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Title

Impaired visual short-term memory capacity is distinctively associated with structural connectivity of the posterior thalamic radiation and the splenium of the corpus callosum in preterm-born adults

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Abstract

Preterm birth is associated with an increased risk for lasting changes in both the cortico-thalamic system and attention; however, the link between cortico-thalamic and attention changes is as yet little understood. In preterm newborns, cortico-cortical and cortico-thalamic structural connectivity are distinctively altered, with increased local clustering for cortico-cortical and decreased integrity for cortico-thalamic connectivity. In preterm-born adults, among the various attention functions, visual short-term memory (vSTM) capacity is selectively impaired. We hypothesized distinct associations between vSTM capacity and the structural integrity of cortico-thalamic and cortico-cortical connections, respectively, in preterm-born adults.

A whole-report paradigm of briefly presented letter arrays based on the computationally formalized Theory of Visual Attention (TVA) was used to quantify parameter vSTM capacity in 26 preterm- and 21 full-term-born adults. Fractional anisotropy (FA) of posterior thalamic radiations and the splenium of the corpus callosum obtained by diffusion tensor imaging were analyzed by tract-based spatial statistics and used as proxies for cortico-thalamic and cortico-cortical structural connectivity.

The relationship between vSTM capacity and cortico-thalamic and cortico-cortical connectivity, respectively, was significantly modified by prematurity. In full-term-born adults, the higher FA in the right posterior thalamic radiation the higher vSTM capacity; in preterm-born adults this FA-vSTM-relationship was inversed. In the splenium, higher FA was correlated with higher vSTM capacity in preterm-born adults, whereas no significant relationship was evident in full-term-born adults.

These results indicate distinct associations between cortico-thalamic and cortico-cortical integrity and vSTM capacity in preterm-and full-term-born adults. Data suggest compensatory cortico-cortical fiber re-organization for attention deficits after preterm delivery.

Keywords: Preterm birth, Theory of Visual Attention, visual short-term memory capacity, diffusion tensor imaging, posterior thalamic radiation, compensation

Abbreviations: vSTM, visual short-term memory; TVA, theory of visual attention; FA, fractional anisotropy; DTI, diffusion tensor imaging; ROI, region of interest; TFCE, threshold-free cluster enhancement; GA, gestational age; IQ, intelligence quotient.

1. Introduction

Preterm birth is associated with an increased risk for lasting impairments in both brain structure and cognitive functions (Baron and Rey-Casserly, 2010; D'Onofrio et al., 2013). Among cognitive functions, attention is particularly affected, as evidenced by pronounced attentional impairments along childhood following preterm delivery (Anderson and Doyle, 2003; Atkinson and Braddick, 2007). Concerning brain structure, white matter integrity is particularly affected, as demonstrated by widespread changes (e.g., in posterior thalamic radiations, corpus callosum, and superior longitudinal fasciculus) in fractional anisotropy (FA) from infancy (Ball et al., 2012, 2013b) to adulthood (Vangberg et al., 2006; Skranes et al., 2007; Constable et al., 2008; Eikenes et al., 2011; Mullen et al., 2011; Meng et al., 2015; for review see Ment et al., 2009; Pandit et al., 2013).

As concerns lasting impairments in attention and their relation with lasting brain changes after preterm delivery, a recent study has linked selective attentional deficits in preterm-born adults to functional connectivity changes of intrinsic posterior brain networks (Finke et al., 2015). Attention parameters were estimated based on the computational Theory of Visual Attention (TVA; Bundesen, 1990). In TVA, visual processing is conceived as a parallel-competitive race of visual objects towards selection, that is, representation in a capacity-limited visual short-term memory (vSTM) store. Bottom-up and top-down biases determine the relative 'attentional weights' for objects. The probability of selection is determined by an object's processing rate *v*, which depends on its attentional weight (*w*), sensory effectiveness, and the capacity of the vSTM store (if the store is filled, the selection process terminates). By means of TVA model- based fitting of performance accuracy in simple psychophysical tasks (requiring verbal report of briefly presented letter arrays), separable, independent latent parameters underlying an individual's performance can be extracted. Finke et al. (2015) showed that specifically parameter vSTM capacity *K*, which reflects the number of items that can be categorized in parallel and transferred to vSTM (Cowan, 2001; Luck and Vogel, 1997), was reduced in preterm- compared to term-born adults, while other parameters, such as visual processing speed *C* and attentional selectivity measures, were preserved. Of note, in the preterm group, vSTM capacity was linked with brain changes in intrinsic networks in a compensatory way: the more pronounced the functional connectivity changes of bilateral posterior brain networks (e.g., dorsal attention network), the higher the individual's vSTM capacity. Similar evidence for compensatory activation following preterm birth comes from a number of other studies (Gimenez et al., 2005; Peterson et al., 2002; Nosarti et al., 2006). For example, Froudist-Walsh and colleagues (2015)

