Modeling the connectome of joint attention in infancy predicts Theory of Mind in preschool-age

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Abstract

A pivotal developmental milestone is reached around 9 months when infants begin to coordinate their attention with others. Joint attention acts as a catalyst for infants' learning and is proposed to predict later social cognitive development, including understanding others' minds (Theory of Mind, ToM). However, neural markers predicting joint attention development and their predictive value for later social cognitive abilities remain unknown. Here, we trained a model to identify whole-brain connectivity patterns predictive of joint attention from resting-state fMRI data of 8-15-month-old infants. The model significantly predicted joint attention scores in an independent infant sample, beyond general development. Dominant connections lay within the default network and its interaction with the ventral attention network. Crucially, this connectome also predicted later ToM in children aged 2-5 years. Beyond providing an early marker for individual differences in social cognitive development, these findings have high potential for the early diagnosis of social cognitive disorders.

The first years of life are a period of intense learning. Infants need to orient themselves in a highly complex environment. Other individuals are central in guiding infants in this difficult task. An important milestone is achieved towards the end of the first year of life when infants begin to coordinate their attention to objects in their environment with other people, termed joint attention[1]. Joint attention critically shapes infants' learning, allowing others to guide them towards relevant learning targets and to inquire information about their environment, for example in language learning[2,3]. Beyond learning, joint attention plays an important role in an infant's understanding of others, correlates with the acquisition of social cognitive skills[4,5], and has been proposed to be a precursor of Theory of Mind (ToM), our capacity to reason about people's mental states. Because of this striking catalyzing effect on learning and social cognitive development, the emergence of joint attention (typically around 9 months of age) has been coined the *9-month revolution*[1].

Despite this central role of joint attention in early development, the neural factors that predict its emergence in infancy are poorly understood. Its pivotal role for social cognitive development suggests that the neural maturation supporting joint attention in infancy may be predictive of later social cognitive outcomes, in particular, of ToM – a cornerstone of mature human social cognition. Identifying the neural footprint that predicts individual differences in joint attention development may thus serve as an early marker of social cognitive development in health and disease. Here, we therefore set out to identify the brain networks predictive of joint attention emergence in infancy by modeling infants' whole-brain connectivity patterns with a connectome-based predictive modeling approach (CPM[6]). We then tested the predictive power of this model for later-developing ToM abilities.

Research on the neural basis of joint attention in infancy has focused on measuring neural activation during joint attention with functional Near Infrared Spectroscopy (fNIRS[7–10]). Despite the limited spatial resolution and coverage of fNIRS, these studies suggest that infants recruit similar brain regions as adults during joint attention. Specifically, in adults, joint attention recruits areas involved in social-cognitive processes, including the medial prefrontal cortex (mPFC), posterior superior temporal sulcus (pSTS), and temporoparietal junction (TPJ)[7–10,14,16–20], as well as the anterior insula, amygdala, and ventral striatum[11–16]. Two studies suggest that connections between some of these regions also correlated with joint attention in early childhood[21,22]. What is unknown is whether brain structures related to joint attention in infancy can serve as a marker for later social cognitive development.

As joint attention entails recognizing what other people attend to, and supports learning about their communicative and action goals, it has been proposed to be a precursor of ToM. Indeed, several longitudinal studies have shown positive behavioral correlations between joint attention and ToM[37–42]. Further, ToM in older children and adults recruits brain regions partly overlapping

with those of joint attention, including the mPFC, STS, and TPJ[43]. We, therefore, hypothesized that a predictive model trained to identify neural networks supporting joint attention in infancy may be predictive of the later development of ToM abilities in preschool children.

