Title:

Impaired structural connectivity between dorsal attention network and pulvinar mediates the impact of premature birth on adult visual-spatial abilities

Running title:

Prematurity and DAN-pulvinar connectivity

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Abstract

The dorsal attention network (DAN), including frontal eye fields and posterior parietal cortices, and its link with the posterior thalamus, contribute to visual-spatial abilities. Very premature birth impairs both visual-spatial abilities and cortico-thalamic structural connectivity. We hypothesized that impaired structural DAN-pulvinar connectivity mediates the effect of very premature birth on adult visual-spatial abilities.

70 very premature (median age 26.6 years) and 57 mature born adults (median age 26.6 years) were assessed with cognitive tests and diffusion tensor imaging. Perceptual organization (PO) index of the Wechsler Adult Intelligence Scale-III was used as a proxy for visual-spatial abilities, and connection probability maps in the thalamus, derived from probabilistic tractography from the DAN, were used as a proxy for DAN-thalamic connectivity.

Premature born adults showed decreases in both PO-index and connection probability from DAN into the pulvinar, with both changes being positively correlated. Moreover, path analysis revealed that DAN-pulvinar connectivity mediates the relationship between very premature birth and PO-index.

Results provide evidence for long-term effects of very premature birth on structural DAN-pulvinar connectivity, mediating the effect of prematurity on adult visual-spatial impairments. Data suggest DAN-pulvinar connectivity as a specific target of prognostic and diagnostic procedures for visual-spatial abilities after premature birth.

Keywords: Premature birth, cortico-thalamic connectivity, visual-spatial abilities, perceptual organization index, probabilistic tractography

Abbreviations

DAN Dorsal Attention Network

DTI Diffusion tensor imaging

iFC intrinsic functional connectivity

MB Mature Born

PO-index Perceptual Organization index

Resting-state fMRI resting-state functional magnetic resonance imaging

VC-index Verbal Comprehension Index

VPB Very Premature Born

WAIS-III Wechsler Adult Intelligence Scale-III

Introduction

Very premature birth (VPB), defined as birth before the completion of 32 weeks of gestation and/or with birth weight below 1500g, affects about 1-2% of all live births [Martin et al., 2008; Volpe, 2009a]. VPB infants are at increased risk of perinatal brain injury due to hypoxia-ischemia, infections, inflammatory processes and/or drug exposure [Deng, 2010; Penn et al., 2016]. This increased risk has been attributed to the fact that premature infants are born at a time when many body systems (e.g. the respiratory system, the cardiovascular system, the immune system, and the central nervous system) are not fully developed making them vulnerable to superimposed injury [Volpe, 2009b]. While for 5-10% of surviving VPB children brain changes lead to major motor deficits (e.g. cerebral palsy), 25-50% of VPB infants do not have major motor impairments but cognitive, attentional, behavioral, and social deficits; therefore, cognitive deficits without major motor deficits are the dominant neurodevelopmental sequelae after VPB [Anderson et al., 2003; Breeman et al., 2015; Eryigit Madzwamuse et al., 2015; Larroque et al., 2008; Platt et al., 2007; Volpe, 2009b; Woodward et al., 2005]. In particular, premature born individuals often show impaired visual-spatial abilities, for example impairments in visual attention, non-verbal reasoning, visual-motor integration, and visual-spatial problem-solving [Bohm et al., 2010; Finke et al., 2015; Foulder-Hughes et al., 2003; Leung et al., 2018; Marlow et al., 2007; Menegaux et al., 2017]. Visual-spatial abilities, in turn, are an important prerequisite for learning and educational and academic performance, and thus highly relevant for socio-economic success and life quality [Aarnoudse-Moens et al., 2011; Johnson et al., 2011; Molloy et al., 2017]. A detailed understanding of brain mechanisms that mediate the impact of premature birth on visual-spatial abilities is necessary, as it might be a critical starting point for the development of targeted treatments or prognostic procedures. These brain mechanisms, however, are poorly understood. Thus, the aim

of the present study was to identify brain systems that may mediate between very premature birth and adult visual-spatial abilities.

Previous studies indicated a relation between premature birth, the development of visual-spatial abilities, and brain regions of the dorsal visual stream i.e., posterior occipital and parietal regions being involved in visual-spatial attention and visual-motor integration [Atkinson et al., 2007; Chaminade et al., 2013]. In terms of large-scale functional brain networks, posterior parietal regions of the visual stream overlap most with the dorsal attention network (DAN). The DAN is an intrinsic brain network of coherent ongoing brain activity of the frontal eye fields and intra-parietal sulci, and it underpins attentional top-down control, spatial attention, and visual-motor control [Corbetta et al., 2008; Corbetta et al., 2002; Vossel et al., 2014]. Critically, the development of visual-spatial abilities is linked with the DAN. For example, a recent study demonstrated that the development of selective visual attention in 4 to 7 years - old children are reflected in functional connectivity changes between frontal eye fields and intra-parietal sulci [Rohr et al., 2017]. Consequences of premature birth, which impair visual-spatial abilities, might therefore be mediated by impaired integrity of the DAN. Toward formulating a more specific hypothesis of how prematurity might impact the DAN, we have to recall two points - the primary impact of prematurity on cortico-thalamic connectivity and the role of cortico-thalamic connectivity for cortico-cortical communication within the DAN. (i) Previous studies showed that premature birth has a preferential and lasting impact on cortico-thalamic connectivity [Ball et al., 2013; Ball et al., 2015; Meng et al., 2016]. These connections are formed typically late in intra-uterine development in gestational weeks of about 18-35 under the guidance of both subplate neurons and oligodendrocyte-progenitor cells [Hoerder-Suabedissen et al., 2015; Salmaso et al., 2014; Volpe, 2009a]. The selective vulnerability of subplate

neurons and oligodendrocyte-progenitor cells to hypoxic-ischemic events is thought to lead to impaired cortico-thalamic connectivity and brain network development after premature birth [Back et al., 2001; Bystron et al., 2008; Lopez-Bendito et al., 2003; Volpe, 2009a], with connectivity and network impairments persisting into adulthood [Bauml et al., 2015; Meng et al., 2016; Sripada et al., 2015]. (ii) Coordinated cortico-cortical communication within the DAN depends on cortico-thalamic control, and thereby on structural cortico-thalamic connectivity [Daitch et al., 2013; Saalmann, 2014; Sherman, 2016]. For example, Saalmann et al. [2012] demonstrated in monkeys, that the pulvinar's structural connectivity with distinct cortical regions of the DAN regulates cortico-cortical communication according to visual attention selection, demonstrating the pulvinar as part of the DAN.