found changes in task-related activity during an N-back task, in which adults who suffered perinatal brain injury exhibited reduced activation in frontoparietal areas, though without differing from controls in performance level. Accordingly, Finke et al. (2015) took their results to suggest that brain alterations following prematurity promote the compensatory recruitment of alternative brain networks. It has been shown that, beyond local activity, functional connectivity depends on underlying white matter structural connectivity (Honey et al., 2009; Hagmann et al., 2008; Kringelbach et al., 2014), which provides a backbone for the coherence of ongoing activity fluctuations. Thus, the question arises whether and how the underlying white matter integrity is linked to vSTM capacity in preterm-born adults. The current study focuses on this question.

According to a neural interpretation of TVA (the Neural TVA, NTVA), visual brain regions, such as thalamus, occipital cortices and posterior parts of temporal and parietal cortices, and their inter-regional structural connectivity subserve vSTM processes in healthy individuals (Bundesen et al., 2005). In line with, for instance, Hebb (1949), it is assumed that when visual objects enter vSTM, the activation of those neurons within posterior parts of the cortex that are initially coding and representing these winner objects is sustained and re-activated in a feedback loop. The thalamus and particularly the thalamic reticular nucleus, where the vSTM map of objects is assumed to be located, are suggested to play a key role in gating these thalamocortical feedback loops (Magen et al., 2009; Todd and Marois, 2004; Xun and Chun, 2006). Given the critical role of such recurrent feedback loop activity, the integrity of cortico-thalamic and cortico-cortical white matter circuits of the thalamo-cortical systems would be expected to be decisive for vSTM capacity (Bundesen et al., 2005). Although Habekost and Rostrup (Habekost and Rostrup, 2007) observed specific alterations in the TVA-based estimates of vSTM capacity following posterior white matter damage, the specific role of posterior cortico-thalamic and cortico-cortical fiber tracts that is implied in NTVA remains to be documented.

As demonstrated by animal studies of prematurity, preterm birth leads to a disturbed brain maturation by impairing the maturation of subplate neurons, GABAergic interneurons, oligodendrocytes and astrocytes (Dean et al., 2013, Komitova et al., 2013). In particular, the premyelinating oligodendrocytes affected by hypoxia or ischemia lead to a loss or a maturational delay of their cellular targets resulting in hypomyelination or axonal damage (Ment et al., 2009). This is reflected in preterm infants by the absence of normal maturational increase in FA (Miller 2002). Correspondingly, cortico-thalamic and cortico-cortical tracts of the thalamo-cortical system are substantially re-organized after preterm delivery (Ball et al., 2012, 2013a). Indeed, using tract-based spatial statistics, Ball and colleagues have

provided evidence that preterm birth altered thalamocortical development through reduction of white matter microstructure and changes in thalamic volume (Ball et al., 2012). Using a similar methodology, Meng and colleagues found lasting changes in white matter microstructure in preterm-born adults, associated with both subcortical grey matter volume reduction and lower IQ (Meng et al., 2015). Using probabilistic tractography, Ball and colleagues (2013) documented a reorganization of connectivity after preterm birth with reduced cortico-thalamic connectivity and increased local cortico-cortical connectivity in infants. These findings suggest a distinct trajectory of brain organization in preterm-, as compared to full-term-, born individuals, with some changes, particularly in cortico-cortical connectivity, potentially reflecting compensation.