Correlational findings with individual brain structures, as observed in previous joint attention studies, do not typically allow predicting individual differences in novel individuals. Firstly, correlational studies tend to overfit the data, resulting in low generalizability to novel data[23]. To determine generalizable neural markers of joint attention, it is therefore critical to use a cross-validated approach that tests identified brain-behavior relationships in an independent sample of infants[23]. Secondly, there is growing consensus that brain regions do not work in isolation. Rather, interactions between multiple distributed brain areas and connections, creating networks, are the neural basis for cognitive functions[24]. Considering patterns of connectivity in the whole brain, referred to as the *connectome*, rather than individual brain regions or connections, has far greater potential for predicting interindividual differences in joint attention in new individuals[23].

To identify generalizable neural markers of joint attention, we therefore trained a cross-validated connectome-based predictive model (CPM[6]) on infants' whole-brain connectivity patterns and joint attention performance. CPM is a powerful method to predict individual behavior from whole-brain patterns of connectivity[6,23]. It has been shown to predict various cognitive and affective functions, such as attention[25,26], executive function[27,28], and creativity[29,30], and has successfully generated predictive models of atypical cognition[31–33]. For development in particular, predictive models have the unique advantage of generating insight into how emerging brain networks give rise to cognition and behavior, as has been shown in childhood and adolescence[33–36].

Leveraging this powerful modeling approach and data from the Baby Connectome Project[44], we constructed a predictive model based on 8- to 15-month-old infants' resting-state fMRI connectivity data and behavioral joint attention performance to predict joint attention capacities in an independent sample of infants. In a next step, we tested whether this model, trained on joint attention in infancy, would be able to predict later ToM performance at 2 to 5 years. In brief, our CPM correlated behavioral joint attention scores with infants' whole-brain connectivity patterns and selected connections that significantly contribute to individual differences in behavior. These selected connections were summed to build a linear regression model that predicts behavioral joint attention scores from resting-state fMRI data of previously unseen individuals. We hypothesized that the connectivity of brain networks involved in social cognition in adults would be predictive of joint attention in infancy, and that the whole-brain connectivity patterns identified for joint attention would also predict the later development of ToM.

Results

Connectome-based model significantly predicts joint attention scores

To investigate whether and which features of the resting-state connectome could predict infants' joint attention scores, we randomly split the data into a training and a test set. A model was then built of the connections associated with joint attention in the training data set. We then tested this model in an independent subset of the data. The model generated on our training set (N = 97) significantly predicted joint attention scores from unseen rsfMRI connectivity in our independent test dataset (N = 47, Spearman rho = .329, p-value = .012, see Fig 1A).

To test for the specificity of this prediction for joint attention beyond general development, we further controlled for the *Mullen Scales of Early Learning*. The resulting model was thus trained to predict joint attention, while controlling for general development. It also significantly predicted behavioral joint attention scores in the independent test data (N = 39, Spearman rho = .328, p-value = .029, see Fig 1B).

