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RESEARCH ARTICLE

Segregation and integration of the functional connectome in neurodevelopmentally 'at risk' children

Jonathan S. Jones | The CALM Team | Duncan E. Astle

MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, UK

Correspondence
Dr Jonathan Jones, Research Associate, 4D Lab, MRC Cognition and Brain Sciences Unit, University of Cambridge, 15 Chaucer Road, Cambridge CB2 7EF.
Email: jonathan.jones@mrc-cbu.cam.ac.uk

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Abstract

Functional connectivity within and between Intrinsic Connectivity Networks (ICNs) transforms over development and is thought to support high order cognitive functions. But how variable is this process, and does it diverge with altered cognitive development? We investigated age-related changes in integration and segregation within and between ICNs in neurodevelopmentally 'at-risk' children, identified by practitioners as experiencing cognitive difficulties in attention, learning, language, or memory. In our analysis we used performance on a battery of 10 cognitive tasks alongside resting-state functional magnetic resonance imaging in 175 at-risk children and 62 comparison children aged 5–16. We observed significant age-by-group interactions in functional connectivity between two network pairs. Integration between the ventral attention and visual networks and segregation of the limbic and fronto-parietal networks increased with age in our comparison sample, relative to at-risk children. Furthermore, functional connectivity between the ventral attention and visual networks in comparison children significantly mediated age-related improvements in executive function, compared to at-risk children. We conclude that integration between ICNs show divergent neurodevelopmental trends in the broad population of children experiencing cognitive difficulties, and that these differences in functional brain organisation may partly explain the pervasive cognitive difficulties within this group over childhood and adolescence.

KEYWORDS
cognitive development, executive function, fMRI, functional connectivity, intrinsic connectivity networks, neurodevelopment

1 | INTRODUCTION

The human connectome is a complex network optimised to minimise wiring cost and maximise efficient communication (Bullmore & Sporns, 2012). This is achieved through a small-world architecture with dense connections between neighbouring brain regions, affording specialisation, and sparser long-range connections, affording global integration (Bullmore & Sporns, 2012). This integration and segregation can be seen in Intrinsic Connectivity Networks (ICNs)—spatially distributed regions of the brain that are highly co-activated and thus functionally connected. ICNs are emergent properties of resting brain activity (Barnes et al., 2016; Yeo et al., 2011), correspond to modules of the connectome, and substantially overlap with major functional systems recruited during task performance (Power et al., 2011).

Importantly, individual ICNs do not operate in isolation, and the integration (increased functional connectivity) and segregation (decreased functional connectivity) between ICNs is important for flexible cognition (J. R. Cohen & D'Esposito, 2016).

This functional topology emerges as the brain develops through childhood and adolescence, coinciding with gross structural changes in the brain (Carlson et al., 2013; Morgan et al., 2018). Over this period there are marked increases in regional specialisation and global integration, as functional connectivity between anatomically proximal regions gradually weakens and longer-range connections strengthen within ICNs (de Lacy & Calhoun, 2018; Fair et al., 2013; Farrant & Uddin, 2015; Satterthwaite et al., 2013; Solé-Padullés et al., 2016; Tomasi & Volkow, 2014). This widely reproduced finding suggests that ICNs become increasingly coherent with age. Functional connectivity between ICNs also changes over development. The default mode network typically segregates from so-called 'task-positive networks', such as the fronto-parietal network, as activity between these ICNs becomes increasingly anti-correlated (Barber et al., 2013; Bo et al., 2014; Chai et al., 2014; de Lacy & Calhoun, 2018; Gu et al., 2015; Sherman et al., 2014). Integration between ICNs generally increases across adolescence and into early adulthood (Betzel et al., 2014; Marek et al., 2015), although notably, the ventral attention network may become integrated with other ICNs earlier in development (Marek et al., 2015).

These developmental changes in functional connectivity within and between ICNs are linked to individual differences in cognition and cognitive development. Integration within specific ICNs is associated with a broad array of cognitive processes (Van Den Heuvel & Pol, 2010), including: executive function (Seeley et al., 2007), numerical cognition (Moeller et al., 2015), working memory (Hampson et al., 2006), and IQ (Abbott et al., 2016; Sherman et al., 2014). Between ICNs, greater segregation of the default-mode network from task-positive networks is associated with attentional control (Barber et al., 2015), working memory (Hampson et al., 2010), and IQ (Sherman et al., 2014). Furthermore, greater integration between the ventral attention network and other ICNs has been associated with better inhibitory control in young people and moderates the effect of age on performance (Marek et al., 2015). These associations with cognitive performance, and particularly age-related changes therein, suggest that the emergence of ICNs, and developing interactions between them, may support cognitive development.

