



The emergence of a theta social brain network during infancy

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ABSTRACT

Infants' socio-cognitive ability develops dramatically during the first year of life. From the perspective of ontogeny, the early development of social behavior allows for parent-child attachment, which in turn enhances survival. Thus, it is theorized that the development of social behavior, driven by social brain networks, forms the core of developmental acquisitions during this period. Further, understanding the maturation within the neural networks during social development is crucial to obtain a better grasp of the development of social developmental disorders. Therefore, we performed a longitudinal study in 854 infants measured at around 5 and 10 months to map the development of functional networks in the brain when infants were processing social and non-social videos. Using EEG, we focused on the frequency bands most commonly connected to social behavior: theta and alpha. We found that alpha networks remained relatively stable over the first year of life and showed no selectivity for social versus non-social stimuli, theta networks, showed strong global reconfigurations. The development of the theta networks progressed from a parietal occipital network in early infancy to a frontoparietal network towards the end of the first year of life. This reconfiguration coincided with selectivity for social versus non-social stimuli, with infants approaching the end of their first year of life showing increased synchronicity of theta communication when watching social videos versus non-social videos. Our findings provide strong evidence for the involvement of a frontoparietal theta network in the development of the social brain.

1. Introduction

Human social behavior develops dramatically during the first year of life. After birth, a newborn shows little social capabilities, but during the development between 4 and 12 months of age, infants start to exhibit signs of joint attention, vocal communication, and participate in complex social constructs, like games. These dramatic developmental changes in behavior are accompanied by equally dramatic changes in the brain, which triples in size during the first year of life (Huttenlocher and Dabholkar, 1997; Huttenlocher and Courten, 1987; Innocenti and Price, 2005; Keunen et al., 2017). Young infants cannot tell us whether they possess certain social capabilities. Therefore, to study the onset of these capabilities, it is useful to detect whether unique neural correlates exist when processing certain social stimuli. For example, the finding that the brain of an infant already responds differently to faces versus houses at three months of age provides evidence that young infants are already primed to detect and process these important social cues (de Haan et al., 2001). Detecting and processing faces, however, is just one facet of social development. As an infant develops, social behavior becomes more complex, requiring input from a wide range of brain areas.

Therefore, when linking the development of the processing of complex cues with neuronal changes, researchers often focus on the development of infant brain networks. After birth, the network features of the infant's brain show many of the macroscopic properties of an adult

brain, with the exception that the infant brain has an overabundance of connections (Huttenlocher and de Courten, 1987) and is unoptimized. Therefore, during childhood and later development, brain networks are optimized through the process of selective pruning of unimportant connections and the strengthening of important (and often long-range) connections (Huang et al., 2015; Yap et al., 2011). This optimization process from a localized to an integrated brain network is already well underway during infancy (Fair et al., 2009; Huang et al., 2015; Tóth et al., 2017), possibly allowing for more complex behaviors to arise over the course of the first year of life.

In this paper, we focus on the development of social behavior during infancy, by analyzing underlying brain networks and communication patterns when infants view complex social stimuli. Early frameworks tackling the relationship between the development of behavior and the brain emphasized the maturation of dedicated brain areas as a prerequisite for specific behavior (Atkinson, 1984; Johnson, 1990), some emphasizing the role of experience herein (Shadmehr and Holcomb, 1997; Spencer et al., 2009). However, more recently, the interactive specialization (IS) framework highlighted the interrelationship between anatomically distinct brain areas (Johnson, 2011). In the IS framework, brain areas respond to a wide array of non-specific cues in the undeveloped brain. During development, interactions between brain areas cause these responses to be more specific towards certain stimuli. Therefore, new behaviors in infants will not arise through the onset of activity in one single region but through changes in the activity of multiple brain regions. Following this framework, the emergence of complex

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social behaviors coincides with the emergence of a so-called social brain network, involved in processing social cues.

In adults, several areas thought to be involved in social processing have been grouped as the ‘social brain’ (Adolphs, 2008; 2003; 2001; 1999). This ‘social brain’ consists of several areas in the prefrontal and the parietal cortex. Most importantly, the fusiform face area, superior temporal sulcus, and the orbitofrontal cortex. Trying to connect the social brain to development, Johnson and colleagues predicted that during infancy the differences in brain activity patterns towards social and non-social stimuli become more distinct in areas associated with the social brain and that the social brain matures as a whole during infancy, rather than maturing region by region (Johnson et al., 2005). Work underlining this increase in social specialization in the infant’s brain is extensive. For example, Farroni and colleagues used fNIRS and found evidence for social cortical specialization as early as a few days after birth (Farroni et al., 2013). Several ERP studies show similar results: infants start showing different ERP responses towards upside down versus right side up faces between 6 and 12-months (Haan et al., 2002; Halit et al., 2003); and start showing distinctly different brain activity patterns in response to fearful faces compared to neutral faces at 6-months but not at 3-months-of age (Hoehl and Striano, 2010). These studies provide compelling evidence that the social brain is undergoing specialization during the first year of life. However, evidence for the interactive part of the IS framework is less commonly described. Most notably, little is known whether entire networks become more specialized towards social stimuli over time. In this study, we, therefore, aim to test this hypothesis by testing infant brain networks in response to animate and inanimate movies in a large-scale longitudinal study.

Networks in the infant’s brain can be studied using the synchronicity of oscillatory EEG rhythms to determine the likelihood of communication between distinct brain areas, as synchrony in oscillatory activity patterns allows for optimized communication between two distinct regions (Fell and Axmacher, 2011). These oscillatory rhythms can be divided into separate frequency bands. We focus on theta and alpha rhythm networks, as these networks can be reliably measured in infants (van der Velde et al., 2019). The theta rhythm (3–6 Hz) is most commonly associated with social processing. Theta power is greater in infants looking at neutral faces compared with smiling faces (Bazhenova et al., 2007) and is increased during infant-directed speech (Orekhova et al., 2006). Most notably, an earlier study comparing the oscillatory response to inanimate versus animate movies found a general increase of theta power that became more pronounced between 6 and 12 months of age (Jones et al., 2015).

Alpha (6–9 Hz) oscillations have also been connected to social processing but in a less specific manner. Alpha power is thought to be an indication of brain ‘idling’. Therefore, alpha suppression is an indication of increased activity in that particular brain area. For example, observing goal-directed actions showed this suppression of alpha power in 8 to 16-month-old infants (Montirosso et al., 2019; Southgate et al., 2009). Also, during live eye contact, alpha band-activity desynchronizes in infants of 6-months-old (Hoehl et al., 2014). Evidence for the involvement of alpha frequency communication in social behavior was also found in infants at risk for ASD, with infants later developing ASD showing distinctly higher alpha connectivity during infancy (Orekhova et al., 2014).

The abovementioned studies show the undoubted connection between the development of social processing and oscillatory activity patterns, but to our knowledge, no longitudinal studies have actively measured the development of functional social brain networks during infancy in a large population. To assess the underlying neurobiology of the emerging social brain, we utilize EEG to study alpha and theta waves in a large group of infants twice during the first year of life. Functional networks were created using EEG data (theta and alpha bands) gathered from infants watching naturalistic social and non-social videos, similar to the ones used in Jones et al. (2015). We set out to test the hypothesis by Johnson and Johnson (2011) that the social brain emerges as a whole during infancy and that the social brain network increasingly

specializes during infancy. Therefore, we expect a significant reconfiguration of the functional connectome during infancy (between 4 and 10 months of age). We expect this reconfiguration to coincide with an increased specificity of global network strength comparing networks of social and non-social cues.