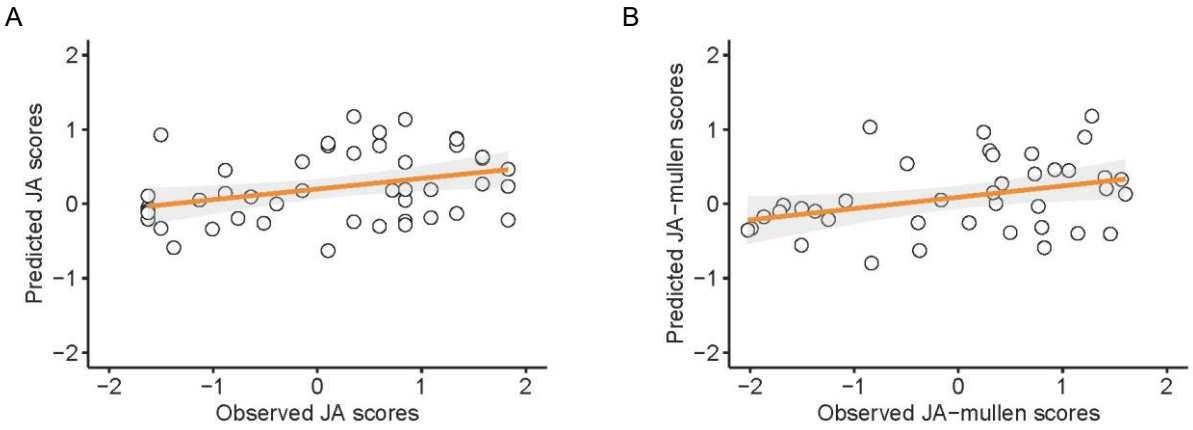

Figure 1. A connectome-based model built on joint attention data in a training dataset significantly predicted joint attention scores in an independent test data set of infants aged 8-15 months. A) Scatterplot of the correlation between predicted joint attention scores from the model and observed joint attention scores in the test data (N = 47, Spearman rho = .329, p = .012). B) Correlation of the joint attention model that controlled for general development by regressing out the *Mullen Scales of Early Learning* (B, N = 39, Spearman rho = .328, p = .029). All scores were z-normalized.

Default mode and ventral-attention network connectivity predicts joint attention

To identify the network interactions that predicted joint attention, we computed network connectivity based on the 7-network parcellation[45]. In the predictive model trained on joint attention scores without controlling for general development, the majority of identified connections lay within sensory and motor networks (somatomotor (SMN) and visual (VIS)) and their interaction with the ventral attention network (VAN) and the default mode network (DMN)

(details see Fig 2A/B). When controlling for infants' general development, connections within the DMN and its interaction with the VAN became dominant, followed by connections between the DMN and SMN and within the VIS (details see Fig. 2C/D).

The connections that contributed to the joint attention model controlling for general development are listed, by network, in Table 1 (see Supplementary Table 1 for connections of the model without controlling for general development). In particular, within-DMN connections had nodes in the left banks of the superior temporal sulcus (bSTS), right rostral anterior cingulate cortex (rACC), right superior frontal gyrus (SFG), right inferior parietal gyrus (IPG), and bilateral middle temporal gyrus (MTG). Connections of the VAN with the DMN were between the right supramarginal gyrus (SMG) to the left bSTS and the bilateral MTG.

