decrease occurs from 2 months to 4 years old and is flat later in child development. By contrast, they also found that short-range inter-electrode phase delays decreased and long-range phase differences increased during development. This maturation pattern was found to be greater for the antero-posterior versus postero-anterior inter-electrode direction and for the left versus right hemisphere. Analyzing delta (1.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz) and beta (12.5–25 Hz) frequency bands in a sample of children between 8 and 12 years old, Barry et al. (2004) reported increments in coherence with age on intra-hemispheric long-range electrode pairs for all the bands considered, except beta, but no age effect for short-medium inter-electrode distances. This study also found higher coherence for left versus right intra-hemispheric short-medium range inter-electrode pairs.

The apparent divergences in the results obtained by Thatcher et al. (2008) and Barry et al. (2004) for long-range electrode configurations in the beta range can be explained by the fact that Barry did not report growing coherence throughout development for the beta band, and Thatcher's decrease in beta coherence as a function of age was found between 2 months and 4 years old, with this effect being almost flat from four to 16 and a half years old (the age range of Barry's sample). Divergences in short-range configurations can be explained by differences in sample sizes (458 vs. 80) and sample ages (2 months–16.67 years vs. 8–12 years), but more fundamentally by the use of different short-range inter-electrode configurations (Fp1/2–F3/4, O1/2–P3/4 for Thatcher; Fp1/2–F3/4, T3/4–T5/6, C3/4–P3/4 for Barry). With regard to the influence of sex during development, a higher coherence has been described in males than in females in the same age range (Barry et al. 2004). Generally, it is assumed that children's multiple decentralized local clusters evolve to more integrated and distributed connections throughout the mature brain (Goldenberg and Galván 2015).

This study is based on previous work by Rodriguez-Martinez et al. (2015). We found an age-dependent correlation between the spectral power of the theta (4–7 Hz) and beta bands (15–20 Hz), and that this covariation was more noteworthy on bilateral antero-posterior electrode sites.

The goal of the present study is to analyze the co-maturation pattern of the theta and beta bands, measured by the IPC, trial-by-trial in individual subjects. This approach makes it possible to observe theta–beta power-to-power–frequency coupling during normal maturation and unravel the characteristics of its topography. To the best of our knowledge, few data are available on how EEG connectivity measures between different EEG bands, such as theta–beta, develop across the lifespan. Our hypothesis is that the theta–beta IPC increases with age, indicating a higher integration of cortical networks with age.

The null hypotheses to be tested in this study will be: (1) there are no differences in IPC as a function of age; (2) there are no differences in IPC as a function of sex; (3) there are no differences in IPC when theta is seeded in anterior, central, or posterior regions; (4) there are no differences between left versus right intra-hemispheric IPC. Based on the literature presented above, a difference in IPC between children and young adults is expected, with higher IPC in the older group. Regarding sex, a higher IPC is expected in males, as well as a higher left hemisphere IPC. We do not have a specific hypothesis about the effect of seeding theta in a given region. Additionally, and by selecting the connections that show a statistically significant increase with age, we expect to establish complementary information (complementary to hypothesis 4) if there are different connectivity maturation dynamics in left and right intra-hemispheric connectivity, and in intra and inter-hemispheric connections. The topography of the connections that change with age, as measured by IPC versus age, will also be described.

Methods

An overview of the method is displayed in Fig. 1.

Subjects

The study included a sample of 160 human subjects between 6 and 26 years old. Three subjects were excluded due to excessive EEG artifacts. 144 subjects were right-handed, and 13 were left-handed. The left-handed subjects were maintained in the analyzed population to increase the generalizability of the results. The group of males consisted of 77 subjects (mean $\pm$ SD age 16.75 ± 5.85), 70 right-handed and 7 left-handed. The female group consisted of 80 subjects (mean $\pm$ SD age 16.74 ± 5.85), 74 right-handed and 6 left-handed. Subjects did not report any neurological diseases or psychological impairments. Both groups were extracted from middle class socioeconomic backgrounds. The children had normal academic records, and the young adults were college students. Experiments were conducted with the informed and written consent of each participant (parents/tutors in the case of the children).