2. Methods and materials

2.1. Participants

The YOUth study is a longitudinal cohort study consisting of two large cohorts differing in age range. The YOUth Baby & Child cohort follows infants from 20 to 24 weeks gestational age until the age of seven years. The YOUth Child & Adolescent cohort follows children from the age of 8 until the age of 16 years. Both behavioral and cognitive development is tracked through numerous tasks and methods (e.g. eye-tracking, EEG, MRI, questionnaires). The YOUth study was approved by the Medical Research Ethics Committee of the University Medical Center Utrecht and all participants’ parents provided written informed consent. A brief overview of the YOUth study including the measurements conducted at each timepoint is available from <https://www.uu.nl/en/research/youth-cohort-study> (Onland-Moret et al., 2020)

The current study only uses data from the YOUth Baby & Child cohort, since this is the only cohort in which EEG was measured in young children from 5 months onwards. In total, 849 5-month-old infants and 642 10-month-old infants were included. Table 1 shows the demographic and attrition information of all subjects in our study. Attrition due to fussiness was counted when the infant was excluded from the analysis for having too little (or no) data due to the infant being too tired, inattentive, started crying, moved too much, or refused to wear the cap. Attrition due to experiment(er) error was counted when the RA logged this or when the resulting data file was corrupted. Attrition rates are well into the expected range (Stets et al., 2012). Only subjects with EEG valid -data sets for both sessions were used in the longitudinal analyses. Table 2 shows the demographic information of these subjects.

2.2. Task design

Infants were seated at 65 cm from a computer screen. Either on the lap of the parent or, when possible, in a highchair. Infants watched videos of either social or non-social content. Each video was 60 s in length and repeated 3 times. In total, the infants viewed 6 videos with the tasks interleaved. The initial video was randomized between subjects. The social video depicted women singing nursery rhymes and the non-social video showed toys that were moving without human interference (meaning that no hands were present on the screen). All moving toys were toys that could move by themselves (for example a spinning top). These movies were highly standardized and adapted from earlier work (Jones et al., 2015; Orekhova et al., 2014; Tomalski et al., 2013) by translating them to Dutch. The videos have earlier been used to detect reliable networks and characteristics (Haartsen et al., 2020; van der Velde et al., 2019). Beyond the content of the videos, the videos were kept as similar as possible. Both videos had comparable luminance and included similar amounts of motion and sound. The videos were meant to provide infants with typical experiences. In between videos, the infant was allowed a short break during the startup of the next video (see Fig. 1A).

2.3. EEG acquisition & cleaning

EEG was recorded using a cap with 32 electrodes (ActiveTwo system, BioSemi) positioned according to the international 10/20 system, at a sampling rate of 2048 Hz. A Common Mode Sense (CMS) and Driven Right Leg (DRL) electrode were used to provide an active ground.

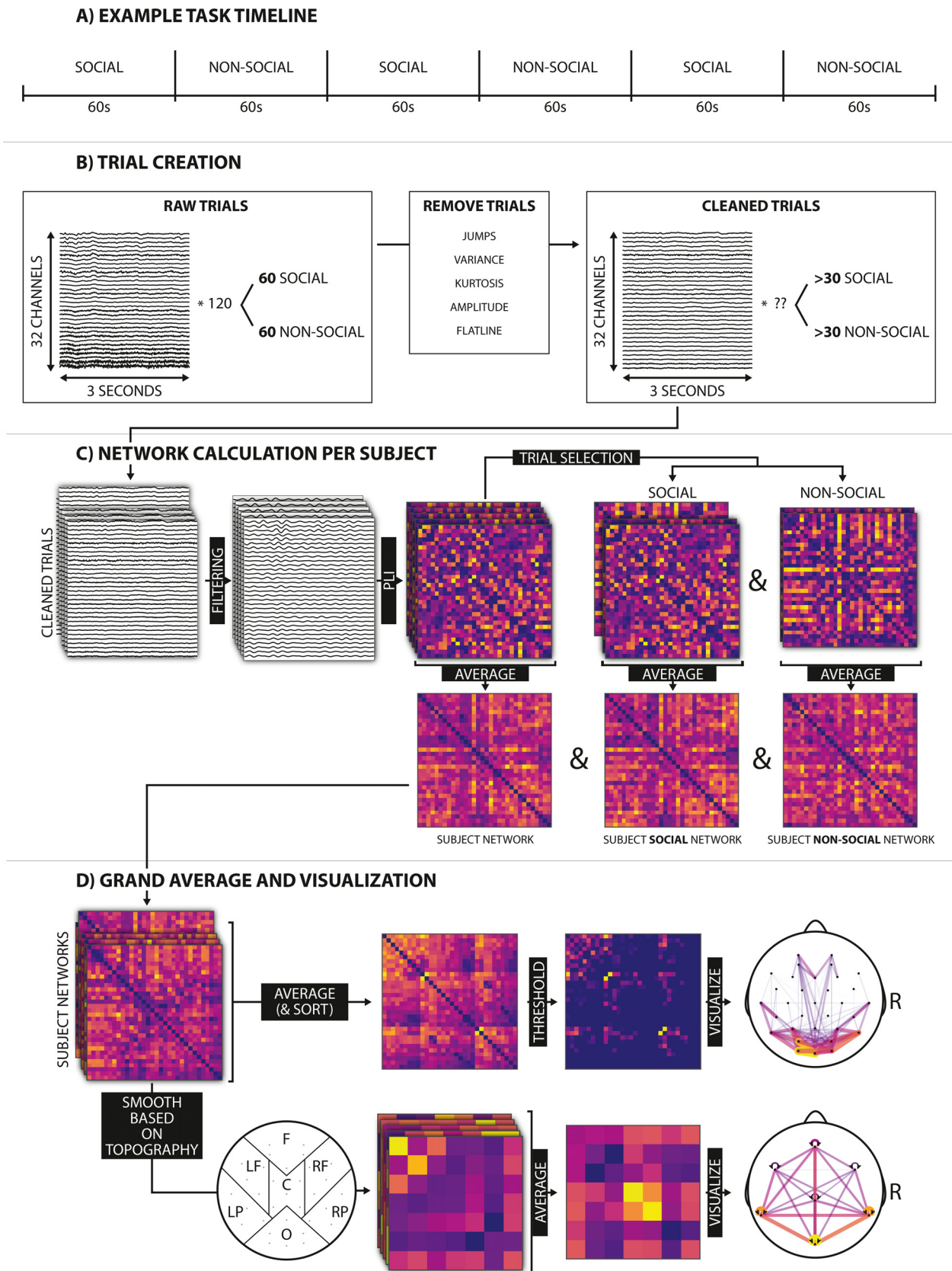


Fig. 1. Overview of analysis steps taken during this study. This figure shows all analysis steps taken during this experiment. From the gathering of data to the visualization of the eventual results. A) depicts an example video order during the experiment for a particular infant. The infant either started with the social or toy video and watched each video three times interleaved. B) Trials were created by cutting the 60 s dataset in 20 3 s trials for each video (so 20x6 = 120 trials in total) and were consequently discarded if problems were found with variance, kurtosis, jumps, absolute amplitude or absence of data. C) Networks were created for each infant by filtering clean trials in theta and alpha frequency band. For each frequency band communication synchrony was calculated between electrodes using the PLI. Resulting adjacency matrices were created for the average synchrony over the entire task, the social videos, and the non-social videos. This results in 2 (frequency bands) * 3 (task options) = 6 adjacency matrices per subject. D) Grand averages were calculated using the average of all subject adjacency matrices for each of the 6 aforementioned categories. Connectomes were used to visualize data, either through thresholding or through averaging connectivity strength over neighbouring electrodes.