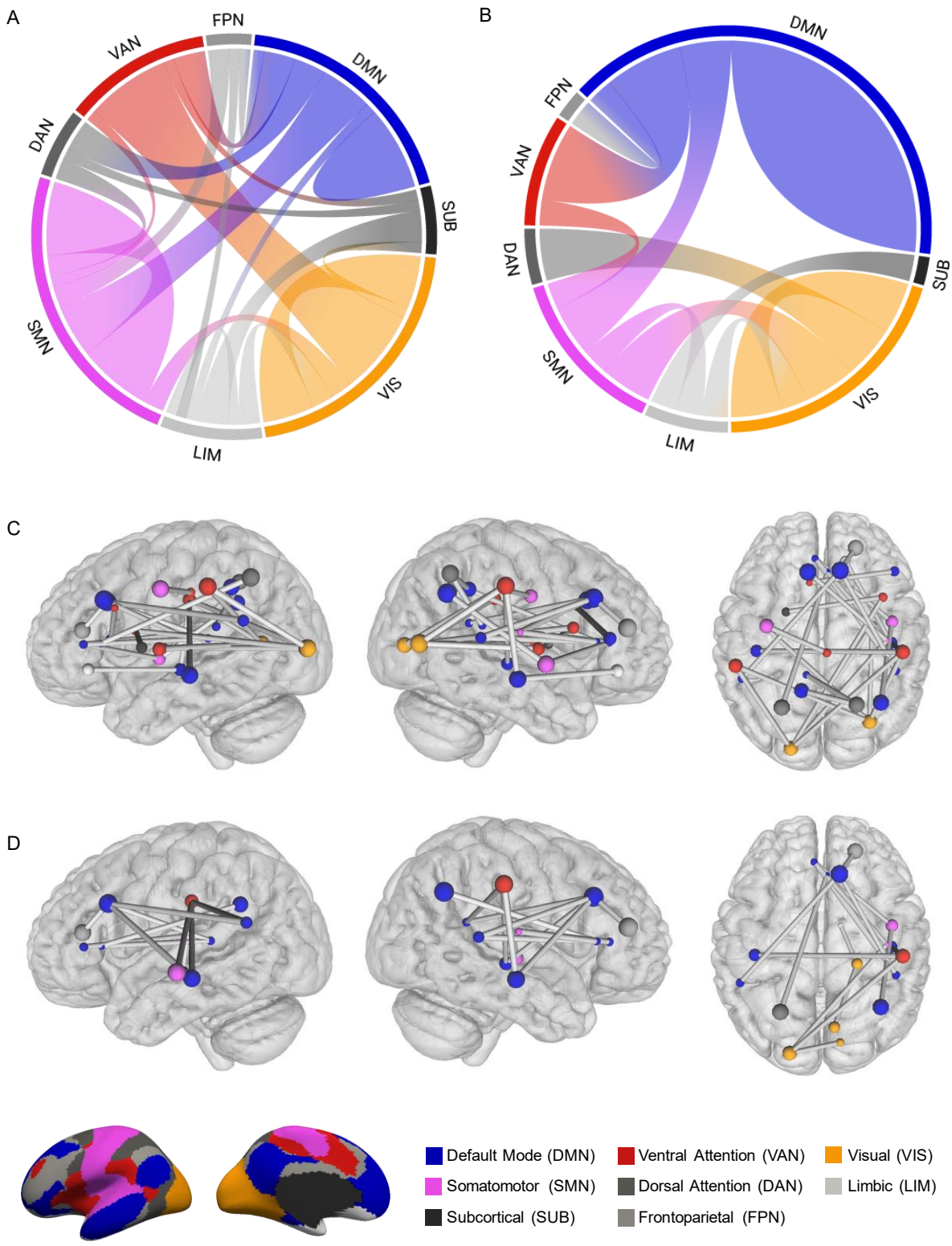

Figure 2 Network connections in the DMN and VAN predict joint attention. Shown are the connections between brain networks for A) the predictive model without controlling for general development and B) the model controlling for general development. Connections with nodes within the DMN and VAN for C) the model without controlling for general development and D) the model controlling for general development. Node size represents node degree, that is, the number of connections linked to this node. Network assignments are based on the Yeo 7-network parcellation (see color legend).

Table 1 List of connections between nodes contributing to the model that controlled for general development. Nodes are based on the UNC4D infant atlas, which uses the Desikan-Kiliany parcellation. Network assignments are based on the Yeo 7-network atlas. Abbreviations: DAN: dorsal attention network, DMN: default mode network, FPN: frontoparietal network, SMN: somatomotor network, SUB: subcortical, LIM: limbic network, VAN: ventral attention network, VIS: visual network; R: right and L: left hemispheres.

Connection between							
Node 1				**Node 2**			
	DMN	L	Bank superior temporal sulcus		DMN	R	Superior frontal gyrus
	DMN	L	Middle temporal gyrus		DMN	R	Superior frontal gyrus
	DMN	L	Bank superior temporal sulcus		DMN	R	Rostral anterior cingulate
	DMN	L	Bank superior temporal sulcus		DMN	R	Superior frontal gyrus
	DMN	R	Inferior parietal gyrus		DMN	R	Rostral anterior cingulate
	DMN	R	Middle temporal gyrus		DMN	R	Superior frontal gyrus
	DMN	L	Bank superior temporal sulcus		VAN	R	Supra marginal gyrus
	DMN	L	Middle temporal gyrus		VAN	R	Supra marginal gyrus
	DMN	R	Middle temporal gyrus		VAN	R	Supra marginal gyrus
	DMN	L	Rostral anterior cingulate		SMN	R	TransverseTemp
	DMN	R	Rostral anterior cingulate		SMN	R	TransverseTemp
	VIS	R	Pericalcarine cortex		DAN	L	Superior parietal gyrus
	VIS	R	Pericalcarine cortex		DAN	R	Superior parietal gyrus
	VIS	R	Fusiform gyrus		VIS	R	Lingual gyrus
	VIS	R	Fusiform gyrus		VIS	R	Pericalcarine cortex
	VIS	L	Lateral occipital cortex		SMN	R	Superior temporal gyrus
	VIS	L	Lateral occipital cortex		SMN	R	TransverseTemp
	VAN	R	Supra marginal gyrus		SMN	L	Superior temporal gyrus
	LIM	L	Entorhinal cortex		SMN	R	Paracentral gyrus
	LIM	L	Frontal pole		SUB	R	Caudate
	LIM	R	Entorhinal cortex		VIS	R	Fusiform gyrus
	DMN	R	Superior frontal gyrus		FPN	R	Rostral middle front gyrus

