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# The association of children's mathematic abilities with both adults' cognitive abilities and intrinsic fronto-parietal networks is altered in preterm born individuals

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Preterm birth, mathematical abilities, general cognitive performance, intrinsic networks, neuro-cognitive development

**Abstract**

Mathematic abilities in childhood are highly predictive for long-term neurocognitive outcomes. Preterm-born individuals have an increased risk for both persistent cognitive impairments and long-term changes in macroscopic brain organization. We hypothesized that the association of childhood mathematic abilities with both adulthood general cognitive abilities and associated fronto-parietal intrinsic networks is altered after preterm delivery.

72 preterm- and 71 term-born individuals underwent standardized mathematic and IQ testing at eight years and resting-state fMRI and full-scale IQ testing at twenty-six years of age. Outcome measure for intrinsic networks was intrinsic functional connectivity (iFC).

Controlling for IQ at age eight, mathematic abilities in childhood were significantly stronger positively associated with adults' IQ in preterm- compared with term-born individuals. In preterm-born individuals, the association of children's mathematic abilities and adults' fronto-parietal iFC was altered. Likewise, fronto-parietal iFC was distinctively linked with preterm and term born adults' IQ.

Results provide evidence that preterm birth alters the link of mathematic abilities in childhood and general cognitive abilities and fronto-parietal intrinsic networks in adulthood. Data suggest a distinct functional role of intrinsic fronto-parietal networks for preterm individuals with respect to mathematic abilities, and that these networks together with associated children's mathematic abilities may represent potential neuro-cognitive targets for early intervention.

**Keywords:**

IQ in adulthood, mathematic abilities in childhood, fronto-parietal intrinsic networks, preterm birth

## Introduction

Preterm born individuals are at increased risk of cognitive impairments in general and mathematic difficulties in particular (Jaekel et al. 2014a; Simms et al. 2013; Taylor et al. 2009). Studies that have followed preterm born children longitudinally report these neurodevelopmental deficits to be persistent throughout childhood, adolescence and adulthood (Allin et al. 2008; Pyhälä 2012; Breeman et al. 2015). As a consequence, research has focused on developing early intervention programs to prevent neurocognitive deficits and educational underachievement in preterm children (McCarton et al. 1997; McCormick et al. 2006; Nordhov et al. 2010). However, the efficacy of these programs is arguable. Current evidence suggests that the benefits of developmental interventions are restricted to short-term gains in cognitive outcome (Orton et al. 2009). In contrast, interventions designed to facilitate children's cognitive development in normal population samples have proven strong positive long-term effects (Clements and Sarama 2011). The lack of observable long-term benefits from intervention programs in preterm born children calls for a more specific and effective intervention planning that is attuned to preterm children's needs. A critical requirement to define such targets is to identify developmental characteristics – and optimally their underlying mechanisms – that may differentially predict later outcomes for term and preterm subjects. The present study tests the association of mathematic abilities with related brain organization in neurocognitive intrinsic networks as potential candidates for such mechanisms.

Mathematic abilities in childhood are a strong predictor for later academic achievement (Duncan et al. 2007), employability and income in adulthood (Ritchie and Bates 2013) as well as social functioning (Geary 2013). Mathematic reasoning is a complex amalgam of cognitive processes comprising both domain-specific (e.g. comprehension of numerical properties, fact retrieval and calculation) and domain-general cognitive resources (e.g. working memory, attention, decision making and sequential mental operations) (Menon 2010). Furthermore, certain aspects of mathematic thinking rely on visuo-spatial abilities (for review see (Hubbard et al. 2005)). Hence, mathematic impairments can arise from deficits in distinct cognitive processes. For instance, mathematic difficulties in preterm born individuals are supposed to be the result of deficits in both domain-specific and domain-general abilities (Aarnoudse-Moens et al. 2013; Simms et al. 2013; Simms et al. 2014), while mathematic difficulties associated with developmental dyscalculia are predominantly a consequence of deficits in domain-specific abilities. Although the nature of mathematic deficits in preterm born individuals is not completely understood, they might be the result of a compromised brain development and associated changes in brain organization (Salmaso et al. 2014; Volpe 2009).

Intrinsic brain networks (IBNs) represent brain organization at the large-scale level (Vincent et al. 2007; Bressler and Menon 2010; Sepulcre et al. 2010) and are consistently altered in preterm born infants (Damaraju et al. 2010; Ball et al. 2012), adolescents (Myers et al. 2010), as well as adults (Bäuml et al. 2014; White et al. 2014). They are characterized by coherent fluctuations in the low-frequency range (<0.1 Hz) of the blood oxygenation level dependent (BOLD) signal measured during resting state functional magnetic resonance imaging (rs-fMRI). IBNs are often referred to as “functional” networks, as their spatial architecture overlaps with networks usually activated during the performance of a particular task (Smith et al. 2009). In line with that, individual differences in cognitive abilities, such as reading (Koyama et al. 2011), attention (Duchek et al. 2013), visual performance (Martin et al. 2012) and intelligence (Song et al. 2011), can be related to intrinsic functional connectivity (iFC) of corresponding IBNs. Insofar, coherent spontaneous fluctuations in the BOLD signal might reflect the history of co-activation between distinct areas of the brain (Laird et al. 2011).

Recently we demonstrated that such functional network organization is affected by preterm birth with some potential for compensatory re-organization for attentional mechanisms in adulthood (Finke et al. 2015). Based on these findings, we suggested that children’s mathematic abilities may predict adults’ general cognitive abilities and associated functional network organization, and – critically – that this link is altered by preterm birth. If so, children’s mathematic abilities and intrinsic brain networks may not only be predictors for later outcome but, more importantly, present potential targets for early intervention. In that sense, our study is a pilot to define more specific hypotheses about potential avenues to intervention after preterm birth.