EEG recording

The EEG was recorded during 3 min of spontaneous activity in an open eyes condition. Open eyes were preferred over closed eyes in order to increase the arousal of the youngest children during the recording period. Subjects were asked to stay calm and look at the screen, blinking as little as possible and keeping their eyes focused on a cross

Fig. 1 Overview of the method. *ICA*: *IPC* inter-electrode power correlation, *FDR* false discovery rate. A complete description in the “Methods” section

presented at the center of the screen. Subjects were recorded at different times of the day between 12 am and 8 pm. No information about previous sleep was required.

Recordings were obtained from an average reference of 32 scalp sites from the 10–20 international system (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, M1, T7, C3, Cz, C4, T8, M2, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, POz, O1, Oz, O2), using tin electrodes mounted in an electrode cap (ELECTROCAP). Eye movements were recorded by two electrodes at the outer canthus of each eye for horizontal movements, and by electrodes placed above and below the left eye for vertical movements. All the scalp electrodes were re-referenced off line to the mastoid average $(M1 + M2)/2$. Impedance was maintained below 10 Kilo-Ohms ($\text{K}\Omega$). Data were recorded in direct current mode at 512 Hz with a 20,000 amplification gain, using a

commercial analog digital acquisition and analysis board (ANT, Refa series). Data were not filtered during registration. The power spectral time analyzed was less than what was initially recorded (90 epochs of 2 s), due to the elimination of epochs containing artifacts. The average time analyzed in the EEG recordings of the sample was 134.3 s (mean $\pm$ SD 134.3 ± 39.7 s; minimum time 22.0 s), whereas the average time recorded in the different age groups was: (a) children: 6–9 years old, 116.9 s (mean $\pm$ SD 116.9 ± 39.3 s, minimum time 40.0 s); (b) pre-adolescents: 10–13 years old, 131.6 s (mean $\pm$ SD 131.6 ± 41.4 s, minimum time 22.0 s); (c) adolescents: 14–17 years old, 140.1 s (mean $\pm$ SD 140.1 ± 32.2 s, minimum time 38.0 s); (d) youngsters: 18–21 years old, 138.9 s (mean $\pm$ SD 138.9 ± 42.8 s, minimum time 38.0 s); and (e) young adults: 22–26 years old, 134.3 s

(mean $\pm$ SD 134.3 ± 40.0 s, minimum time 30.0 s). Three participants whose corrected EEG durations were below 22.0 ms were excluded from the study. An ANOVA was computed, with the number of rejected trials as independent variable and the age group as between-subjects factor, in order to show any statistical differences between groups in the analyzed time. This control ANOVA revealed that the five age groups did not show any differences in the number of rejected trials. ($F [4] = 1.68$, $p = 0.156$).

Data analysis

EEG recordings were analyzed with EEGLAB (Delorme and Makeig 2004) and Matlab 2010a software packages. The segmented epochs had a duration of 2.0 s. All epochs for which the EEG exceeded $\pm 150 \mu\text{V}$ in any channel were automatically discarded. The Power Spectral Density (PSD) of individual epochs was computed by Fast Fourier Transform (FFT), using the *spectopo* function of the EEGLAB software. The PSD function provides the energy of the signal in each frequency (Smith 1999). This function uses the *pwelch* script of Matlab, which applies a hamming window and computes PSD. The Hamming window, by multiplying each single epoch by the Hamming function reduces the leakage of frequencies in the abrupt border of the time epochs. The window function is adjusted to have a value near zero in the epochs border producing zero values when the window is multiplied by the EEG epoch, eliminating the distortion of applying the FFT to finite epochs. The PSD was computed in windows of 2 s and expressed in decibels.

