Differerent brain networks underlying intelligence in Autism Spectrum Disorders and Typically Developing Children

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Abstract
There has been sustained clinical and cognitive neuroscience research interest in the neural basis of intelligence. The characterisation of brain structure and function underlying cognitive performance is necessary to understand the neurodevelopment of intelligence across the lifespan, and how associated neural correlates could be perturbed in atypical populations. As most work in this area has focused on neurotypical adults, the nature of functional brain connectivity underlying intelligence in paediatric cohorts with or without abnormal neurodevelopment requires further investigation. We use network-based statistics (NBS) to examine the association between resting-state functional Magnetic Resonance Imaging (fMRI) connectivity and fluid intelligence ability in male children with Autism Spectrum Disorders (ASD; M=10.45, SD=1.58 years, n=26) and in matched controls (M=10.38, SD=0.96 years). Compared to typically developing controls strictly matched on age, sex and fluid intelligence scores, boys with ASD displayed a subnetwork (network size=24, p=.0373, FWE-corrected) of significantly increased associations between functional connectivity and fluid intelligence performance. Between-group differences remained significant at a higher edge threshold of t=4 (size=6, p=.0425, FWE-corrected). Results were validated in independent-site replication analyses representing a similar male cohort with ASD (network size=14, p=.0396, FWE-corrected). Regions implicated in atypical ASD fluid intelligence connectivity were the angular gyrus, posterior middle temporal gyrus, occipital and temporo-occipital regions. Across all sites, within-group analyses failed to identify functional connectivity subnetworks associated with fluid or general intelligence performance in matched typically developing males. Findings suggest a prematurely accelerated but aberrant development of fluid intelligence neural correlates in young ASD males, possibly as a compensation mechanism that supports equivalent task performance to controls. The absence of whole-brain network correlates of general and fluid intelligence in young neurotypical males may represent the shift from local to global integration in the development of cognitive ability.
Introduction
Fluid intelligence, or fluid reasoning, refers to the broad cognitive ability to solve novel problems and is typically estimated from composite scores of non-verbal or abstract tests (Barbey, Colom, Paul, & Grafman, 2014; Reynolds & Keith, 2017; Schneider & McGrew, 2012). As a cognitive construct, fluid intelligence is distinct from but strongly correlated with general intelligence (Blair, 2006). The neural architecture of human cognition likely comprises of complex large-scale networks with dynamic interactions and co-functioning between distributed cortical and subcortical regions (Bressler & Menon, 2010; Petersen & Sporns, 2015). However, associated neural correlates could be differentially expressed in neurodevelopmental conditions (Gray, Chabris, & Braver, 2003; Kosslyn et al., 2002).

The autism spectrum disorders (ASD) are a group of heterogeneous neurodevelopmental conditions associated with deficits in social communication, social interaction, and restricted and repetitive behaviours. Compared to typically developing controls, fluid intelligence in children and adults has been suggested to be increased in Asperger’s disorder, an associated ASD condition, as well as elevated within ASD groups relative to crystallized intelligence scores on verbal tasks (Ehlers et al., 1997; Happé, 1994; Hayashi, Kato, Igarashi, & Kashima, 2008). The observed strengths in ASD fluid ability were attributed to theorized disorder-specific deficits such as weak central coherence in autism, although others have argued that measured performance in ASD represent valid estimates of fluid intelligence (Dawson, Soulières, Gernsbacher, & Mottron, 2007). Early studies have reported deficits in executive functioning in ASD but were limited in methodology and sampling (Pennington & Ozonoff, 1996). An important note is that these findings should not be taken as indicative of any diagnostic profile for ASD, more so given the highly heterogeneous and variable nature of the condition (Ehlers et al., 1997). On the other hand, failure to account for variability in fluid intelligence performance in ASD can contribute to estimation errors of group effects in brain-behaviour models (Hazlett, Poe, Gerig, Smith, & Piven, 2006).

Individuals with ASD demonstrate an atypical reliance on enhanced visuospatial processes in extrastriate and parietal regions when engaging in fluid tasks (Koshino et al., 2005; Mottron et al., 2013). Increase in fluid task complexity modulated stronger activity in occipital and temporal regions in ASD, coupled with higher connectivity between major lobar regions (superior frontal gyrus, superior parietal lobe, inferior temporal gyrus, middle and inferior occipital gyrus; Simard, Luck, Mottron, Zeffiro, & Soulières, 2015; Soulières et al., 2009). Connectivity to prefrontal cortical areas observed in controls during fluid tasks were either altered or absent in ASD, suggesting aberrant functional segregation and integration in neural mechanisms underlying ASD fluid intelligence ability that are primarily characterized by increased occipito-parietal and temporal activity. (Sahyoun, Belliveau, Soulières, Schwartz, & Mody, 2010; Yamada et al., 2012). ASD performance on
visual search tasks show a similar pattern of atypically increased occipito-temporal but absent prefrontal activity, indicating a predisposition for local rather than global processing that could explain differences in brain activity and connectivity related to higher level cognition in this population. The atypical emphasis on constituent features in ASD could however be an efficient strategy for the processing of complex stimuli, consistent with observations of increased performance on fluid tasks in individuals with ASD (Ring et al., 1999).