To test the association of mathematic abilities in childhood and cognitive and brain function in adulthood, we evaluated both mathematic competence and general cognitive abilities at 8 years of age as well as general cognitive abilities and intrinsic brain networks at 26 years of age in preterm and term born individuals. Intrinsic functional connectivity (iFC) within and between math-related networks was derived from resting-state fMRI. We selected IBNs based on their behavioral domain characterization as identified by a study of Smith and colleagues (Smith et al. 2009) (see below for details). Specifically, we identified intrinsic networks that overlapped with cognitive domains relevant for mathematics. Adult outcomes were predicted by preterm vs. term birth group status and children's mathematic abilities within an ANCOVA framework controlling for general cognitive abilities in childhood. We hypothesized that (i) individual differences in mathematic performance at age eight years predict individual differences in both general cognitive abilities and intra- and inter-network-iFC of mathematic-related intrinsic brain networks at the age of twenty-six years and that (ii) these predictions are influenced by a history of preterm birth. Finally, we were interested whether iFC that is distinctively predicted by childhood maths scores in preterm and term born individuals is associated with general cognitive abilities at age 26 years.

## Materials and Methods

### Participants

Participants were recruited as part of the prospective whole population based Bavarian Longitudinal Study (BLS) of neonatal at-risk children (Riegel et al. 1995; Wolke and Meyer 1999). All live-birth infants that were born between February 1985 and March 1986 in southern Bavaria and who required admission to one of 19 neonatal units in 17 children's hospitals within the first ten days of life comprised the target sample (Wolke and Meyer 1999). A total of 7505 children (10.6% of all live births) were classified as neonatal at-risk children, whereupon 2759 children were born before 37 weeks of gestation (Riegel et al. 1995). During the same period, 916 healthy term infants (>36 weeks gestation; normal postnatal care) born in the same hospital centres were recruited as control infants. Over the years, subjects of both groups were repeatedly assessed with neurological and psychological test batteries, and parental interviews to monitor development. Full details of the sampling criteria and dropout rates are provided elsewhere (Wolke and Meyer 1999; Gutbrod et al. 2000). At age 26 years, 83 preterm and 79 full term control participants agreed to undergo functional and structural MRI. MRI assessments were carried out at two different sites: The Department of Neuroradiology, Klinikum Rechts der Isar, Technische Universität München, Germany (N=91), and the Department of Radiology, University Hospital Bonn, Germany (N=55). The study was approved by the local ethics committees of the Klinikum rechts der Isar and University Hospital Bonn. All study participants gave written informed consent and received travel expenses. Subsequent analyses involving MRI data were based on 74 preterm and 72 term born subjects due to imaging artefacts described in detail below. Analyses additionally involving adult full-scale IQ were further reduced to 143 subjects since full-scale IQ was only available for 72 preterm and 71 term born adults.

### Birth-related variables and family socio-economic background (SES)

Gestational age (GA) was estimated from maternal reports of the last menstrual period and serial ultrasounds during pregnancy. Maternal age and birth weight (BW) were obtained from obstetric records.

Neonatal medical complications were assessed with a standardized optimality scoring system (Opti neonatal) including 21 items (e.g. ventilation or intubation, sepsis, neonatal seizures, cerebral haemorrhage) (Prechtl 1967). Items were coded as 1 (yes) or 0 (no) and summed into an index score with higher values being less optimal.

Family SES was collected through structured parental interviews within 10 days of child birth. It was computed as a weighted composite score based on the profession of the self-identified head of each family together with the highest educational qualification held by either parent (Bauer 1988).

**Assessment of mathematic abilities and general cognitive performance**

Cognitive assessments and tests were performed by trained assistant psychologists who were blind to participants' background characteristics.

***Mathematic abilities at 8 years of age.*** To assess numerical representations and reasoning, children were administered a comprehensive mathematic test at primary school age. Test tasks were presented to children in book form with 79 items assessing numerical estimations, calculation, reasoning, and mental rotation abilities: 12 estimation tasks measured children's accuracy in estimating numbers and comparing distances between numbers. Retrieval of arithmetic facts and procedural competence were measured with 50 calculation tasks (simple addition), whereas application of these 2 ability dimensions on real-world problems was assessed with 6 reasoning tasks. Finally, children's visual-spatial problem solving was tested with 11 mental rotation tasks. Item responses were scored for accuracy and subscale scores were then summed into a comprehensive total score (Jaekel et al. 2014a; Jaekel and Wolke 2014).

***Cognitive assessment at 8 years of age.*** At 8;5 years of corrected age, children's general cognitive abilities were assessed with the German version of the Kaufman Assessment Battery for Children, K-ABC MPC score (Kaufman and Kaufman 1983; Melchers and Preuss 1991). All test scores were z-standardized according to the scores of the healthy term control children.

***Cognitive assessment at 26 years of age.*** Prior to and independent from the subsequent MRI examination, subjects were asked to take part in an assessment of general cognitive functioning. This included a short version of the German version of the Wechsler Adult Intelligence Scale-III (WAIS-III) (Von Aster et al. 2006). Scores were converted to age-normed full-scale IQ scores (Eryigit Madzwamuse et al. 2014).

