Tracking the Development of Functional Connectomes for Face Processing

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Abstract

Face processing capacities become more specialized and advanced during development, but neural underpinnings of these processes are not fully understood. The present study applied graph theory-based network analysis to task-negative (resting blocks) and task-positive (viewing faces) functional magnetic resonance imaging data in children (5–17 years) and adults (18–42 years) to test the hypothesis that the development of a specialized network for face processing is driven by task-positive processing (face viewing) more than by task-negative processing (visual fixation) and by both progressive and regressive changes in network properties. Predictive modeling was used to predict age from node-based network properties derived from task-positive and task-negative states in a whole-brain network (WBN) and a canonical face network (FN). The best-fitting model indicated that FN maturation was marked by both progressive and regressive changes in information diffusion (eigenvector centrality) in the task-positive state, with regressive changes outweighing progressive changes. Hence, FN maturation was characterized by reductions in information diffusion potentially reflecting the development of more specialized modules. In contrast, WBN maturation was marked by a balance of progressive and regressive changes in hub-connectivity (betweenness centrality) in the task-negative state. These findings suggest that the development of specialized networks like the FN depends on dynamic developmental changes associated with domain-specific information (e.g., face processing), but maturation of the brain as a whole can be predicted from task-free states.

Keywords: connectome; face perception; fMRI; functional connectivity; graph theory

Introduction

FACE PROCESSING IS one of the most fundamental human cognitive abilities. Infants are born with an inherent preference to view faces versus other objects (Johnson, 2007), even within a few minutes after birth, they display a remarkable sensitivity to visual face-like stimuli (Wilkinson et al., 2014). Face processing, like some other specialized cognitive capacities, matures over a prolonged developmental time line (Joseph et al., 2015; Kadosh and Johnson, 2007) and requires synchronized interaction among diverse brain systems (Atkinson and Adolphs, 2011; Kadosh and Johnson, 2007).

At the same time, specialized capacities require neural resources devoted to processing domain-specific information. Hence, capacities like face processing in the developed brain likely require an optimal configuration of both functional integration to coordinate activity and synthesize information across multiple brain regions and segregation of brain systems to process domain-specific information.

However, given the protracted developmental time line for face processing, how the brain achieves functional specialization during typical development is still an unanswered question. Moreover, altered integration and segregation in brain maturation may be a characteristic of neurodevelopmental disorders such as autism (Rudie et al., 2012). Therefore, understanding the brain as a complex network with many interacting and connected elements is a promising approach to illuminate both typical and atypical developmental changes in the functional architecture of specialized brain systems like face processing.

Graph theory-based network analysis has become an increasingly popular approach to describe the functional architecture of the human brain based on functional magnetic resonance imaging (fMRI) data (Rubinov and Sporns, 2010; Sporns, 2014). The brain can be envisioned as a set of nodes (regions) that form highly intracommunity modular communities, which are largely segregated from each other except through a few critical connector regions. Numerous

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graph theory measures are available to characterize brain network topology and connectivity.

In this study, three measures were chosen based on the fact that they capture somewhat nonoverlapping and conceptually distinct properties of network organization and information flow. Another motivation for selecting these three measures was that they should be linked to the ideas of segregation and integration within networks. Finally, these network measures have neurobiological interpretations (Bullmore and Sporns, 2009). The degree of *segregation* in a network can be described by the clustering coefficient (CC), which reflects how many of a given node's neighbors are also neighbors of each other (Rubinov and Sporns, 2011; Saramaki et al., 2007; Watts and Strogatz, 1998).

The degree of *integration* in a network can be described in various ways. For example, connections among local communities are often characterized by central nodes or hubs. Betweenness centrality (BC) is one network metric that reflects integration because connector hubs represent the fraction of shortest paths passing through a particular node (Freeman, 1979; Freeman et al., 1991; Kintali, 2008). Hub regions thus allow for otherwise disconnected local neighborhoods to communicate with each other.

Another important network measure, eigenvector centrality (EC), is also considered a metric for network integration. It reflects the influence of a node on the network by characterizing the number and importance of connections a given node's connections has (Bonacich, 2007; Lohmann et al., 2010; Newman, 2008). EC can also be considered a measure of information diffusion in a network. A node that has neighbors that are also highly connected has the capacity to convey information further in a network.