In contrast, fluid intelligence performance in neurotypical individuals involve broad recruitment across frontal, parietal, temporal and occipital cortices, as well as subcortical striatal and thalamic regions (Burgaleta et al., 2014; Geake & Hansen, 2010; Gong et al., 2005; Kroger et al., 2002; Perfetti et al., 2009; Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997). Lateral prefrontal and parietal regions could mediate between-subject variability in the association between fluid intelligence and task performance (Gray et al., 2003). Psychometrically unidimensional tasks with high factor loadings on fluid intelligence also share similar patterns of associations with superior frontal, inferior and posterior parietal and temporal-occipital regions (Ebisch et al., 2012). Overall, it is not surprising that these pattern of findings are consistent with the parieto-frontal integration theory (P-FIT) of general intelligence neural correlates, given that fluid intelligence ability is related to a higher-order general intelligence factor (Carroll, 1993; Colom et al., 2009; Jung & Haier, 2007; Reynolds & Keith, 2017). The recent voxel-based meta-analysis of Basten, Hilger, and Fiebach (2015) on brain structural and functional correlates of intelligence lends further support to the P-FIT hypothesis.

Functional connectivity refers to the temporal dependency between the time series of measured neurophysiological signals and can express network mechanisms of high level cognitive processes (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995). Resting-state or intrinsic functional connectivity provide data about the functional architecture of the brain that also correspond to individual differences during task-dependent active states (Smith et al., 2009; Tavor et al., 2016). Intrinsic functional connectivity profiles have been shown to predict fluid intelligence ability, although existing investigations on brain networks in cognition are mostly limited to general intelligence in typically developing adult populations (Finn et al., 2015; Haász et al., 2013; Malpas et al., 2016; Penke et al., 2012).

Previous investigations on the neural correlates of ASD fluid intelligence ability have mainly relied on functional Magnetic Resonance Imaging (fMRI) task-based paradigms using blood oxygen level dependent (BOLD) as an estimate of brain activity to infer the role of local brain regions. Consequently, current knowledge about the neural basis of cognition for different intelligence constructs is limited especially in paediatric populations, and the neural correlates of fluid intelligence in children with ASD are not well-defined. The
common use of a priori specified seed-target correlations to examine brain-cognition relationships may be associated with a bias for the identification of task-positive regions, and there is a need for network-based investigations across the whole-brain to be integrated with localization-focused findings on the neural mechanisms of fluid intelligence. Approaches that investigate brain-wide activity related to intelligence have recently been recommended (Basten et al., 2015; Langeslag et al., 2013). The nature and developmental trajectory of whole-brain fluid intelligence connectivity networks in ASD therefore merits further investigation. Given that ASD fluid task performance is characterized by aberrant activity in local anatomical regions-of-interest, we expect whole-brain intrinsic functional connectivity networks associated with fluid intelligence to be altered in the ASD group in comparison to typically developing controls matched on age, sex and fluid intelligence ability.

**Methods**

**Participants**

Data was obtained from the Kennedy Krieger Institute (KKI, ABIDE-II) sample (n=148) from the Autism Brain Imaging Database Exchange (ABIDE I and II; Di Martino et al., 2014). Full protocol details for sampling, image acquisition and phenotyping are available for public access. Participants in the KKI sample were recruited as part of a study run by the Center for Neurodevelopment and Imaging Research (CNIR) at the KKI. All eligible participants received an MRI scan and cognitive assessment with the Wechsler Intelligence Scale for Children (Fourth Edition, WISC-IV; Fifth Edition, WISC-V). Handedness was assessed using the Edinburgh Handedness Inventory. Inclusion criteria were an age range of 8 years and 0 months to 12 years, 11 months and 30 days, and WISC-IV or WISC-V Full Scale Intelligence Quotient >80. For participants with a discrepancy of 12 points or more across indexes, the Verbal Comprehension Index (VCI), and the Perceptual Reasoning Index (PRI) score (or Visual Spatial Index and Fluid Reasoning Index in the WISC-V) had to be greater than 80 points, with the lowest index score above 65 points. Diagnosis of ASD was determined using the Autism Diagnostic Interview-Revised (ADI-R), Autism Diagnostic Observation Schedule-Generic (ADOS-G) module 3 or the ADOS-2 module 3. Instruments were administered by psychologists with graduate training. ASD classification criteria was based on the ADOS-G and/or ADI-R and clinical assessment by an expert paediatric neurologist with extensive experience in autism diagnosis. ASD participants were excluded if they had an identifiable cause of autism. For the control group, participants with a history of developmental or psychiatric disorders or with a first-degree relative with ASD were excluded. For all participants, exclusion criteria were the presence or history of a

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1 Public access ABIDE protocol: [http://fcon_1000.projects.nitrc.org/indi/abide/](http://fcon_1000.projects.nitrc.org/indi/abide/)
neurologic disorder, major visual impairment, history of alcohol or substance use, and a developmental level of 3 or above on the Physical Development Scale.