Based on both the impact of premature birth on cortico-thalamic connectivity and the role of the pulvinar for DAN cortico-cortical communication, we hypothesized that structural connectivity between pulvinar and the DAN mediates the impact of premature birth on visual-spatial abilities. As a proxy for visual-spatial functioning, we used the perceptual organization (PO) index of the Wechsler Adult Intelligence Scale [Von Aster M, 2006] – an integrative measure which reflects visual-spatial processes, problem-solving, non-verbal reasoning and visual-motor integration [Lange, 2011]. As a proxy for structural connectivity between the pulvinar and the DAN, we used connection probability maps in the thalamus, which were derived from diffusion tensor imaging (DTI) data, and probabilistic tractography from the DAN into the thalamus. The DAN was defined for each participant by individual resting-state functional connectivity maps, derived from resting-state functional MRI (resting-state fMRI); the thalamus was defined by canonical anatomical atlas. PO-index assessment, resting-state fMRI, and DTI were applied in a sample of 70 VPB and 57 mature-born (MB) adults at the age of

26 years. Connection probability values were associated with prematurity at birth and PO-index at the age of 26 years via correlation and mediation analysis. Finally, to investigate the relevance of PO-index and DAN structural connectivity for educational performance, we explored the possible link between structural alterations, PO-index and educational success at the age of 26 years as well as the role of structural alterations as a potential mediator between prematurity and educational success.

Materials and Methods

Sample and clinical-cognitive measures

Participant description

Participants were recruited as part of the prospective Bavarian Longitudinal Study (BLS) [Riegel et al., 1995; Wolke et al., 1999]. The BLS investigates a geographically defined whole-population sample of neonatal at-risk children and healthy term born controls. All live-birth infants who were born between January 1985 and March 1986 in Southern Bavaria and required admission to a neonatal unit of 17 children's hospitals within the first ten days of life comprised the target sample [Wolke et al., 1999]. A total of 7505 children (10.6% of all live births) were classified as neonatal at-risk children, of whom 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 hospitals were recruited as control infants. Over the following years, subjects of both groups were repeatedly assessed via neurological and psychological tests and parental interviews. Full design of the BLS is provided elsewhere [Gutbrod et al., 2000; Wolke et al., 1999]. At 26 years of age and based on the study design of premature born population versus reference population, all eligible 411 surviving VPB and 308 MB adults, similar regarding the overall distribution of gender, family socioeconomic status (SES), and maternal age, were invited for a follow-up assessment and of these 260 VBP and 229 MB adults participated at 26 years of age [Eryigit Madzwamuse et al., 2015]. 183 subjects underwent structural T1- and diffusion-weighted MRI as well as resting-state fMRI. MRI assessments were carried out at two different sites: The Department of Neuroradiology, Klinikum Rechts der Isar, Technische Universität München, Germany, and the Department of Radiology, University Hospital Bonn, Germany. The study was approved by the local ethics committees of the Klinikum rechts der Isar and University Hospital Bonn in

accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. All study participants gave written informed consent and received travel expenses and a payment for attendance. The following inclusion criteria were applied: normal or corrected-to-normal vision, free from non-correctable reduction of sight in either eye, from medication, from psychiatric or neurological diseases at the assessment or qualitative signs of brain injury (such as ventriculomegaly or polymicrogyria). Exclusion criteria were poor structural, diffusion, or functional MRI data quality, or dropout of MRI acquisition.

A full description of the sample, which underwent DTI (n=183), and corresponding details about exclusion (n=29) can be found in [Meng et al., 2016]. Further 27 subjects were excluded because of missing resting state fMRI acquisition (n=11) and/or head motion artifacts (n=16) in the resting state fMRI acquisition. Thus, the current study sample consists of 70 VPB adults and 57 MB adults (see Table 1 for more details).

Birth-related variables

Gestational age was estimated from maternal reports of the last menstrual period and serial ultrasounds during pregnancy. Further clinical assessment with the Dubowitz method was applied in case of a variation of these two measures by more than two weeks [Dubowitz et al., 1970]. Birth weight was obtained from obstetric records. The intensity of neonatal treatment index as a measure of neonatal complications was ascertained by daily assessments of care level, respiratory support, feeding dependency and neurological status [Casaer P, 1985].

Assessment of Cognitive Performance and Educational Success

Cognitive performance at the age of 26 years was assessed by independently trained psychologists using the German version of the Wechsler Adult Intelligence Scale-III (WAIS-III), including our measure-of-interest, namely PO-index [Von Aster M, 2006]. The psychologists were blinded to group membership. Full-Scale Intelligence Quotient (IQ) as a measure of global cognitive functioning as well as Verbal Comprehension Index (VC-index) was additionally derived from WAIS-III.

Educational and occupational accomplishments were asked at the age of 26 years in a life course interview, similar to the German Socioeconomic Panel Study [Frick JR, 2007; Wagner et al., 2007]. Educational success was categorized into four levels: 1=basic educational level (up to 10 years of schooling; no further education or apprenticeship), 2=middle educational level (up to 10 years of schooling and profession-oriented education (10+ years)), 3=higher educational level (high school (12+ years) giving access to higher education, i.e. university access qualification), and 4=university degree (undergraduate or postgraduate).