Although network analysis has already been used to examine neurotypical developmental changes with continuous resting-state paradigms (Cao et al., 2014; Dosenbach et al., 2010; Fair et al., 2009; Song et al., 2015; Stevens et al., 2009; Supekar et al., 2009), fewer studies have applied network analysis to task-driven functional connectome development for face processing (Joseph et al., 2012; Rudie et al., 2012). Collectively, the resting state studies suggest that functional brain maturation likely involves a dynamic interplay of functional segregation and integration (Betz et al., 2014; Cao et al., 2017; Fair et al., 2009; Hwang et al., 2013; Zuo et al., 2012) from childhood to adulthood.

Although a dynamic interplay of functional integration and segregation is likely at play for maturation of domain-specific connectomes, network properties that are important for maturation of intrinsic functional connectivity, as measured with continuous resting state, may not necessarily be the same network properties that characterize maturation of specialized functional networks, such as those involved in face processing. To the best of our knowledge, no studies to date have differentiated the network properties that are most important for maturation of face processing.

Because so few studies have applied network analysis to study the development of the functional connectome for face processing, the present study will examine this by using network measures of functional segregation (CC) and two different measures of functional integration: information diffusion (based on EC) and hub topology (based on BC). The goal is to determine which of these network properties is mostly strongly associated with functional connectome

development in task-positive (face viewing) versus task-negative (visual fixation) states and within a whole-brain versus face-specific network.

The primary hypothesis is that the development of a specialized network for face processing is driven by (a) task-positive processing more so than task-negative processing and by (b) both progressive and regressive changes in network properties. Predictive modeling will be used to determine which network properties are most strongly associated with face network (FN) versus whole-brain network (WBN) development.

Materials and Methods

Participants

Fifty-nine neurotypical adults (mean age = 26.5 years, SD = 6.0 years, range = 18–42 years; 29 males) and 42 neurotypical children and adolescents (mean age = 9.9 years, SD = 3.5 years, range = 5–18 years; 21 males) completed the study. Exclusion criteria were left-handedness, central nervous system medications, prior neurological or psychiatric diagnosis, learning disability, and contraindications for MRI scanning. Neurotypical status was established by scores on the Peabody Picture Vocabulary Test and Expressive Vocabulary Test (Dunn and Dunn, 2007; Williams, 1997) in children and adults. All subjects provided informed consent or assent in accord with the University's Institutional Review Board.

Face localizer stimuli and task

In a face localizer task (4.5 min), subjects passively viewed blocks of faces, objects, or textures and pressed a button at the onset of each stimulus to ensure active participation. Stimuli consisted of 30 grayscale photographs each of unfamiliar high-school yearbook faces (15 females and 15 males), objects (e.g., tools, household objects), and textures constructed by blurring and scrambling the face and object photos. The face stimuli were head shots, mostly Caucasian individuals with smiling or neutral expressions and no facial hair or glasses. Each stimulus was presented individually in the center of the screen (vertical visual angle of 5.8°). In each of 9 task blocks (3 each of face, object, and texture), 10 stimuli appeared for 1 sec each, followed by a fixation cross for 750 ms. Nine rest blocks consisted of 12.5 sec of a fixation cross.

MRI data acquisition

A 3T Siemens Trio MRI scanner equipped for echo-planar imaging was used (repetition time [TR] = 2500 ms, echo time [TE] = 30 ms, flip angle = 80°, 38 axial slices, field of view [FOV] = 224 × 224 mm, 3.5 mm³ voxels; 109 volumes). A high-resolution T1-weighted anatomical scan (MPRAGE [Magnetization Prepared Rapid Gradient Echo Imaging]; TE = 2.56 ms, TR = 1690 ms, TI [inversion time] = 1100 ms, FOV = 256 × 224 mm, 1 mm³ voxels, flip angle = 12°, 176 contiguous sagittal) and a 1-min field-map scan were also collected.

fMRI data preprocessing

The full preprocessing pipeline is illustrated in Supplementary Fig. S1. Using FMRIB's FSL package (www.fmrib.ox.ac.uk/fsl), images in each participant's time series were corrected for geometric distortion and head motion, spatially smoothed with a 3D Gaussian kernel (FWHM [full width

half maximum] = 7 mm) and high-pass filtered (100 sec cut-off). The first four volumes were eliminated from each time series to achieve steady-state magnetization.