The EEG frequencies in the range from 4 to 7 Hz for theta and from 15 to 20 Hz for the beta band were selected for analysis. These frequency ranges for theta and beta bands were chosen in a previous study by our group with a very similar sample (Rodriguez-Martinez et al. 2015). Once the PSD for each trial had been obtained from each subject, the mean power of the theta and beta bands was correlated using Spearman's rank correlation coefficient for all the trials between all the electrodes. Please note that theta and beta power were obtained in each single epoch of 2 s, making it possible to obtain the theta versus beta correlation for any subject on a trial-by-trial basis. This is an important difference from Rodriguez-Martinez et al. (2015), in which average theta power versus average beta power were correlated between different subjects.

This operation was repeated for each pair of electrodes, including the theta versus beta correlation in one given electrode with itself. Therefore, the data matrix obtained consisted of 900 empirical variables in the columns (30×30 electrodes), corresponding to the inter-electrode theta–beta power correlation, and 157 subjects in the rows. Thus, each single piece of data represents the power

correlation between theta and beta bands of two single electrodes in one subject during the recording time. We defined this variable as the IPC, which corresponds to the correlation between theta versus beta bands in each single subject and pair of electrodes. An example of IPC analysis can be found in Fig. 2.

Statistical analysis

Using the Statistical Package for the Social Sciences (SPSS) 20.0, a mixed-model Analysis of Variance (ANOVA) was applied to the IPC in order to observe differences due to age and sex (between-subjects factors). The 900 IPC variables ($30 \text{ electrodes} \times 30 \text{ electrodes}$) were the within-subject variables. In order to organize the data matrix in a feasible manner to compute the ANOVA, two within-subject factors were considered: the first factor corresponded to the electrode in which theta was seeded and the second factor to the whole array of electrodes. Both factors had 30 levels (electrodes). Age, as between-subject factor, was organized in five groups (children: 6–9 years old; pre-adolescents: 10–13 years old; adolescents: 14–17 years old; youngsters: 18–21 years old; and young adults: 22–26 years old), considered as the age-group levels. Male and females corresponded to the sex factor levels. Bonferroni comparisons were computed between the different groups of subjects in order to establish which age group comparisons presented different IPC values. As the sex factor was not statistically significant as a main factor or in interaction with the age group factor, sex was not included as a between-subject factor in the next ANOVAs carried out on the IPC dependent variable.

In order to determine whether there was differences in IPC when theta is seeded in anterior, central, or posterior regions, first we define each region by electrodes, with the anterior region being formed by Fp1, Fpz, Fp2, F7, F3, Fz, F4 and F8, the central region by FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2 and CP6, and the posterior region by P7, P3, Pz, P4, P8, POz, O1, Oz and O2. We selected 6 representative electrodes from each group, and so the anterior group was finally formed by Fp1, Fpz, Fp2, F3, Fz and F4, the central group by FC1, FC2, C3, C4, CP1 and CP2, and the posterior group by P3, Pz, P4, O1, Oz and O2. These electrodes were selected to be in the midline or nearby the midline, given that they are less influenced by muscle artifacts than more peripheral electrodes. The 324 IPCs used were those formed by all the possible combinations of these 18 electrodes (6 electrodes in each region where theta was seeded $\times$ 18 electrodes with beta values to compute IPC in 3 regions). Then, this second ANOVA was applied with posterior, central, and anterior IPC groups as within-subject factors and age groups as between-subject factor. Bonferroni comparisons were applied when needed.

Fig. 2 Example of computation of IPC. In this example, the PSD is computed for all the trials and electrodes in Subject 1. To determine Fp1 (theta) versus Fp1 (beta) IPC, the mean power of theta and beta bands was correlated using Spearman's rank correlation coefficient. Trials 1 to n are used for this computation. To determine Fp1 (theta) versus Fpz (beta) IPC, the PSD of theta in electrode Fp1 is correlated with the PSD of the beta band in electrode Fpz in each trial. Note that this computation also gives us the Fpz (beta) versus Fp1 (theta) IPC, which in fact corresponds to the same correlation. This procedure was applied to the 30×30 ($= 900$) possible inter-electrode configurations in each subject

In order to determine whether differences between left versus right intra-hemispheric IPCs were statistically significant, a third ANOVA was computed, with left versus right intra-hemispheric IPC as within-subject factors and age groups as between-subject factor. Midline electrodes were excluded from this analysis.