MRI Data Acquisition

MRI data were acquired on 3T Philips scanners in Munich and Bonn (Achieva (Philips Medical System, Netherlands) and Ingenia (Philips Medical System, Netherlands)) with standard 8 channel head coils using consistent sequences and parameter settings across scanners. To account for different scanners in data analyses, scanner identities were included in the analyses as covariates of no interest. (i) For all subjects, diffusion images were acquired using a single-shot spin-echo echo-planar imaging sequence, resulting in one non-diffusion weighted image (b = 0 s/mm2) and 32 diffusion weighted images (b = 1000 s/mm2, 32 non-collinear gradient directions) covering whole brain with following parameters: echo time (TE) = 47 ms, repetition time (TR) = 20,150 ms,

flip angle = 90°, field of view = 224 x 224 mm^2, matrix = 112 x 112, 75 transverse slices, slice thickness = 2 mm, and 0 mm interslice gap, voxel size = 2 x 2 x 2 mm^3. (ii) A whole-head, high-resolution 3D gradient echo T1-weighted image was acquired using the following parameters: echo time (TE) = 3.9 ms, repetition time (TR) = 7.7 ms, flip angle = 15°, field of view = 256 x 256 mm^2, matrix = 256 x 256, 180 sagittal slices, slice thickness = 1 mm, and 0 mm interslice gap, voxel size = 1 x 1 x 1 mm^3. (iii) Resting-state fMRI data were 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 × 63, 41 slices, thickness 3.58 and 0 mm interslice gap, reconstructed voxel size = 3.59 × 3.59 × 3.59 mm^3) resulting in 250 volumes of BOLD fMRI data for each subject. Immediately before undergoing the resting-state sequence, subjects were instructed to keep their eyes closed and to restrain from falling asleep.

Individual DAN definition via resting-state fMRI analysis

To identify for each participant individual DAN as the mask for subsequent structural connectivity tractography, we performed resting-state fMRI data analysis, including group independent component analysis and dual regression analysis via FSL (FMRIB Software Library, Oxford, UK, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki, [Jenkinson et al., 2012]). For each participant, the first 5 functional scans of each resting-state fMRI session were discarded due to magnetization effects. Data were then preprocessed using FSL [Jenkinson et al., 2012]. Functional volumes were realigned to correct for head motion [Jenkinson et al., 2012] and non-brain tissue was removed using BET [Smith, 2002]. Following, spatial smoothing was applied using a Gaussian kernel of FWHM 5 mm, and data were high-pass temporal filtered (200s). Each subject's fMRI data were subsequently coregistered to that subject's high-resolution structural T1 image by using boundary-based registration [Greve et al., 2009]. The remaining data

were then transformed to MNI space at 2 x 2 x 2-mm resolution using nonlinear registration [Andersson et al., 2007]. To ensure comparable data quality across groups, particularly concerning motion-induced artifacts, point-to-point head motion was estimated for each subject [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 ($P = 0.43$).

Individual DAN maps were derived from resting-state fMRI data following a multi-step procedure: first, we parcellated the cortex into distinct intrinsic brain networks (IBNs) using independent component analysis (ICA). For this purpose, preprocessed data from both groups were concatenated in time and entered into a single group ICA framework as implemented in FSL MELODIC [Beckmann et al., 2005]. We used a fixed dimensionality of 25 spatially independent components. To identify the DAN component, the spatial correlations between the DAN template, provided by Allen and colleagues [2011], and the components identified in our sample were calculated. The sub-component with the highest correlation score (Allen IC72; $r = 0.32$) was used for further analysis. The DAN component was then mapped back to each subject's dataset through dual regression [Filippini et al., 2009] to obtain subject-specific DAN maps. Specifically, back-projected maps were thresholded ($Z > 5$) and the resulting DAN maps were used as regions-of-interest (ROIs) for fiber tracking.

We performed the same procedure in order to identify further networks (namely, the posterior and anterior Default Mode Network (DMN, IC50/53/25), sensorimotor network (SMN, IC23/24/29), salience network (SN, IC55), auditory network (IC17), visual (IC46) and lateral visual network (IC48) and frontal networks (IC42/20)), which

were used later to test for specificity of impaired structural connectivity between DAN and pulvinar and its mediating role for the effect of VPB on adult PO-index.

Functional connectivity analysis – control analyses

(i) In order to control that DANs across groups were comparable and do not confound group differences in structural connectivity between DAN and thalamus, we compared DANs' intra-network connectivity. We used ICA/dual-regression based individual DAN maps as proxies for intra-network functional connectivity of the DAN, and applied firstly, one sample t-tests for DANs' of MB and VPB adults, respectively, to visualize DAN of each group (see supplemental Figure 1). After that we used a two-sample t-test to compare DANs' functional connectivity across groups.

(ii) In order to control whether *structural* connectivity changes between DAN and pulvinar in the VPB group were specific for modality, we analyzed the functional connectivity between DAN and thalamus and compared it across MB and VPB groups. To define cortico-thalamic functional connectivity, we relied on previously applied partial correlation approach of our group on functional connectivity as described in [Avram et al., 2018]. More specifically, we used a voxel-wise partial correlation approach to map intrinsic functional connectivity (iFC) between each voxel in the thalamus and characteristic time series associated with a specific cortical ROI, in each case regressing out the time series of all other cortical ROIs, the signal in white matter and cerebrospinal fluid as well as head motion parameters [O'Reilly et al., 2010]. These analyses were performed in native space to reduce spatial inaccuracy introduced by suboptimal normalization [O'Reilly et al., 2010]. For each subject the component maps (i.e. the ROIs) were thresholded at $Z > 5$, and the remaining voxels inside the mask were used to extract the first Eigen time series from the preprocessed individual

functional data. In a second step, masks representing white matter and cerebrospinal fluid were created using FSL tissue segmentation tool FAST [Zhang et al., 2001] and transformed into individual functional space. Both WM and CSF masks were thresholded at $P > 0.5$, and the remaining voxels inside each mask were used to extract the first Eigen time series from the preprocessed individual functional data. For every subject, these procedures resulted in 12 component Eigen time series (i.e. one per component) and two Eigen time series representing WM and CSF. In a last step, we extracted the subject-specific 6 head motion parameters which were estimated with MCFLIRT [Jenkinson et al., 2002]. Finally, a thresholded thalamus mask ($P > 0.3$) was created using the Harvard-Oxford Subcortical Structural Atlas in FSL and transformed back into individual functional space. This partial correlation procedure resulted in one partial r-map per component and subject (total: 12 x 176) that were subsequently converted to Z values using Fisher's r-to-z transformation.