Functional images were fit to the MNI template using each subject's high-resolution anatomical image and affine transformations. In our experience, using nonlinear transformations to fit functional images from children to an adult template is more distorting than affine transformations. The automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) was used to define regions-of-interest (ROIs) or network nodes, excluding cerebellar regions. By using large ROIs from the AAL atlas, small errors in the spatial normalization of these ROIs in different brains are less likely to affect the average time series in a region given that the ROI is large.

In each of 90 AAL cerebral regions, time series were extracted for the entire functional run and time censored (Power et al., 2012). Time points with fractional displacement (FD) greater than 0.5 mm were eliminated from analysis. Because the time series were short, only the volumes at a single time point were removed, surrounding volumes were not removed. Subjects with 25% or more scrubbed time points were excluded from analyses. Each time series was shifted by one TR to more closely link the time points with the conditions of interest by accounting for the hemodynamic lag (Pouratian et al., 2002).

The full time series for the task were then broken into four separate time series, one for each condition: faces, objects, textures, and rest (similar to Joseph et al., 2012), but only the face and rest states were analyzed in this study. Each of the experimental conditions' time series consisted of a maximum of 21 time points and the rest condition consisted of 45 time points.

Connectivity matrices and graph theory metrics

As shown in Supplementary Figure S1, for each subject and each condition, a connectivity matrix was computed from all pairwise correlations across the 90 regions, using partial correlation (Fransson and Marrelec, 2008; Marrelec et al., 2009; Salvador et al., 2005). We used shrinkage because partial correlation (rather than Pearson) was used to create connectivity matrices, but in all cases, we had fewer observations (time points) than nodes (brain regions).

Partial correlation requires matrix inversion, which in "large p small n" cases require some sort of regularization to stabilize the inversion. We applied a shrinkage factor as developed by Ledoit and Wolf (2003) and implemented in MATLAB by Schafer and Strimmer (2005) to create a well-conditioned covariance estimate. The mixing parameter is largely an optimal weight as a function of N to combine the observed covariance and a target matrix such as a diagonal (i.e., no covariance/correlation between regions).

The brain connectivity toolbox (Rubinov and Sporns, 2010, 2011) was used to generate several graph theory measures (www.brain-connectivity-toolbox.net). We only considered edges with positive weights and used the weighted alternatives of graph theory measures. Node strength was normalized by dividing each node's strength by the sum of all strengths across nodes for a given subject.

For CC, a weighted alternative was used that defined that sums over the triangle intensities, $C_i = \frac{2}{s_i(s_i - 1)} \sum_{j,k} (e_{ij}e_{jk}e_{kj})^{1/3}$, where s_i is the strength of that node (Saramaki et al., 2007).

The BC of a node i was defined as $b_i = \frac{1}{(n-1)(n-2)} \sum_{j,k} \frac{\rho_{jk}^i}{\rho_{jk}}$, where ρ_{jk} is the number of shortest paths between j and k , and ρ_{jk}^i is the number that also pass through i . This function also requires distances, rather than measures of similarity, and inverts the values of the edges on the graph.

EC is a strength measure that is recursively weighted by the strength of those nodes in its neighborhood. A vector representation of a graph can result in an adjacency matrix A , and with the decomposition $Ax = \lambda x$, the vector corresponding to the greatest eigenvalue results in the EC, with the v th component giving the respective nodes centrality score. This is further normalized by dividing each component by the sum of the entire vector.

Connectivity measures were always calculated using all 90 nodes, but different numbers of nodes were used as predictors in predictive modeling for the WBN (all 90 nodes minus those that were excluded due to FD; see the Results section) and FN (30 nodes minus those that were excluded due to FD). Hence, each node reflected connectivity with respect to the whole network irrespective of whether the analysis was for the WBN or FN. In addition, each node's association with age was the same for the WBN and FN analyses.

The 30 regions that were included in the FN were based primarily on a previous study (Joseph et al., 2011), which reported these regions as activated in either children or adults during a passive face viewing task but also on other sources that outline a "face network" (Haxby et al., 2001): bilateral amygdala, precentral gyrus, inferior frontal gyrus–opercular portion, inferior frontal gyrus–orbital portion, insula, hippocampus, calcarine sulcus, inferior occipital cortex, fusiform gyrus, postcentral gyrus, inferior parietal cortex, angular gyrus, superior temporal gyrus, middle temporal gyrus, and inferior temporal gyrus. As the regions were activated in either adults or children, they represent nodes where developmental change is possible.