**MRI: data acquisition and analysis**

***Acquisition.*** MRI data acquisition was performed on Philips Achieva 3T TX systems (Achieva, Philips, The Netherlands), using an 8-channel SENSE head coil, in departments of neuroradiology and radiology, respectively, in Munich and Bonn. Due to a scanner upgrade, data acquisition in Bonn was switched to Philips Ingenia 3T system with an 8-channel SENSE head coil after N = 17 participants. To account for possible confounds introduced by scanner differences, analyses included scanner identities as covariates-of-no-interest. Across all scanners, sequence parameters were kept identical. Scanners were controlled regularly providing optimal and constant scanning conditions. Signal-to-noise was not significantly different between scanners (one-way ANOVA with factor "scanner-ID" (Bonn 1, Bonn 2, Munich); p=.63). Resting-state data was collected for 10 min 52 s from a gradient-echo echo-planar sequence (TE = 35 ms, TR = 2608 ms, flip angle = 90°, FOV = 230 $mm^2$, matrix size = 64 x 63, 41 slices, thickness 3.58 mm and 0 mm interslice gap, reconstructed voxel size = 3.59 x 3.59 x 3.59 $mm^3$) resulting in 250 volumes of BOLD fMRI data per subject. Subsequently, a high-resolution T1-weighted 3D-MPRAGE sequence (TI = 1300 ms, TR = 7.7 ms, TE = 3.9 ms, flip angle = 15°; 180 sagittal slices, FOV = 256 x 256 x 180 mm, reconstruction matrix = 256 x 256; reconstructed voxel size = 1 x 1 x 1 $mm^3$) was acquired. Immediately before undergoing the resting-state sequence, subjects were instructed to keep their eyes closed and to restrain from falling asleep. We verified that subjects stayed awake by interrogating via intercom immediately after the rs-fMRI scan.

***MRI data preprocessing.*** Functional fMRI data were preprocessed according to an automated in-house pipeline (Meng et al. 2013) using SPM8 (Wellcome Trust Centre for Neuroimaging, University College London, UK: http://www.fil.ion.ucl.ac.uk/spm). For each participant, the first five functional scans of each resting-state fMRI-session were discarded to account for magnetization effects. Resulting volumes were then realigned to correct for head motion and coregistered to the structural T1-image. Subsequently, the T1-weighted image was segmented into its different compartments using Unified Segmentation (Ashburner and Friston 2005). To transform the individual images into common MNI (Montreal Neurological Institute) space, segmentation-based normalization parameters were applied to the coregistered structural and functional data. Furthermore, normalized EPI images were smoothed using a Gaussian kernel with a full-width at half-maximum of 6 mm to increase signal-to-noise ratio. In a final step, preprocessed functional time-series for each voxel were despiked using ANFI's 3dDespike motion censoring procedure (http://afni.nimh.nih.gov/afni) to further remove motion-induced artifacts. Nine subjects had to be excluded due to excessive head motion which was defined as a cumulative motion translation or rotation > 3 mm or 3° and mean point-to-point translation or rotation > 0.15 mm or 0.1°. Furthermore, data of four subjects were removed from the data set due to severe hardware owing image artefacts. Three further subjects had different scanner parameters in the resting-state sequence and hence were not included in the final sample. The final imaging sample consisted of 74 preterm and 72 term subjects. To ensure data quality, particularly concerning motion-induced artifacts, temporal signal-to-noise ratio (tSNR) and point-to-point head motion were estimated for the remaining 146 subjects (Murphy et al. 2007; Van Dijk et al. 2012). Point-to-point motion was defined as the absolute displacement of each brain volume compared to its previous volume. Two-sample t-tests yielded no significant differences between groups regarding mean point-to-point translation or rotation of any direction ($p = 0.46$) as well as tSNR ($p = 0.09$).

***Intrinsic network analysis**.* To investigate intrinsic networks of interest, we performed spatial independent component analysis (ICA) on resting-state fMRI (rs-fMRI) data (Sorg et al. 2007; Bäuml et al. 2014). Spatial ICA decomposes rs-fMRI data into components reflecting intrinsic networks (Fox and Raichle 2007). ICA is a model-free multivariate data analysis approach that - assuming linear mixtures of independent sources - decomposes data into temporally coherent spatial components by estimating statistically maximally independent spatial sources (Beckmann et al. 2005). Preprocessed data from both groups was entered into a single group ICA framework as implemented in the GIFT toolbox (http://icatb.sourceforge.net). We chose a high model order ICA (number of independent components [ICs] = 75; (Allen et al. 2011)) since it has been shown, that such models decompose data into components that are in best agreement with known anatomical and functional networks (Kiviniemi et al. 2009). Before performing ICA, a two-step data reduction approach was conducted using principal component analysis (PCA). First, PCA was done on the single subject level retaining 100 principal components. Large numbers of subject-specific principal components preserve most of the individual variance and have been shown to stabilize subsequent back-reconstruction (Erhardt et al. 2011). In a second step, each of the subject's reduced data was concatenated in time to perform a second PCA on the group level followed by independent component analysis with the infomax algorithm. ICs were depicted as spatial maps and corresponding IC time courses. To estimate the reliability of the decomposition, ICA was repeated 20 times by using the Icasso-toolbox (http://research.ics.aalto.fi/ica/icasso/). Reliability was quantified using the Icasso cluster quality index Iq, ranging from 0 to 1. The group ICA framework in GIFT results in a set of average group components, which are then back reconstructed into single subject space using the GICA3 back-reconstruction method. Each back-reconstructed component consists of a spatial map reflecting component's functional connectivity pattern across space and an associated time course reflecting component's activity across time. Spatial maps were used as surrogates of networks' intra-network intrinsic functional connectivity, time courses as surrogates for network activity along time. Time courses were the base for later calculated inter-network iFC (see below).