Based on (i) such complex and permanent patterns of brain re-organization, (ii) on the altered relationship between vSTM capacity and functional connectivity in the posterior brain (Finke et al., 2015), and (iii) on the fact that functional connectivity depends on underlying structural connectivity (e.g. Honey et al., 2009), we hypothesized that the linkage of microstructure of posterior brain circuits with vSTM capacity might be changed, too, in preterm-, as compared to full-term-, born adults. Furthermore, we assumed that the way these relationships are changed might differ between cortico-thalamic fibers microstructure on the one hand and cortico-cortical fibers on the other. Specifically, (i) with respect to cortico-thalamic tracts microstructure in full-term-born adults, based on the NTVA thalamo-visual cortex vSTM loop model, we expected greater integrity of tracts connecting thalamus and posterior cortex, that is, of the posterior thalamic radiations, to be associated with higher vSTM capacity. Accordingly, we used the posterior thalamic radiations as a proxy for cortico-thalamic structural connectivity. Given profound changes of cortico-thalamic connectivity in preterm-born adults (Meng et al., 2015), this relationship could be changed in the preterm group. (ii) Based on findings of changes in CC connectivity in preterm-born infants (Ball et al., 2014) and compensatory functional connectivity changes in bilateral posterior intrinsic networks in preterm-born adults (Finke et al., 2015), we hypothesized that the role of cortico-cortical structural connectivity for vSTM capacity might also be changed (i.e., be potentially enhanced) for preterm- as compared to term-born adults. We analyzed FA in a main cortico-cortical fiber tract, the splenium of the corpus callosum, as a simple proxy for cortico-cortical connectivity. The corpus callosum is classically regarded as important for compensatory functional recovery following brain damage, as it provides an interhemispheric connection to contralateral homologous brain systems (Bartolomeo and Thiebaut de Schotten, 2016). We focused on the splenium of the corpus callosum as it supports interactions between bilateral posterior visual intrinsic networks. Parallel activation of homologous vSTM systems has been shown to improve vSTM storage in healthy

individuals (Delvenne and Holt, 2012; Umemoto et al., 2010) and, notably, also to enhance parameter *K* in TVA-based paradigms (Kraft et al., 2013; 2015). FA in the splenium of the corpus callosum has been shown to be related to the degree of such a bilateral processing advantage (Davis and Cabeza, 2015). Thus, especially in preterm-born adults, FA of the corpus callosum might be critical for a potential compensatory hemispheric interaction between parallel vSTM storage systems with relatively independent resources in both hemispheres (e.g., Sereno and Kosslyn, 1991).

In order to test these hypotheses, 28 pre- and 27 full-term born young adults were assessed by both diffusion tensor imaging (DTI) and a TVA-based whole-report task. To sample white matter structural connectivity, fractional anisotropy (FA) of water diffusion was investigated using tract-based spatial statistics in the mentioned regions of interest (ROI), specifically, posterior thalamic radiations (proxy for cortico-thalamic connectivity) and the splenium of the corpus callosum (proxy for cortico-cortical connectivity). Parameter *K*, representing vSTM capacity in TVA, was estimated based on whole report of briefly presented letter arrays. White matter FA values of both ROIs, respectively, were explored in relation to vSTM capacity and prematurity using ANCOVA.

2. Material and methods

2.1. Participants

2.1.1. Sample description

Participants were recruited from the Bavarian Longitudinal Study (BLS) (Riegel et al., 1995; Wolke and Meyer, 1999), which investigates a geographically defined whole-population sample of neonatal at-risk children and healthy term controls. 28 preterm-born and 27 term-born young adults were recruited, all born between January 1985 and March 1986 (25 to 27 years old) (for demographics and clinical data, see table 1). Participants represent a sub-sample of a previous study of our group, for which DTI data were assessed beyond attention assessment (Finke et al., 2015). While the previous study aimed at answering which particular attention functions are impaired in preterm-born adults (i.e. vSTM capacity), the current study focused on the underlying structural connectivity of vSTM capacity deficits. Full-term- and preterm-born participant groups were matched in terms of sex, age, visual acuity, socioeconomic background, and maternal age. Exclusion criteria for participating in the study were non-correctable reduction of sight in either eye and the presence of psychiatric disorders that are known to affect attention, such as ADHD, autism, schizophrenia, or major depression. All participants had normal or corrected-to-normal vision and were not color-blind. Participants were examined at the Department of Neuroradiology, Klinikum rechts der Isar, Technische Universität München, Germany. The study was approved by the local ethics committee of the Klinikum Rechts der Isar. All participants provided informed consent to be entered in the study.

2.1.2. Measure of Prematurity

Gestational age (GA) was estimated from maternal reports of the last menstrual period and serial ultrasounds during pregnancy. When the two measures differed by more than two weeks, clinical assessment using the Dubowitz method was applied (Dubowitz et al., 1970)

2.1.3. Cognitive evaluation

All participants were tested for global cognitive functioning at the age of 26 years by trained psychologists. This included a short version of the German Wechsler Adult Intelligence scale-III (WAIS-III) (Von Aster et al., 2006), permitting computation of Full Scale Intelligence Quotient (IQ).