Predictive modeling

The combination of 3 network properties (EC, BC, and CC) $\times$ 2 states (task positive and task negative) $\times$ 2 networks (WBN and FN) yielded 12 separate models (see final step of pipeline in Supplementary Fig. S1). Each model was built using the automatic linear modeling (ALM) function in IBM SPSS Statistics (v. 19, Chicago, IL). Detailed processing steps employed by ALM are illustrated in Supplementary Figure S2. ALM is a linear modeling approach in which a set of variables (i.e., network properties in each of the 90 AAL regions/nodes) predict an outcome (i.e., age). ALM also automatically trims outliers and transforms variables, if needed.

ALM divides the full sample of subjects into a training set (70% of the data) and a test set, called the overfit prevention set (30% of the data). In ALM, all variables are first entered into a forward stepwise regression on the training set, with the average squared error (ASE) calculated using the overfit prevention set after the addition of each variable. If ASE is reduced, the variable is retained; otherwise, the variable is removed from the model.

After the forward stepwise regression, ALM yields a set of variables that are further examined using the "best subsets" option, which examines all possible subsets of variables (Schatzoff et al., 1968) and determines the best subset

using the ASE of the overfit prevention set. All possible subsets are examined if the number of variables from the forward stepwise regression is 20 or fewer. If the number of variables is between 21 and 40, the $n - 20$ variables with the minimum p -value based on Type III Sums of Square are entered into the model, then an exhaustive search of all remaining 20 variables is conducted.

If the number of variables from the forward stepwise regression exceeds 40, then those variables are selected as the best subset. The model with the lowest ASE is chosen by ALM as the best model. ALM yields a measure of model accuracy, which is 100 times the adjusted R^2 of the final model, as well as the importance and weight (coefficient) of each predictor.

Predictor importance is a relative measure of how important each variable was in the prediction. IBM SPSS Statistics uses the leave-one-out method to compute importance, based on the residual sum of squares by removing one predictor at a time from the final full model. The importance values all sum to 1.

Note that the 12 different models in the present analysis were derived from different data sets, that is, each model used a different network metric (BC, CC, EC), pool of predictors (all nodes for WBN and 40 nodes for FN), or task state (face viewing, task-negative). Therefore, formal model comparisons were not conducted, but models were compared qualitatively based on model fit (accuracy or adjusted R^2), number of predictors as an index of parsimony, and prediction accuracy (ASE). Based on a combination of these indices, a highest ranking model for each network (WBN or FN) was determined. For the highest ranking model for each network, age functions were fit to linear, quadratic, or growth (von Bertalanffy, 1966) curves in MATLAB and the adjusted R^2 and root mean squared error (RMSE) were used to compare developmental trajectories from the same set of data.

Results

Although the data were time censored, it was important to address any residual effects of head movement in predicting age given that age was highly correlated with FD ($r = -0.58$, $p = 0.0001$). Initial ALM analyses that included FD as a predictor of age revealed that FD dominated the regressions and

yielded essentially the same accuracy across models. To control for effects of head motion, nodes that showed high correlations with FD over and above the correlation with age were identified for each network metric (BC, CC, EC) and state (task-positive or task-negative) using partial correlation between FD and each node's value, controlling for age. Nodes that showed a significant partial correlation ($p < 0.05$, uncorrected) for either the task-positive or task-negative state for a given metric were omitted as predictors in the models for that metric.

Eleven nodes were omitted for BC (left caudate, left anterior cingulate, left middle frontal, right mid-orbital frontal, left superior medial frontal, left Heschl, left inferior occipital, left paracentral, right precentral, left rectus, and left thalamus), 11 nodes were omitted for CC (right caudate, left anterior cingulate, left inferior frontal triangular, left lingual, left inferior occipital, right inferior parietal, left paracentral, left postcentral, right precentral, left rectus, and right thalamus), and 8 nodes were omitted for EC (left angular, left and right Heschl, right hippocampus, left middle occipital, right postcentral, and left and right thalamus).

Predictive modeling results for each graph theory metric (BC, CC, EC) for each state (face or task-negative) and for each network (WBN and FN) are shown in Table 1.

WBN results

The WBN yielded four significant models that ranged in accuracy from 25.2% to 37.3%. Among the significant models, the 95% confidence intervals calculated for R^2 (www.danielsoper.com/statcalc/calculator.aspx?id=28) were overlapping, indicating no single best model. However, the model with the highest accuracy (BC in the task-negative state) was also the most parsimonious, having the fewest predictors ($n = 19$). In contrast, CC in the task-negative state had the best prediction accuracy, with the lowest ASE from cross-validation. Models constructed in the face state were not significant for BC or CC.