Before performing group analyses, thalamic Z maps were transformed back into Montreal Neurological Institute space using nonlinear registration implemented in FNIRT. To statistically evaluate network-specific thalamic iFC, for each group (term and preterm) and each cortical ROI, we calculated voxel-wise one-sample t-tests on participants' thalamic Z maps using SPM 8 controlling for sex and scanner-ID ($P < 0.05$, FDR corrected). Group differences in DAN-thalamus iFC were tested via voxel-wise two-sample t-tests using SPM 8 controlling for sex and scanner-ID ($P < 0.05$, FDR corrected).

To relate between group differences in DAN-thalamus iFC to PO-indices, we used the following approach: voxels whose iFC differed significantly between groups were saved as images in SPM 8. After binarization, ROI-restricted network-specific iFC was extracted and averaged subject-wise with Matlab-based in-house software. This procedure resulted in one mean iFC Z-value per cluster and subject. Then, this

thalamo-cortical iFC was used to predict PO-index within a multiple regression model using SPSS 24 with further regressors being sex and scanner-ID.

Diffusion MRI Data Processing

DTI data were processed using FSL [Jenkinson et al., 2012] applying the following steps: DTI preprocessing including eddy current and head motion correction by coregistrating all diffusion-weighted images to b0 image, DTI data quality check based on visual inspection by several independent raters (B.M., B.J., C.S.), reconstruction of the distribution of diffusion directions at each voxel, probabilistic tractography and analysis of connection probability as explained in the following.

DTI preprocessing and quality check

Diffusion data were preprocessed using FSL's FDT toolbox. Eddy-current distortion and head motion were corrected by linear registration of all diffusion-weighted images to the first b0 volume using FSL "eddy_correct". Brain-tissue extraction was performed by removing the skull and non-brain tissue using FSL BET [Smith, 2002].

Each image was visually checked by three independent raters (C.M., C.S., A.M.) and fitting residuals (the sum-of-squared-error maps generated by FSL DTIFIT) were used to identify data corrupted by artifacts. Detailed information about the exclusion process can be found in Meng et al. [2016].

Seed and target definition for tractography

Before applying probabilistic tractography, seed and target ROIs were defined, based on the study´s hypothesis. The seed for tractography was placed in individual DAN derived from resting-state fMRI data analysis (see above), its target into the bilateral thalamus. The target ROI was taken from the Oxford thalamic connectivity atlas, based

on the probability of anatomical connections between thalamus and cortex in MNI space [Behrens et al., 2003].

Each subject´s native 3D T1-weighted image was brain extracted by removing the skull and non-brain tissue using FSL BET [Smith, 2002] as well as bias-corrected using FAST (FMRIB's Automated Segmentation Tool). A two-step transformation procedure was used to register these T1-weighted images to the MNI ICBM 152 non-linear (6th Generation) symmetric standard-space T1-weighted average structural template image [Grabner et al., 2006]. In the first step, linear (affine) transformation was performed using FLIRT (FMRIB's Linear Image Registration Tool), then the generated affine transform was used as a guide for non-linear registration using FNIRT (FMRIB's Non-Linear Image Registration Tool). The output of this transformation procedure was an individual native to standard (MNI space) non-linear warp field.

The brain-extracted b0-image of each subject was registered to the corresponding brain extracted and bias-corrected T1 image in native space using linear registration (FLIRT) with twelve degrees of freedom and correlation ratio cost function. This individual diffusion-to-native transformation matrix was combined with the above described native-to-standard non-linear transformation matrix, that resulted in diffusion-to-standard space transformations and their corresponding inverses. These warp-fields were then applied to the ROI masks of seed and target (in standard MNI space), namely DAN and thalamus, to align them into each subject’s individual diffusion space with the implementation of nearest neighbor interpolation, followed by a visual check by an experienced neuroradiologist (M.B.).

Probabilistic fiber tracking and connection probability

Probabilistic tractography was used to get cortico-subcortical connection probabilities between DAN and thalamus (Figure 2A). To estimate the fiber orientations, the distribution of diffusion directions at each voxel was reconstructed by the use of BEDPOSTX (Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques, FSL) with two crossing fibers modeled per voxel [Behrens et al., 2007]. Probabilistic tractography was performed using PROBTRACKX2 (probabilistic tracking with crossing fibres, FSL) using the following parameters: number of samples = 5000, step length = 0.5 mm, curvature-threshold = 0.2, subsidiary fiber volume fraction threshold = 0.01. By creating probabilities of an existing path in the diffusion field of each subject between individual DAN, used as seed ROI, and thalamus, used as waypoint ROI, a surrogate measure of white matter connectivity was created [Behrens et al., 2007; Jbabdi et al., 2011]. As a previously used step of normalization, the resulting individual streamline maps were divided by the total number of generated tracts of each individual tractography ("waytotal"), taking into account the high inter-subject variability of these tracts as well as ROI-sizes [Arnold et al., 2012; Rus et al., 2017; Zhang et al., 2010].