2.2. Theoretical TVA framework and TVA-based behavioural assessment of vSTM capacity

2.2.1.Computational TVA framework

In TVA, visual processing is conceived as a race: objects are processed in parallel and compete for being selected, that is, represented in vSTM for conscious report. VSTM capacity *K* quantifies the number of items that can be categorized and selected in parallel and transferred into the vSTM store (Cowan, 2001; Habekost and Starrfelt, 2009; Luck and Vogel, 1997; Sperling, 1960). Note that three additional parameters, visual processing speed *C*, minimum effective exposure duration (visual threshold) *t0*, and effective additional exposure duration in unmasked displays μ, were also determined. While not being in the focus of the present study, these parameters play a role for valid estimation of parameter vSTM capacity *K*. All parameters are obtained from the fitting of the accuracy of letter report across the different conditions of a so-called whole-report task. For a formal description of TVA and the TVA equations, maximum likelihood model fitting and software, see Kyllingsbæk (2006).

2.2.2. Assessment Procedure

As described previously in Finke et al., (Finke et al., 2015), we used a whole-report task (conducted in a dimly lit room). Stimuli were presented briefly to participants on a 17 inch screen (1024 x 1280 pixel resolution, 60-Hz refresh rate). A chin rest was used to maintain viewing distance at 50 cm. Participants were instructed to fixate a central white cross (0.3° visual angle) presented for 300 ms. Then, after a gap of 100 ms, red and/or green letters (0.5° high × 0.4° wide) were briefly presented on a black background. Three different individual letter exposure durations were determined in a practice session prior to the experiment proper to meet a set criterion value (i.e., about one letter named correctly at the intermediate, unmasked exposure duration). The letters were randomly chosen from a pre-specified set ("ABEFHJKLMNPRSTWXYZ"), with the same letter appearing only once on a given trial. Each participant received the same displays in the same sequence. Stimuli were either masked at the end of the exposure duration or unmasked. In unmasked conditions, the effective exposure durations are prolonged by several hundred milliseconds due to "iconic" memory buffering. Participants were asked to identify and verbally report as many stimuli as possible. They were free to report individual letters in any order they liked, without stress on response speed. The experimenter entered the responses on the keyboard. The total number of trials was 192, separated into blocks of 48 trials each. Within each block, the different trial types were presented equally often in randomized order. For more details regarding the assessment procedure see Kyllingsbæk (2006).

2.2.3. Statistical analysis

As *K* was not normally distributed, we used a permutation test with 10^5 iterations to confirm that *K* was lower in the preterm group than in the term group, as shown previously by Finke and colleagues (2015). In the same way, a permutation test was used to assess between-group differences in *C*, *t0*, and μ.

2.3. Diffusion imaging and data analysis.

2.3.1. Image Acquisition

Both T1 and diffusion tensor imaging were obtained using a 3 T Philips scanner with an 8-channel phased-array head coil. A whole-head, high-resolution T1-weighted image was acquired using a magnetization-prepared rapid acquisition gradient echo sequence with 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 inter-slice gap, voxel size = 1 x 1 x 1 mm^3. Diffusion images were acquired using a single-shot spin-echo echo-planar imaging sequence, resulting in one non-diffusion weighted image (b = 0 s/mm^2) and 32 diffusion weighted images (b = 1000 s/mm^2, 32 non-collinear gradient directions) covering whole brain with: 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 inter-slice gap, voxel size = 2 x 2 x 2 mm^3

2.3.2. Quality Check

Each image was visually checked by three independent raters (C.M., C.S., A.M.) prior to further processing (see also Meng et al., 2015). Beyond visual inspection of raw data, we also used the fitting residuals (the sum-of-squared-error maps generated by DTIFIT) to identify data corrupted by artifacts. Artifacts include motion-induced artifacts and insufficient fat suppression (ghosting) artifacts. DTI data were classified as data with none, moderate, and severe visible artifacts, respectively. Only data without artifacts were included in the study, that is, out of the 28 preterm- and 27 term-born participants, seven subjects were excluded due to ghost artifacts and one subject due to a motion artifact. Our final cohort consisted of 26 preterm- and 21 term-born young adults.