The predictors for the most parsimonious and most accurate model (BC task negative) are provided in Table 2. Figure 1a shows the top predictors (i.e., nodes) of age for the model with the highest accuracy and least number of variables needed to predict age for the WBN (BC in the

TABLE 1. RESULTS FROM AUTOMATIC LINEAR MODELING

Network	Metric	State	Accuracy (adjusted R^2), %	F-test	Overfit prevention criterion (ASE)
WBN	BC	TN	24.6 < 37.3 < 50.0	$F(19, 75) = 3.30$, $p = 0.0001^{**}$	20.3
		Face	4.8 < 14.6 < 24.6	$F(22, 81) = 1.63$, $p = 0.07$	33.6
	CC	TN	15.9 < 27.7 < 39.5	$F(23, 75) = 2.25$, $p = 0.008^{*}$	10.3
		Face	6.4 < 16.5 < 26.6	$F(25, 81) = 1.64$, $p = 0.063$	17.6
	EC	TN	17.9 < 30.4 < 42.9	$F(20, 75) = 2.64$, $p = 0.002^{**}$	13.8
		Face	13.3 < 25.2 < 37.1	$F(21, 81) = 2.30$, $p = 0.006^{*}$	11.5
FN	BC	TN	0 < 10.6 < 21.8	$F(10, 76) = 1.89$, $p = 0.063$	57.1
		Face	6.9 < 19.9 < 32.9	$F(12, 81) = 2.68$, $p = 0.005^{*}$	53.9
	CC	TN	7.4 < 21.4 < 35.4	$F(10, 76) = 3.04$, $p = 0.003^{**}$	56.4
		Face	3.1 < 16.0 < 28.9	$F(8, 81) = 2.93$, $p = 0.007^{*}$	67.9
	EC	TN	8.5 < 22.2 < 35.9	$F(12, 76) = 2.78$, $p = 0.004^{**}$	33.3
		Face	16.3 < 30.5 < 44.7	$F(11, 81) = 4.20$, $p = 0.0001^{**}$	18.8

*Model is significant at $p < 0.05$.

**Model is significant at $p < 0.0042$.

ASE, average squared error; BC, betweenness centrality; CC, clustering coefficient; EC, eigenvector centrality; FN, face network; TN, task negative; WBN, whole-brain network.

TABLE 2. PREDICTORS OF AGE FOR THE WHOLE-BRAIN NETWORK AND BETWEENNESS CENTRALITY

Region	Coefficient	Importance	p
L superior orbitofrontal	257.52	0.058	0.006
R supramarginal	−304.30	0.057	0.017
R olfactory	110.08	0.054	0.098
L superior temporal	−259.77	0.053	0.135
R inferior orbitofrontal	−173.08	0.053	0.114
R superior parietal	−121.00	0.053	0.181
R caudate	144.76	0.053	0.129
R putamen	285.41	0.053	0.142
L cuneus	−119.52	0.052	0.450
L temporal pole superior	−59.58	0.052	0.454
R superior orbitofrontal	92.18	0.052	0.370
L middle temporal	122.83	0.052	0.355
R anterior cingulate	189.03	0.052	0.320
R mid-orbitofrontal	−101.33	0.051	0.491
R middle frontal	−100.46	0.051	0.554
L postcentral	−33.73	0.051	0.800
R temporal pole mid	48.57	0.051	0.588
R superior frontal	105.19	0.051	0.559
R lingual	129.01	0.051	0.465

L, left; R, right.

task-negative state), with the importance of each predictor indicated by the size of the sphere. Progressive changes (blue) mean that network metric increased with age, whereas regressive changes (red) mean that the network metric decreased with age.

Figure 2a shows the age predictions for this model, with three different curves. Ranking the fits according to the adjusted R^2 or RMSE yields quadratic as the top-ranking fit, followed by growth curve fit, followed by linear. Cook's distance in SPSS detected six outliers. We omitted those outliers and then reran the ALM, and model accuracy improves and the rank ordering of fits changed. Linear (RMSE = 3.79, adjusted R^2 = 66.0%) and quadratic (RMSE = 3.81, adjusted R^2 = 65.6%) are essentially the same, but now the growth curve fit is about 8% worse than the others in terms of RMSE (RMSE = 4.09, adjusted R^2 = 60.3%).