Joint attention model in infancy predicts later Theory of Mind at preschool age

To test whether brain networks that predict joint attention in infancy are also predictive of later-developing ToM in the preschool years, we applied the joint attention model that controlled for general development to the resting-state data of preschool children aged 2 to 5 years (N = 37). Notably, the joint attention model, which was initially trained in infants aged 8 to 15 months, significantly predicted the emergence of ToM reasoning in an independent sample of preschool-aged children several years later (N = 37, rho = .336, p = .021, Fig 3).

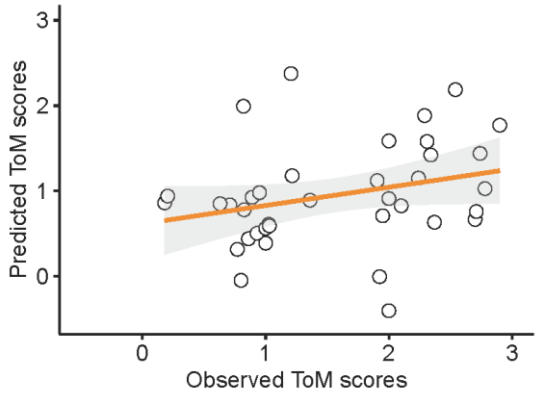

Figure 3 A connectome-based model built on joint attention data in infancy significantly predicted ToM capacity in preschool children. Scatterplot of the correlation between predicted ToM scores from the model and observed ToM scores (N = 37, rho = .336, p = .021).

Discussion

Joint attention marks a pivotal developmental milestone in infancy that plays a catalyzing role for infants' learning and social cognitive development. Joint attention thus has high potential as a predictor for individual differences in cognitive development in health and disease. Here, we therefore set out to investigate neural markers that are predictive of joint attention. To this end, we modeled 8- to 15-month-old infants' whole brain connectivity with connectome-based predictive modeling to identify brain network patterns that predict infants' engagement in joint attention. Importantly, our model significantly predicted joint attention scores in an independent cohort of individuals. An initial model of joint attention relied on connections within sensory networks and their interactions with the DMN and VAN. However, when accounting for children's general cognitive development, within-DMN connectivity became the dominant predictive contributor, followed by its interaction with the VAN. Connections within the somatomotor network, in turn, diminished. This indicates that these connections likely pertain to general developmental processes, such as motor coordination, that may facilitate joint attention but lack specificity to it. Remarkably, this model, trained on joint attention in infants, not only predicted joint attention performance in new infants but also the development of ToM – a milestone of social cognitive development several years later.