Divergent ICN development may itself be a risk factor for cognitive or behavioural difficulties. Indeed, under-connectivity within the default-mode network (Nomi & Uddin, 2015; Sripada et al., 2014), and over-connectivity between the default-mode and task-positive networks, has been associated with cognitive difficulties in childhood (Cai et al., 2018; Francx et al., 2015; Lin et al., 2018; Sripada et al., 2014). Segregation of the default-mode and task-positive networks are developmentally delayed in children with poorer attention performance, and those with greater difficulties show greater delay (Cai et al., 2018; Francx et al., 2015; see also Kessler et al., 2016; Lin et al., 2018; Mills et al., 2018; Sripada et al., 2014). Similarly, children with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) do not show a maturational strengthening between the ventral attention and right fronto-parietal networks compared to non-ADHD controls (de Lacy & Calhoun, 2018). Crucially, these differences do not appear to be tied to any particular neurodevelopmental condition. In fact, differences in functional connectivity between the fronto-parietal, ventral attention and default mode networks have been implicated in multiple neurodevelopmental conditions (Menon, 2011) and associated with difficulties even in those without a diagnosis (e.g. Sripada et al., 2014). Taken together, these findings suggest that divergent ICN development is significantly associated with cognitive and behavioural difficulties in childhood. One plausible explanation is that differences in the emergence and timing of ICN development may itself put children at increased neurodevelopmental risk of these difficulties. Although it should be noted early that it is difficult to establish causality—alterations in network development could drive differences in cognitive development, or the relationships could be bidirectional.

In the present study, we explored ICN development in a sample that reflects the large heterogeneous population of children experiencing neurodevelopmental difficulties in cognition and behaviour (Astle et al., 2019; Bathelt, Gathercole, Butterfield et al., 2018; Bathelt, Gathercole, Johnson et al., 2018; Bathelt, Holmes et al., 2018; Holmes et al., 2019, 2020; Mareva & Holmes, 2019; Siugzdaite et al., 2020). These young people were recruited on the basis of experiencing difficulties in attention, learning, language and/or memory, as identified by practitioners across a variety of children's professional services. Hereafter we refer to this cohort of children as being neurodevelopmentally 'at-risk', referring to their broad heterogeneous nature, and the elevated likelihood that they will experience educational underachievement (Gathercole et al., 2016), underemployment (Emerson & Hatton, 2008) and mental health difficulties (Emerson & Hatton, 2007). Exploring resting functional connectivity in this large mixed sample of children, we wanted to answer the following questions: *Firstly, can we replicate reported patterns*

RESEARCH HIGHLIGHTS

- We investigated functional brain organisation and its development in 175 children who experience neurodevelopmental difficulties in cognition and behaviour, relative to a comparison sample ($n = 62$).
- We replicated common neurodevelopmental trends across the samples: functional connectivity increased within Intrinsic Connectivity Networks and the default-mode network increasingly segregated with age.
- Neurodevelopmentally at-risk children also showed different age-related changes in functional connectivity between the ventral attention and visual networks and between the fronto-parietal and limbic networks.
- Furthermore, the integration between the ventral attention and visual networks in comparison children mediated age-related changes in cognition, relative to at-risk children.

TABLE 1 Group characteristics in the final fMRI sample

	At-risk ($n = 175$)	Comparison ($n = 62$)
Age in years: *M* (*SD*)	10.72 (2.20)	11.03 (2.05)
Boys: *n*	115 (65. 71%)	28 (45.16%)
Girls: *n*	60 (34.29%)	34 (54.84%)
Ethnicity: *n*		
Asian/Asian British	0 (0%)	0 (0%)
Black/African/Caribbean/Black British	0 (0%)	1 (2.63%)
Mixed/multiple ethnic groups	7 (10.45%)	2 (5.26%)
White	59 (89.39%)	35 (92.11%)
No diagnosis: *n*	109 (62.29%)	59 (95.16%)
ADHD: *n*	35 (20%)	1 (1.61%)
Suspected ADHD: *n*	10 (5.71%)	0 (0%)
Autism: *n*	13 (7.43%)	0 (0%)
Dyslexia: *n*	17 (9.71%)	2 (3.23%)
IMD: *M* (*SD*)	−0.40 (0.78)	−0.88 (0.91)

Note: Age at MRI assessment. The Index of Multiple Deprivation (IMD) was available for 231 children, the rank data were reversed and normalised to the population mean (0) so that higher scores indicate greater deprivation. Ethnicity data were available for 104 children.

of age-related changes in ICNs? Secondly, do age-related changes in ICNs distinguish children 'at risk', relative to a comparison sample? And, thirdly, are age-related changes in ICNs associated with cognitive development and do these ICN-cognition relationships differ in neurodevelopmentally at-risk children?

2 | METHOD

2.1 | Sample characteristics

Behavioural data were collected from 957 children and adolescents from the Centre for Attention Learning and Memory (CALM; Holmes et al., 2019). Children in the 'at-risk' sample were referred by educational and health practitioners for having one or more difficulties in attention, memory, language, literacy, and numeracy. The comparison sample was recruited from the same schools but were not identified as struggling in these areas. Children were excluded from the study if they had an uncorrected hearing or visual impairment, pre-existing neurological condition, a known genetic cause for their difficulties, or if they were a non-native English speaker.

Resting-state fMRI data were available for 348 children and adolescents who opted to take part in the MRI study. High motion scans ($n = 111$) were excluded from the analysis (see 'fMRI Preprocessing' for details). The final fMRI sample consisted of 237 children and adolescents aged 5–17 years ($M = 10.80$, $SD = 2.16$; see Figure S1 for age distribution): 175 at-risk and 62 comparison children (see Table 1 for group characteristics). The demographics of the MRI sample were comparable to the full sample (see Table S1).