FN results

The FN yielded five significant models that ranged in accuracy from 16.0% to 30.5%. Among the significant models, the 95% confidence intervals calculated for R^2 were overlapping, indicating no single best model. However, the model with the highest accuracy (EC in the face state) also had the best prediction accuracy (lowest ASE), but this model was not the most parsimonious, having 11 predictors as opposed to 10 predictors for CC in the task-negative state. Models constructed in the face state were not significant for BC or CC. The predictors for the model with the highest model accuracy and prediction accuracy (EC face state) are provided in Table 3 and Figure 1b.

Figure 2b shows the age predictions for this model. Quadratic was the top-ranking fit, followed by linear and then growth curve. Cook's distance identified four cases that were outliers. Removal of those cases from curve-fitting did not change the rank ordering of fits. Linear (RMSE = 4.18,

FIG. 1. (a) Nodes that predicted age for the WBN based on BC. Nineteen predictors are shown because these were the predictors included in the model. (b) Nodes that predicted age for the FN based on EC. Eleven predictors are shown because these were the predictors included in the model. The size of each node reflects the importance of the node in the prediction. The biggest sphere is the most important predictor. The size of subsequent nodes is dictated by node size = $\frac{x - x_{\min}}{x_{\max} - x_{\min}} + \xi$, where $x_{\min}$ and $x_{\max}$ are the smallest and largest importance values, respectively, and ξ is an arbitrary constant to avoid zero values (which would not be drawn); here, $\xi = 0.5$. In this way, the values range in the [0.5, 1.5] interval where the smallest node is 0.5 and the biggest one is 1.5. Figures were constructed using BrainNet Viewer (Xia et al., 2013). The color of the node reflects whether it positively predicted age (progressive change; blue) or negatively predicted age (regressive change; red). BC, betweenness centrality; EC, eigenvector centrality; FN, face network; WBN, whole-brain network. Color images are available online.

FIG. 2. Curve fits for the prediction of age from observed age using automatic linear modeling for the (a) WBN and (b) FN. Dotted lines indicate the 95% confidence interval. The adjusted R^2 value and RMSE is provided for each curve fit. RMSE, root mean squared error. Color images are available online.

adjusted $R^2 = 53.4\%$) and quadratic (RMSE=4.21, adjusted $R^2 = 52.9\%$) are essentially the same when outliers are removed, but the growth curve fit is worse (RMSE=4.48, adjusted $R^2 = 46.6\%$).

Discussion

The present study used graph theory-based network analysis and predictive modeling to characterize typical developmental changes in the functional connectome for face processing. An important novel contribution of the present study was to examine differences in the functional connectome development in two different behavioral states: face viewing versus task-negative resting state.

Previous studies of functional connectome development have primarily employed continuous resting-state paradigms, which may not be directly relevant to study domain-specific cognitive processing like face processing. Network properties that are important for the development of resting-state connectomes may be different from network properties that are involved in development of the face processing connectome. Consequently, the present study examined functional connectome development for face and resting states.

The primary hypothesis was that the development of a specialized network for face processing is driven by (a)

task-positive processing (viewing faces) more so than task-negative processing (visual fixation) and by (b) both progressive and regressive changes in network properties. Maturation of a more generalized network, like the WBN, was not expected to be linked to specialized information processing. These hypotheses were largely confirmed.

First, prediction of age for the FN was most accurate in the face state. Second, the predictors of age for the FN using EC indicated both progressive and regressive changes. Third, maturation of the WBN was more strongly driven by the task-negative state.

We also explored whether one network metric performed better in terms of predicting age than other network metrics for the same task state and network. Another exploratory goal was to determine whether linear, quadratic, or growth functions ranked higher in describing age trajectories. The relevance of these findings with respect to the state of the current literature and future studies is discussed below.

Is maturation of the FN driven by domain-specific processing?

The best-performing model for age prediction for the FN was in the face state (for the EC measure). This finding that a specialized functional network, like the FN, is driven more strongly by domain-specific processing than by a task-negative state is novel, given that few prior studies of functional brain network development have examined active task states. Future studies should determine whether the greater reliance on domain-specific processing also applies to functional network maturation of other kinds of cognitive specializations, such as reading or speech.