Table 1
Cross-sectional demographic and attrition information.

	Gender	Total	Attrition		Exp. Error		Fussiness		Age (in days)	
		N	N	%	N	%	N	%	mean	sd
5m		849	125	14.7	27	3.2	98	11.5	167.2	22.9
	Boy	421	63	15	17	4	46	10.9	168.3	23.0
	Girl	428	62	14.5	10	2.3	52	12.1	166.2	22.7
10m		642	76	11.8	26	4	50	7.8	315.7	24.7
	Boy	318	32	10.1	14	4.4	18	5.7	316.8	25.0
	Girl	324	44	13.6	12	3.7	32	9.9	314.6	24.5

Table 2
Longitudinal demographic information.

Session	Gender	N	Age (mean)	Age (sd)
5m		428	315.1	25.2
	Boy	227	315.3	25.5
	Girl	201	314.9	24.9
10m		428	167.3	22.3
	Boy	227	168.0	21.7
	Girl	201	166.5	23.0

EEG data was analyzed using MATLAB, using the FieldTrip toolbox (Oostenveld et al., 2011). The original 2048 Hz data was downsampled to 512 Hz, using chip interpolation and band-pass filtered at 0.1–70 Hz with a two-way Butterworth filter. Artifact removal was similar to work done earlier in our lab (van der Velde et al., 2019). The continuous EEG data was cut into 1 s. trials. Trials were selected for removal if they: contained too high amplitudes (> 250 μV); contained jumps (detected with *ft_jump_removal.m*); were excessively non-normal (kurtosis > 7); contained flatlining electrodes (inverse of variance > 0.1); or contained excessive noise (variance > 1500). The trials before and after bad trials were also selected for removal. Channels were removed if more than 40 percent of the trials in a channel contained artifacts. If no more than two bad channels were found in a single subject, the two channels were interpolated utilizing weighted averaging of the neighboring channels. If more than two bad channels were found in a subject's EEG dataset or if the two bad channels in question were neighbors, that subject's session was removed from the analysis. After cleaning, the continuous parts of the clean EEG data longer than 3 s were cut into 3-second trials. The sampling points to be included were stored for later use. The PLI can be prone to overestimation bias if the total amount of trials is low. Therefore, subjects were required to have at least 30 trials in the non-social condition and 30 trials in the social condition (see Fig. 1B). After cleaning, 125 5-month-old infants and 76 10-month-old infants were removed (see Table 1). The remaining 724 5-month-old infants and 566 10-month-old infants were used for further analysis. Data quality characteristics of the EEG of the entire cohort are reported elsewhere (van der Velde and Junge, 2020).

2.5. Network calculation

Network calculation was similar to earlier studies of our group (van der Velde et al., 2019). To limit the influence of filter edge-effects, the raw EEG data was bandpass filtered into theta (3 up to, but not including 6 Hz.) and low alpha (6 up to, but not including 9 Hz.) frequency bands. Since individual theta and alpha peaks are influenced by development, alpha1 and theta bands were chosen to encompass all theta and alpha peaks ± 1 Hz. After filtering, the three-second trials were created based on the earlier stored sampling data for clean trials. For each epoch, connectivity between pairs of electrodes ($32 \times 31 / 2 = 496$) was calculated with the phase lag index (PLI), relying on the same principle of phase locking or phase synchrony (Tass et al., 1998). The PLI was chosen over the debiased weighted PLI (Vinck et al., 2011), as previous work has shown the PLI to be slightly more reliable in an infant

population (van der Velde et al., 2019). The PLI, proposed by Stam and colleagues, (Stam et al., 2007), describes the asymmetry of the distribution of phase differences between pairs of signals:

$$\text{PLI} = |\langle \text{sign}[\sin(\Delta\varphi(tk))] \rangle|,$$

where $\Delta\varphi$ is the instantaneous phase difference between signals at time point t for $k = 1 \dots N$ per epoch ($N = 5 \times 512 = 2560$), determined using the Hilbert transformation. $|\cdot|$ stands for absolute values, $\langle \cdot \rangle$ for the mean values, and the sign for a signum function (phase difference is either -1 , 0 , or 1). The resulting PLI can range from 0 to 1. One of the key strengths of the PLI is that it is relatively resistant to volume conduction. Activity from a single strong source will likely appear in both electrodes as having a phase difference of close to zero. Maybe jumping from phase lagging to phase leaping every once in a while under the influence of noise. This centering around zero phase lag will cause the PLI to be calculated as zero. The PLI is certainly not completely immune to volume conduction. It is, however, one of the most important tools we have to limit the influence of it on calculated connectivity.

The 496 connectivity values per epoch were used to create an adjacency matrix for every epoch for a subject. These adjacency matrices were used to calculate three separate subject connectivity matrices for both frequency bands: 1) An average of the entire experiment, 2) an average over the entire social experiment, and 3) an average over the entire non-social experiment (see Fig. 1C). In addition to these adjacency matrices, global network strength was calculated for each subject connectivity matrix by averaging all connections in the network.

2.6. Network visualization

Grand averages were calculated for each of the six categories, by averaging each subject's connectivity matrix for each category over all subjects. To visualize these grand averaged connectivity matrices, connectomes were created using in-house MATLAB scripts. Two separate visualization processes were undertaken. In the first process, the grand averaged connectivity matrices were thresholded, to only include the strongest 25 percent of all connections. The remaining connections were visualized as connectomes based on electrode location. In the second process, neighboring nodes were grouped and connections between these nodes averaged to create average connectivity between areas. The following areas were created through averaging: Frontal (F), consisting of electrodes Fp1, Fp2, AF3, AF4, Fz; Left Frontal (LF), consisting of electrodes F3, F7, FC5, FC1; Right Frontal (RF), consisting of electrodes F4, F8, FC6, FC2; Central (C), consisting of electrodes C3, C4, CP1, CP2, Cz; Left Parietal (LP), consisting of electrodes T7, CP5, P7, P3; Right Parietal (RP), consisting of electrodes T8, CP6, P8, P4; and Occipital (O), consisting of electrodes PO3, PO4, O1, Oz, O2, Pz. A graphical overview of the grouping can be seen in Fig. 1D. In the paper, these networks are labeled 'smoothed connectomes' to distinguish them from the full connectomes, since the process of taking together the connectivity of neighboring nodes essentially smoothes the connectome.

2.7. Spectral analysis

Previous work has underlined the possibility of overestimating and overinterpreting functional connectivity results due to the strong re-

relationship between functional connectivity measures and EEG power (Demuru et al., 2020). This is even true for the phase lag index, which is calculated without the involvement of signal amplitude. However, increases in amplitude likely increase signal-to-noise ratios and with it the likelihood to calculate increases in connectivity. Therefore, we have included a spectral analysis and will use both theta and alpha power as dependent variables to compare to our main outcomes studying functional connectivity.