For the present study, inclusion criteria applied to the KKI sample were male participants satisfying DSM-IV-TR\(^2\) Pervasive Developmental Disorder criteria (Autistic Disorder, Asperger’s or Not Otherwise Specified), assessed with the WISC-IV, and with MRI data acquired under the same scanning protocol. Continuous variables in the phenotype data were demeaned. Non-parametric propensity matching was conducted using the MatchIt package (Ho, Imai, & King) in the R environment (Team, 2014). Male participants with ASD were matched with TD controls on the following variables: sex, age in years [ASD: \(M=10.45\) (SD=1.58); TD: \(M=10.38\) (SD=0.96)], and PRI score from the WISC-IV [ASD: 108.65 (13.57); TD: 108.83 (14.14)]. The matching procedure resulted in a final sample of 50 male participants (ASD: n=26; TD: n=24).

**Image Acquisition**

MRI data was acquired on a 3 Tesla Philips scanner (Achieva; Philips Healthcare, Best, The Netherlands). T1-weighted images were obtained through a 200 slice three-dimensional acquisition (Turbo Field Echo [TFE] MPRAGE; acquisition time = 8min 8sec; coronal slice orientation; flip angle =8°; repetition time (TR) = 8ms; echo time (TE) = 3.7ms; minimum inverse time (TI) delay = 843.25ms; field of view (FOV) = 256; matrix = 256 x 200; slice thickness = 1mm, in-plane resolution = 1mm x1.28mm). BOLD-weighted resting-state functional MRI volumes were acquired using echo planar imaging (EPI; number of volumes = 128; TE = 30ms; TR = 2500ms; slices = 47; flip angle = 7°; FOV = 256; matrix = 84x81; slice thickness = 3mm, in-plane resolution = 3mm x3.1mm; transverse slice orientation). During the resting-state scan, participants were instructed to relax and focus on a crosshair while remaining as still as possible with their eyes open. For the structural scan, participants watched a movie of their choice. Images were inspected after each processing step for quality control.

**Image Processing and Analysis**

Functional connectivity analysis and visualizations were generated with the Functional Connectivity Toolbox v.16.b (Whitfield-Gabrieli & Nieto-Castanon, 2012) pipeline, Matlab R2010b (The MathWorks, Inc., Natick, MA, USA) and NeuroMArVL (http://immersive.erc.monash.edu.au/neuromarvl/). The initial 4 functional volumes per session were removed to account for T1 saturation effects. Slice-timing correction and first-volume realignment (using a six rigid-body parameter spatial transformation) were applied to adjust for temporal and motion artefacts. Functional volumes were normalized

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\(^2\) DSM-IV-TR: Diagnostic and statistical manual of mental disorders, text revision. American Psychiatric Association, & American Psychiatric Association. (2000). DSM-IV-TR: Diagnostic and statistical manual of mental disorders, text revision. Washington, DC: American Psychiatric Association, 75.
to MNI-space, and smoothed with a full-width half-maximum Gaussian kernel of 8mm. Structural images were co-registered and segmented into grey-matter, white-matter and cerebrospinal fluid for later use in the removal of physiological noise from the functional volumes. In the first-level BOLD model, identified outliers from head motion parameters and global signal intensities (Artifact Detection Tool scrubbing) were regressed from the BOLD signal. Using the aCompCor approach (Behzadi, Restom, Liau, & Liu, 2007), confounds from non-neuronal sources such as cardiac, respiratory and physiological activity were removed. The residual BOLD time series were detrended and band-pass filtered (0.008-0.09Hz) to reduce noise in the detection of gray-matter signals.

Regions-of-interest (ROI) were defined using the FSL Harvard-Oxford Atlas (http://www.fmrib.ox.ac.uk/fsl/) for cortical and subcortical areas, and the Anatomical Automatic Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) for cerebellar regions, resulting in 132 ROIs. The mean BOLD time series for all voxels in each ROI were extracted to compute pairwise correlations between all ROIs with the Fisher r-to-z transformation to construct a 132x132 connectivity matrix. Brain networks showing between-group differences in functional connectivity were identified with network-based statistic (NBS; Zalesky, Fornito, & Bullmore, 2010). Fluid intelligence performance scores (PRI) were regressed onto individual edges in the functional connectivity matrix and one-way ANCOVA covariate models were used to test for between-group differences in functional connectivity associated with cognitive performance scores (PRI by group interaction), or between-group differences in functional connectivity. Handedness and age were included as covariates for all analyses. To identify connected subnetworks, a breadth first search (Ahuja, Magnanti, & Orlin, 1993) was performed among connections surviving a t-statistic threshold of at least t=3.0 and permuted to generate a null distribution of largest network sizes. Each permutation randomly reassigns group labels and identifies the size of the largest interconnected subnetwork. The family-wise error (FWE) corrected p-value for a given subnetwork of size $m$ reflects the proportion of permutations for which the largest subnetwork size is equal to or greater than $m$. The FWE rate is therefore controlled non-parametrically through the use of a randomized null distribution of maximum component size. Finally, subnetworks with a corrected p-FWE<0.05 value were retained.