2.2 | Measures

Children completed a battery of 10 computerised and paper-based cognitive assessments that evaluated phonological processing, working memory, episodic memory, nonverbal reasoning, attention, and processing speed. The battery included: the Alliteration subtest of the Phonological Assessment Battery (Frederickson et al., 1997); the Children's Test of Nonword Repetition (Gathercole et al., 1994); the Hector Cancellation/Balloon Hunt subtest of the Test of Everyday Attention for Children II (Manly et al., 2016); the Digit Recall, Dot Matrix, Backwards Digit Recall, and Mr X subtests of the Automated Working Memory Assessment (Alloway, 2007); the Following Instructions task (Gathercole et al., 2008); delayed recall of the Stories subtest on the Children's Memory Scale (M. Cohen, 1997); and the Matrix Reasoning subtest of the Wechsler Abbreviated Scale of Intelligence II (Wechsler, 2011). Measures of learning were also collected for the Word Reading and Numerical Operations subtests of the Wechsler Individual Achievement Test II (Wechsler, 2005). The full protocol and details of the measures are described in Holmes et al. (2019). Summary statistics of the age-standardised cognitive and learning measures are provided in Table 2.

The dimensionality of the raw data was reduced using Principal Components Analysis (PCA) with varimax rotation using the principal function from the psych package (version 2.0.9) in R (version 4.0.3). The raw cognitive scores from the full sample of children with behavioural data ($N = 957$) were first scaled to unit variance and mean-centred. Missing data were then imputed using K-nearest neighbours with the knn function from the impute package ($K = 10$, version 1.64.0). Across all variables and participants, 6.02% of data were missing and imputed (see Tables S2–S4 for a summary). From the PCA, we extracted component scores for the first two rotated components, which explained 64.8% variance in the data. Two components were extracted because additional components were primarily defined by a high loading on only one variable and adding a third component only explained an additional 6.1% of variance in the data. The first component predominantly loaded on executive measures of working memory, non-verbal reasoning, and selective attention; whereas the second component predominantly loaded on verbal measures of phonological processing and memory (see Figure 1). The executive vs. phonological interpretation of these component loadings is consistent with a recent factor analysis in the same sample (Holmes et al., 2020). At-risk children had significantly lower scores on the executive component ($M = 0.09$, $SD = 0.93$) relative to comparison children ($M = 1.03$, $SD = 1.17$) with age and gender included as covariates, $F(1, 233) = 52.27$, $p = 6.87 \times 10^{-12}$, $\eta^2_p = 0.18$. Similarly, at-risk children had significantly lower scores on the phonological component ($M = 0.18$, $SD = 0.83$) relative to comparison children ($M = 0.73$, $SD = 0.69$), $F(1, 233) = 20.69$, $p = 8.67 \times 10^{-6}$, $\eta^2_p = 0.08$. Component scores were used in subsequent analyses to

TABLE 2 Cognitive and learning characteristics in the final fMRI sample

	At-risk		Comparison		ANOVA		
	n	*M* (*SD*)	*n*	*M* (*SD*)	*F*	*p*	η^2_p
AWMA digit recall	174	94.08 (16.43)	62	110.21 (15.88)	48.50	<0.001	0.17
AWMA backwards digit recall	175	92.94 (12.25)	62	108.67 (15.71)	78.90	<0.001	0.25
AWMA dot matrix	175	93.13 (14.94)	62	105.18 (15.65)	34.92	<0.001	0.13
AWMA Mr X	175	96.08 (14.64)	62	110.15 (18.56)	42.02	<0.001	0.15
CMS stories delayed recall	174	8.24 (3.19)	61	11.30 (3.36)	39.13	<0.001	0.14
CNRep	85	86.95 (19.90)	62	98.56 (16.74)	13.75	<0.001	0.09
Following instructions	165	98.71 (13.28)	58	109.71 (13.35)	30.84	<0.001	0.12
PhAB alliteration	175	92.94 (9.35)	62	98.08 (8.21)	17.92	<0.001	0.07
TEA-Ch-II cancellation	170	10.47 (3.39)	57	12.40 (2.66)	17.15	<0.001	0.07
WASI-II matrix reasoning	175	44.16 (10.36)	62	53.92 (8.95)	46.10	<0.001	0.16
WIAT-II word reading	173	87.63 (17.71)	61	108.38 (11.69)	76.65	<0.001	0.25
WIAT-II numerical operations	151	88.89 (18.23)	62	116.34 (20.32)	107.43	<0.001	0.34

Note: Age-normalised scores are reported for all tests with normative data, except for the following instructions test where scores have been age-residualised, mean-centered and scaled ($M = 100$, $SD = 15$). Analysis of variance tests examined group differences in age-standardised scores including gender as an effect of no interest. Automated Working Memory Assessment (AWMA), Children's Memory Scale (CMS), Children's test of Nonword Repetition (CNRep), Phonological Assessment Battery (PhAB), Test of Everyday Attention for Children II (TEA-Ch-II), Wechsler Abbreviated Scale of Intelligence II (WASI-II), Wechsler Individual Achievement Test II (WIAT-II).