Since mathematic reasoning is an amalgam of different cognitive processes (see above), we selected IBNs of interest based on their behavioral domain characterization as described in a study by Smith and colleagues (Smith et al. 2009). Smith and colleagues performed ICA both on resting state fMRI data and on thousands of activation maps for tasks of several cognitive domains derived from the BrainMap database (http://www.brainmap.org). Out of twenty networks, ten networks in both data sets showed a strong spatial overlap, indicating the functional nature of the corresponding intrinsic network (of rs-fMRI data). From these, four networks were shown to be involved in such cognitive processes as cognition, attention, working memory, reasoning and visuo-spatial abilities. Networks comprised left and right frontoparietal networks (FPN), the executive control network (ECN) and a lateral visual network (LVN) (see Figure S1). To identify the corresponding networks in our data, we performed a two-step procedure. We first chose the respective spatial maps described in the study by Smith and colleagues and assigned them to the spatial maps described in the study by Allen and colleagues via multiple spatial regressions (Allen et al. 2011). Allen's T-maps (Fig. 4 in (Allen et al. 2011)) were based on 603 healthy adolescents and adults and were made available online by the Medical Image Analysis Lab (MIALAB) (http://mialab.mrn.org/data/hcp/RSN_HC_unthresholded_tmaps.nii.). Second, we used these maps of Allen to identify intrinsic networks in our data, again via spatial regression. For each network, the independent component with the largest regression coefficient was chosen (see Supplements).

**Statistical analysis**

***Association of children's mathematic abilities with adults' full-scale IQ.*** To test the predictive link of children's mathematic abilities with adults' general cognitive abilities, a univariate general linear model approach was used as implemented in IBM SPSS Statistics 22 (IBM Corp., Armonk, NY). Full-scale IQ at age twenty-six was the dependent variable. Independent variables were the factor group (term vs. preterm) and the continuous covariate-of-interest of subject-specific, z-transformed maths scores at age eight. To investigate the specific effect of maths on adults' full-scale IQ, subject-specific, z-transformed IQ scores at age eight were included as covariate of no-interest. Likewise, sex was included as another covariate of no-interest. Contrasts of interest were the main effects of preterm group status and maths and the interaction of preterm group status with maths, controlling for IQ at age eight and child sex.

***Association of children's mathematic abilities with adults' intrinsic functional connectivity.*** To test whether maths scores at age eight predicted intra-network-iFC of intrinsic networks-of-interest in adulthood, a univariate general linear model approach was used as implemented in SPM8. For each independent component of interest, voxel-wise, subject-specific spatial maps reflecting intra-network iFC served as the dependent variable. Independent variables were the factor group (term vs. preterm) and subject-specific z-transformed maths scores. As mentioned above, subject-specific, z-transformed IQ scores at age eight were included as further covariate to investigate the specific effect of maths on adults' iFC. Additional covariates of no interest were sex and scanner-ID (Bonn 1, Bonn 2, Munich). To correct for multiple comparisons across multiple voxels, we used the program AlphaSim as implemented in the REST-toolbox (Song et al. 2011). AlphaSim uses the Monte Carlo simulation as implemented in AFNI (see the AlphaSim command description at http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim). A combination threshold of $P<0.001$ on the voxel level and a cluster size $>243\ mm^3$ was considered significant, which corresponded to a corrected $P<0.05$. The simulation was performed within a user-defined probability gray matter mask (threshold at 0.3) covering 28,254 voxel.

To test the association of children's mathematic abilities with inter-network-iFC, we set up the same model as described above using SPSS 22. Inter-network-iFC was canonically defined by Pearson's correlation between ICA-derived timecourses of pairs of components (Jafri et al. 2008). Subject-specific component timecourses were extracted, de-trended and filtered using a fifth-order Butterworth low-pass filter, with a high-frequency cut-off set at 0.15 Hz (Allen et al. 2011). Subsequently, preprocessed timecourses were correlated with each other using Pearson's correlation and transformed to z-scores using Fisher's transformation using a Matlab-based in-house script. Fisher's z-transformed correlations between each pair of independent component timecourses served as the dependent variable.

For both models, contrasts of interest were the main effect of maths and interaction of group and maths, controlling for group, IQ at age eight, sex and scanner-ID; i.e. we were interested whether mathematic abilities at the age of eight – adjusted for IQ– were associated with intrinsic functional connectivity of neurocognitive networks at age 26, and whether such a relationship was modulated by preterm birth. Additional post-hoc t-tests were performed to uncover the direction of effects.

***Linking maths-related network iFC to general cognitive abilities in adulthood.*** To further assess whether iFC that was differentially associated with children's mathematic abilities in term and preterm individuals was relevant for general cognitive performance in adulthood (i.e. linked with full-scale IQ), we extracted respective cluster values voxel-wise, calculated the mean for each cluster and subsequently correlated iFC with adults' full-scale IQ in a partial correlation approach. To rule out that the correlation between iFC and IQ at 26 is driven by the same variance that has been explained by IQ or mathematic abilities at eight years, we controlled for scanner-ID, sex as well as IQ and mathematic abilities in childhood, respectively. For the association of maths-related inter-network-iFC with full-scale IQ in adulthood, we related respective Fisher's z-transformed correlations between pairs of independent component timecourses to full-scale IQ using the same partial correlation approach as described above.

## Results

Demographic and medical information of the preterm and full term participants are shown in Table 1. Both maths scores at age eight, IQ at age eight and full-scale IQ in adulthood were significantly lower in preterm born individuals ($p<0.001$; $p=0.002$; $p=0.002$) (Table 1).