2.3.3. Preprocessing

Diffusion data preprocessing was performed using FMRIB Diffusion Toolbox in the FSL software (www.fmrib.ox.ac.uk/fsl) after converting data from DICOM to niftii format by using dcm2nii as described in previous work (Meng et al., 2015). All diffusion-weighted images were first corrected for eddy current and head motion by registration to b0 image. Using the Brain Extraction Tool (BET), skull

and non-brain tissue were removed. The tensor model was then applied voxel by voxel to obtain FA maps.

2.3.4. Skeletonized FA generation

Voxel-wise statistical analysis of the FA data was carried out using Tract Based Spatial Statistics (TBSS). All subjects' FA were non-linearly registered and aligned to the Montreal Neurological Institute Standard Space (MNI 152). Next, the mean FA image of all subjects was created and used to generate an across-all-subjects skeleton, which represents the white matter tracts common to all subjects. We thresholded the skeleton for FA > 0.2 to keep the main white matter tracts only and then projected each subject's FA image onto the skeleton to obtain individual FA maps.

2.3.5. Region of interest (ROI) generation

We used the whole-brain skeleton to create our ROIs (Fig.1). Using fslstats command, we extracted the splenium of the corpus callosum as well as bilateral posterior thalamic radiations including optic radiations separately, from the JHU-ICBM-DTI-81 white matter labels atlas (Mori et al., 2005). Using fslmaths command, we first combined the splenium of the corpus callosum with the FA skeleton obtained previously to obtain a splenium of the corpus callosum skeleton mask. We repeated the process using both posterior thalamic radiations instead of the splenium of the corpus callosum to obtain a posterior thalamic radiation skeleton mask.

2.3.6. Statistical analysis

General linear model and nonparametric permutation testing (5000 random permutations) were adopted to perform statistical analyses on the ROI's FA using FSL's *randomize* script (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/randomise/) (Anderson and Robinson 2001). The design matrix we used was representative of an ANCOVA with main effects of group and vSTM storage parameter *K* and the interaction effect of group and *K* on FA. The statistical threshold was set at $P_{FWE} < 0.05$, with multiple comparison correction threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009). In order to control for the influence of general cognitive performance, we added in a second analysis IQ as a covariate-of-no-interest in the ANCOVA model. In order to visualize the association between vSTM storage *K* and FA in each group separately, we used fslmeants command to extract for each subject a mean FA value from TBSS significant interaction voxels of each ROI. Then we plotted each individual FA value and its vSTM storage *K* score, and applied linear fitting and Spearman correlation in each group

separately using Matlab (MathWorks). Group differences in mean FA were analysed by ANCOVA including Full-scale IQ as additional co-variate using SPSS statistics package version 21 (IBM).

3. Results

3.1. VSTM capacity is reduced in preterm-born adults

As previously reported by Finke and colleagues (2015), vSTM capacity *K* was significantly lower in the preterm- compared to the full-term-born group (p =0.023) (see Table 1). Also in line with Finke et al. (2015), visual processing speed (*C*) and minimum effective exposure duration (*t0*) did not differ significantly between the two groups. There was also no difference for the parameter of no interest, effective additional exposure duration in unmasked displays (μ).

3.2. Preterm birth modulates the relationship between vSTM capacity and FA in posterior thalamic radiation

To investigate whether there was a distinct association between vSTM capacity *K* and cortico-thalamic fibers' integrity in preterm- and full-term-born adults, we performed a voxel-wise analysis of the interaction between prematurity (preterm-born group, term-born group) and vSTM capacity *K* on posterior thalamic radiation FA values by means of ANCOVA modeling and permutation testing (Fig. 2). We found a significant interaction between prematurity and vSTM capacity *K* on FA in a cluster of voxels (264 voxels) in the posterior part of the right posterior thalamic radiation (Fig. 2a, P_{FWE}<0.05 TFCE corrected).

Control analyses. (i) To assess whether the interaction between prematurity and vSTM capacity *K* arises independently of general cognitive performance, we repeated the interaction analysis including Full-scale IQ as additional co-variate of no interest (Fig. 2b). The interaction effect remained significant, indicating the specificity of the distinct link between cortico-thalamic fibers' FA and vSTM capacity *K* across preterm- and full-term-born adults. To examine the direction of this interaction, we extracted the average FA value within that cluster separately for the term-born and the preterm-born group, plotted it and correlated it to vSTM capacity *K*, using Spearman correlation. In full-term-born adults, the association between vSTM capacity *K* and FA was significantly positive (ρ = 0.57; p < 0.01), whereas in preterm-born subjects it was significantly negative (ρ = -0.49; p = 0.01) (Fig. 2c). (ii) To examine FA group differences for the relevant (interaction) cluster, we tested for the main effect of prematurity. We found a significant main effect of prematurity on mean FA, with FA being reduced in preterm-born adults (p<0.016), which is in line with previous findings (Meng et al., 2015). We did not find any significant difference in mean FA between groups over the whole tract (p = 0.34).