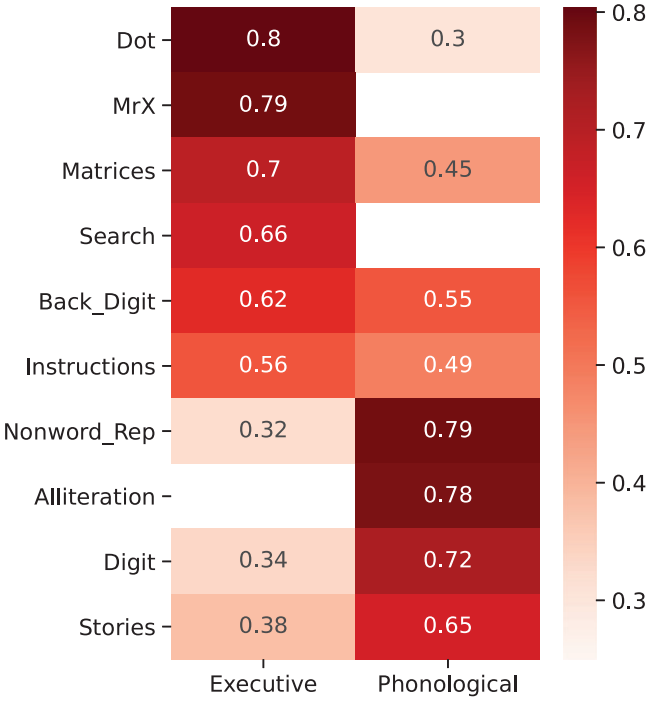

FIGURE 1 Loadings of cognitive variables on the two rotated principal components

Loadings lower than 0.3 are suppressed for visualisation purposes. Dot (Dot Matrix), Matrices (Matrix Reasoning), Search (Hector Cancellation/Balloon Hunt), Back_Digit (Backwards Digit Recall), Instructions (Following Instructions), Nonword_Rep (Children's test of Nonword Repetition), Digit (Digit Recall).

examine whether age-related changes in cognition are mediated by functional connectivity.

2.3 | Image acquisition

Magnetic resonance imaging data were acquired at the MRC Cognition and Brain Sciences Unit, University of Cambridge. All scans were obtained on a Siemens 3T Prisma-Fit system (Siemens Healthcare, Erlangen, Germany) using a 32-channel head coil.

In the resting-state fMRI, 270 T2*-weighted whole-brain echo planar images (EPIs) were acquired over 9 min (time repetition [TR] = 2 s; time echo [TE] = 30 ms; flip angle = 78°, 3 × 3 × 3 mm). The first four volumes were discarded to ensure steady state magnetization. Participants were instructed to lie still with their eyes closed and to not fall asleep. For registration of functional images, T1-weighted volume scans were acquired using a whole-brain coverage 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MP RAGE) sequence acquired using 1-mm isometric image resolution (TR = 2.25 s, TE = 2.99 ms, flip angle = 9°, 1 × 1 × 1 mm).

2.4 | fMRI pre-processing

Available resting-state fMRI data from 348 children was minimally pre-processed in fMRIPrep version 1.5.0 (Esteban et al., 2019), which implements slice-timing correction, rigid-body realignment, boundary-based co-registration to the structural T1, segmentation, and normalisation to the MNI template. The data were then smoothed by 6 mm full-width at half-maximum. Many methods exist to denoise

motion and physiological artefacts from resting-state fMRI; however, the effectiveness of these strategies varies depending on the sample (Ciric et al., 2017; Parkes et al., 2018). We evaluated the performance of several denoising strategies (head movement regressors, aCompCor, ICA-AROMA, motion spike regression, white matter [WM] and cerebrospinal fluid [CSF] regression, and global signal regression) on several quality control metrics (edge weight density, motion-functional connectivity correlation, distance-dependence, and functional degrees of freedom lost) using the fmridenoise package in Python (Finc et al., 2019; see Supplementary materials). The most effective confound regression procedure included a band-pass filter between 0.01 and 0.1 Hz, 10 aCompCor components from the WM and CSF signal (Behzadi et al., 2007), linear and quadratic trends, and motion spikes (framewise displacement > 0.5 mm; Power et al., 2012). Simultaneous confound regression was performed in the Nipype (version 1.2.0) implementation of AFNI's 3dTproject (Cox, 1996). Children were first excluded for high average motion (mean framewise displacement >0.5 mm, $n = 93$) and then for a large number of motion spikes (>20% spikes, $n = 18$), where few temporal degrees of freedom would have remained. The final functional connectome sample included 237 children (at-risk $n = 175$, comparison $n = 62$) with mean framewise displacement 0.20 mm ($SD = 0.09$ mm).

2.5 | Network functional connectivity

The denoised fMRI data were parcellated into 100 cortical regions that were assigned to seven ICNs (Schaefer et al., 2018). Pearson correlations were computed for the regional time-series within each individual generating 100 × 100 connectivity matrices. Edge weights were transformed using Fisher's *z*-transformation. In line with standard practice, proportional thresholding was used to remove noisy edges with small statistical relations and to control for the number of edges across participants (Fornito et al., 2013; Marek et al., 2015). Specifically, positive and negative connectomes were generated for each individual by thresholding the connectivity matrices to retain the top 25% of positive or negative edges at the group level (see Figure S2–S9), to ensure that the same edges across individuals are retained for comparison in subsequent analyses, as in Baum et al. (2017). To test the robustness of brain-behaviour results, connectomes were generated at additional cost thresholds (1% intervals between 15%–35%). Average functional connectivity was calculated within and between seven pre-defined ICNs: visual, somatomotor, dorsal attention, ventral attention, fronto-parietal, default mode, and limbic (Yeo et al., 2011). Finally, global intra- and inter-network functional connectivity were calculated by averaging these values within and between networks respectively.