### Children's mathematic abilities are distinctively associated with adults' general cognitive abilities in term and preterm individuals

A significant main effect of mathematic abilities revealed that across both groups mathematic abilities in childhood predicted full-scale IQ in adulthood ($F(1, 136) = 9.08$; $p = 0.003$; Figure 1). A subsequent post-hoc t-test showed that the association of children's mathematic abilities and adults' full-scale IQ was positive ($T(136) = 2.90$; $p = 0.004$), indicating that the higher the maths score in childhood, the higher the full-scale IQ in adulthood. A significant interaction effect of preterm group status with mathematic abilities revealed that mathematic abilities in childhood were differently linked with adults' IQ in preterm and term born subjects ($F(1, 136) = 4.27$; $p = 0.041$). A post-hoc t-test showed that preterm birth increased the positive association of mathematic abilities in childhood with general cognitive abilities in adulthood ($t(136) = -2.07$; $p = 0.041$) (Figure 1).

### Children's mathematic abilities are distinctively associated with adults' fronto-parietal intra-network, but not inter-network iFC in term and preterm individuals

Independent component analysis of rs-fMRI data revealed intrinsic networks for full- and preterm born adults that have been described previously (one-sample t-test, $p < 0.05$ FWE-corrected; Fig. S1) (Beckmann et al. 2005; Kiviniemi et al. 2009; Smith et al. 2009; Allen et al. 2011).

Significant interaction effects of preterm group status with mathematic abilities revealed that mathematic abilities in childhood were differently linked with intra-network iFC of left and right fronto-parietal networks in preterm and term born individuals ($p<0.05$, corrected; Figure 2; Table S2). For the right fronto-parietal network, post-hoc t-tests revealed that in preterm born adults maths scores in childhood were positively associated with iFC in the left lateral occipital/middle temporal cortex while the relationship was reversed for term adults. In the left fronto-parietal network, post-hoc t-tests revealed a similar pattern, i.e. in preterm born adults higher z-transformed maths scores were associated with increased iFC in the right angular gyrus/middle temporal cortex, while the opposite was true for term born adults. In contrast, higher mathematic abilities were associated with decreased iFC in the superior frontal gyrus of the left fronto-parietal network of preterm adults, while this association was reversed for term born adults. As described in the methods part the analysis was controlled for IQ in childhood, suggesting that the moderator effect of preterm birth on the association between childhood math ability and iFC was independent from childhood IQ. In a subsequent control analysis, we then replaced IQ in childhood by IQ in adulthood and found identical results, indicating that the moderating effect of preterm birth on the link between childhood math and iFC was not influenced by adult IQ.

Neither a main effect of maths, nor a significant association between preterm group status and children's mathematic abilities was found for inter-network iFC.

**iFC which is distinctively associated with children's mathematic abilities in term and preterm subjects is linked with adults general cognitive abilities**

In a final step, we investigated whether adults' iFC, which is distinctively associated with early mathematic abilities in term and preterm subjects (Figure 2), is also linked with adults' general cognitive abilities. For this purpose, we performed two partial correlation analyses, firstly controlling for sex, scanner-ID and IQ in childhood and secondly controlling for sex, scanner-ID and mathematic abilities in childhood. Partial correlations were calculated for preterm and term born individuals separately. Results showed that when controlling for IQ at eight, intra-network iFC of the right fronto-parietal network (i.e. left middle temporal/lateral occipital gyrus) was significantly correlated with adults' full-scale IQ – particularly in preterm born individuals ($r = 0.40$, $p = 0.001$; Table S3). In contrast, when controlling for children's mathematic abilities, this association disappeared ($p > 0.05$), indicating that the association between iFC changes and IQ at 26 years is partly explained by mathematic abilities in childhood, i.e., specifically linked with childhood math ability.

## Discussion

To investigate the effect of preterm birth on the association of childhood mathematic abilities with adulthood general cognitive abilities and maths-related fronto-parietal intrinsic network organization, we evaluated childhood mathematic competence and IQ as well as full-scale IQ and intrinsic functional connectivity of neurocognitive brain networks at twenty-six years of age in 72 preterm and 71 term born individuals. In comparison to the term group, preterm born individuals' mathematic abilities and IQ in childhood and general cognitive abilities in adulthood were lower. Importantly, children's mathematic abilities were distinctively associated with both adults' full-scale IQ and fronto-parietal intrinsic connectivity in term and preterm born individuals, even when controlling for IQ in childhood. Likewise, iFC of the right fronto-parietal network that was distinctively associated with term and preterm born children's mathematic abilities was distinctively linked with adults' general cognitive abilities. The present study provides first evidence that term and preterm born children's mathematic abilities are distinctively predictive for both cognitive outcome and fronto-parietal brain organization in adulthood. Our data suggest (i) a distinct functional role of fronto-parietal iFC in term and preterm born individuals with respect to mathematic abilities and (ii) that early mathematic competence and maths-related fronto-parietal network organization may serve as potential targets for specific intervention to reduce adverse long-term effects after preterm delivery.

### *Preterm birth alters the predictive link of children's mathematic abilities for long-term general cognitive abilities*

Both preterm individuals' mathematic abilities and IQ in childhood and full-scale IQ in adulthood were lower compared to term born individuals (Table 1). This is in line with previous findings (Eryigit-Madzwamuse et al. 2014; Jaekel and Wolke 2014) supporting the view that preterm birth leads to long-term cognitive impairments (Hack et al. 2002; Allin et al. 2008; Breeman et al. 2015). Although IQ at the age of eight significantly predicted full-scale IQ in adulthood ($P < 0.001$) (Table S1), maths scores at eight years explained some additional variance in full-scale IQ at twenty-six years. Importantly, this prediction was modulated by a history of preterm birth suggesting that childhood mathematic abilities have a higher predictive value for general cognitive abilities in adulthood in preterm born individuals. We made sure that results were not confounded by group differences in IQ at eight years, age, sex or SES by matching groups with respect to these variables (see Table 1). A study by Duncan and colleagues has shown that term born children's mathematical competence at school age is a strong predictor for academic achievement (Duncan et al. 2007). We complement this finding by showing that preterm birth even increases the predictive value of children's mathematic abilities for long-term general cognitive outcome (Figure 1). This might be attributed to a more fixed developmental trajectory in preterm born individuals supposedly due to reduced neuronal plasticity (Anderson et al. 2009). In line with that, a recent study demonstrated IQ scores to be more stable over time in preterm compared with term born individuals (Breeman et al. 2015).