Based on Behrens et al. [2003], a map of thalamic voxels containing information about the probability of connectivity with the DAN was extracted for each subject. That was used for identification of thalamic substructures that exhibit group differences, and also for correlation analyses between these connectivity values and clinical-neuropsychological data. To enable inter-subject comparisons, the thalamic connectivity maps were warped into MNI space using the above-mentioned diffusion-to-standard space transformations with the implementation of nearest neighbor interpolation.

Statistical Analysis

Concerning voxel-wise connection probability maps in the thalamus, voxel-wise one- and two-sample t-tests were performed for VPB and MB adults, using SPM8 and controlling for sex and scanner identities ($P < 0.05$, FWE-cluster corrected). Connection probability values of group difference clusters were extracted and averaged using Matlab-based in-house software and used for further correlation and mediation analyses.

Mediation analysis

Mediation analysis was carried out to test whether structural connectivity alterations between individual DAN and pulvinar mediate the effect of group (VPB vs. MB adults) on PO-index. In the mediation model, group affiliation was entered as the causal variable, PO-index as the outcome variable and residuals from structural connectivity values as the mediator variable. These residuals were calculated by regressing out the effects of sex and scanner identities, in order to control for effects of these variables on mediation. Path coefficients were estimated using (unstandardized) regression coefficients of multiple regression analyses. Statistical significance of the indirect pathway, reflecting the impact of mediation, was evaluated using a non-parametric bootstrap approach with 10.000 replication samples to obtain a 95% confidence interval [Hayes et al., 2017; Preacher et al., 2004].

Analyzing the relevance for educational success

To explore, whether adult PO-index and DAN-pulvinar connectivity might be relevant for educational performance after premature birth, we tested the relationship between prematurity, educational success, PO-index, and DAN-pulvinar connectivity, respectively. Mann-Whitney-U-test was used to estimate the impact of premature birth

on educational success. Spearman rank correlation was applied to quantify the relationship between PO-index and educational success. After performing linear regression to get residuals of the connectivity values (corrected for sex and scanner identities), Spearman rank bivariate correlation was performed with PO-index and educational success. Mediation analysis was carried out to test whether structural connectivity alterations between individual DAN and pulvinar mediate the effect of group (VPB vs. MB adults) on educational success.

Results

Lowered perceptual organization index in very premature born adults

PO-index in VPB adults (93.78 ± 14.11) was lower than in MB adults (106.39 ± 12.11, $p<0.001$, two-sample t-test) (Figure 1).

Reduced connection probabilities from the DAN to the pulvinar of very premature born adults

Qualitatively, connection probability maps of the DAN into the thalamus were similar between VPB and MB groups, justifying group comparison (Figure 2B; one-sample t-tests, $p<0.05$ FWE-cluster corrected). In more detail, peak voxels of both groups were located in the pulvinar and the overall pattern covered posterior thalamic parts. However, quantitative two-sample t-test revealed decreased connection probability from the DAN to the pulvinar in VPB adults ($p < 0.05$, FWE-cluster corrected) (Figure 2C). To control that group different DAN-pulvinar structural connectivity was not due to group different DANs as defined by functional connectivity (see Supplemental Figure 1), we compared DAN functional connectivity maps across groups. We did not find any group difference, suggesting that DANs were comparable across groups, with distinct spatial outline of DANs being unlikely to confound group differences in DAN-pulvinar structural connectivity.

Structural connectivity changes mediate the effect of prematurity on perception

In a mediation analysis (Figure 3), the effect of group (VPB vs. MB) on adult PO-index (total effect $c = 12.61 \pm 2.38$, $p < 0.001$) was still present, but reduced when controlling for DAN-pulvinar connection probability (direct effect $c' = 10.84 \pm 2.55$, $p<0.001$); critically, the bootstrapped 95% confidence interval for the indirect effect (i.e., mediation: total - direct effect) was different from zero (CI: 0.26 – 4.03), indicating that

DAN-pulvinar connectivity significantly mediated the relationship between very premature birth and PO-index performance.

Control analyses – specificity: (i) Next, we tested whether the mediating role of impaired DAN-pulvinar connectivity for the association between premature birth and visual-spatial functioning was specific for visual-spatial functioning i.e., PO -index. Therefore, we repeated our mediation approach on DAN-pulvinar connectivity but now focusing on verbal instead of non-verbal visual-spatial abilities. Specifically, we performed again a mediation analysis for DAN-pulvinar connectivity but with the VC-index of the WAIS as outcome/dependent variable, which reflects verbal abilities. Verbal functioning is thought to depend more on lateral fronto-parieto-temporal networks than the dorsal fronto-parietal DAN [Lau et al., 2008]. First, we found a significant reduction of the VC-index in the VPB group ($p<0.05$; Table 1). Then we performed path analysis for VC index in the exact same way as for PO index. Critically, we found, that the bootstrapped 95% confidence interval for the indirect effect of DAN-pulvinar on VC index covered the zero (CI: -1.35 – 3.27), indicating that DAN-pulvinar connectivity does not mediate the link between prematurity and verbal intelligence. This finding supports the notion of the specificity of DAN-pulvinar connectivity to mediate prematurity effects on PO-index, with respect to other cognitive impairments such as verbal abilities in VPB.

(ii) Next we tested whether DAN-pulvinar connectivity plays a specific role for distinguishing VPB from MB adults. Therefore, we tested global network connectivity, defined by averaging the connectivities of all networks, except DAN-pulvinar, for each individuum at thalamus connectivity map level, and searched for group difference in the global connectivity map between VPB and MB adults. No group difference ($p<0.05$,

FWE-cluster corrected) could be found, indicating no main difference in the global cortico-thalamic connectivity between VPB and MB adults. By analyzing the single networks (such as posterior and anterior DMN, sensorimotor network (SMN), salience network (SN), auditory network, visual networks and frontal network) and their connectivity to the thalamus, we found decreased connection probability from the lateral visual network, the salience network, and the anterior DMN into the posterior thalamus for VPB adults ($p < 0.05$, FWE-cluster corrected).