2.6 | Analyses

First, we examined whether age correlations with global intra- and inter-network functional connectivity aligned with previously reported trajectories in childhood development. We then tested whether group (at-risk vs. comparison) moderated these associations in linear models. Second, we examined whether age associations with functional connectivity between or within specific ICNs differed between the two groups. Multiple comparisons across network pairs were corrected for using the False Discovery Rate (FDR) Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995). Third, we tested whether any of these age-related changes were associated with cognitive development. Specifically, whether functional connectivity mediated age-related changes in the cognitive components identified from the PCA, and whether this was moderated by group (see Figure 3a). Statistical significance was ascertained by computing 95% confidence intervals (CI) of the moderated mediation beta from 1000 bootstrapped estimates and by comparing this to the null hypothesis. In addition, we calculated the area under the curve (AUC) for beta estimates jointly across all connectome thresholds (15%–35%) and compared this to estimates expected by chance in 10,000 samples with randomly shuffled group labels. All models including age*group interaction terms included gender, motion, and mean functional connectivity (pre-thresholding) as nuisance covariates. To account for group differences in deprivation, the IMD was included as an additional nuisance covariate in analyses of group effects (see Supplementary materials). Linear regression ('ols') and mediation analyses ('Mediation') were conducted with statsmodels 0.12.1 in Python 3.8.6. The analysis code is available at https://osf.io/zaecd/ (DOI: 10.17605/OSF.IO/ZAECD).

3 | RESULTS

3.1 | Age-related changes in integration and segregation

We first examined whether average functional connectivity within networks and average functional connectivity between networks correlated with age across both groups. In the positive connectome, age significantly positively correlated with average intra-network functional connectivity in the combined sample across all thresholds ($r = 0.130$–142, $p = 0.028$–045) but not with average inter-network functional connectivity ($r = 0.016$–071, $p = 0.279$–802). Age was also significantly associated with intra-network functional connectivity across all but two thresholds when controlling for gender, motion and mean functional connectivity ($\beta = 0.101$–111, $SE = 0.051$–054, $p = 0.038$–0.052). In the negative connectome, age was not associated with average intra-network functional connectivity, which was limited to default-mode connections ($r = -0.066$–096, $p = 0.141$–313), or average inter-network functional connectivity at any threshold ($r = -0.037$–104, $p = 0.111$–570).

Next, we investigated age associations with functional connectivity between or within specific ICNs when controlling for gender, motion and mean functional connectivity. When considering both groups together, no positive connections between or within specific ICNs were significantly associated with age. The negative connection (anti-correlation) between the dorsal attention and default-mode networks significantly strengthened with age across all but two thresholds

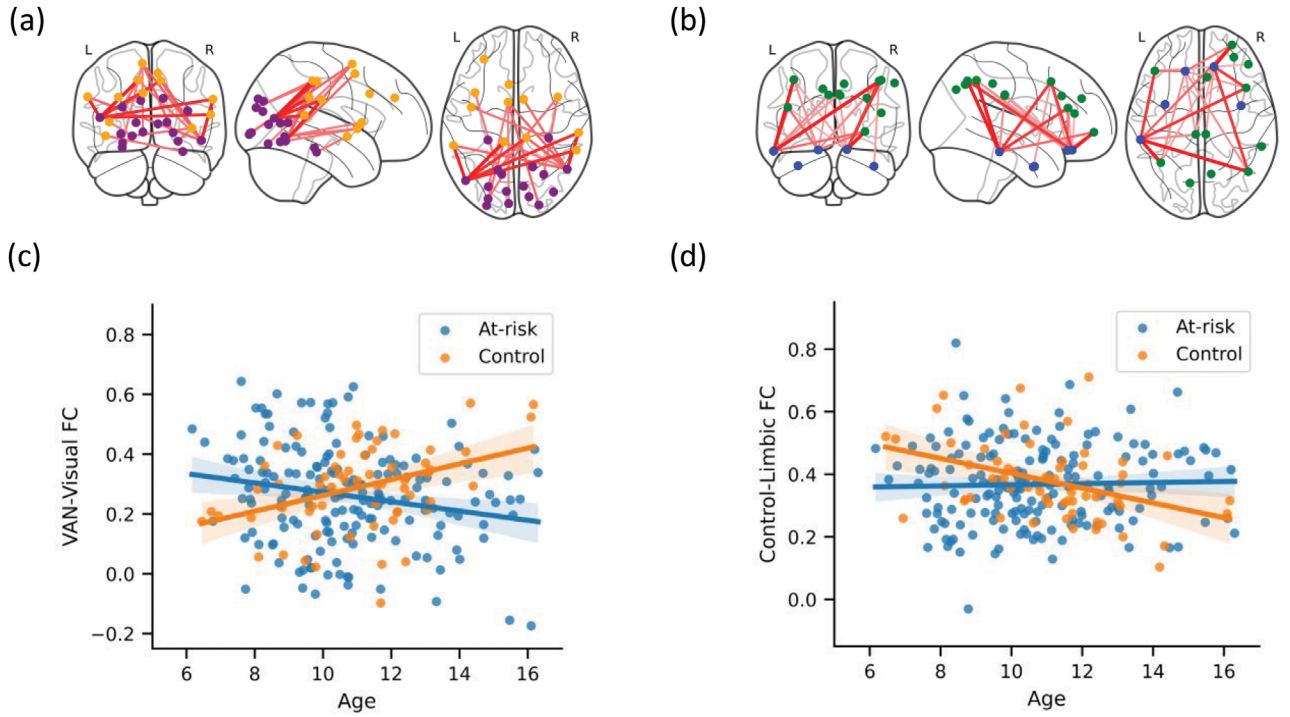

FIGURE 2 Age-by-group interactions on functional connectivity between ICNs

Positive edges between the visual (purple) and ventral attention networks (orange; a) and the limbic (blue) and fronto-parietal networks (green, b) at 25% cost threshold. Age associations with positive functional connectivity between the visual and ventral attention networks (c) and the limbic and fronto-parietal networks (d).