***Preterm birth alters the predictive link of children's mathematic abilities for long-term fronto-parietal intra-network brain organization***

Preterm birth altered the association of children's mathematic abilities with intra-network iFC of fronto-parietal intrinsic brain networks in adulthood (Fig. 2). The distinctive association of children's mathematic abilities with term and preterm born adults' functional brain organization was specific for intra-network iFC, since we did not find any association with inter-network iFC. In the right fronto-parietal network, preterm individuals' maths scores in childhood were positively correlated with adults' iFC in the left lateral occipital/middle temporal cortex while they were negatively correlated with adults' iFC in term born individuals. In the left fronto-parietal network, the same pattern was present in the right angular gyrus/middle temporal cortex. In contrast, higher mathematic abilities in childhood were associated with decreased left fronto-parietal network iFC in the superior frontal gyrus of preterm adults, while this association was reversed for term born adults. Importantly, these findings were independent of IQ in childhood for which we controlled in our analysis. This suggests a specific effect of preterm birth on the association of children's mathematic abilities with young adults' fronto-parietal network organization. Moreover, our results implicate a distinct functional role of fronto-parietal iFC for term and preterm born individuals with respect to mathematic abilities.

Both left and right fronto-parietal networks have been implicated in several cognitive processes such as attention, working memory and reasoning (Smith et al. 2009) which are essential to mathematic reasoning (Menon et al. 2010) and often impaired in preterm born individuals (Aarnoudse-Moens et al. 2009). Moreover, these networks cover the angular gyrus, intraparietal sulcus and superior parietal gyrus which have been associated with distinct mathematic abilities (Dastjerdi et al. 2013; Dehaene et al. 2003; Gerstmann 1940). In line with that, Alavash and colleagues have recently documented in a normal population sample that visual-spatial and numerical abilities are differently associated with functional integration of resting state brain networks particularly of the parietal cortex (Alavash et al. 2015). Recently we showed that parietal network organization is altered in preterm born adults and that such networks show some potential to compensate attentional shortfalls by functional network re-organization (Finke et al. 2015). This finding suggests a capacity for neuronal plasticity in the parietal cortex of preterm born adults and raises the question whether similar compensatory network organization could be observed in the context of maths performance. Moreover, it implicates neuronal plasticity in the parietal cortex as a potential target for intervention in preterm born individuals. Previous studies implicated that both cognitive abilities and iFC of IBNs follow different developmental trajectories in term and preterm born individuals. For instance, Allin and colleagues report different cognitive trajectories for semantic verbal fluency in term and preterm born individuals from adolescence to adulthood (Allin et al. 2008). Moreover, a recent study using the BLS cohort demonstrated that cognitive abilities in preterm born individuals are rather stable over time while they are more variable in term born peers (Breeman et al. 2015). Complementary, several fMRI studies showed altered functional brain organization in preterm born individuals in infancy (Damaraju et al. 2010), childhood (Wilke et al. 2013), adolescence (Schafer et al.

2009), as well as adulthood (Bäuml et al. 2014; White et al. 2014). Although cross-sectional in design, these studies suggest different neurodevelopmental trajectories with respect to preterm born individuals' IBNs. Future studies may investigate both development of mathematic abilities and iFC of IBNs in parallel.

Finally, reduced fractional anisotropy of both commissural and association tracts connecting frontal and parietal areas has been linked to cognitive impairments in preterm born adults (Allin et al. 2011; Eikenes et al. 2011). It is conceivable that this also holds true for deficits in mathematic abilities – yet this has to be tested. Future studies may focus on the question whether mathematic impairments in preterm born individuals are the result of aberrant structural and/or functional brain connectivity (see next paragraph) as more and more studies suggest brain dysconnectivity to be a fundamental long-term consequence of preterm birth (Bäuml et al. 2014; White et al. 2014; Meng et al. 2015).

***The nature of mathematic deficits in preterm born individuals***

As stated in the introduction, mathematic difficulties in preterm born individuals are thought to result from deficits in both domain-specific and domain-general abilities (Aarnoudse-Moens et al. 2013; Simms et al. 2013; Simms et al. 2014). Consequently, mathematic deficits may be attributed to alterations in brain circuits that subserve both domain-general and domain-specific cognitive functions. A recent study that used the duration of mechanical ventilation as a proxy measure for potential hypoxia-ischemia (and hence perinatal brain injury) demonstrated that prolonged ventilation predicted specific impairments in mathematic abilities (Jaekel et al. 2014). In animal models of premature brain injury hypoxia-ischemia is typically associated with diffuse white matter injury (WMI) and arrest of premyelinating oligodendrocyte lineage cell differentiation (see (Back and Rosenberg 2014) for review). In preterm cohorts born before the 1990s, hypoxic-ischemic events were additionally accompanied by a significant loss of cortical and subcortical neurons (Volpe 2009). Which of these cellular alterations uniquely contribute to mathematic difficulties is unknown so far. However, given the complex pattern of brain development (Bystron et al. 2008) and the widely distributed brain alterations associated with preterm birth (Bourgeois et al. 1989; Salmaso et al. 2014; Penn et al. 2015; Bäuml et al. 2014; Meng et al. 2015), we speculate that mathematic deficits in preterm individuals result from aberrant brain connectivity rather than from alterations in singular regions (however see (Isaacs et al. 2001)). As such, different associations of term and preterm children's mathematic abilities with iFC in adulthood may point to a distinct functional role of fronto-parietal networks in preterm populations.