Using Spearman's rho, a correlation was calculated between each theta versus beta IPC and age, measured in days. This correlation matrix (900 elements) made it possible to determine which electrode pairs showed a significant IPC versus age correlation, indicating maturational changes in the age range considered (6–26 years old). Then, a Benjamini–Hochberg procedure was applied as a multiple testing error protocol (Benjamini and Hochberg 1995) in order to define a p threshold value. The False Discovery Rate was set at 0.01, which gave a statistical

significance value for type I error of $p = 0.00137$. This p value was applied as the thresholding value to make the thresholded correlation matrix.

Construction of power correlation maps and map analysis

Once the IPC thresholded correlation matrix had been obtained, the IPC significant correlation maps were drawn. On the maps, a line between the seed electrode and another electrode means there is a significant theta–beta correlation with age, with beta represented by a red spot. For the map analysis, only the theta–beta Maps were used because beta–theta maps would include the same information.

For the maps and statistical analysis of the topography of the significant increase in IPC versus age correlations,

Fig. 3 Mean values of IPC in the different age groups (IPC values of the different electrodes are collapsed, taking into account the gender and the age group). Mean IPC values for males and females in each age group are represented. Please note the increase in IPC values with age, and that no gender effect was found. Error bars represent 2 SE (SE standard error)

the electrodes were grouped into frontal electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8), central electrodes (FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6), and parietal electrodes (P7, P3, Pz, P4, P8, POz, O1, Oz, O2). Then, each statistically significant correlation between IPC and age was classified as Fronto-Frontal (FF), Fronto-Central (FC), Fronto-Parietal (FP), Centro-Frontal (CF), Centro-Central (CC), Centro-Parietal (CP), Parieto-Frontal (PF), Parieto-Central (PC), or Parieto-Parietal (PP). Likewise, the correlations (IPC vs. age) were also classified as intra-hemispheric or inter-hemispheric. All the correlations that included midline electrodes were excluded from the intra and inter-hemispheric classification because it was not possible to determine their category. The correlations were counted. Then, because the number of possible correlations differs from one to another category, a weighted percentage was calculated. To show statistically significant differences in the number of significant IPC versus age correlations between intra and inter-hemispheric and left and right intra-hemispheric connections, the Wilcoxon Rank Sum test was used. To show possible differences in the spatial distribution of IPC versus age correlations between intra and inter-hemispheric and left and right intra-hemispheric connections, the two-sample Kolmogorov–Smirnov test was used. Please note that these analyses are complementary to those from the ANOVA on age group effects because, in the former, only significant IPC versus age values are considered, whereas in the ANOVAs, all IPC values are analyzed.

Results

The first ANOVA showed that the mean IPC values presented an increase during development ($F [4,147] = 4.44$, $p = 0.002$, $\eta_p^2 = 0.108$, Fig. 3), although as Table 1 indicates, only the comparisons between groups 1 and 5 and groups 2 and 5 were statistically significant.

The gender factor did not show statistically significant differences as a main factor or in interaction with the effects of the age group. Therefore, gender was not included as a between-subject factor in the next ANOVAs computed on the IPC dependent variable.