Spectral preprocessing was performed analogously to the spectral analysis in (Jones et al., 2015). Using Matlab the cleaned epochs were subjected to an FFT, creating power spectra for all electrodes. Power values were averaged across all epochs and averaged across theta (3–6 Hz.) and alpha (6–9 Hz.) frequency bands. Only participants with enough clean trials and enough non-noisy channels were included in the analysis. The logged theta and alpha power was used for statistical analysis. The resulting power measures were strongly correlated with global connectivity. Theta power correlated strongly with theta global connectivity ($r = 0.61$) and alpha power correlated strongly with alpha global connectivity ($r = 0.75$).

2.8. Statistical analysis

A major difficulty in assessing longitudinal effects is the almost unavailability of missing data (Ibrahim and Molenberghs, 2009). Analyzing this type of data with a repeated measurements ANOVA (rmANOVA) forces the researcher to throw any subject away with missing data in one session, due to the rmANOVA requirement of MCAR (Missing Completely at Random). A linear mixed model (LMM), in contrast, assumes missing at random (MAR). This means, in practice, that even if a single session is missing, we can still use the participant's data points that were observed in other sessions for the analysis. Additionally, rmANOVAs assume sphericity and require independent variables to be categorical. Therefore, rmANOVAs are an effective procedure, easy to implement with statistical software, but only if the above assumptions are met, the variances between repeated measures are relatively equal, and we have complete data of all subjects. Since missing data is not MCAR in our study and additionally we include participant age (which is a continuous variable) as an independent variable, using a rmANOVA is not possible. Therefore, we opt to use LMMs to test our hypotheses.

LMMs can be seen as an extension of the linear regression models, but also include random effects and correlated errors (Bates, 2005; Jiang, 2007; McCulloch and Neuhaus, 2005). Similar to ANOVAs, LMMs include fixed effects (observed variables, like in our case connectivity strength towards social or toys videos; or time). The most common LMMs include at least a subject random effect. This random subject effect, also called random intercept, captures the differences in starting point between subjects. A subject that has a higher value in session 1 is assumed to also be higher in session 2. If necessary, additional random effects can be added to capture additional variance or correlation. This all allows for greater flexibility in the correlations between sessions. One additional important positive aspect of LMMs is that time does not have to be categorical: it can be added as a continuous measure. Therefore, in our case, where the age of infants is continuously noted in days, using an LMM provides an additional benefit (Krueger and Tian, 2004).

For our first research question, we evaluated how theta and low alpha networks developed over the first year of life. The research question can be split into two subquestions: 1) How does the average connectivity strength of EEG networks develop during the first year? 2) Does the network reconfigure over the first year, and if so, how? To answer these questions, we used the above described LMMs. The first subquestion evaluates how average connectivity strength develops over infancy. We created two LMMs: one for theta average connectivity and one for low alpha average connectivity. With both LMMs, age was used as a fixed effect in addition to random intercept for participants. Since the PLI can induce a bias based on the number of trials, for each frequency band we compared two models: one with the number of trials as an extra fixed

effect and one without. We used the Akaike information criterion (AIC) to select the most appropriate statistical model (lower is better). In both frequency bands, the model with the added fixed effect for the number of trials did not yield a significantly better model (theta: 3116.3 versus 3116.6; and alpha: 2990.0 versus 3007.2). The final model formula was: $\text{averageConnectivity} \sim \text{age} + (1|\text{subject})$.

With the second subquestion, we want to look at network reconfiguration over time. This is slightly different from our first subquestion. If the first subquestion determines that the network as on average increases in connectivity during the first year, we are not necessarily interested in that all the connections increase during this period. That would be redundant. What we are most interested in, is whether some connections become on average more or less important in the individual networks. Therefore, we center and scale the networks per subject for each session (also known as z-scoring). These z-scored connections are then used to perform LMMs. To do LMMs on all the connections in a network with 32 nodes would lead to multiple comparison issues. Therefore, we use the smoothed connectome of connectivity between 7 large areas in the brain (see above). In an undirected 7-node network, there are 28 connections. For each of the 28 connections, LMMs were fitted with age as a fixed effect, zscored connection as a dependent variable, and a random intercept for participant. This was done both for theta and for low alpha networks. Once again, model fit was compared between the inclusion of the number of trials as a fixed effect or not. No models fitted better with the number of trials as a fixed effect. AIC of chosen models for theta connections varied between 2900.3 and 4520.9. For alpha connections, AIC varied between 2671.4 and 4596.8. Due to space constraints, the AIC outcomes are in the supplementary material. The final formula use was $\text{connectionConnectivity} \sim \text{age} + (1|\text{subject})$. All p-value thresholds were Bonferroni corrected.

For our second research question, we want to understand whether during development these theta and low alpha networks show an increase in sensitivity for social stimuli versus non-social stimuli. That is to say, whether network differences in processing social versus non-social cues become more distinct. Once again this question was first answered globally: are there differences in average connectivity strength in processing social cues versus non-social cues and how does this develop over the first year of life. And then locally: are there differences in individual connections in processing social cues versus non-social cues and how does this develop over the first year of life. We try to answer the first subquestion by constructing an LMM with average connectivity (for social or non-social trials) as a dependent variable and age and social contrast (whether the infant was watching a social video or a toys video) as fixed effects. Once again a random intercept for the participant was used. The inclusion for the number of trials did not yield a better fitting model (theta: AIC = $-14,469.88$ versus AIC = $-14,449.14$; and alpha: AIC = $-13,955.92$ versus AIC = $-13,929.38$). The final formula used was $\text{averageConnectivity} \sim \text{age} * \text{socialContrast} + (1|\text{subject})$.

For the second subquestion, we constructed a similar LMM as in the first subquestion, but now for every connection in the smoothed connectome separately. The 28 LMMs were created both for the theta and the low alpha networks. No improvement was found when adding the number of trials to the model fit. For theta AIC varied between $-13,215.97$ and $-10,619.19$. For low alpha, AIC varied between $-14,263.85$ and $-11,261.27$. Due to space constraints, the AIC outcomes are in the supplementary material. The final formula use was $\text{connectionConnectivity} \sim \text{age} * \text{socialContrast} + (1|\text{subject})$. All p-value thresholds were Bonferroni corrected.

Analyses were performed using the lmer4 package in R (Bates et al., 2014; 2007). Relative effect sizes were computed following Brysbaert and Stevens (2018). Effect size of $d < 0.2$ were deemed small, $0.2 < d < 0.5$ were deemed small-medium, $0.5 < d < 0.8$ were deemed medium-large, and $d > 0.8$ were deemed large.

For the models including an interaction, pairwise contrasts were calculated for every month of age of a subject. Since data is non-normal, these pairwise contrasts were calculated using the Wilcoxon signed-rank

Table 3
Linear Mixed Model with age (in days) as a fixed effect and global network strength as the dependent variable.

Frequency Band	Parameter	Estimate	Test (df)	p^*	Effect size
Theta	Age	0.48	$t = 19.47$ (833.21)	<0.0001	$d = 1.35$
Low Alpha	Age	0.53	$t = 25.31$ (715.96)	<0.0001	$d = 1.89$

* Bonferroni corrected.