Another relevant finding was that the task-negative state was predictive of age for the WBN. Although the highest ranking model for the WBN had the highest model accuracy and was more parsimonious than the next ranking model, it was not the highest ranking model in terms of prediction error. Therefore, the model with the highest accuracy appears to perform better in explaining the present data set but may not be as useful for prediction. Despite this, it is interesting to note that across all three network metrics, the task-negative state yielded higher ranking models than the face state for the WBN, in

TABLE 3. PREDICTORS OF AGE FOR THE FACE NETWORK AND EIGENVECTOR CENTRALITY

Region	Coefficient	Importance	p
L insula	3730.768	0.100	0.002
R angular	-2287.035	0.095	0.011
L calcarine	-2443.001	0.093	0.018
R inferior occipital	-1641.243	0.092	0.034
R superior temporal	-2229.039	0.090	0.073
R insula	-1978.801	0.090	0.097
L superior temporal	-1844.308	0.090	0.095
L inferior parietal	-1181.607	0.089	0.115
R amygdala	-641.023	0.087	0.408
R middle temporal	892.520	0.087	0.338
R inferior frontal opercular	347.861	0.086	0.710

terms of adjusted R^2 , and the models were not significant in the face state for two of the metrics (CC and EC).

The finding that the task-negative state yielded better performing models than the face state for the WBN lends further credibility to the already popular approach of using task-free states to understand the functional brain organization. Essentially, resting-state networks reflect the parcellation of the WBN into functional subsystems like the default mode network, salience network, and dorsal attention networks. The present study and others (Betzel et al., 2014; Cao et al., 2014; Dosenbach et al., 2010; Fair et al., 2009; Hwang et al., 2013; Uddin et al., 2010; Wang et al., 2012; Yang et al., 2014; Zuo et al., 2010) have shown that functional organization revealed in task-free states undergoes significant developmental change.

A practical implication of this is that task-free states can be measured in pediatric populations without the additional concern of greater demands on cognitive processing and concomitant effects on performance, which is often a concern with developmental studies. However, the novel contribution of the present study is that understanding typical development of domain-specific networks, like the FN, may be better addressed when domain-specific information must be processed, whereas understanding maturation of the WBN may be better addressed using task-free states.

Do both progressive and regressive changes contribute to functional network maturation?

Both the FN and WBN showed progressive and regressive changes. An influential framework of brain development, the Interactive Specialization account (Johnson, 2005), suggests that as certain functional capacities develop, a brain region may increase its tuning to specific kinds of information or reduce tuning to other kinds of information. A consequence of this is that there is significant reorganization at the network level across development, with some regions being more important for specific kinds of information processing at one point in development and less important at another stage.

With respect to the FN, the majority of changes with age were regressive (eight nodes vs. three progressive nodes), which suggests that the primary developmental changes in the FN were a *reduction* in functional integration with respect to the rest of the brain. Regressive changes indicate that a given brain region is important early in development but not later in development for face processing. With respect to EC, this means that some nodes play an integrative role during childhood through their strong global influence and information diffusion in the network (which is the main characteristic of EC), but these nodes decrease in their global influence by adulthood.

We speculate that such changes may reflect the development of a more specialized network devoted to face processing with age, such that many of the nodes in the FN shift from being globally integrated with the rest of the brain to being less integrated. This would allow for the FN to largely process domain-specific information (like faces), which was also demonstrated by the finding that the face state was most predictive of age for the FN.

What is the best network metric for predicting age?

For the FN, the highest ranking model emerged for EC in the face state. For the WBN, the highest ranking model emerged for BC in the task-negative state. Models based on CC were not the

highest ranking model for any network. Given that the two measures of functional integration (BC and EC) seemed to fare better than the measure of functional segregation (CC); this finding seems consistent with the idea that functional brain development involves maturation of long-range connections to enable more global communication and integration of information processing across diverse brain systems (Fair et al., 2009; Hwang et al., 2013). However, this is only true for those nodes that showed progressive changes in integration measures. Many nodes showed regressive changes in both the FN and WBN, suggesting *reduced* integration of those nodes with age.

For the WBN, the best predictor of age was BC, which reflects the degree to which a region can be considered a hub in a network. Interestingly, in a resting-state fMRI study, Hwang et al. (2013) found that the hub architecture of the human brain is stable from childhood to early adulthood in that the regions that were designated as hubs did not change throughout development. They also found both progressive and regressive significant changes in the strength of 26 connections between hub and spoke regions.