(β = −0.172–0.187, SE = 0.057–0.060, p = 0.019–0.055 FDR-corrected). Together, these results in the combined sample replicate commonly reported findings in typical development: strengthening integration within ICNs and segregation of the default-mode and task-positive networks.

3.2 | Age-by-group interactions

Next, we investigated whether age associations with functional connectivity differed between the groups whilst controlling for gender, motion, and mean functional connectivity. Age associations with average intra- (β = −0.066, SE = 0.053, p = 0.213 FDR-corrected) and inter-network functional connectivity (β = 0.038, SE = 0.042, p = 0.368 FDR-corrected) did not significantly differ between the groups. However, significant age*group interactions were found for positive connections between the visual and ventral attention networks (β = 0.219, SE = 0.060, p = 0.005 FDR-corrected) and between the limbic and fronto-parietal networks (β = −0.198, SE = 0.065, p = 0.033 FDR-corrected). Older children in the comparison sample showed greater functional connectivity between the visual and ventral attention networks and reduced connectivity between the limbic and fronto-parietal networks relative to younger children, whereas at-risk children did not show these age-related changes (see Figure 2). The interaction effects were significant across multiple cost thresholds for the visual and ventral attention networks (thresholds 21%–34%, β = 0.191–219, SE = 0.057–061, p = 0.004–015 FDR-corrected) and the limbic and fronto-parietal networks (thresholds 22%–34%, β = −0.190–214, SE = 0.064–065, p = 0.013–048 FDR-corrected). Information about the edges included at each threshold are presented in Tables S5 and S6. We also tested whether the area under the curve for these effects jointly across all thresholds significantly exceeded that expected by chance when group labels were randomly shuffled 10,000 times. This too indicated a significant age*group interaction on functional connectivity between the visual and ventral attention networks (AUC = 3.32, mean permuted AUC = 0.009, p = 0.0002) and between the limbic and fronto-parietal networks (AUC = −3.86, mean permuted AUC = −0.015, p = 0.0012). Age associations with negative connections within and between specific ICNs, including between the dorsal attention and default-mode networks, did not significantly differ between the groups. All of these results were replicated when additionally controlling for deprivation, except that the age*group interaction for positive connections between the limbic and fronto-parietal networks was statistically significant at fewer individual thresholds (see Supplementary materials).

3.3 | Links with cognition

Finally, we examined whether these age-by-group interactions predicted cognitive ability. Specifically, we examined whether age-related changes in comparison children's executive function were mediated

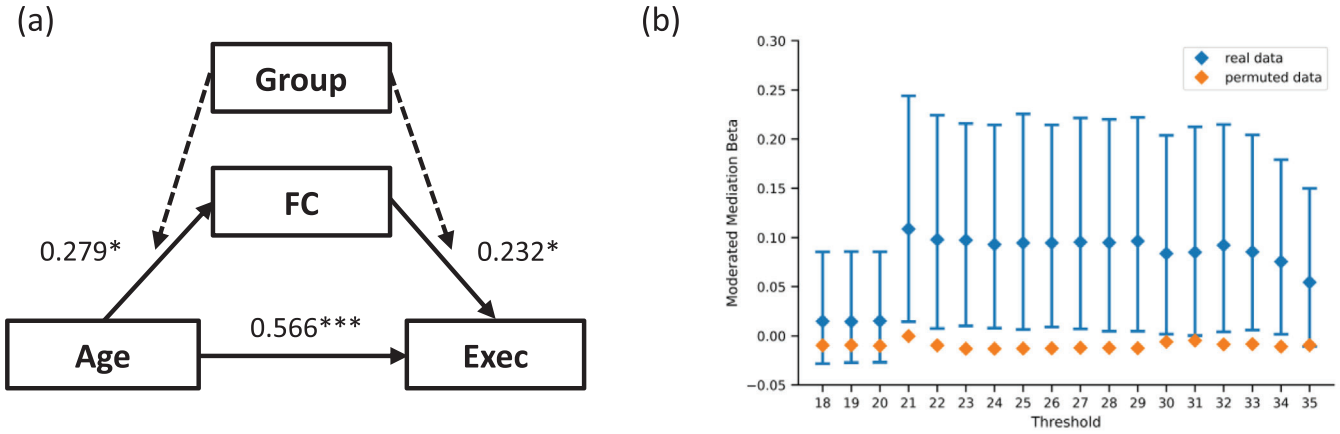

FIGURE 3 Moderated mediation of visual-ventral attention network functional connectivity on age-related changes in executive function