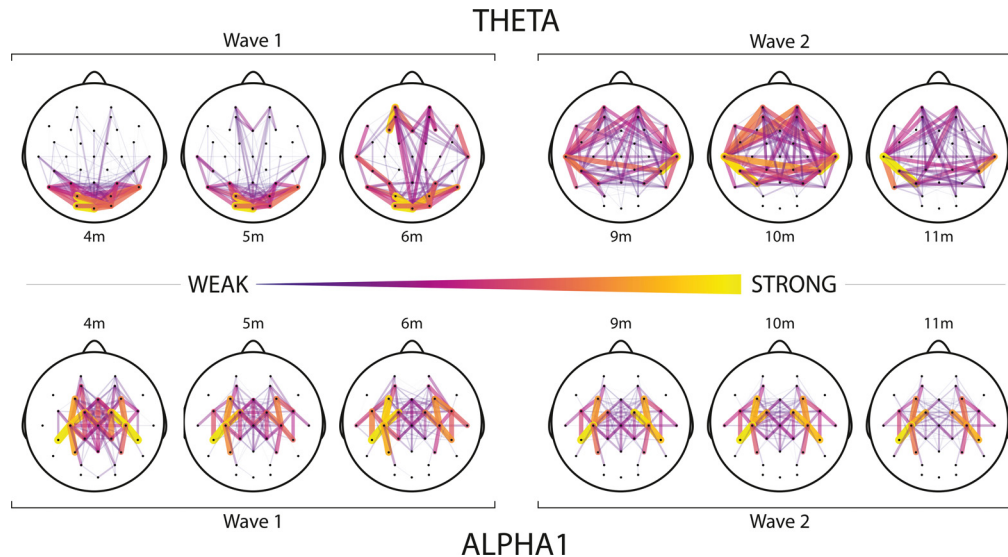


Fig. 2. Normalized thresholded network topologies during infant development. Depicted here average network topologies between 4 and 11 months old viewed top down. The networks are normalized per age group to enhance the focus on network configuration instead of network strength. Stronger connections are thicker and more yellow. The low alpha networks show little reconfiguration. The theta networks do show a distinct reconfiguration from an occipitoparietal network towards a frontoparietal network. This switch seems to come online gradually, with 5 and 6-month-old infants already showing distinctly more frontoparietal connectivity compared to the 4-month-old infants. Note that infants were tested in 2 waves (4 to 6-month-old and 9 to 11-month-old), so every infant is represented twice in this figure.

test. P-value thresholds were Bonferroni corrected. Since Cohen's d calculated effect size is calculated using means, which is non-optimal in non-normal data, Pearson's R was used to calculate the effect size. We used the following notions for effect size: $r < 0.1$ is small effect size, $0.1 < r < 0.3$ is small-medium effect size, $0.3 < r < 0.5$ is medium-large effect size, and $r > 0.5$ is large effect size.

3. Results

3.1. The development of global network strength over time

For global network strength, the estimated subject variance was 0.11 with an estimated residual variance of 0.67. For low alpha global network strength, the estimated subject variance was 0.22 with an estimated residual variance of 0.47. For the theta global network strength LMM, a significant main effect was found for infant age in days ($\hat{\beta} = 0.48$, $p < 0.0001$, $d = 1.35$). For the low alpha global network strength LMM, a significant main effect of infant age in days was also found ($\hat{\beta} = 0.53$, $p < 0.0001$, $d = 1.89$). See [table 3](#) for the summary of the results.

3.2. The reconfiguration of the theta network

[Figs. 2 and 3](#) show the development of network topology in the infant's brain between 4-months-old and 11-months-old. The low alpha network configuration remains relatively stable over time, with high frontocentral connectivity. The theta network, however, reconfigures from an occipitoparietal network towards a frontoparietal network. To overcome the problems of choosing a threshold to depict networks, [Fig. 3](#) shows simplified "smoothed" network topologies. Connections are

averaged according to the location on the scalp. Here a clear reconfiguration in the theta network can be seen as well, with clear interconnectivity appearing at 9 months old between the frontal areas and the left and right parietal areas. Note

To focus on the reconfiguration of the network, we evaluated the developmental pattern of individual connections in the network. To simplify the analysis, we used the smoothed networks, consisting of 28 connections in total. Above, we showed that age has a strong effect on global connectivity. To control for general connectivity strength increase due to age, individual networks were scaled and centered. A high value of connectivity now indicates that the connection is relatively more important compared to the other connections in the individual's network. The LMMs used single connection strength as the dependent variable, with age (in days) as a fixed variable and random intercepts for subject. The results are shown in [Fig. 4](#). The red connections indicate an increase in relative connectivity at the $p < 0.0001$ level (Bonferroni corrected), the blue connections indicate a decrease in relative connectivity at the $p < 0.0001$ level (Bonferroni corrected). In line with the earlier visualizations of the networks over the first year of life, a clear reconfiguration can be seen in the theta network, from an occipitoparietal network towards a frontoparietal network. In the alpha network, such a change was not found. If anything, the frontocentral network becomes more prominent over time. For the full linear mixed models of all 28 connections and both frequency bands, please refer to the supplementary materials.

3.3. The infant EEG network and social processing

To understand whether this reorganization of the theta network coincided with an increase in sensitivity for the processing of social stimuli, we again utilized LMM (see [Tables 4 and 5](#)). This time, global connec-

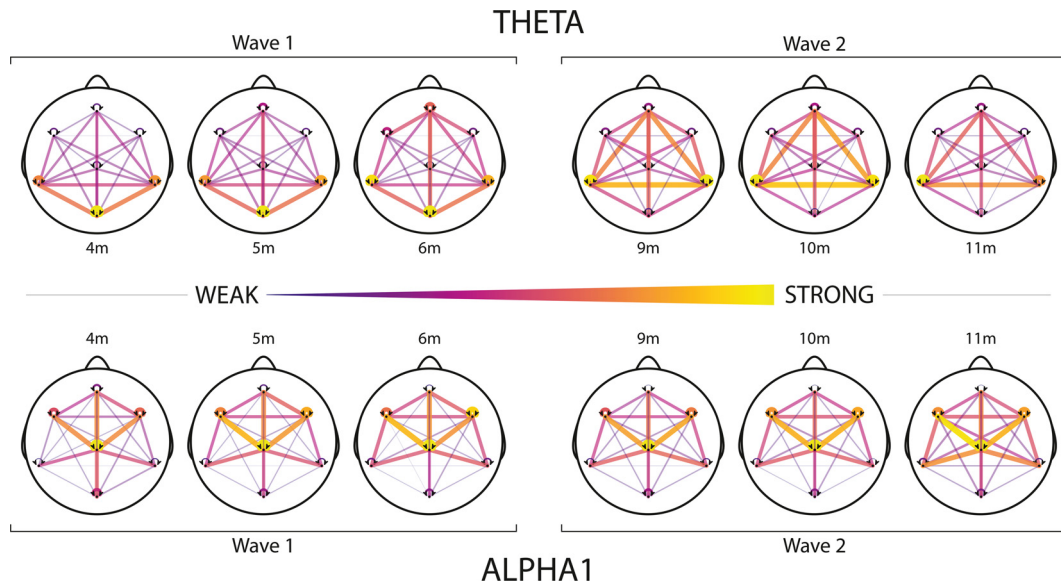


Fig. 3. Normalized smoothed network topologies. Depicted here smoothed average network topologies between 4 and 11 months old viewed top down. Connections are averaged according to location on the scalp (see Fig. 1d). Double ended arrows represent interconnectivity within a certain area. Low alpha shows a clear pattern across the first year of development, with high connectivity within the central areas and all areas with central areas in the brain. For the theta networks, however, a clear reconfiguration takes place with the occipitoparietal network slowly morphing into a frontoparietal network, which can be clearly spotted from 9-months-old onwards with a clear triangle of connectivity between the frontal and left and right parietal areas in the brain. Also note the increase in interconnectivity between parietal areas.