Table 1 Bonferroni statistical comparisons between age groups for the IPC mean

Theta low beta	
IPC mean	
1–2	1.000
1–3	1.000
1–4	1.000
1–5	0.003*
2–3	1.000
2–4	1.000
2–5	0.011*
3–4	1.000
3–5	0.099
4–5	0.264

*Significant comparison using the Bonferroni Correction

Fig. 4 a Mean IPC values when theta was seeded in an anterior, central, and posterior sample of electrodes in the different age groups (IPC values of the different electrode groups are collapsed, taking into account the electrodes and age groups). Higher IPC values were found when theta was seeded in posterior electrodes. No interactions with age were observed. Bars represent 2SE. *F* frontal, *C* central, *P* posterior. **b** Mean IPC values when theta is seeded in one electrode and correlated with the beta values in the full set of electrodes, including itself. Results are displayed for the five age groups

The second ANOVA performed showed that IPC values were different when the theta seed was positioned in different scalp areas ($F [1.61, 237.9] = 20.63$, $p = 0.001$, $\eta_p^2 = 0.123$, Fig. 4a). No interaction with age was observed. All comparisons between electrode groups were statistically significant using Bonferroni Correction. (Table 2, with IPC values showing a pattern of posterior > central > anterior IPC (posterior, central, anterior refer to the position where the theta values were seeded to obtain the IPC values). For descriptive purposes, all the IPC seeded in all the electrodes in the five age groups considered are displayed in Fig. 4b. Higher IPC values in posterior electrodes and older subjects, compared to younger subjects and anterior electrodes, can be observed.

Table 2 Statistical comparisons of anterior, central, and posterior theta-seeded IPC

Theta low beta	
IPC mean	
Anterior-central	0.024*
Anterior-posterior	0.001*
Central-posterior	0.001*

*Significant comparison using the Bonferroni Correction

When ANOVA was applied to all the possible left versus right intra-hemispheric IPC, no statistical differences were obtained for the left versus right comparison or the Hemisphere x Group interaction ($F [4,147] = 0.40$;

Fig. 5 Mean values of IPC for right and left intra-hemispheric configurations for each age group. (IPC values of the different electrodes groups are collapsed, taking into account the hemisphere and the age group). No hemispheric effects and no interactions with age were found. Bars represent 2 SE

Fig. 6 The IPC versus age matrix shows the values of IPC versus age correlations (Spearman's Rho) for each inter-electrode pair. Please note that all the correlations between IPC and age were positive or close to zero

$p = 0.805$, $\eta_p^2 = 0.011$). Figure 5 shows the mean IPC values for the left and right hemispheres in each age group.

The Spearman correlation values for IPC versus age for each inter-electrode pair are represented in the inter-electrode power correlation matrix (Fig. 6). The extreme correlation values were -0.04 and 0.41 (mean $\pm$ SD 0.166 ± 0.08). Interestingly, all the correlations between IPC and age were positive or close to zero. Figure 7 shows

a few IPC versus age examples in selected electrodes with different Rho values.

The 129 significant correlations obtained, out of 900 total relationships, are shown in the thresholded IPC versus age correlation matrix (Fig. 8). The threshold p value obtained by False Discovery Rate (FDR) protocol was 0.00137. Rho values for the significant IPC versus age relationships were comprised between 0.25 and 0.41 (mean $\pm$ SD 0.29 ± 0.032), and all of them corresponded to positive significant correlations, indicating that IPC increased systematically with age. Table 3 summarizes the significant number and percentage of statistically significant IPC versus age correlations in frontal, central, and posterior areas of the scalp, differentiating between intra-hemispheric and inter-hemispheric relationships. The Wilcoxon test showed that there were no statistically significant differences ($p = 0.95$) in the number of intra and inter-hemispheric significant IPC versus age correlations. The two-sample Kolmogorov–Smirnov test indicated that the spatial distribution of Intra and inter-hemispheric significant IPC versus age correlations was not different ($p = 0.5608$).

Table 4 summarizes the significant number and percentage of statistically significant IPC versus age correlations in frontal, central, and posterior areas of the scalp, differentiating between left intra-hemispheric and right intra-hemispheric relationships. The Wilcoxon test showed statistically significant differences ($p = 0.03$) in the number of left and right intra-hemispheric significant IPC (vs.