The moderated mediation model (a) examining group-moderated mediation effect of positive functional connectivity (FC) between the visual and ventral attention networks on age-related changes executive function (Exec). Beta weights are shown for the control group. 1000 bootstrapped estimates of the moderated mediation effect (b) across proportional thresholds compared to mean permuted point estimates when group labels were shuffled 10,000 times. Error bars denote 95% confidence interval. Thresholds 15–17 are not displayed because no edges were present. $^{*}p < 0.05$, $^{***}p < 0.001$

by functional connectivity between the visual and ventral attention networks, relative to at-risk children. Indeed, group significantly moderated the mediation effect of functional connectivity on age-related changes in executive function (β = 0.095, 95% CI [0.008, 0.214], p = 0.03; see Figure 3), such that the partial mediation effect was larger in comparison children, relative to at-risk children (difference in proportion of effect mediated = 12.17%, 95% CI [1.02, 30.94]). The moderated mediation was significant across multiple cost thresholds (21%–34%; see Figure 3). Further, the area under the curve across all thresholds (AUC = 1.36) significantly exceeded that expected by chance when group labels were randomly shuffled 10,000 times (mean permuted AUC = −0.17, p = 0.0004). As the number of edges between networks were equal across some thresholds, using only thresholds with a unique number of edges also revealed a significant effect (AUC = 0.76, mean permuted AUC = −0.07, p = 0.0008). Similar results were obtained when using the first principal component from four tasks that were previously identified as measures of a latent executive component (Holmes et al., 2020). This moderated mediation was significant at the 25% cost threshold (β = 0.066, 95% CI [0.004, 0.160], p = 0.036), jointly across all thresholds (AUC = 0.869, mean permuted AUC = −0.134, p = 0.0031), and jointly across all thresholds with a unique number of edges (AUC = 0.760, mean permuted AUC = −0.057, p = 0.005). The effect was specific to executive function and did not generalise to phonological ability at any threshold examined (β = −0.033–0.006, p = 0.346–1.000). Similarly, the effect was specific to functional connectivity between the visual and ventral attention networks. Functional connectivity between the limbic and fronto-parietal networks did not significantly mediate age-related changes in comparison children's executive function (β = −0.049–0, p = 0.302–990) or phonological ability at any threshold (β = 0.027–0.062, p = 0.182–604), relative to at-risk children. These results were replicated when additionally controlling for deprivation (see Figure S10).

4 | DISCUSSION

We investigated whether age-related changes in ICN integration and segregation differed between neurodevelopmentally at-risk children and a comparison sample. The at-risk children were identified by practitioners as experiencing difficulties in cognition, whereas the comparison sample were not referred but attended the same schools. Across the samples we replicated common neurodevelopmental trends: increasing integration within ICNs (de Lacy & Calhoun, 2018; Farrant & Uddin, 2015; Satterthwaite et al., 2013; Sherman et al., 2014; Solé-Padullés et al., 2016; Tomasi & Volkow, 2014) and segregation of the default-mode network from the dorsal attention network (Barber et al., 2013; Bo et al., 2014; Chai et al., 2014; de Lacy & Calhoun, 2018; Gu et al., 2015; Sherman et al., 2014). However, at-risk children showed significantly different age-related changes, relative to the comparison sample. Specifically, older comparison children had greater functional connectivity between the visual and ventral attention networks and reduced functional connectivity between the limbic and fronto-parietal networks than younger children. In contrast, 'at-risk' children did not show these developmental trends. Importantly, these age-related changes in connectivity significantly predicted cognitive development: functional connectivity between the visual and ventral attention networks significantly mediated age-related changes in executive function in comparison children, compared to 'at-risk' children.

Our findings suggest that the developing integration and segregation between ICNs differs in children and adolescents with difficulties in the domains of attention, learning, language, and memory. Specifically, at-risk children showed a lack of increasing integration with age between the visual and ventral attention networks and an absence of increasing segregation with age between the limbic and fronto-parietal networks, relative to comparison children. This is

consistent with evidence that the ventral attention network typically becomes increasingly integrated with other ICNs in late childhood (Marek et al., 2015). It also converges with reports of differential development of integration and segregation between ICNs in neurodevelopmental conditions, such as autism and ADHD, which have commonly implicated the ventral attention, fronto-parietal, and default-mode networks (Abbott et al., 2016; de Lacy & Calhoun, 2018; Kessler et al., 2016; Mills et al., 2018; Sripada et al., 2014). Altered connectivity between these networks has been highlighted as a key transdiagnostic marker of multiple neurodevelopmental and mental health conditions (Menon, 2011). Our findings provide direct evidence for common neurodevelopmental patterns in a large mixed sample of children who commonly experience cognitive difficulties in childhood.

The absence of increasing integration between the visual and ventral attention networks with age in at-risk children may indicate differences in functional brain organisation and cognitive development. In the comparison sample the integration between these two networks mediated age-related changes in executive function relative to at-risk children, whilst controlling for differences in gender, in-scanner motion, mean functional connectivity and deprivation. This mirrors previous work that demonstrated increasing cross-network integration of the ventral attention network was a moderator of age-related improvements on a visual inhibitory control task (Marek et al., 2015). Notably, tasks requiring visual attention/processing also loaded heavily on the executive component in the current study. Thus one possibility is that this developmental change in integration may reflect the emerging role of the ventral attention network in bottom-up attention (Corbetta & Shulman, 2002; Vossel et al., 2014) and cognitive control (Dosenbach et al., 2007; Wu et al., 2021). As development unfolds working memory performance is less associated with activity in fronto-parietal cortex, and progressively more associated with activity in visual regions, again suggesting that the integration of specialised regions is important to developing control processes (Simmonds et al., 2017). Whilst maturing integration of the ventral attention and visual networks may support the development of cognitive control and/or visual attention across development, this effect is missing in our large mixed sample of children with cognitive difficulties. This may contribute to the enduring cognitive difficulties experienced in this group. Crucially, it is difficult to establish causality. It may well be that these neural differences reflect, *rather than drive*, these differences in cognitive development. We cannot disentangle the directionality, but future longitudinal data may provide a means of inferring directionality or bidirectional relationships across development.