However, the relationships between PO-index and the group different structural connectivity probability clusters from the lateral visual network into the thalamus ($r=0.05$, $p=0.66$), anterior DMN ($r=0.001$, $p=0.99$), and the salience network ($r=-0.23$, $p=0.06$), respectively, were not significant, supporting the specificity of DAN-pulvinar connectivity and its link with PO-indices.

(iii) Finally, we tested whether the mediating role of DAN-pulvinar structural connectivity for the VPB effect on PO-index was specific with respect to DAN-pulvinar *structural* connectivity. As control modality of connectivity, we chose functional connectivity between DAN and the thalamus. Voxel-wise two-sample t-tests indicated that DAN-thalamus iFC was not significantly different between MB and VPB adults (see supplemental Figure 2). However, our results suggest a trend to significance ($p = 0.071$) where VPB adults show an increased DAN-pulvinar iFC. Moreover, correlation analyses indicated that aberrant DAN-pulvinar iFC was not associated with PO-index measures, neither within term ($r = -0.11$, $p = 0.40$), nor within VPB adults ($r = -0.01$, $p = 0.94$). This result indicates that specifically the impaired structural connectivity between DAN and pulvinar is linked with PO-indices.

DAN-pulvinar connectivity, premature birth, and educational success

Finally, to investigate the relevance of reductions in both visual-spatial abilities and related DAN-pulvinar connectivity for educational performance after premature birth, we analyzed whether PO-index and DAN-pulvinar connectivity are related to educational success after premature birth. First, we found a positive correlation between PO-index and educational success in VPB adults ($r = 0.3$, $p = 0.012$), demonstrating a link between visual-spatial abilities and educational success. Then, we saw that DAN-pulvinar connectivity was associated with both PO-index ($r = 0.27$, $p = 0.03$) and educational success ($r = 0.28$, $p = 0.02$) for VPB adults. This final result supports the idea that prematurity, educational success, and PO-index abilities are linked by impaired DAN-pulvinar connectivity. Indeed, in a mediation analysis, the effect of group (VPB vs. MB) on educational success (total effect $c = 0.28 \pm 0.15$, $p = 0.06$) was still present, but reduced when controlling for DAN-pulvinar connection probability (direct effect $c' = 0.13 \pm 0.16$, $p = 0.43$). The bootstrapped 95% confidence interval for the indirect effect was different from zero (CI: 0.04 – 0.30), indicating that DAN-pulvinar connectivity significantly mediated the relationship between very premature birth and educational success.

In order to estimate which type of ability is more linked to educational success, we compared correlation coefficients for both VC- and PO-indices by the use of Fisher-z-testing. We found no significant differences between the two correlations ($z=-1.7$, $p=0.09$). This indicates that not only visuo-motor but also verbal comprehension abilities are relevant for educational success.

Discussion

Using cognitive assessment and diffusion MRI in very premature and mature born adults, we tested the hypothesis that aberrant structural connectivity between the pulvinar and dorsal attention network mediates the effect of very premature birth on impaired visual-spatial functioning in adulthood. In VPB adults, the perceptual organization index, which reflects visual-spatial skills and problem-solving, was reduced, as well as DAN-pulvinar connectivity. Critically, DAN-pulvinar connectivity partially mediated specifically the link between prematurity and adult PO-index. To the best of our knowledge, this result is the first one outlining a specific neural system mediating adverse effects of very premature birth on visual-spatial functioning. Our finding defines a specific target – DAN-pulvinar connectivity – to develop focused treatment or prognostic strategies to improve long-term visual-spatial functioning after premature birth. Next, we discuss these points in more detail.

Aberrant DAN-pulvinar connectivity mediates prematurity effects on adult visual-spatial abilities

The main result of the current study is that impaired DAN-pulvinar connectivity mediates the effect of very premature birth on adult PO-index (Figure 3). This finding is based on three elements – (i) the effect of prematurity on PO-index, (ii) impaired DAN-pulvinar connectivity, and (iii) the proper mediation function of this connectivity.

(i) Impaired PO-index after premature birth. PO-index was reduced in VPB adults (Figure 1). PO-index is derived from the Wechsler Adult Intelligence Scale (WAIS) [Von Aster M, 2006], and measures visual-spatial processes and problem-solving, nonverbal fluid reasoning, and visual-motor integration [Lange, 2011]. Therefore, PO-index is an integrative measure of visual-spatial functioning, which interacts with more specific functions such as visual attention (including for example visual short-term

memory capacity or top-down attentional weighting) or visuo-motor integration (including for example control of eye movements) [Kimchi, 2009]. Impaired visual attention and visuo-motor integration, in turn, are common findings in premature born children [Butcher et al., 2012; Foulder-Hughes et al., 2003; Goyen et al., 2011; Marlow et al., 2007] and seem to persist into adulthood [Breeman et al., 2015]. Correspondingly, specifically impaired visual short-term memory capacity was found for a subsample of the current sample [Finke et al., 2015]. It might be that these attentional and visuo-motor deficits trace back to early impairments in newborns; for example, Papageorgiu and colleagues demonstrated that the individual differences in eye fixation duration of newborns predict attentional and visuo-motor control deficits in childhood [Papageorgiou et al., 2014].