Validation
To investigate if results from the present study (age range: 8 to 13 years) could be generalized to similar or older age cohorts, the above analyses were replicated on independent samples of data from other ABIDE sites. The University of Utah School of Medicine (USM, ABIDE-I), NYU Langone Medical Center (NYU, ABIDE-I) and Georgetown University (GU, ABIDE-II) sites were selected based on cohort age range and adequate sample size for analysis. This resulted in three independent samples representing a broad range of age cohorts (GU: 8 to 13 years; USM: 15 to 24 years; NYU: 6 to 39 years) of
individuals with ASD and typically developing controls. Table 1 provides descriptive statistics for all samples used for present analyses. Diagnostic criteria, imaging acquisition protocols and parameters differed between sites. To investigate the findings of a general intelligence subnetwork in neurotypical adults (Malpas et al., 2016) but in younger cohorts with or without ASD, we further ran the above analyses to identify between-group differences in functional connectivity networks that were associated with estimate scores of general intelligence ability.

Table 1. Descriptive statistics of samples by site

| Site  | Sample size | Age in years [M(SD)] | Age range in years | PRI [M(SD)] | Test type |
|-------|-------------|-----------------------|--------------------|-------------|-----------|
| KKI   |             |                       |                    |             |           |
| ASD   | 26          | 10.45 (1.58)          | 8 to 13            | 108.65 (13.57) | WISC-IV  |
| TD    | 24          | 10.38 (0.96)          | 8.9 to 12.8        | 108.83 (14.14) | WISC-IV  |
| GU    |             |                       |                    |             |           |
| ASD   | 25          | 11.04 (1.44)          | 8.28 to 13.08      | 109.68 (14.06) | WASI     |
| TD    | 25          | 10.6 (1.46)           | 8.06 to 12.7       | 118.52 (13.45) | WASI     |
| USM   |             |                       |                    |             |           |
| ASD   | 15          | 20.32 (1.48)          | 18.41-22.88        | 102.67 (13.98) | WASI     |
| TD    | 15          | 18.46 (2.45)          | 15-23.95           | 111 (10.39) | WASI     |
| NYU   |             |                       |                    |             |           |
| ASD   | 68          | 13.95 (6.51)          | 7.13-39.10         | 110.29 (17.40) | WASI     |
| TD    | 68          | 14.86 (5.77)          | 6.47-31.78         | 109.44 (14.32) | WASI     |

Notes. ASD: Autism Spectrum Disorders; FSIQ: Full Scale Intelligence Quotient, or general intelligence score estimate; GU: Georgetown University; KKI: Kennedy Krieger Institute; M= mean; NYU: NYU Langone Medical Center; PRI: Perceptual Reasoning Index, or fluid intelligence score estimate; SD=standard deviation, TD: typically developing; USM: The University of Utah School of Medicine; WASI: Weschler Abbreviated Scale of Intelligence; WISC-IV: Weschler Intelligence Scale for Children – Fourth Edition.
Results

Between-group differences in the association of resting-state fMRI subnetwork connectivity with fluid intelligence performance was identified in ASD males aged 8 to 13 years (network size=24 links, t-statistic threshold=3.5, p=.0373, FWE-corrected), with higher strength in ASD compared to typically developing matched controls (Figure 1). The fluid intelligence subnetwork involved regions in the left temporo-occipital middle temporal gyrus, left posterior middle temporal gyrus, bilateral paracingulate gyrus, posterior cingulate gyrus, right frontal pole, right inferior frontal gyrus pars triangularis, bilateral angular gyrus, left lateral occipital cortex (superior division) and precuneus (Table 2). Between-group differences remained significant at a higher network edge threshold (t=4, size=6, p=.0425, FWE-corrected) with nodes of the left temporo-occipital middle gyrus, bilateral angular gyrus, precuneus, posterior cingulate gyrus. Within-group edge associations in ASD also survived higher thresholding (t=4.5, size=48, p-FWE=0.0017). No networks associated with fluid intelligence were found in the matched control group, even when initial statistical thresholding was relaxed (t=2.5).

Table 2. Nodes identified in atypical subnetwork connectivity association with fluid intelligence in Autism Spectrum Disorders compared to matched controls (Site KKI)

| Lobe                      | Node                                | Position | Node Label | MNI Coordinates |
|---------------------------|-------------------------------------|----------|------------|-----------------|
|                           |                                     |          |            | x   y   z       |
| Frontal                   | Paracingulate gyrus                 | Left     | PaCiG l    | -6.21 36.65 20.79 |
|                           | Paracingulate gyrus                 | Right    | PaCiG r    | 6.55 36.57 22.69 |
|                           | Frontal pole                        | Right    | FP r       | 26.16 52.14 8.26 |
|                           | Inferior frontal gyrus,             | Right    | IFG tri r  | 51.87 27.76 7.71 |
|                           | pars triangularis                   |          |            |                 |
| Temporal                  | Middle temporal gyrus, posterior    | Left     | pMTG l     | -60.91 -27.36 -11.00 |
|                           | division                            |          |            |                 |
|                           | Temoporo-occipital middle           | Left     | toMTG l    | -57.64 -53.00 0.82 |
|                           | temporal gyrus*                     |          |            |                 |
| Occipital                 | Lateral occipital cortex, superior  | Left     | sLOC l     | -31.96 -72.89 37.97 |
|                           | division                            |          |            |                 |
| Parietal                  | Angular gyrus*                      | Right    | AG r       | 51.93 -51.80 32.36 |
|                           | Angular gyrus*                      | Left     | AG l       | -50.35 -55.70 29.76 |
|                           | Precuneous*                         | -        | Precuneous | 0.95 -59.29 38.02 |
|                           | Posterior cingulate gyrus           | -        | PC         | 0.78 -36.62 29.98 |