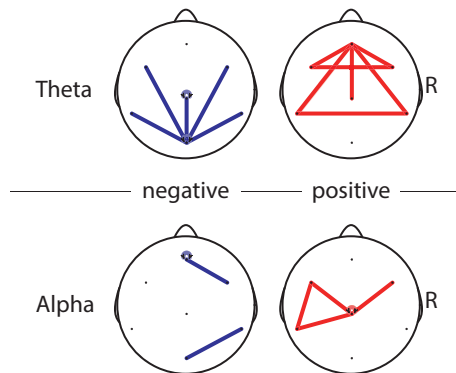


Fig. 4. Development of important connections during infancy. Depicted here are the connections of the smoothed connectomes which become significantly more or less important in the connectome during the first year of life. A linear mixed model was run over each connection with normalized connection strength as dependent variable and age as fixed variable. The red connections indicate a significant increase in importance at the $p < 0.0001$ level (Bonferroni corrected). The blue connections indicate significant decrease in importance at the $p < 0.0001$ level (Bonferroni corrected). For theta, a clear switch can be seen, where connections to the occipital cortex become less important during the first year of life and the frontoparietal connection become more important. In the alpha network the opposite is true, where the already important frontocentral connectivity becomes increasingly prominent, while other connections become less involved.

tivity when watching social or toy videos was used as the dependent variable. Since we were interested in whether the development of the theta network increased sensitivity for social processing, we used both ‘age’ and ‘social versus toy’ contrasts as fixed effects. Once again, a random intercept for subject was included.

For the theta networks (Table 4), the estimated subject variance was 0.33 with an estimated residual variance of 0.47. Not surprisingly, a significant main effect was found for age ($\beta = 0.37, p < 0.0001, d = 0.81$). Additionally, a significant main effect was found for the social versus

Table 4

Linear mixed model with age and social vs toys videos as the fixed effects and theta global connectivity as the dependent variable (pairwise contrasts are indented).

Parameter	Estimate	Test (df)	p^*	Effect size
Age	0.37	$t = 17.27 (1924.88)$	< 0.0001	$d = 0.81$
Social	0.24	$t = 8.58 (1503.96)$	< 0.0001	$d = 0.42$
Age \times Social	0.19	$t = 6.80 (1500.11)$	< 0.0001	$d = 0.35$
04 m (Social vs Toys)		$Z = 0.95$	n.s.	$r = 0.10$
05 m (Social vs Toys)		$Z = 2.05$	n.s.	$r = 0.11$
06 m (Social vs Toys)		$Z = 2.83$	< 0.05	$r = 0.24$
09 m (Social vs Toys)		$Z = 7.07$	< 0.0001	$r = 0.49$
10 m (Social vs Toys)		$Z = 7.79$	< 0.0001	$r = 0.52$
11 m (Social vs Toys)		$Z = 5.34$	< 0.0001	$r = 0.42$

* Bonferroni corrected.

Table 5

Linear mixed model with age and social vs toys videos as the fixed effects and low alpha global connectivity as the dependent variable (pairwise contrasts are indented).

Parameter	Estimate	Test (df)	p^*	Effect size
Age	0.52	$t = 30.26 (1852.00)$	< 0.0001	$d = 1.40$
Social	-0.06	$t = -0.74 (1545.80)$	n.s.	$d = -0.04$
Age \times Social	-0.01	$t = -0.38 (1542.76)$	n.s.	$d = 0.01$

* Bonferroni corrected.

toys contrast ($\hat{\beta} = 0.24, p < 0.0001, d = 0.42$). Lastly, and most importantly, a significant interaction effect was found between age and social contrast ($\hat{\beta} = 0.19, p < 0.0001, d = 0.35$) indicating that as the infant’s brain develops, the difference in theta network synchronicity increases. Further analyzing this effect, we performed 6 post-hoc Wilcoxon signed-rank tests, separating the infants per age in months. We found that from 6 months onwards, a significant difference in global connectivity strength in the social versus non-social condition could be found. From 9-months-old onwards, a medium-large effect was detected ($0.42 < r < 0.52$). For more detailed statistics, please see Table 4.

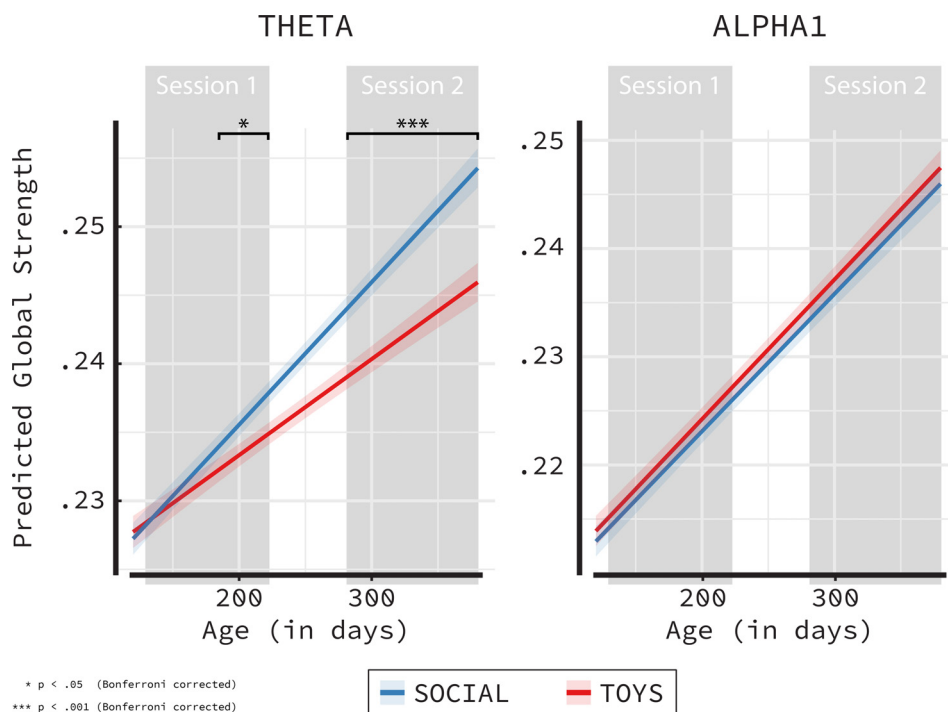


Fig. 5. Interaction effect age and watching social videos. During the first year of life, theta global connectivity differences between watching social and toys videos become more distinct. This effect is significant from 6 months onwards, but becomes more pronounced over the first year of life. No such effect can be seen in alpha1 global connectivity. Session 1 and 2 are depicted as light gray to visualize the age range the prediction of the LMM is based on.