(ii) Impaired DAN-pulvinar structural connectivity. We found reduced connection probabilities in the pulvinar from the DAN in VPB adults (Figure 2). In the mature born adults, peak values of connection probabilities from the DAN focused on the posterior thalamus (Figure 2B), being in line with both anatomical connections between the posterior parietal cortex and the pulvinar [Fischer et al., 2012] and recent diffusion-based tractography results of thalamo-cortical connectivity [Kumar et al., 2017]. In the VPB group, connection probability maps were qualitatively similar to those of the mature born group, indicating that DAN-thalamus connectivity was not substantially re-organized in the VPB group, but with changes being focused on the pulvinar (Figure 2B and C). Our analysis of cortico-thalamic structural connectivity was based on individually defined DANs via resting-state fMRI and corresponding ICA/dual regression analysis (Figure 2A). We performed this approach in order to increase individual specificity of DAN tractography. One should note that such an approach includes the possibility for individual DAN detection by resting-state fMRI, a possibility that might be relevant for individual treatments of the DAN-pulvinar system (see below

for more details). The finding of impaired DAN-pulvinar structural connectivity corresponds with more generally impaired thalamo-cortical structural connectivity after premature birth, as explicitly shown in premature born newborns [Kostovic et al., 2010] and children [Ball et al., 2013; Ball et al., 2015], and implicitly suggested in adults [Meng et al., 2016; Sripada et al., 2015]. In more detail, only extended white matter changes have been demonstrated for premature born adults so far, but the current study demonstrates directly impaired thalamo-cortical connectivity.

(iii) Impaired DAN-pulvinar connectivity as mediator for the prematurity effect on PO-index. DAN-pulvinar connectivity partly mediated the effect of very prematurity on PO-index (Figure 3). The mediating role of DAN-pulvinar structural connectivity was threefold specific - specific for PO-index but not for reduced VC-index, specific for the DAN but not for global connectivity or other networks - thalamic connectivities, and specific for structural connectivity but not for the functional connectivity between DAN and the thalamus. The absent group differences between VPB and MB adults for global connectivity values show that the DAN-pulvinar connectivity changes are specific for VPB and not simply a reflection of a wider reduction of cerebral connectivity. The functional connectivity analysis showed a trend to increased DAN-pulvinar iFC for VPB adults, maybe due to increased variance in regional BOLD fluctuations on the basis of a structural integrity change with decreased structural connectivity.

Furthermore, impaired DAN-pulvinar connectivity was unlikely confounded by distinct DANs across groups, as we did not find any group differences for DANs' functional connectivity maps. The pulvinar is known to control cortico-cortical communication, especially within the dorsal attention network [Saalmann, 2014; Shipp, 2003]. For example, in monkeys, the pulvinar's structural connectivity with the DAN is associated with attention selection via controlling cortico-cortical communication [Saalmann et al., 2012]. Reduced structural connectivity between DAN and pulvinar after premature birth

may reflect impaired development of thalamo-cortical connectivity and consequently impaired coordination of cortico-cortical communication. For example, Ball and colleagues showed that impaired thalamo-cortical connectivity of neonates was predictive for cognitive performance at the age of 2 years [Ball et al., 2013; Ball et al., 2015]. Future studies have to test this idea in more detail.

One should note that our analysis revealed a partial mediation effect of DAN-pulvinar on the association between prematurity and PO-index, suggesting further brain mechanism to mediate prematurity effects on visual-spatial functioning. Due to the complexity of visual-spatial functioning in general and PO-index in particular, it is not surprising that multiple mechanisms underpin these abilities. For example, we previously found impaired visual attention, specifically reduced visual short-term memory capacity in VPB adults, that was associated with impaired integrity of connections between the posterior thalamus and the primary occipital gyri [Menegaux et al., 2017]. This result indicates that structural connectivity of more posterior occipito-thalamic systems also contributes to prematurity effects on visuo-motor functioning. Furthermore, beyond structural connectivity, coherence of ongoing slowly fluctuating activity in both DAN and occipital networks covering primary occipital gyri has been shown to modulate impaired visual short-term memory after premature birth, indicating that physiological mechanisms on top of structural connectivity link with impaired visual-spatial abilities in the context of prematurity [Finke et al., 2015]. An example for such physiological mechanism might be alterations in local temporal variability of ongoing activity within the thalamus - as being found in premature born adults (Shang et al., 2019) -, which impair functional integration in cortico-thalamic networks (Garrett et al., 2018). It is clear, that this list of potential mechanisms is not exhaustive; in order to increase potential targets for ‘clinical’ procedures such as treatment or prognostics

of visual-spatial deficits, future studies are necessary to reveal further brain mechanisms mediating prematurity effects on visual-spatial functioning.

Relevance for educational success

Visual-spatial abilities are basic abilities for other cognitive functions, learning, and thereby for educational success, which in turn are important determinants of socio-economic status [Fernandes et al., 2016; Haapala et al., 2014; Piaget, 1952]. In line with this knowledge, we found a positive correlation between PO-index and educational success in adulthood, suggesting a link between PO-index relevant abilities such as visual-spatial skills, problem-solving and educational performance.

By comparing correlation coefficients for both VC- and PO-indices, no significant differences indicate that bot visuo-motor and verbal comprehension abilities are relevant for educational success. This result specifies our finding for PO-index and its dependence on DAN-pulvinar connectivity further, in terms of partial relevance amongst other factors such as verbal comprehension.

Furthermore, DAN-pulvinar connectivity, that was found to be impaired for VPB adults, is positively correlated with PO-index and educational success. This finding suggests that structural connectivity alterations caused by prematurity contribute to perceptual as well as educational outcome.

A link between premature birth and less favorable academic outcome has been demonstrated for several times [Aarnoudse-Moens et al., 2011; Johnson et al., 2011; Leung et al., 2018; Molloy et al., 2017]. In the present study, this correlation between prematurity and lower educational outcome in adulthood was mediated by adult DAN-pulvinar connectivity. This finding together with the role of DAN-pulvinar connectivity for visual-spatial functioning after premature birth suggests the model that prematurity-

induced changes in DAN-pulvinar connectivity lead to impaired visual-spatial functioning, which in turn is relevant for educational success. This model is supported by above-mentioned findings of Ball and colleagues, indicating the predictive role of neonatal thalamo-cortical connectivity for later attention functioning [Ball et al., 2015]. Furthermore, changes in functional connectivity within the DAN were linked with both DAN development from 4-7 years and corresponding development in selective attention of 4-7 years old girls [Rohr et al., 2017].