3.3. Preterm birth modulates the relationship between vSTM capacity and FA in the splenium of the corpus callosum

To investigate the distinct association between vSTM capacity *K* and cortico-cortical fibers' integrity in preterm- and full-term-born adults, we performed a voxel-wise analysis of the interaction between prematurity and *K* on splenium FA values by using the same approach as for the posterior thalamic radiations (Fig. 3). We found a significant interaction between prematurity and *K* on FA in two clusters of voxels (354 voxels in total) within the posterior part of the splenium (Fig. 3a, $P_{FWE}<0.05$ TFCE corrected).

Control analyses: (i) To test whether the interaction between prematurity and vSTM capacity *K* occurs independently of general cognitive performance, we repeated the ANCOVA-based interaction analysis including Full-scale IQ as additional co-variate of no interest. We found a trend towards significance for the interaction between *K* and prematurity (Fig. 3b, $P_{FWE} < 0.06$, TFCE corrected), suggesting specificity of the distinct link between cortico-cortical fibers' FA and vSTM capacity across preterm- and full-term-born adults. To examine the direction of interaction, we extracted the average FA value within that cluster separately for the term-born and the preterm-born group, plotted it and correlated it to vSTM capacity *K*, using Spearman correlation. This showed that within these clusters, average FA was significantly positively associated with vSTM capacity *K* in the preterm-born group ($\rho = 0.51$; $p < 0.01$), while no significant association was found in the term-born group ($\rho = -0.14$; $p = 0.56$) (Fig. 3c). (ii) To examine FA group differences for the relevant (interaction) cluster, we tested for the main effect of prematurity. We found a significant main effect of prematurity on mean FA, with FA being reduced in preterm-born adults ($p = 0.046$), which is in line with previous findings (Meng et al., 2015). We did not find any significant difference in mean FA between groups over the whole tract ($p = 0.59$).

4. Discussion

The present study tested the hypothesis that cortico-cortical and cortico-thalamic fibers' integrity of posterior brain circuits would be distinctively linked with vSTM capacity in preterm-born, in comparison with full-term-born, adults. Diffusion tensor imaging and TVA-based whole-report were applied in preterm- and full-term-born adults. We found that prematurity modulated the relationship between vSTM capacity and cortico-cortical and cortico-thalamic fibers' microstructure, respectively. For cortio-thalamic connectivity we found a reversed relationship between FA and vSTM storage capacity in preterm- compared to full-term born adults: Full-term-born adults with higher FA in a posterior part of the right posterior thalamic radiation exhibited higher vSTM capacity, while a significantly negative relationship was revealed for preterm-born adults. For cortico-cortical connectivity, too, we found a change in the FA-vSTM-relationship between full-term and preterm-born adults: preterm-born adults with higher FA in a right part of the splenium exhibited higher vSTM capacity, while no significant relationship was evident for full-term-born adults. This pattern of results provides first evidence of distinct structural connectivity underlying vSTM capacity in preterm-born adults compared to term-born individuals. The data suggest that, in preterm-born adults, the re-organization of cortico-cortical and cortico-thalamic tracts is differentially linked with vSTM capacity, and that the splenium in particular plays a role in compensatory re-organization.

4.1 Prematurity modulates the relationship between vSTM capacity and posterior thalamic radiation microstructure

Our hypothesis of a distinct link of posterior brain white matter with vSTM capacity *K* in preterm-born, in comparison with full-term-born, adults was supported by the finding that the association between FA in a posterior part of the posterior thalamic radiation and K differed significantly between the two groups (Fig 2a). Since this result remained significant even when we controlled for the influence of IQ (Fig 2c), this interaction appears to be independent of the general level of cognitive ability. Our finding of a significant association of FA in part of the right posterior thalamic radiation of healthy full-term-born adults with TVA parameter *K* goes beyond previous TVA-based studies that documented a relationship between posterior white matter microstructure and vSTM capacity *K* (Habekost and Rostrup, 2007; Espeseth et al., 2014) and the relevance of right hemispheric tracts in particular (Chechlacz et al., 2015). We establish a role for a specific tract: the posterior thalamic radiation, which connects the thalamus with the posterior visual brain. We thus provide direct empirical support for the NTVA notion of a

recurrent thalamo-cortical feedback loop that sustains the activity in visual areas representing objects in vSTM (Bundesen et al., 2005). Our findings are in line with those of Golestani and colleagues (Golestani et al., 2014), who reported an association between visual working memory performance in a different paradigm and white matter microstructure of the optic radiations (as part of the posterior thalamic radiations) and posterior thalamus in healthy adults.