We performed a similar LMM analysis for the low alpha networks. The estimated subject variance was 0.22 with an estimated residual variance of 0.47. A significant main effect was found for age ($\hat{\beta} = 0.52, p < 0.0001, d = 1.40$). No effect for social contrast or interaction effect between age and social contrast was found. Since we did not find an interaction effect, no post-hoc analyses were performed. For more detailed statistics, please see Table 5. Fig. 5 shows the predicted global strength over the first year of life, based on these LMMs. A clear interaction effect can be seen in the theta networks, but not in the low alpha networks.

We once more zoomed in on the interaction effect between age and the contrast type (social versus toy) to find out which connections, between which areas in the brain showed a similar interaction effect over the first year of life. With the theta networks, 28 LMMs with the age (in days) \times social contrast interaction effect with single connectivity strength as the dependent variable were calculated for each connection in the smoothed connectivity matrix. The resulting findings are presented in Table 6. The significance levels are Bonferroni corrected for multiple comparisons. Significant interaction effects were found in connections throughout the brain, except for the interconnectivity in the frontal regions. We plotted the connections with at least a small-medium effect size ($d > 0.2$) in Fig. 6. Fig. 6 nicely illustrates the frontoparietal triangle showing and the occipitoparietal connections both having a significant interaction effect. For the alpha networks, no significant interaction effects were found for single connections. Therefore, the resulting LMMs are presented in the supplementary materials.

3.4. Infant EEG power and social processing

To provide a comparison, similar models were calculated with theta and alpha power as dependent variables. For the theta power, the estimated subject variance was 0.49 with an estimated residual variance of 0.29. A significant main effect was found for age ($\hat{\beta} = 0.46, p < 0.0001, d = 1.47$). Additionally, a significant main effect was found for the social versus toys contrast ($\hat{\beta} = 0.17, p < 0.0001, d = 0.39$). Lastly, a significant interaction effect was found between age and social contrast ($\hat{\beta} = 0.14, p < 0.0001, d = 0.29$). Note that both the scaled estimation and the effect size of theta power are lower for the interaction effect compared to interaction effect with theta global connectivity as dependent variable.

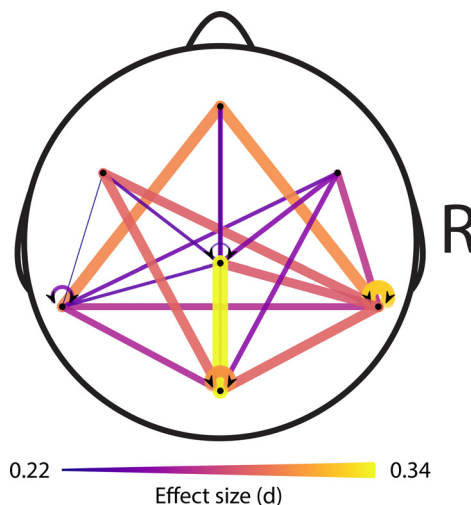


Fig. 6. The theta connections with significant age \times social interaction effects. Depicted here are the connections with a significant interaction effect between age and social contrast. These connections developed an increase in synchronicity for social stimuli over the course of the first year of life. Connections are scaled in color and thickness according to their effect size. Only connections with an effect size higher than the cut off for small effect size (0.2) are shown. Opposed to the development of the theta connectome, social specialization happens all throughout the brain, with the exception of frontal interconnectivity. Note the clear frontoparietal triangle and the strong connectivity between the occipital and the parietal areas.

We performed a similar LMM analysis for the low alpha power. The estimated subject variance was 0.44 with an estimated residual variance of 0.22. A significant main effect was found for age ($\hat{\beta} = 0.59, p < 0.0001, d = 1.87$). No effect for social contrast or interaction effect between age and social contrast was found. Additionally, tables and figures detailing this interaction effect were created. These can be found in the supplementary materials. Lastly, a figure was create showing the scalp

Table 6
Linear mixed model interaction effect between the fixed effects of age and social vs toys with θ individual connections as the dependent variable.

Connectivity Pair		Estimate	Test (df)	p^*	Effect size
Frontal	Frontal	-0.01	$t = -0.19$ (1761.49)	n.s	$d = -0.01$
Frontal	Left Frontal	0.08	$t = 2.76$ (1730.68)	n.s	$d = 0.13$
Frontal	Right Frontal	0.10	$t = 3.53$ (1739.68)	< 0.05	$d = 0.17$
Frontal	Left Parietal	0.18	$t = 6.47$ (1720.44)	< 0.0001	$d = 0.31$
Frontal	Right Parietal	0.18	$t = 6.49$ (1701.93)	< 0.0001	$d = 0.31$
Frontal	Central	0.15	$t = 5.36$ (1721.69)	< 0.0001	$d = 0.26$
Frontal	Occipital	0.15	$t = 5.02$ (1781.50)	< 0.0001	$d = 0.24$
Left Frontal	Left Frontal	0.10	$t = 3.26$ (1722.31)	< 0.05	$d = 0.16$
Left Frontal	Right Frontal	0.10	$t = 3.74$ (1725.42)	< 0.01	$d = 0.18$
Left Frontal	Left Parietal	0.13	$t = 4.66$ (1725.74)	< 0.0001	$d = 0.22$
Left Frontal	Right Parietal	0.17	$t = 6.14$ (1716.51)	< 0.0001	$d = 0.30$
Left Frontal	Central	0.14	$t = 5.07$ (1727.79)	< 0.0001	$d = 0.24$
Left Frontal	Occipital	0.19	$t = 6.29$ (1767.83)	< 0.0001	$d = 0.30$
Right Frontal	Right Frontal	0.10	$t = 3.48$ (1726.44)	< 0.05	$d = 0.17$
Right Frontal	Left Parietal	0.15	$t = 5.18$ (1724.39)	< 0.0001	$d = 0.25$
Right Frontal	Right Parietal	0.15	$t = 5.74$ (1707.95)	< 0.0001	$d = 0.28$
Right Frontal	Central	0.15	$t = 5.35$ (1723.18)	< 0.0001	$d = 0.26$
Right Frontal	Occipital	0.16	$t = 5.41$ (1740.73)	< 0.0001	$d = 0.26$
Left Parietal	Left Parietal	0.15	$t = 5.23$ (1721.07)	< 0.0001	$d = 0.25$
Left Parietal	Right Parietal	0.15	$t = 5.65$ (1696.48)	< 0.0001	$d = 0.27$
Left Parietal	Central	0.14	$t = 5.06$ (1722.69)	< 0.0001	$d = 0.24$
Left Parietal	Occipital	0.17	$t = 5.71$ (1764.39)	< 0.0001	$d = 0.27$
Right Parietal	Right Parietal	0.20	$t = 6.94$ (1707.56)	< 0.0001	$d = 0.34$
Right Parietal	Central	0.17	$t = 6.10$ (1714.08)	< 0.0001	$d = 0.29$
Right Parietal	Occipital	0.19	$t = 6.30$ (1776.24)	< 0.0001	$d = 0.30$
Central	Central	0.15	$t = 4.89$ (1751.40)	< 0.0001	$d = 0.23$
Central	Occipital	0.22	$t = 7.30$ (1750.73)	< 0.0001	$d = 0.35$
Occipital	Occipital	0.21	$t = 6.65$ (1763.05)	< 0.0001	$d = 0.32$

* Bonferroni corrected.

topography of alpha and theta power in response to the social and toys videos. This figure can also be found in the supplementary materials.