Fig. 7 Examples of IPC versus age correlations obtained (in days): **a** two of the highest significant IPC versus age correlations; **b** two examples presenting a nearly statistically significant correlation; **c** two examples of non-significant correlations

Fig. 8 Thresholded power correlation matrix of IPC versus age, showing 129 significant IPC versus age correlations. Rho values were all positive and comprised between .25 and .41. The threshold p value was obtained with the False Discovery Rate method ($p = 0.00137$)

age), due to a higher number of left intra-hemispheric significant IPC versus age relationships. The two-sample Kolmogorov–Smirnov test indicated that the spatial

Table 3 The number and percentage (of possible cases) of IPC versus age significant correlations are shown for the different scalp area relationships

	Total	Intra-hemispheric	Inter-hemispheric
FF	3/64 (4.69%)	1/18 (5.56%)	1/18 (5.56%)
FC	12/104 (11.54%)	4/36 (11.11%)	6/36 (16.67%)
FP	4/72 (5.56%)	2/18 (11.11%)	1/18 (5.56%)
CF	37/104 (35.58%)	13/36 (36.11%)	12/36 (33.33%)
CC	16/169 (9.47%)	10/72 (13.89%)	5/72 (6.94%)
CP	0/117 (0%)	0/36 (0%)	0/36 (0%)
PF	23/72 (31.95%)	6/18 (33.33%)	4/18 (22.22%)
PC	30/117 (25.64%)	8/36 (22.22%)	6/36 (16.67%)
PP	4/81 (4.94%)	1/18 (5.56%)	0/18 (0%)

The most frequent relationships were Centro-Frontal, Postero-Frontal, and Postero-Central. A relatively low number of relationships were found in Fronto-Frontal, Fronto-Posterior, and Postero-Posterior areas. No correlations were found between IPC and age in the Centro-Posterior area. There are almost no differences between Intra-hemispheric and Inter-hemispheric relationships. Note that the missing numbers between Intra-hemispheric plus Inter-hemispheric and total relationships correspond to the exclusion of midline electrodes and their IPC versus age correlations from the Intra-hemispheric/Inter-hemispheric categories. *FF* Fronto-Frontal, *FC* Fronto-Central, *FP* Fronto-Posterior, *CF* Centro-Frontal, *CC* Centro-Central, *CP* Centro-Posterior, *PF* Postero-Frontal, *PC* Postero-Central, *PP* Postero-Posterior

Table 4 The number and percentage (of possible cases) of IPC versus Age significant correlations are shown for the left and right intra-hemispheric relationships in the different scalp areas

	Left intra-hemispheric	Right intra-hemispheric
FF	0/9 (0%)	1/9 (11.11%)
FC	4/18 (22.22%)	0/18 (0%)
FP	2/9 (22.22%)	0/9 (0%)
CF	10/18 (55.56%)	3/18 (16.67%)
CC	9/36 (25%)	1/36 (2.78%)
CP	0/18 (0%)	0/18 (0%)
PF	6/9 (66.67%)	0/9 (0%)
PC	7/18 (38.89%)	1/18 (5.56%)
PP	1/9 (11.11%)	0/9 (0%)

The observation of the maps shows a greater number of left versus right intra-hemispheric IPC versus age correlations, mostly for Centro-Frontal, Centro-Central, Postero-Frontal, and Postero-Central relationships. *FF* Fronto-Frontal, *FC* Fronto-Central, *FP* Fronto-Posterior, *CF* Centro-Frontal, *CC* Centro-Central, *CP* Centro-Posterior, *PF* Postero-Frontal, *PC* Postero-Central, *PP* Postero-Posterior

distribution of left and right intra-hemispheric significant IPC (vs. age) was not different ($p = 0.077$).