Notes. *Nodes surviving increased thresholding (T=4) in network-based statistics analysis (NBS); KKI: Kennedy Krieger Institute.
Figure 1. A: P-value heatmaps representing second-level within-group associations of pairwise BOLD ROI-ROI edges (132x132 matrix) with fluid intelligence performance (Site: KKI). ASD: Autism Spectrum Disorders group; ASD vs TD: Group interactions between functional connectivity and fluid intelligence performance association; KKI: Kennedy Krieger Institute; TD: matched typically developing controls. B: Visual model of subnetwork representing within-group associations in functional connectivity and fluid intelligence performance in ASD. C: Effect of increased thresholding in network-based analysis (NBS) before network construction. In C1, only pairwise edge association with fluid intelligence of at least t=3.5 were retained for network construction. In C2, the t-statistic threshold was further increased to t=4. Components that survived increased thresholding involved the angular gyrus, temporo-occipital middle temporal gyrus, precuneus and the posterior cingulate gyrus. AG: angular gyrus; FP: frontal pole; IFG tri: inferior frontal gyrus, pars triangularis; PaCiG: paracingulate gyrus; PC: posterior cingulate gyrus; sLOC: Lateral occipital cortex, superior division; toMTG: temporo-occipital middle temporal gyrus.
Repeat analyses for replication in independent samples from different sites presented a similar pattern of findings in the same age cohort (site GU; age range 8 to 13 years), showing a fluid intelligence subnetwork with increased association in ASD compared to controls (network size=14 links, t-statistic threshold=3.5, $p=0.0396$, FWE-corrected, alternate hypothesis: ASD>controls; Figure 2). Implicated regions were the bilateral occipital pole, right temporo-occipital middle temporal gyrus, right anterior middle temporal gyrus, left posterior middle temporal gyrus, right angular gyrus and the cerebellum (Table 3). No fluid intelligence subnetworks were found in the matched control group, consistent with initial findings. Across replicated analyses from independent sites in age-matched samples, the right angular gyrus, left posterior middle temporal gyrus, occipital and temporo-occipital regions were consistently implicated in fluid intelligence subnetwork differences.

Findings failed to replicate in older age cohorts from two independent sites of ages 15 to 24 years (site USM; $p>0.05$, FWE-corrected) and ages 6 to 39 years (site NYU; $p>0.05$, FWE-corrected). Fluid intelligence subnetworks were not identified in older cohorts with ASD, even when the initial thresholding of pairwise functional connectivity links and FWE-corrected p-values were relaxed. No intrinsic connectivity subnetworks associated with general intelligence were identified in cohorts across all sites in our study.

Table 3. Nodes identified in atypical subnetwork connectivity association with fluid intelligence in Autism Spectrum Disorders compared to matched controls (Site GU)

| Lobe          | Node                                | Position | Node Label       | MNI Coordinates | x   | y   | z   |
|---------------|-------------------------------------|----------|------------------|-----------------|-----|-----|-----|
| Frontal       | -                                   | -        | -                | -               | -   | -   | -   |
| Temporal      | Middle temporal gyrus, anterior division | Right    | aMTG r           | 57.89           | -1.529 | -24.51 |
|               | Middle temporal gyrus, posterior division* | Left     | pMTG l           | -60.91          | -27.36 | -11.00 |
|               | Temporo-occipital middle temporal gyrus* | Right    | toMTG r          | 58.18           | -49.22 | 1.59   |
| Occipital     | Occipital pole                      | Right    | OP r             | 17.73           | -95.13 | 8.31   |
|               | Occipital pole                      | Left     | OP l             | -16.85          | -96.50 | 6.74   |
| Parietal      | Angular gyrus*                      | Right    | AG r             | 51.93           | -51.80 | 32.36 |
| Cerebellar    | Cerebellum, crus II                 | Left     | Cereb2 l         | -28.64          | -73.26 | -38.20 |
|               | Cerebellum, vermis 8                | -        | Ver8             | 1.15            | -64.43 | -34.08 |