4. Discussion

Our goal was to describe the relationship between the development of social capabilities and the development of the infant's brain. Since behavior is embedded within functioning networks in the human brain, and since there is considerable social cognitive development within the first year of life, we focused on the development of infant brain networks over this period. We described the development of alpha and theta networks in the infant's brain with its relationship to the processing of social stimuli. As a measure of the total synchronicity of the brain, we used global connectivity. We found that theta networks, but not alpha networks, show increased sensitivity in differentiating social versus non-social videos, with an increase in global connectivity found when looking at social compared to non-social videos. Notably, this increase was only found in infants when they reached approximately 9-months of age. This period of time coincided with a striking reconfiguration of the theta network. This reconfiguration, in addition to the increased sensitivity to social videos, provides important evidence for the emergence of the social brain during infancy.

4.1. Network development

Both alpha and theta networks show a general increase in network strength. This indicates greater synchronicity between brain regions, which likely reflects increase neural communication between distant brain areas, and is related to the global maturation of neural networks. Supporting this, Xie and colleagues (Xie et al., 2018) studied sustained attention in infants and found that global connectivity both in the alpha and in theta networks increased over the course of development during the first year of life. Maturation of global networks during infancy has also been shown in fMRI studies (Gao et al., 2015; 2014). This is possibly caused by an increase in myelination, which progresses at a rapid

pace during the first year of life (Keunen et al., 2017). Together with the strengthening of important connections, this could lead to increased global connectivity. It is important to note that increases in network strength do not necessarily indicate the optimization of networks. Increases in theta have been connected to immaturity (Orekhova et al., 2006), however, during the first year of life increases in theta communication appear to be related to typical development.

Together with a global increase in synchronicity, theta networks also underwent considerable reconfiguration during the first year of life. Theta synchronicity evolved from a predominant occipitoparietal network to a more balanced pattern that included the addition of a frontoparietal network. Prior studies have found that frontoparietal brain networks are related to attention (Gao et al., 2015), working memory (Short et al., 2013), and, noteworthy for this study, the social brain (Frith, 2007; Frith and Frith, 2010). Fig. 3 shows this especially clear, with a clear increase in the synchrony in the triangle between the prefrontal cortex and the bilateral parietal cortex.

The change in network configuration occurred quite rapidly. This supports the hypothesis of Johnson et al. (2005), who hypothesized that through the lens of the IS framework, networks should mature in unison rather than area by area. Note, however, that we did not study the infants consistently for all ages and that the sudden shift in configuration coincides with a 3-month hiatus between waves of data collection (between 6 and 9-months-old). Thus, we do not know how rapidly the theta network develops within this 3-month window of time. Future research is warranted to better understand the precise temporal characteristics and importantly, environmental factors that contribute to the functional network organization in the infant's brain.

Per our hypothesis, the theta network showed a considerable reconfiguration of important connections in the whole brain network. The alpha network, however, did not show this reconfiguration. On average alpha showed the strongest synchronicity in the frontocentral areas of the brain. As the infant developed, these frontocentral connections in the network strengthened and became an even more important focal point of the network. The alpha network did show a similar increase in

global connectivity as the theta network. This underlines the uniqueness of the reconfiguration of the theta network during infancy.

4.2. Social selectivity

In addition to the considerable reorganization of the theta network in the infant's brain, we also showed that this reorganization coincided with an increase in global connectivity when watching social stimuli compared to non-social stimuli. This increase only was identified in the 10-month-old infants, and not in the 5-month-old infants, so after the reorganization took place. Increases in global connectivity are an important indication that areas in the brain increase in communication with each other when looking at social images. As global connectivity is also found to be a reliable brain network metric (van der Velde et al., 2019), this is important evidence that the theta network is connected to the development of the social brain.

This is in agreement with earlier work from Jones et al. (2015), who studied EEG-power in response to similar videos as used in the current paper and found that theta power increased when looking at social videos versus non-social videos. However, contrary to their work, in our paper increases in synchronicity were found throughout the entire brain network (excepting frontal interconnectivity) and not specifically in parietal and frontal regions. A possible explanation for this is that the reorganized theta network has a strong backbone of frontal and parietal regions, these communications are projected throughout the brain, leading to significant differences in synchronicity in the whole-brain network. Extra evidence for this topography of theta power while watching social and non-social videos can be found in the current paper. As our spectral analysis yielded very similar results compared to Jones et al. (2015) work (supplementary materials). The alpha network did not show any selectivity for social versus non-social stimuli, with synchronicity between signals remaining equal for both the 5-month-old and the 10-month-old infants.

4.3. Limitations and future directions

The above-described work comes with some limitations. First, it is difficult to determine whether the network 'comes online' suddenly (as hypothesized by the IS framework, Johnson, 2011). We demonstrate that the reconfiguration of the core theta network takes place between 6 and 9 months of age, but how rapidly within this period of time is not known. Additionally, infants in the current study were tested twice, limiting the ability to test non-linear trajectories of brain network development. Future studies, with greater temporal sampling, will shed light on these issues.

Also, in our study, we did not find any relationship between alpha synchronicity and social development. What is important to note, however, is that studies that did find a relationship between alpha depression and social processing were using live conditions of social interaction (Jones et al., 2015). Future research is necessary to study in what way the development of alpha connectivity influences social brain processing during infancy, including the addition of live social interactions.

Lastly, it is important to note that it is difficult to pull apart EEG power and EEG connectivity. As mentioned before, there is a clear relationship between functional connectivity measures and EEG power. This is also the case in our paper. Therefore, we have included spectral results for inspection. Both effect sizes and estimates are lower in the models based purely on power measurements compared to global connectivity measures, but it is currently unclear whether this means that connectivity measures tell us more than just the power measures. Related to this is the possibility of entrainment caused by speech during the social videos (Leong et al., 2017). This would cause EEG power to increase, but not due to connectivity. However, this should not be the case in our study, as we find similarly structured networks in both the social and the toys condition. Indicating that the measurement of communication in the social condition does not just arise due to entrainment.

Additionally, entrainment should cause brain waves to have the exact same phase, which should lower their measured PLI connectivity.

5. Conclusion

We showed that theta networks in the brains of infants undergo a large reconfiguration during the first year of life; from an on average parieto-occipital network towards a frontoparietal network. This reconfiguration coincides with an increase in sensitivity for social versus non-social stimuli, which is represented by an increase in synchronicity of brain activity when looking at social videos compared to non-social videos. The alpha network neither shows this reconfiguration or this increase in sensitivity for social stimuli. This provides important evidence for the development of the social brain network during the first year of life and its probable relationship to theta communication. Also, this study provides evidence for the interactive specialization framework (Johnson, 2011), as the reconfiguration appears to develop in unison, rather than piecewise between different regions. Future studies can hopefully shed light on whether this theta network reconfiguration can be used to predict behavioral outcomes and whether enhancing these network connections in children with delayed social development can improve their social cognitive abilities.

Data availability statement

As a result of the General Data Protection Regulation (GDPR), in principle, the data will not be accessible to third parties. Nevertheless, the data could be made available after consent from patients and approval of a protocol submitted by the user. The data is managed by the Utrecht University which can approve access to the data, if it complies with Dutch privacy laws. Matlab and R-scripts are available upon request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Credit authorship contribution statement

Bauke van der Velde: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Tonya White:** Supervision, Methodology, Writing – review & editing. **Chantal Kemner:** Supervision, Project administration, Funding acquisition, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118298.

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