Figures 9, 10 and 11 show the spatial distribution of the significant IPC versus age relationships. A clear increase

Fig. 9 Statistically significant IPC versus age correlations, displayed as maps and using theta power as a seed in frontal scalp regions. *FF* Fronto-Frontal, *FC* Fronto-Central, *FP* Fronto-Posterior, *intra* intra-hemispheric, *inter* inter-hemispheric. Left row of maps corresponds to the total number of significant IPC versus age correlations, including midline electrodes. The electrodes in gray color represent the theta seed, and those in red are the electrodes where beta values are measured. (Color figure online)

can be observed in left compared to right inter-hemispheric significant relationships. In addition, the most frequent IPC versus age relationships were Centro-Frontal, Postero-Frontal, and Postero-Central. By contrast, the number of correlations for the Fronto-Frontal, Fronto-Posterior, Centro-Posterior, and Postero-Posterior areas was relatively low. Fronto-Central and Central-Central presented intermediate values. From Tables 3 and 4 and Figs. 9, 10 and 11, two main trends of theta–beta IPC changes with age can be observed: (1) Long-range connections tend to increase with age; (2) the only short-range connections that increase with age are central to central connectivity.

Discussion

The co-maturation of theta and beta bands from early childhood to young adulthood, reported by Rodriguez-Martinez et al. (2015) with a subject-to-subject approach, is confirmed in the present report on a trial-by-trial basis. The maturational trend is an increase in theta versus beta correlations with age, suggesting an increase in connectivity with age. When the value of IPC was analyzed taking IPC

across the whole scalp into account, no gender or hemispheric differences were obtained. The posterior sites showed higher IPC values than anterior sites. When only significant IPC versus age correlations were considered, left intra-hemispheric connections presented a higher number of significant IPC versus age than right intra-hemispheric, and no significant differences were obtained between intra and inter-hemispheric connections. The obtained results that most IPC versus age correlations were positive and that the statistically significant IPC versus age were very frequent for long distance pairs of electrodes, permit to suggest that the increase in IPC values with age is not due passive volume conduction, and can be interpreted as an increase of functional connectivity.

The first null hypothesis tested in this study was rejected, and the expectation was confirmed that young adults have higher IPC than children and pre-adolescents. This implies that a theta–beta IPC increase with age is a possible marker for normal EEG development. The fact that almost no negative correlations between IPC and age were found probably means that brain development oscillations positively tend to reach a higher degree of functional connectivity, measured both by phase coherence (Barry et al.

Fig. 10 Statistically significant IPC versus age correlations displayed as maps and using theta power as a seed in central scalp regions. *CF* Centro-Frontal, *CC* Centro-Central, *CP* Centro-Posterior, *intra* intra-hemispheric, *inter* inter-hemispheric. Left row of maps corresponds to the total number of significant IPC versus age correlations, including midline electrodes. The electrodes in gray color represent the theta seed, and those in red are the electrodes where beta values are measured. (Color figure online)

2004, 2005; Thatcher et al. 1986, 2007, 2008) and by power correlation, as obtained in the present report. The increase of functional connectivity with age has also been demonstrated using the phase-lag index, and by the demonstration that small-world network level was higher in children than in adults (Dimitriadis et al. 2015). The positive IPC values may indicate that the increase in IPC with age is not due to changes in head, skull, and/or brain size, which would produce a reduction in IPC if this parameter were entirely due to volume conduction. The latter argument is based on the decrease in influence of a common source when the distance between the electrodes increases, and also on the fact that brain volume is relatively steady from 5 years old on (Lebel et al. 2008), and the contribution of distance must not be significant in EEG connectivity measures during development.

The second hypothesis was accepted. No statistically significant differences were observed between males and females. The divergence between the results found by Barry's team (Barry et al. 2002, 2004) and those presented here could be explained by the fact that connectivity measures such as IPC and coherence are independent electrophysiological measures. The lack of IPC differences

with gender contrasts with the differential developmental pace of girls and boys in different brain metrics as: cortical thickness (Giedd et al. 2009), global and local patterns of connectivity (reviewed in Cao et al. 2016) and in inter-electrode coherence (Hanlon et al. 1999; Barry et al. 2004). The great individual differences in IPC values, as can be observed in Figs. 3 and 7, would be one of the possible causes of accepting the null hypothesis of no differences in IPC values by gender.