Notes. *Nodes consistent across independent-site replication GU: Georgetown University
Figure 2. A: Cortical and subcortical regions involved in atypical neural correlates of ASD fluid intelligence in replicated analyses, configured by lobe. The subnetwork represents between-group differences in edge connectivity and fluid intelligence performance association in ASD compared to matched controls (Site: Georgetown University, GU). B: Network components implicated in atypical neural correlates of ASD fluid intelligence (B1; Site: Kennedy Krieger Institute, KKI) and in independent-site replication (B2; Site GU). Nodes consistent in the replicated subnetwork were the angular gyrus, posterior and temporo-occipital middle temporal gyrus. AG: angular gyrus; aMTG: anterior middle temporal gyrus; Cereb2: cerebellum, crus II; FP: frontal pole; IFG: inferior frontal gyrus; OP: occipital pole; PaCiG: paracingulate gyrus; PC: posterior cingulate gyrus; pMTG: posterior middle temporal gyrus; sLOC: Lateral occipital cortex, superior division; toMTG: temporo-occipital middle temporal gyrus; Ver8: cerebellar vermis 8.
Discussion
This is the first study to investigate the neural correlates of intelligence in paediatric cohorts using a sophisticated functional connectivity modelling technique with multi-site replication. We identified a resting-state functional connectivity subnetwork of fluid intelligence that showed atypical increased strength of association with fluid intelligence ability in young ASD males relative to matched controls. Findings were replicated in an independent sample of a similar matched cohort. This subnetwork was not found in older ASD samples, or in typically developing controls across all age groups in the present investigation. In the context of inter-site differences in sampling, phenotyping, diagnostic classification, MRI scanner and acquisition parameters, and the inherent heterogeneity within ASD neurobiology, the consistency of findings with replication support the robustness of a dysfunctional fluid intelligence subnetwork in individuals with ASD between 8 to 13 years of age. A unique strength of this study is the use of a network-based analysis approach to identify fluid intelligence intrinsic subnetworks controlling for whole-brain multiple comparisons, together with replication of analyses in independent samples for validation. Controls were further matched on age, sex and fluid task performance for equivalency.

Primary nodes implicated in atypical ASD fluid intelligence connectivity were the angular gyrus, posterior middle temporal gyrus, occipital and temporo-occipital regions. These regions remained consistent across independent-site replication and increased network thresholding. The strength of association between fluid intelligence and functional connectivity was greater in ASD compared to controls. Typical dorsolateral prefrontal involvement in fluid performance was notably absent in relation to fluid intelligence ability in children with ASD in replicated results when compared to controls, and did not survive increased thresholding in the initial analyses.

These findings are consistent with investigations of localized functional BOLD activity during fluid task performance that report atypical increases in occipito-temporal activity coupled with decreased prefrontal activation in ASD (e.g. Yamada et al., 2012). A recent meta-analysis of grey-matter abnormalities in paediatric ASD reported grey-matter alterations in the right angular gyrus, left inferior occipital gyrus and right inferior temporal gyrus, as well as in frontal, medial parietal and cerebellar regions. Increased grey-matter volume of the right angular gyrus was further associated with increased severity of repetitive behaviours, a core symptom in ASD (Liu et al., 2017). The distinct overlap of specific patterns of grey-matter abnormalities with our present study in similar age cohorts could suggest a structural morphometric basis for the identified atypical fluid intelligence functional connectivity subnetwork in children with ASD.
Independent component analysis of task-based fMRI metadata in previous work on neurotypical subjects show that temporo-occipital and inferior parietal regions constitute a cluster of intrinsic connectivity networks related to visual perception of complex stimuli higher-level visual processing, visual tracking, mental rotation and spatial discrimination (Laird et al., 2011). The angular gyrus and temporal-occipital cortex also demonstrate shared activity even among different fluid intelligence tasks, suggesting their role as potential neural correlates of fluid intelligence ability (Ebisch et al., 2012). In task-free states, connectivity between the angular gyrus and occipital regions form part of a temporally independent functional mode (Smith et al., 2012). Functionally, the angular gyrus serves as a cross-modal hub that combines and integrates multisensory information for attentional reorientation to critical information, comprehension of environmental events, manipulation of mental representations and problem solving (Seghier, 2013). The role of the angular gyrus according to the P-FIT hypothesis of information processing stages involves integration and abstraction of information, followed by parietal-frontal interactions that support problem solving and evaluation of solutions (Colom et al., 2009; Jung & Haier, 2007). That our present findings cohere with known resting-state and task-dependent functional connectivity networks in relation to fluid ability in typical controls suggest that components of the dysfunctional fluid intelligence subnetwork subserve similar functions in ASD, but are susceptible to alterations in local activity and global connectivity.

The dysfunctional fluid intelligence subnetwork in 8 to 13 year-old males was absent in older ASD cohorts. Age-dependent alterations in brain structure and function with inter- and intragroup heterogeneity are characteristic of atypical neurodevelopment in ASD (Uddin, Supekar, & Menon, 2013). A pattern of early increased functional connectivity followed by a decline in later stages has been reported in other disorders such as schizophrenia, possibly related to dysregulation of brain activity due to aberrant neurodevelopment of structural connectivity of hub regions in the association cortices (Fornito & Bullmore, 2015). Similarly in ASD, significant hypoactivation of the middle frontal gyrus during nonsocial tasks in children compared to adults suggest age-dependent trajectories of atypical changes in task neural correlates, and may account for discrepant findings between age cohorts in the present study (Dickstein et al., 2013). As dysfunctional subnetworks related to general intelligence were not detected in our ASD cohorts, the age-dependent aberrant network structure of cognitive correlates may be specific to fluid intelligence ability in this population.