The predictive power of our model likely rests on the cross-validated whole-connectome predictive modelling approach that allowed the discovery of whole-brain network patterns predictive of joint attention, rather than being limited to individual connections or brain regions. As the networks identified for joint attention also predicted ToM reasoning several years later, these findings suggest a causal relation in which the maturation of these networks drives ToM development. This is in line with the proposed role of joint attention as a catalyst for social cognitive development and ToM[1] and with partly overlapping brain regions observed for joint attention and ToM[43]. The dominant connections in the model lay within the DMN, linked to

various domains of higher-order cognition and largely overlapping with the network activated for ToM[46,47]. This supports the notion that the DMN's capacity to integrate sensory signals and external attention[48] within social contexts is already in place in infancy. The DMN was previously shown to be active during real-time synchronization in social interactions[49], allowing a mutual attunement to one another, which is highly relevant for infants and their caregivers[50]. In particular, during moments of mutual gaze, smiling, and joint attention, local neural couplings in infants and caregivers were observed in the mPFC, a core region of the DMN[51]. Moreover, the emergence of mature ToM in the preschool years was associated with increased structural connectivity of the DMN and its connection to regions involved in language and executive function[52].

Next to within-DMN connectivity, its interaction with the VAN, followed by sensory network interactions contributed to the predictive model. This interplay of sensory input processed in the VIS and SMN and information filtering in the VAN may contribute to the integration of sensory input (e.g., the others' gaze or pointing and target of attention), attentional control (to focus on the attentionally guiding cues), and coordination of one's movements (to follow these cues) required for joint attention. Thereby, bottom-up, stimulus-driven processing in the VAN may allow infants to attune and react to striking and attention-grabbing cues in their environment. For example, the gaze cues of another person and the highlighted objects are particularly salient, and therefore facilitate infants learning in social interactions in a bottom-up fashion[53–55]. This interplay of higher-order, attention, and sensory networks may contribute to infants' development beyond joint attention, giving rise to the 9-month revolution[1], a period of developmental leaps across different social cognitive domains. Indeed, our results suggest that these networks already play a foundational role in the emergence of joint attention, which then, in turn, seems to set the stage for later-developing ToM.

While joint attention is a directly perceivable activity, the later-developing skill of ToM is used to infer *invisible* mental states, that is, content which is decoupled from perceptual input. Our finding that the networks predictive of joint attention also predicted later ToM reasoning fit with the recent suggestions that the interaction between bottom-up networks and the DMN may contribute to decoupling content from perceptual input[56,57]. This possible shift from perceptual access to higher, perceptually decoupled cognition is reflected in the maturational trajectories of brain networks. Indeed, sensory networks mature first, with adult-like functional patterns by 9 months, while attention networks and the DMN mature later[58,59]. In line with this idea, a study correlating behavioral joint attention scores with functional connectivity found that 24-month-old infants showed decreased coupling between sensory networks and higher-order networks compared to 12-month-olds[21].

Given its predictive power for joint attention and ToM, our model and the employed CPM approach has high potential of providing early neuro-markers of atypical development with impairments in joint attention and ToM, such as in autism spectrum disorder (ASD)[60,61]. Because of its function as a catalyst, joint attention impairments at this early stage in life have far-reaching and negatively cascading consequences[39,42]. Thus, early diagnosis and intervention are of great importance. Indeed, imaging-based models have been used to predict ASD[62,63] and ADHD[64]. Our connectome-based approach, specifically modeling joint attention, could extend the diagnostic power of such models. Applying our model to these disorders could reveal early interventions targeting the contributing brain networks predictive of joint attention and ToM.

In conclusion, we have demonstrated that a predictive model of joint attention, trained on the whole-brain connectome of 8- to 15-month-old infants, significantly predicted both joint attention in a new sample of individuals and ToM capacity several years later. Dominant connections of the model lay within the DMN and its interaction with the VAN. We propose that the development of joint attention is underpinned by increased connectivity of the DMN and its coupling to bottom-up processing in the VAN, bridging the transition from perceptually-based processing to more abstract social cognitive processes that are decoupled from perception, such as ToM. The possibility to predict joint attention and ToM at this early stage in development reveals intriguing potential for the early diagnosis of social cognitive disorders like ASD, ADHD, and delayed language development. An exciting avenue for future research is whether a similar approach can predict other cognitive developments linked to joint attention, such as language and other social cognitive functions.