Integrating these findings, we suggest that DAN-pulvinar connectivity after premature birth might have some potential for targeted clinical procedures such as specific treatment of developing visual-spatial and visual-motor functioning or predicting the development of visual-spatial abilities at birth. (i) Concerning treatment: Targeted brain stimulation, especially transcranial magnetic stimulation (TMS) of cortical DAN structures might be of interest when combined with appropriate visual-motor training. (ii) Concerning prediction of visual-spatial abilities at birth: use at birth DAN-pulvinar structural connectivity could be helpful to predict later visual-spatial abilities, that is in line with the above-mentioned studies. However, based on these preceding as well as current findings, further studies are needed to derive a concrete concept useful for the prediction of visual-spatial abilities.

Strength and limitations

Some points should be considered when interpreting our results. First, the current sample might be biased to VPB adults with less severe neonatal complications and less functional impairments. Individuals with stronger birth complications and/or severe lasting impairments in the initial BLS sample were more likely to be excluded in the initial screening for MRI or to reject MRI scanning or even continuation in the study.

Thus, reported differences in outcomes including DAN-pulvinar connectivity between VPB and MB adults are conservative estimates. Second, the current sample size is rather large (70 VPB, 57 MB), enhancing the generalizability of our findings.

Third, the study was performed with the existing methodologies of structural connectivity analysis to the point of time when acquiring the data and postprocessing them with well-established software. Recently developed techniques are not possible to apply on these data but should be performed for consequential studies in future, e.g. correction for susceptibility-induced geometric distortions.

A further limitation of the study is the use of three distinct MRI scanners to acquire diffusion data. However, all of them were 3T Phillips scanners of the same type with standard 8 channel head coils using identical sequences and parameter settings. Furthermore, to account for potential confounds induced by different scanners, scanner identities were statistically integrated as covariates of no interest in distinct data analyses, demonstrating no essential influence of scanner types in our findings.

Conclusion

Impaired DAN-pulvinar structural connectivity makes a major contribution to the impact of very prematurity.

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Tables:

Table 1 Demographics and neuropsychological data

		VPB (n = 70)			**MB (n = 57)**			
Age (year)		median 26.57 (range 25.72-27.76)			median 26.60 (range 25.58-27.89)			
Gender (m/f)		n (41/29)			n (35/22)			
		mean	**SD**	**IQR**	**mean**	**SD**	**IQR**	**p-value**
Gestational age (week)		30.23	1.95	29-31	39.63	0.99	39-40	<0.001
Birth weight (g)		1300.57	321.81	1045-1496	3471.39	358.01	3210-3715	<0.001
INTI		6.44	2.09	4.27-8.09	-			
intracranial hemorrhage		n=13			-			
Full-scale IQ		94.41	12.86	86-100	102.88	12.16	95-111	<0.001
PO-index		93.78	14.11	83-104	106.39	12.11	96-114	<0.001
VC-index		104.23	14.51	95-111	109.54	15.03	98-122	0.048
Educational success		2.79	0.85	2-4	3.07	0.88	2-4	0.08
MRI center								
Scanner MUC		n = 45			n = 37			0.94
Scanner BN1		n = 3			n = 8			0.05
Scanner BN2		n = 22			n = 12			0.19

Group comparisons: two-sample t-tests for age, gestational age, birth weight, full-scale IQ, PO-index and VC-index; Mann-Whitney U test for educational success; chi-squared statistics for gender and MRI centers (first and second MRI scanner in Bonn as well as the scanner in Munich, respectively coded as BN1, BN2, MUC). Data are presented as mean ± standard deviation as well as the interquartile range; Abbreviations: VPB: very premature born, MB: mature born, INTI: Intensity of Neonatal Treatment Index, IQ: intelligence quotient, PO-index: perceptual organization index

Figure Legends:

Figure 1: Perceptual organization index in very premature and mature born adults

The boxplot shows the median and interquartile range of PO-indices, a sub-scale of the Wechsler Adult Intelligence Scale-III, for VPB adults on the left (96, 83-104) and MB adults on the right (107, 96-114). Groups are different in PO-index (two-sample t-test, $p < 0.001$). Abbreviations: VPB, very premature born; MB, mature born; PO-index, perceptual organization index.

Figure 2: Structural connectivity between dorsal attention network and thalamus - probabilistic tractography and group comparisons

A) Seeds of probabilistic tractography in individual DAN (in red, spatial maps are generated via independent component analysis and dual regression analysis of resting state fMRI data) and target in the thalamus (in blue, atlas based on [Behrens et al., 2003]), and an example of connectivity distributions (produced via probtrackx (FSL) [Behrens et al., 2007]) on the right, displayed in individual diffusion space of a representative VPB adult. B) Connection probability (between DAN and thalamus) with DAN of the thalamic voxels (one sample t-test for MB and VPB adults on a significance level of 0.05, FWE corrected, extracted from SPM8), the peak is marked in the pulvinar, overlaid to a T1-weighted sequence in MNI space. C) Thalamic voxels of reduced structural connection probability with the DAN in VPB adults compared to MB adults, located in the right pulvinar (two-sample t-test, $p<0.05$, FWE corrected), overlaid to a T1-weighted sequence in MNI space. Abbreviations: VPB, very premature born; MB, mature born.

Figure 3: Structural connectivity changes mediate the effect of prematurity on perception

Structural connectivity alterations between thalamus (located in right pulvinar) and individual DAN mediate the effect of group (VPB vs. MB adults) on PO-index. Paths are labeled with the (unstandardized) regression coefficients of the respective effect (± SE). a, effect of causal variable on mediator; b, direct effect of mediator on outcome; c, total effect of causal variable on outcome; c´, direct effect of causal variable on outcome. Abbreviations: VPB, very premature born; MB, mature born; PO-index, perceptual organization index.