**Intelligence in Typically Developing Children**

Using the network-based analysis pipeline, a single subnetwork broadly distributed across regions in fronto-parietal and default-mode resting-state networks are associated with general intelligence in neurotypical adults (Hearne, Mattingley, & Cocchi, 2016; Malpas et
The developmental trajectory of global neural architectures underlying intelligence ability in younger populations is less defined. Based on findings with replication in our present study, the absence of both general and fluid intelligence intrinsic connectivity subnetworks in typically developing boys suggests that whole-brain network correlates of intelligence ability in younger male cohorts are not yet robustly connected enough to be detected with fMRI.

Typical brain maturation from infancy through adolescence involves a decrease in short-range functional connectivity coupled with increases in long-range connections that reflect increased integration and segregation of brain networks with age. (Richmond, Johnson, Seal, Allen, & Whittle, 2016). The development of network topology is characterized by the reorganization of functional networks with a shift from local anatomical clustering to distributed function-dependent segregation, through which specific cognitive abilities co-evolve with modular specialization and selective cross-network integration (Fair et al., 2009; Grayson & Fair, 2017). The absence of a whole-brain intrinsic functional connectivity subnetwork of intelligence in our analyses of typically developing children could reflect the ongoing shift from local to global networks observed in adulthood. In neurotypical adults, individual variation in general intelligence is associated with a large functional subnetwork, diffuse white-matter organization and increased global network efficiency (Li et al., 2009; Malpas et al., 2016; van den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009). Consistent with this hypothesis are findings of intelligence-related differences in nodal but not global brain network properties in children between 5 to 19 years of age (Wu et al., 2013). Functional network properties however showed age and sex differences, highlighting the need for cohort-specific groups to investigate network connectivity and age-dependent developmental trajectories of brain-behaviour associations with cognitive ability. (Shaw et al., 2006).

In contrast, both global and local network properties of structural connectivity estimates of axonal white-matter tracts are related to fluid intelligence measures in children aged 6 to 11 years. Better performance on measures of perceptual reasoning was associated with greater communication capacities of structural networks from both whole-brain and specific regions (Kim et al., 2016). Because anatomical networks determine pathways of neuronal signalling, structural connectivity drives and constrains functional connectivity throughout development (Petersen & Sporns, 2015; Vertes & Bullmore, 2015). Our findings could suggest that structural network development precedes the complete deployment of global intrinsic functional connectivity networks underlying intellectual ability in children and adolescents. Cross-modal network analysis that integrates structural and functional data will be necessary to delineate the mechanisms of cognitive development and their abnormal nature and trajectory over time in neurodevelopmental disorders (Grayson & Fair, 2017).
Implications

There are several key points to draw from our analyses across distinct age and disorder-specific samples. Importantly, between-group differences in intrinsic connectivity networks underlying fluid intelligence performance remain significant between ASD and controls even when groups were matched on fluid intelligence ability. The degree of association between subnetwork connectivity and fluid ability observed in ASD is therefore more likely related to disorder-specific effects, rather than differences in fluid performance ability (Gray et al., 2003; Perfetti et al., 2009). According to the neural efficiency hypothesis, differential cortical activity may be observed among subjects with discrepant neural resources in relation to cognitive performance. The degree of brain activity associated with cognitive processing could therefore be interpreted as a measure of neural efficiency that varies as a function of individual ability or task complexity, although findings have been ambiguous and may be region-specific (Haier et al., 1988; Neubauer & Fink, 2009; Perfetti et al., 2009). Abnormally increased activation of brain regions during cognitive tasks in atypical populations may indicate a mechanism of neural compensation, and often involves mediation by hub nodes that integrate multiple neural systems, such as the angular gyrus in the parietal association cortex. Dedifferentiation, the failure of neural processes to specialize due to neurodevelopmental abnormalities could also underlie early aberrant increases in hub activity (Fornito, Bullmore, & Zalesky, 2017). Consistent with this framework, our results complement previous findings of increased BOLD signal changes with increased fluid task difficulty in the inferior parietal lobule including the angular gyrus, and the left temporo-occipital junction in healthy individuals (Preusse, van der Meer, Deshpande, Krueger, & Wartenburger, 2011). Increased resting-state connectivity was also associated with higher intelligence scores (Hearne et al., 2016). Given the aberrant brain structure and function in ASD, atypically increased strength of association in the ASD fluid intelligence subnetwork may reflect a compensatory effect to achieve the same level of fluid task performance as ability-matched controls in our analyses.

Consequently, the common approach of controlling for performance variables based on matching of test scores may still remain fallible to sources of variation across different scales of brain structure and function. The general assumption behind matching groups on performance variables is that the neural architecture supporting covariates of interest also remain equivalent across groups, and therefore presumably do not contribute to variation in comparison analyses. However, observed between-group differences in neuroimaging measures in atypical neurodevelopmental conditions could be explained by variation at the level of associated neural correlates of cognitive ability, such as altered subnetwork connectivity underlying ASD fluid intelligence performance as we have shown. Matching groups on general intelligence ability without careful considerations could introduce artefactual differences in case-control comparisons biased by differential associations with neural correlates in ASD (Lefebvre, Beggiato, Bourgeron, & Toro, 2015). The critical point is
that group differences in brain structure and function should demonstrate covariation with variables of interest such as clinical symptom severity, beyond rudimentary matching on performance variables as a method for confound control (Picci, Gotts, & Scherf, 2016).