***Potential targets for intervention after preterm birth***

Our study may help generate new hypotheses about potential targets for developmental intervention after preterm birth. Intervention may take place in the form of specific training programs to support children's cognitive and/or motor development (Orton et al. 2009; Melby-Lervåg and Hulme 2013; Løhaugen et al. 2011). Although some studies report beneficial effects of early interventions in very low birth weight children (Grunewaldt et al. 2013; Grunewaldt et al. 2015), the long-term effects of such programs are arguable and raise questions about the biological and educational underpinnings that facilitate sustained intervention effects (McCormick et al. 2006; Jaekel et al. 2014b). Here we demonstrate that mathematical competence in elementary school is specifically linked to adults' fronto-parietal iFC and a valuable prognostic factor for later cognitive outcome, especially for preterm born children. This suggests both mathematic abilities and fronto-parietal networks as potential targets for early intervention. For instance, cortical regions where children's mathematic abilities were positively linked with adults' intra-network iFC in preterm born individuals while they were negatively linked in term born adults (i.e. angular gyrus, middle temporal gyrus), were located in heteromodal association cortices. In this regard, a study by Mueller and colleagues demonstrated both that heteromodal association cortices show the highest inter-subject variability in functional connectivity and are among the regions that best predict inter-individual differences in various cognitive domains (Mueller et al. 2013). Since the phylogenetic and ontogenetic maturation course of such areas is relatively longer compared to that of primary sensory or motor areas, the authors suggest that heteromodal association cortices might be more amenable to the input of variable extrinsic experience, and thus to the input of special educational care. Hence, training programs that foster mathematic reasoning in preterm born children might help to prevent long-term cognitive underachievement. For instance, a recent study in primary-grade normal population school children investigated behavioral and neural predictors of individual differences in maths performance improvements with tutoring (Supekar et al. 2013). Neither pretutorial intelligence, nor working memory or mathematic abilities were able to predict performance improvements. Instead, pretutorial hippocampal volume and hippocampal iFC with basal ganglia and other structures predicted individual performance improvements. However, both hippocampus and basal ganglia are often reported to be affected by preterm birth (Nosarti et al. 2008; Nagy et al. 2009; Bäuml et al. 2014) and thus possibly impairing preterm born children's learning success. Alternatively, intervention programs could target fronto-parietal network development, for example via transcranial magnetic brain stimulation (TMS). For instance, a study by Pitcher and colleagues used TMS to stimulate term and preterm born adolescents' motor cortices (Pitcher et al. 2012). Motor and sensory areas are particularly sensitive to events in late pregnancy and the most common sites of perinatal brain damage (Eyre 2003; Kapellou et al. 2006). Accordingly, Pitcher and colleagues reported reduced motor cortex plasticity in preterm born adolescents in response to TMS stimulation. However, according to the findings by Mueller and colleagues (Mueller et al. 2013), heteromodal fronto-parietal network organization might be more amenable for such kind of in-vivo stimulation assuming that its development is not finished until early adulthood (for review see (Casey et al. 2005)). The question whether preterm birth leads to reduced neuronal plasticity impeding postnatal intervention (Anderson et al. 2009; Anderson et al. 2011) or enabling neural network re-organization over time (Schafer et al. 2009; Myers et al. 2010; Finke et al. 2015) is still unresolved. Future studies should address this question to get new insights into possible intervention strategies.

**Limitations and methodological considerations**

*Study Sample*. The majority of preterm born adults in our sample was born very preterm (< 32 weeks of gestation; 79,7%), yet a significant number of our participants were born moderately or late preterm (32-26 weeks of gestation; 20,3%). We included those participants to cover the whole spectrum of preterm birth and to have a sample that is maximally representative. However, previous studies have shown that depending on the time of birth, different cellular compartments of the brain display a different vulnerability to the deleterious effects of premature brain injury (Kostović et al. 2014a; Kostović et al. 2014b). To pool subjects with different developmental stages during birth together may thus carry the risk of non-uniform brain alterations in the respective sample (Fischi-Gómez et al. 2015). To rule out possible between-group differences in iFC between very preterm (VP; < 32 weeks GA) and moderately to late preterm (MLP; 32-36 weeks GA) adults, we performed post-hoc two-sample t-tests comparing the means of those clusters where we had found a significant interaction of group status and mathematic abilities (see Figure 2, Table S2). There were no significant differences between groups for any of the clusters ($p$ > 0.05).

*ICA.* Despite many advantages, some limitations of the use of ICA to identify intrinsic networks have to be considered. First, our selection of a model order was empirical. Although it has been demonstrated that a model order of about 75 components (as used in this study) seems to be an optimal choice (Kiviniemi et al. 2009; Allen et al. 2011), no clear computational or objective criterion for that number is available. Second, the selection of networks of interest from ICA-derived components is intricate, particularly due to subjective bias. To address this problem, we performed maximally controlled spatial regression analysis of ICs of interest on network templates, based on a previous study using the exactly same analysis approach and based on a large sample of 603 healthy subjects (Allen et al. 2011).