STAR Methods

Baby Connectome Project Dataset

For this study, we used open-access data from the Baby Connectome Project (BCP[44]), available via the NIMH Data Archive (ID: 2848). We were interested in participants with resting state data and behavioral assessments of joint attention and theory of mind. Our joint attention analysis included N=92 infants (51 female) aged 8 to 15 months (median 11 months) with a total of 144 scans. Furthermore, for the prediction of Theory of Mind scores in preschool-aged children, N=37 children (21 female) aged 24 to 60 months (median 34 months) with a total of 38 scans were included.

Behavioral Assessment

Joint Attention

Joint attention was assessed with the *Dimensional Joint Attention Assessment*[22] in infants aged 8 to 15 months. Several novel toys were distributed in a room. The experimenter sat in

front of the infant and initiated four joint attention prompts with decreasing difficulty. First, the experimenter shifted their gaze and head toward a toy. Secondly, the experimenter additionally said, “Look at that”. Then, the experimenter shifted their gaze and head and pointed at the toy. Last, the experimenter used all cues of shifting gaze and head, pointing, and verbalization. If the infant responded to one prompt, the series was accomplished, and the infant was allowed to play with the toy. If the infant did not respond, the experimenter continued with the next level of difficulty. These maximal four prompts were repeated with four different toys. For each series, the infant was scored from 0 (no response) to 4 (responding to the first, most difficult prompt), and the mean of all series was used for further analysis. Joint attention assessment and MRI data acquisition occurred within a timespan of two weeks.

General Development

The general development of infants was assessed with the *Mullen Scales of Early Learning*[65]. The scale spans the domains of gross motor, fine motor, visual reception, receptive language, and expressive language. The scale comprises interactive tasks and was administered in a standardized format. For our analysis, an aggregated score across all subdomains was used.

Theory of Mind

Theory of Mind skills in preschool-aged children was assessed with the *Children's Social Understanding Scale* (CSUS[66], which is a parent-report questionnaire that was cross-validated in several studies with children’s performance in different ToM tasks. The scale comprises evaluating various aspects of Theory of Mind, including children’s understanding of other people’s beliefs, knowledge, perceptual access, desires, intentions, and emotions. Theory of Mind and MRI data were acquired within one month.

MRI Data Acquisition

Infants under 3 years of age were scanned during natural sleep (for a review see[67], for detailed procedures[44]). Parents of children above 3 years could choose between sleep and awake MRI. All images were acquired on a Siemens 3T Prisma with a 32-channel head coil. Sequences used in the BCP were specifically tailored to the needs of infant MRI (e.g., by using quieter and shorter sequences). Anatomical MRI was acquired with MPRAGE (0.8 mm isotropic, TE=2.24 ms, TR=2400/1060 ms, 6:38 minutes). Resting-state fMRI was acquired with a single-shot EPI sequence (2 mm isotropic, TE=37 ms, TR=800 ms, 5:47 min). For further details, see the BCP acquisition pipeline[44].

MRI Data Preprocessing

MRI data from the BCP were preprocessed using the state-of-the-art infant-specific pipeline niBabies 22.0.1, derived from fMRIPrep[68] with the UNC 4D volumetric atlas[69] in *MNIInfant*

space. Preprocessing was performed with the respective age-group-specific template to account for age-related brain size differences. Preprocessed data were quality controlled by checking for proper brain extraction, T1w/T2w registration and quality of functional data. For details, see supplements. For additional details, see Supplementary Methods 1 for pipeline-generated boilerplate.