The strength of the present study design based on variable matching also comes with inherent limits to generalizability of findings. The degree and structure of neural correlates of cognition could vary as a function of both task complexity and individual differences in intelligence ability (Gray et al., 2003; Khundrakpam et al., 2017; Perfetti et al., 2009; Preusse et al., 2011). ASD research is unfortunately biased towards the sampling of high-functioning individuals, likely under-representing subgroups with lower nonverbal intelligence ability. The proportion of cohorts with neuroimaging data available is even smaller (Jack & Pelphrey, 2017). Interpretations of findings are generally limited to sampled cohorts, and extension of assumptions to understudied ASD populations should be done with caution. This is reflected in ASD samples in our study with intelligence ability in the average range. Previous work has shown that intelligence estimates in ASD based on the Raven’s Progressive Matrices (RPM) were higher than scores derived from the Wechsler intelligence scales, suggesting an under or over-estimation of intelligence in this population (Dawson et al., 2007). However, others have postulated that findings may only be specific to ASD subgroups with low intelligence ability, emphasizing the need to consider the implications of individual differences in task performance in clinical research (Bölte, Dziobek, & Poustka, 2009).

With the wide range of tasks and instruments used to interrogate the neural mechanisms underlying cognition, test construct validity should be carefully evaluated in the selection of dependent variables. That is, the validity of neuroimaging and psychometric task measures of brain structure, function and performance should warrant equal consideration when investigating the neural correlates of cognition. For our study, we relied on full and abbreviated forms of the Wechsler intelligence scales with established construct validity and reliability in both typically developing and ASD populations (Minshew, Turner, & Goldstein, 2005; Scott, Austin, & Reid, 2007; Weiss, Keith, Zhu, & Chen, 2013). Others have suggested that the abbreviated form may overestimate nonverbal intelligence ability, and the PRI has also been recently separated into two independent factors representing fluid intelligence and visual processing in the latest iteration of the WISC (Axelrod, 2002; Reynolds & Keith, 2017). Varying definitions and measurement of cognitive constructs might account for inter-site differences in findings, such as the prominent occipital mediation in ASD that we observed in replication analyses. The nomenclature of brain regions also tend to differ between studies depending on the cognitive domain of interest (Seghier, 2013). Despite discrepancies in task, image acquisition and site, in addition to the heterogeneous nature of ASD, the consistent finding of a single atypical subnetwork
associated with fluid intelligence in independent ASD samples is remarkable evidence that the neural correlates of fluid performance are altered in this population.

A final consideration are the constraints of NBS. The technique yields increased power over link-based FWE control to detect connected components with whole-brain multiple comparisons, but at the cost of localizing resolution for independent links (Zalesky et al., 2010). We have thus refrained from directly interpreting individual edge links in the identified subnetworks. Connectivity strength and network topology are distinct properties of the brain connectome that can demonstrate mutually exclusive perturbations (Hong et al., 2013). While we have focused on between-group differences in functional connectivity, these findings establish a framework for subsequent investigations into the multi-scale configuration of connections fundamental to cognition. Apart from identifying fundamental units or collective features of network topology, graph-based measures allow the identification of intermediate mesoscale structures through community detection techniques and across multiple timescales. Importantly, the function of network nodes may differ depending on the scale of analysis (Betzel & Bassett, 2016). The characterization of the neural architecture of intelligence in both typical and atypical populations will require an appreciation of brain structural and functional network topology across multiple scales, and their integration with valid measurement of cognitive constructs of interest.

**Conclusion**

We demonstrate preliminary evidence with replication for an atypical intrinsic connectivity brain network underlying fluid intelligence in male ASD children matched on fluid task ability to controls. Together with the absence of such a network in typically developing children, the neural architecture of fluid intelligence in ASD children may involve prematurely accelerated but aberrant network integration of distributed regions to support equal task performance with same-aged peers. There is potential for longitudinal investigations to delineate inter- and intra-individual variation and between-sex differences in the neurodevelopment of cognitive ability across different populations.

**Acknowledgements**

Data used in this research study was acquired from the Autism Brain Imaging Data Exchange (ABIDE; http://fcon_1000.projects.nitrc.org/indi/abide/). Data analysis and interpretation was conducted within the Developmental Imaging research group, Murdoch Childrens Research Institute and the Children’s MRI Centre, Royal Children’s Hospital, Melbourne, Victoria. It was supported by the Murdoch Childrens Research Institute, the Royal Children’s Hospital, Department of Paediatrics The University of Melbourne and the Victorian Government’s Operational Infrastructure Support Program. The project was
generously supported by RCH1000, a unique arm of The Royal Children's Hospital Foundation devoted to raising funds for research at The Royal Children's Hospital.

Declaration of Conflicting Interests
The authors received no financial support for the research, authorship, and/or publication of this article. The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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