*Maths-related networks.* We found a distinct association of term and preterm children's mathematic abilities and adults' fronto-parietal intra-network iFC. Although this association was specific for left and right fronto-parietal networks (i.e. there was no such association with the executive control and lateral visual networks), it cannot be ruled out that other neurocognitive networks (e.g. the dorsal and ventral attention networks, frontal networks etc.)

showed a similar relation with mathematic abilities in childhood.  Yet, our network selection process was based on a defined behavioral domain characterization (Smith et al. 2009). We used this criterion for two reasons: (i) the four networks identified by Smith and colleagues overlapped with activation networks involved in maths-related domain-general processes such as cognition, attention, working memory, reasoning and visuo-spatial abilities, and (ii) fronto-parietal networks comprised such regions as the angular gyrus, intraparietal sulcus, and superior parietal gyrus that are known to be essential for mathematic reasoning (Dehaene et al. 2003). Future studies could focus on different IBNs to test their relation to cognitive abilities in childhood.

*Neuroradiological abnormalities*: Nine preterm born adults (13%) that took part in our fMRI experiments were diagnosed with intracranial hemorrhage based on cerebral ultrasound findings at the time of birth (n=2 with stage 3, n=4 with stage 2, and n=3 with stage 1). Additionally, some participants exhibited abnormalities on T2* weighted MR images (see Table S5). Abnormalities were present in both term (N = 4) and preterm (N = 9) born adults. To test if these influenced our findings, we repeated our analysis excluding individuals with brain abnormalities; results remained the same.

*Strengths.* Despite these limitations the specific strengths of the present study are noteworthy. The population studied is large, the design is longitudinal, and the link of children's mathematic abilities with adults' iFC considerable. Integrating behavioral and brain measures allows a more comprehensive picture of the long-term consequences of preterm birth.

***Conclusion***

The present study provides first evidence that term and preterm born children's mathematic abilities are differently linked with both cognitive outcome and fronto-parietal brain organization in adulthood. Our data suggest a different functional role of fronto-parietal networks for term and preterm born individuals with respect to mathematic abilities and indicate both early mathematic competence and maths-related fronto-parietal network organization as potential targets for early intervention.

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***Table 1. Sample characteristics***

| | Term group n=72 | | | Preterm group n=74 | | | Statistical comparison |
|---|---|---|---|---|---|---|---|
| sex, (f/m) | 25/47 | | | 31/43 | | | p=.377 |
| | *M* | *SD* | *Range* | *M* | *SD* | *Range* | |
| age (years) | 26.6 | ±0.63 | 25.6-28.9 | 26.6 | ±0.50 | 25.7-27.8 | p=.89 |
| GA (weeks) | 39.76 | ±0.90 | 38-41 | 30.53 | ±2.11 | 25-36 | p<.001 |
| BW (grams) | 3483 | ±410.60 | 2120-4200 | 1381 | ±350.02 | 730-2330 | p<.001 |
| Opti neonatal | 0.33 | ±0.58 | 0-2 | 8.66 | ±2.74 | 1-14 | p<.001 |
| SES | 1.93 | ±0.74 | 1-3 | 1.86 | ±0.75 | 1-3 | p=.59 |
| maternal age | 29.18 | ±5.14 | 18-40 | 29.99 | ±4.29 | 17-41 | p=.31 |
| IQ at age 8 (z) | 0.20 | ±0.92 | -2.17-2.07 | -0.32 | ±1.03 | -2.47-2.27 | p=.002 |
| Maths at age 8 (z) | 0.09 | ±0.67 | -1.4-1.5 | -0.33 | ±0.72 | -2.2-1.1 | p<.001 |
| Full-scale IQ at age 26* | 103 | ±12 | 77-130 | 96 | ±13 | 71-132 | p=.002 |

Abbreviations: m: male; f: female; GA: gestation age; BW: birth weight; Opti neonatal: Optimality score of neonatal conditions; SES: socio-economic status at birth; maternal age: Maternal age at birth; Statistical comparisons: sex, SES: chi-squared statistics; age, GA, BW, maternal age, maths, IQ: t-tests; Opti neonatal: nonparametric Mann-Whitney-U-tests.

*data are based on 72 preterm and 71 full-term subjects, respectively

**Figure Captions:**

**Fig. 1 Association of children's mathematic abilities and adults' full-scale IQ for term and preterm born subjects**

The black line represents the regression line regressing children's mathematic abilities on adults' full-scale IQ for all subjects (term and preterm) (univariate general linear model, factors maths and term birth, control for sex, $p<0.05$). The red/blue lines represent the same regression lines for preterm/term subjects only

Abbreviations: FT: full-term; PT: preterm; y: years

**Fig. 2 Children's mathematic abilities differently predict fronto-parietal intra-network iFC in adulthood in preterm and term born adults**

Voxel-wise ANCOVA of intra-network iFC with factors group and maths was performed controlling for IQ in childhood, sex and Scanner-ID ($p<0.05$, corrected for multiple comparisons). A1. Sagittal, coronal, and axial slices show the post-hoc t-test (blue cluster) of the significant interaction of preterm group status and maths in the left superior frontal gyrus overlaid on a binarized one sample t-test mask ($p<0.001$, uncorrected) of the left FPN (red) for visualization purposes. The color bar below reflects the magnitude of post-hoc t-values with brighter blue colors indicating higher t-values. A2: For visualization scatterplot of the regression lines (red/blue: interaction of preterm group status and maths) regressing children's mathematic abilities on adults' intranetwork iFC are shown (iFC values are based on mean iFC within the respective colored cluster). B1. and C1. The same presentation style for the significant interactions of preterm group status and maths for the clusters in the right angular/middle temporal gyrus (B1.) and left lateral occipital/middle temporal gyrus (C1.). Correspondingly, B2 and C2 depict scatterplots of the regressions depicted in B2 and C2, respectively.

Abbreviations: left/right FPN: left/right fronto-parietal network; FT: full-term; PT: preterm; iFC: intrinsic functional connectivity; a.u.: arbitrary units