Connectome Construction

To obtain connectivity matrices from the preprocessed rsfMRI data, CONN toolbox 21.a (RRID:SCR_009550[70]) was used. As suggested, an additional functional smoothing step with a Gaussian kernel of 6 mm full-width half maximum (FWHM)[71] was performed after importing the preprocessed rsfMRI data. Furthermore, CONN's default denoising pipeline, including linear regression of potential confounding effects in the BOLD signal and temporal bandpass filtering, was performed. ROI-to-ROI connectivity was calculated with the UNC-4D[69] infant atlas containing a cortical parcellation of 82 regions based on the Desikan-Killiany parcellation[72]. For additional details, see Supplementary Methods 2 for pipeline-generated boilerplate.

Connectome Predictive Modeling

Building a model predictive of joint attention in the training data

Connectome predictive modeling (CPM) was used to predict behavioral JA scores from resting-state connectivity matrices. CPM involves the steps of feature selection, model building, and model validation described below (for details see[6]). We randomly split our data into a training (N=97) and test (N=47) set to obtain independent datasets. In the first step of CPM, connections whose individual variations could explain differences in behavior were obtained. To achieve this, we correlated joint attention scores with the edges (functional connections) of rfMRI connectivity matrices in the training set. Edges above a correlation threshold of p=0.005 were selected for the model. We used a leave-one-out cross-validation approach, repeating the edge selection step 97 times while always leaving out one participant. The final set of edges that make up the joint attention network was based on edges found in 90% of all leave-one-out iterations. Each participant's connectivity strength was summed for the selected edges, and this summed network strength was used to build linear regressions that model the relation between connectivity strength and joint attention.

Predicting joint attention scores and validating the model

The built joint attention model was validated by applying the model to the unseen, independent test dataset (N=47). In the test dataset, individual network strength for the selected joint attention edges was computed as described above. Then, joint attention scores were predicted based on resting-state connectivity, and the predictive performance of the model was

evaluated with a one-sided Spearman correlation between the predicted scores and the measured joint attention scores.

Controlling for general development

To ensure the specificity of our joint attention model, we controlled for the general development of children. For this, we built a model as described above in the training data but regressed out the *Mullen Scales of Early Learning* from the joint attention scores (N=79). The model was validated in the independent test data as described above for the uncontrolled model (N=39).

Predicting Theory of Mind scores

To test whether the built models predict ToM scores in older children (N=37), we applied the model predictive of joint attention and controlled for general development on the resting-state data of children with ToM measures to predict ToM scores. Model performance was assessed with a Spearman correlation between the predicted and the actual ToM scores.

Optimizing the Feature Selection Threshold

As suggested by Shen et al.[6], we determined the optimal feature selection threshold that determines which edges are considered in the model. For this, we split the original dataset into a training (N=97) and test (N=47) set. In our training dataset, we tested four different, commonly used, feature selection thresholds (p=0.05, p=0.01, p=0.005, p=0.001) with a leave-one-out cross-validation approach. We evaluated each model built with a different feature selection threshold by comparing their predictive performance (Spearman rho). For all analyses in the test set, we used the feature selection threshold of p=0.005 obtained from the training dataset. See performance of the tested feature selection thresholds in Supplementary Table 2.

Controlling for Motion

As suggested by Shen et al.[6], we controlled for motion by correlating motion parameters (framewise displacement according to Power) with behavior and resting state connectivity. Neither a correlation of motion with behavior (Spearman rho=.017, p=.825) nor a prediction of motion by the predictive model (Spearman rho=-.133, p=.372) was found.

Network Connectivity

Brain network connectivity was investigated by using the mapping of the 7-network atlas[45] and the Desikan-Kiliany parcellation, on which the UNC 4D infant atlas[69] is based. This mapping between different atlases was computed with spatial permutations[73]. We assigned each node in the UNC 4D atlas to one of the seven networks based on its highest overlap. For network connectivity, the sum of connections between networks was computed for visualization.

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Conceptualization – CS, CGW, and PB. Data curation, Formal analysis, Methodology, Validation, and Visualization – CS. Supervision – CGW. Writing, original draft – CS. Writing, review and editing – CGW and PB.

Competing interests.

We declare no competing interests.