This group difference in the mediating role of ICN integration on age-related changes in cognition was specific and robust. Age-related increases in integration between the visual and ventral attention networks was specifically associated with an executive/visual component of cognition. This component loaded heavily on measures of working memory, non-verbal reasoning, and attention, which have previously been identified as measures of an executive latent variable in a recent factor analysis of the same sample (Holmes et al., 2020). By contrast, age-related increases in ICN integration were not associated with improvements in the phonological component. Phonological processing is established earlier in development, whereas executive functions show a protracted development over childhood and adolescence (Carlson et al., 2013), which may explain these differential developmental trends. The effect on executive function was reproducible when extracting only the first unrotated principal component from the subset of four tasks that were previously identified as measures of executive function (Holmes et al., 2020). This demonstrates that the effect is robust to the precise rotation and composition of tasks used to generate the cognitive component scores.

We also observed altered development of connectivity between the limbic and fronto-parietal networks in at-risk children, such that they did not segregate with age. This was not associated with the development of executive or phonological cognition; however, it may be associated with the development of 'hot' executive function or emotion regulation (Zelazo & Carlson, 2012) that we did not measure. Elevated levels of behavioural difficulties have been reported in neurodevelopmentally at-risk children (Bathelt, Holmes et al., 2018) and functional connectivity in the limbic system has been associated with emotion regulation (Posner et al., 2013), emotional lability (Hulvershorn et al., 2014), temperament (Karalunas et al., 2014), aggressiveness and conduct problems (Ho et al., 2015), and depressive symptoms (Posner et al., 2014). Furthermore, impulsivity has been associated with interactions between key nodes of the limbic and fronto-parietal networks (Li et al., 2013; Zhai et al., 2015), whereby the fronto-parietal network modulates activity in the limbic network (Baumgartner et al., 2011). The increasing segregation of these networks over typical development could indicate greater down-regulation of the limbic network emanating from the fronto-parietal network; which, speculatively, may be associated with the development of hot executive function.

Our study has several limitations. First, the data are cross-sectional. We studied development by measuring age effects over the group rather than within individuals over time. Despite this, we replicated several neurodevelopmental findings from longitudinal studies, including: increasing intra-network functional connectivity and increasing segregation of the default-mode and dorsal attention networks (e.g. Sherman et al., 2014). Second, the at-risk sample included a greater proportion of boys compared to the comparison sample. This is consistent with the prevalence of neurodevelopmental conditions in boys and girls (Russell et al., 2014). Gender differences in functional connectivity have been observed, but boys and girls do not appear to show different age-related changes from childhood into early adulthood (Satterthwaite et al., 2015). Nonetheless, gender was included as a covariate in our analyses. Third, the ICNs were based on a parcellation of adult resting-state networks. Using a standard parcellation and group-thresholding ensured that the same anatomical regions and edges were compared across individuals. However, the cortical topography of ICNs has been shown to vary between individuals and with age (Cui et al., 2020), thus it is possible that the extent to which an adult parcellation captures children's functional connectivity may vary as a function of age (i.e. worse in younger children). This would not explain

why we observed differences between the groups, but it is possible that at-risk children conform less well to the template, and this in turn drives the differences. A crucial future step would be to create functionally homogenous individualised parcellations (Cui et al., 2020; Gordon et al., 2017). Fourth, neurodevelopmentally at-risk children may show heterogeneous development of integration and segregation between ICNs. With no clear categorical distinction between at-risk children this is difficult to test in the current study. However, future work with longitudinal data could investigate whether distinct neurodevelopmental sub-groups exist according to changes in ICN integration and segregation over time. Fifth, we only investigated linear relationships with age, yet cognitive and brain development can be non-linear (Luna et al., 2004; Marek et al., 2015). Our linear approach is less likely to overfit, but it may oversimplify complex neurodevelopmental changes.

In summary, neurodevelopmentally at-risk children with difficulties in the domains of attention, learning, language, and memory showed different age-related changes in ICN integration and segregation compared to a comparison sample. Integration between the ventral attention and visual networks in comparison children mediated age-related changes in executive function, compared to at-risk children. The effect was specific to this component of cognition and robust to different degrees of connectome thresholding and dimension reduction choices. We propose that the absence of increasing integration between the visual and ventral attention networks may be a marker of enduring cognitive difficulties in this large mixed population of children.

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CONFLICT OF INTERESTS STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The ethics approval for the cohort data used (CALM) does not currently permit open data access. External access to the raw data by application is in the process of being set up. All analysis code for this study is available at: DOI https://doi.org/10.17605/OSF.IO/ZAECD.

ETHICS APPROVAL STATEMENT

We confirm that the study conformed to ethical standards set out in the Declaration of Helsinki (2013). The Centre for Attention Learning and Memory (CALM) was granted ethical approval from the National Health Service (REC: 13/EE/0157). This secondary analysis study was subsequently approved by the CALM Management Committee.

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