Hubs are central regions that are highly interconnected with many other regions; spoke regions are nonhub regions or the regions that are less important to the network's integrity and information traffic. Hence, even though overall hub topology did not change with age in the Hwang et al.'s (2013) study, the connections to hub regions did change in strength with age. This suggests that BC can change in magnitude with age, which is consistent with some findings in the present study. When hub-spoke connectivity was considered in the Hwang et al.'s (2013) study, some of our results for the task-negative state overlap with their results. In particular, both studies showed developmental change in the inferior parietal, orbital frontal, and superior frontal cortex.

Interestingly, the highest ranking model for the FN emerged for EC, which had fewer nodes removed due to correlations with head motion (only 8 nodes removed vs. 11 nodes removed for both BC and CC). This, of course, means that more predictors were available for model selection. But the adjusted R^2 adjusts for the number of predictors so we do not think the highest ranking model performed better for this reason. Instead, we suggest that EC may be less contaminated by head movement than some other network metrics, such as BC or CC. This finding may be useful for future developmental studies that examine network maturation using graph theory measures.

Are developmental trajectories best described as growth curves?

Dosenbach et al. (2010) reported that prediction of age based on network features (edges) followed a growth curve function. In the present study, no single curve best described the age prediction for the WBN, the growth curve was the lowest ranking curve for the FN, and growth curves were more sensitive to outliers than linear or quadratic curves for the WBN. Many of the outlier cases were some of the older subjects in the sample (over 30 years), but these cases were not as well represented in the present sample. Future studies should have a more equal sampling of the entire age range when determining age-related trajectories.

It is important to note that Dosenbach et al. (2010) used edges as features to predict age and the present study used

nodes. It is possible that edge strength tapers off at a certain age such that a growth curve would faithfully reflect that asymptotic behavior. In contrast, it is possible that node measures, which reflect higher order properties that depend on edge weights like topological features and information flow through a network, may continue to change and reorganize even if the strength of individual connections levels off. Clearly, this possibility will need to be tested in future studies, but it presents an intriguing hypothesis about functional reorganization of the brain during development.

Limitations

Although there are several novel contributions of the present study, some limitations need to be noted. One potential limitation was that we defined our ROIs based on the AAL atlas (Tzourio-Mazoyer et al., 2002), which defines nodes based on an anatomical model and the nodes are quite large, often encompassing several gyri. The risk of such node definition is that there may be some functionally distinct entities within the anatomical components, leading to a potential distortion from the true properties of the network (Butts, 2009). There is some debate about whether the specific atlas used can significantly alter connectome results (Cao et al., 2014). We suggest that the use of AAL atlas regions might be a better choice when both pediatric and adult subjects comprise the sample because larger ROIs defined by anatomical boundaries may reduce errors during spatial normalization.

To examine a task-positive state (face viewing), the present study necessarily relied on short time series to establish functional connections. A concern with short time series, however, is that they may not be reliable estimates of functional connections given the few time points.

However, this concern is likely more relevant to continuous resting-state paradigms (Birn et al., 2013) than to task-constrained time series. Studies that examine dynamic network connectivity in task-driven states have found that short time windows (<75 sec) can be informative. Short windows reflect individual differences in flexibility of networks, but they are not as sensitive to network shifts due to changing cognitive states (Telesford et al., 2016). Importantly, although the present study did not examine dynamic functional networks, it would be important for future studies to examine developmental changes in static network properties in task-positive states with longer time series.

Conclusions

The present study showed that the development of functional brain networks is characterized largely by changes in information diffusion (EC) and hub topology (BC) rather than changes in functional segregation (CC). Few previous studies have compared different network properties and behavioral states in functional connectome development. Importantly, developmental changes in the FN were driven by different network properties and behavioral state than changes in the WBN. Hence, understanding how specialized networks develop may be advanced by considering different information processing states in addition to resting or task-negative states.

The present study also showed that functional connectome development was marked by both regressive and progressive changes with age. These bidirectional changes reflect strengthening and weakening of functional connections with maturation

and are suggestive of a highly interactive and dynamic system over development, in which some components are being added and others being pruned away as the specialized functions become more advanced and refined (Johnson, 2005). By understanding the role of domain-specific processing in functional connectome development, the present study characterized developmental trajectories of typical face processing maturation, which can also provide insight into disrupted functional organization in atypical development.

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Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Figure S1
Supplementary Figure S2

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