Our finding of a negative association in preterm-born adults as well as a reduction of FA in the preterm group indicates that the relationship between this central fiber tract in the thalamo-cortical loop system and short-term memory maintenance is compromised after preterm delivery. Prior studies on the role of FA in the posterior thalamus and the optic radiation with visual functions in preterm newborns found that, at this stage of development, changes in FA are related to impaired visual and attentional functions (Bassi et al., 2008; Groppo et al., 2014). These findings support the assumption that the thalamo-cortical system is critically damaged following preterm birth. Our results are in line with those of Karolis and colleagues (2016), who reported altered cortico-thalamic loops in adults born preterm. Additionally, our results are in agreement with those of Meng and colleagues (2015), who reported a widespread reduction of white matter microstructure in preterm-born adults in several tracts (e.g., in the splenium of the corpus callosum) and in cortico-thalamic tracts such as the posterior thalamic radiations. Moreover, although the negative association between *K* and FA in the preterm group might seem somewhat surprising, other studies have previously reported different directions of correlations (positive vs. negative) between microstructural properties of WM pathways and individual differences in cognitive abilities (Tuch et al., 2005; Roberts et al., 2010; Chechlacz et al., 2015). Jones and colleagues (2013), reported that changes in FA can reflect changes in myelination, axon diameter, packing density or membrane permeability, that is, higher FA might not invariably reflect higher integrity of a tract. Nevertheless, the well-known impairment in white matter microstructure demonstrated after preterm birth (Ball et al., 2012; Meng et al., 2015) leads us to suggest that lower FA is associated with lower integrity of the posterior thalamic radiations in preterm-born adults.

This, in summary, provides evidence that posterior thalamic radiations support vSTM capacity in the healthy adult brain. Following preterm delivery, this support is compromised.

4.2 Prematurity modulates the relationship between vSTM capacity and the splenium of the corpus callosum microstructure

We found evidence that prematurity increases the relevance of FA in a right part of the splenium of the corpus callosum for vSTM capacity *K* (Fig3a) as only in the preterm (but not in the full-term) group, higher FA was associated with higher storage capacity *K* (Fig3b). These interaction results remained near-significant even when we controlled for IQ (TFCE corrected, $p < 0.06$), implying that they are relatively independent of general cognitive abilities. The splenium FA was reduced in preterm-born adults, indicative of compromised microstructure. Thus, the positive correlation between *K* and FA suggests that, when the splenium of the corpus callosum is still relatively intact despite preterm delivery, the role of this fiber tract can be reorganized so as to supports the vSTM system in a compensatory manner. Our results are in agreement with findings of compensatory intrinsic functional connectivity changes in bilateral posterior brain networks in the same cohort of preterm-born adults (Finke et al., 2015). Finke and colleagues (2015) found that preterm-born adults with relatively preserved vSTM storage functions exhibited a stronger difference in intrinsic functional connectivity compared to term-born adults. While these results had already implied complex reorganization of intrinsic connectivity in posterior networks, the current results suggest that structural cortico-cortical and cortico-thalamic changes reflect, and support, this reorganization. More specifically, reduced cortico-thalamic connectivity as reflected by a reduction of FA in the posterior thalamic radiation in preterm-born adults is in line with intrinsic functional connectivity changes in typical vSTM networks previously documented by Finke et al. (2015). Furthermore, the splenium might play an enhanced role in interhemispheric transfer especially between those compensatory bilateral posterior intrinsic networks that had also been documented in the Finke et al. (2015) study. This is in line with a role of the corpus callosum in functional recovery following brain damage by interconnecting homologous brain systems (Bartolomeo and Thiebaut de Schotten, 2016). In preterm-born adults in particular, the splenium might support transfer between otherwise relatively independent vSTM systems in the two hemispheres (e.g., Kraft et al., 2013; 2015), thus providing a means to activate bilateral systems and so increase storage capacity resources. – Taken together, the findings of the two studies provide converging evidence for the proposal that the damaged original, or typical, vSTM network is not functional to the same degree by adults born preterm as compared to full-term-born adults. Furthermore, it appears that especially adults with relatively preserved vSTM storage function might rather employ a compensatory bilateral posterior intrinsic network that at least in part relies on structural connections provided by the splenium of the corpus callosum. Studies on task-related activation during performance of N-back working memory tasks appear to support our proposal: Froudist-Walsh and colleagues (2015) found that preterm-born adults who suffered perinatal brain injury and who, despite reduced activation in typical frontoparietal working memory areas, displayed relatively normal N-back performance exhibited enhanced activity in the perisylvian cortex. And Daamen and