The third null hypothesis was rejected. IPC values were higher when theta was seeded in posterior electrodes, decreasing when theta was seeded in anterior scalp areas. One possible explanation for this observation is related to the fact that the EEG was recorded in an open eyes condition. Slow rhythms, such as theta, are assumed to involve and coordinate populations of neurons driving local faster rhythms, such as beta (Buzsáki 2006). It is possible that in an open eyes condition, posterior visual areas and the hippocampus might be exhibiting higher activity and, thus, could be driving local computation, based on beta activity, in central and anterior areas.

Surprisingly, the fourth null hypothesis was accepted. Higher IPC was expected in the left hemisphere due to

Fig. 11 Statistically significant IPC versus age correlations displayed as maps and using theta power as a seed in posterior scalp regions. *PF* Postero-Frontal, *PC* Postero-Central, *PP* Postero-Posterior, *intra* intra-hemispheric, *inter* inter-hemispheric. Left row of maps corresponds to the total number of significant IPC versus age correlations, including midline electrodes. The electrodes in gray color represent the theta seed, and those in red are the electrodes where beta values are measured. (Color figure online)

previous results obtained for coherence measures (Barry et al. 2004; Thatcher et al. 2008), but the test of IPC in the present report failed to reach significance. However, when the number of significant IPC versus age correlations was considered, a higher number of left intra-hemispheric IPC versus age significant correlations was obtained (Table 4). This does not mean that IPC in the left hemisphere reaches higher mean values than the right hemisphere, but rather suggests that maturation of connectivity in the left hemisphere, as measured by IPC, occurs with a steeper rise and with a more localized pattern than in the right hemisphere.

The comparisons of intra and inter-hemispheric connections did not show a difference in IPC maturation, suggesting a similar maturation for callosal and intra-hemispheric tracts. Tarokh et al. (2010) showed a linear increase with age in intra-hemispheric and diagonal (non-homologous inter-hemispheric pairs of electrodes) coherence during sleep, but no age-related changes in inter-hemispheric connections between pairs of homologous electrodes. In the present report, most of the inter-hemispheric significant IPC versus age connectivity was between non-homologous inter-hemispheric connections, in consonance with Tarokh et al. (2010). Lebel et al.

(2008), in a longitudinal tractography study measuring the increase with age of fractional anisotropy and the decrease with age of mean diffusivity, showed a steeper rise and an earlier maturation of callosal fibers than intra-hemispheric tracts. This result would justify the preponderance of intra-hemispheric and diagonal (non-homologous inter-hemispheric pairs of electrodes) significant IPC versus age connectivity over inter-hemispheric homologous electrodes. These results would imply a protracted intra-hemispheric functional connectivity compared to callosal connectivity, as measured by the IPC parameter.

Finally, to indicate that the IPC values obtained in present report are lower than those described for coherence values (Barry et al. 2004; Thatcher et al. 2008). These differences between IPC and coherence being more clear for short-distance interelectrode coherence than for long distance coherence. The lower values of IPC with respect to coherence would suggest that the development of functional integration in the brain relies more in phase coherence than in power-to-power theta–beta frequency coupling.

Conclusions

The present results support the current notion that an increase in functional connectivity with age occurs during development (Barry et al. 2004; Thatcher et al. 2008; Stevens 2009; Tarokh et al. 2010). The increase in functional integration with age would be one of the key elements in improving cognitive abilities. This report adds the frequency coupling concept in theta–beta coupling to the increase in the functional integration of brain rhythms with age. The results agree with studies on development default networks that show an increase in functional integration with age (reviewed in Goldenberg and Galván 2015).

The cross-sectional nature of the data limits the conclusions, given that the samples grew up in different socio-cultural backgrounds. In addition, the high inter-individual variability, due to the cross-sectional design, would reduce the possibility of the null hypotheses being refuted.

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Compliance with ethical standards

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

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