colleagues (2015) found enhanced deactivations of posterior parietal areas of the default mode network in preterm- compared to term-born adults. Finally, with respect to the relationship between structural connectivity and cognition, and similar to the present findings, Lindqvist and colleagues (2011) found a positive correlation between FA in the splenium of the corpus callosum and visual performance in preterm-, but not in full-term-, born adolescents. Importantly, however, in our participants, visual screening prior to inclusion and normal visual thresholds (*t0*) and visual processing speed (*C*) in the TVA-based testing rule out that the reduced vSTM capacity is attributable to more basic visual deficits. Given this, the findings of Lindqvist and colleagues and of our study are complementary in indicating that at least from adolescence and up to adulthood, the splenium of the corpus callosum plays an important role in the compensatory recruitment of structural networks supporting both perception and short-term storage of visual information in preterm-born individuals.

Finally, Ceschin and colleagues (2015) proposed that thalamo-cortical and interhemispheric connectivity are likely playing a synergistic role in the development of visual functions in preterm-born infants. In line with this assumption, we found a significant modulation of the relationship between vSTM capacity and cortico-cortical and cortico-thalamic connectivity by preterm birth. Thus, in light of our results, it appears likely that a compensatory vSTM network, in preterm-born adults, relies less on cortico-thalamic connectivity (as this "original" network is disrupted in preterm infants) and more on interhemispheric cortico-cortical, that is, the splenium of the corpus callosum, connectivity.

4.3. Methodological issues and limitations.

First, individuals with severe impairments or multiple complications in the initial BLS sample were more likely to be excluded in the initial screening for MRI and visual attention testing (e.g., visual acuity) or they declined to participate in MRI scanning. Accordingly, there is sample bias in the current study towards preterm-born adults with reduced neonatal complications and higher IQ. Therefore, our findings of linked structural connectivity and vSTM capacity, and in particular of 'compensatory' splenium integrity, might not hold for preterm-born adults in general. Severely impaired preterm-born individuals might not have the same compensatory mechanisms, or such mechanisms might be disrupted. Further studies on subgroups and longitudinal studies are necessary to clarify this. Second, despite many advantages, the use of TBSS-based analysis of fiber integrity combine with the use of the JHU-ICBM atlas has several limitations, as reported by Bach and colleagues (2014). Most prominently, skeletonised structural connectivity approaches mainly investigate major fiber pathways across subjects, but it is

nevertheless difficult to label the white matter skeleton for specific tracts due to crossing fibers or high inter-subject variability. Indeed, although the ROI we used is labeled posterior thalamic radiation, we cannot exclude the possibility that other tracts might be present within it. Additionally, although TBSS uses nonlinear registration to align each subject's individual FA to the FMRIB58 FA 1mm standard template, the registration might not be optimal for individuals with large ventricles such as preterm-born adults. Given this, the region-of-interest labels we used to link white matter with vSTM capacity should be evaluated with care. Furthermore, all our results were obtained using TFCE and are thus also influenced by the size of the skeleton sheet structure. Moreover, we found differences in the relationship of FA and vSTM storage only in subparts of both posterior thalamic radiations and the splenium of the corpus callosum. Accordingly, our findings do not indicate that the role of these fiber tracts is, in general, changed; rather, they imply that some fibers of these bundles are restructured following preterm delivery.

Finally, we interpreted higher FA representing higher integrity of the tract. However, as mentioned by Jones and colleagues (Jones et al., 2013), it is under debate whether FA is a sufficient measure of fiber integrity. Given that FA is a measure influenced by axon diameter, axon density, and myelination, interpretations of reduced FA in terms of reduced microstructure should be considered with care.

4.4. Conclusion

The Splenium and posterior thalamic radiation integrity are distinctively linked with vSTM capacity in preterm-born adults, in comparison with full-term born adults. In particular, the splenium integrity is positively associated with vSTM capacity exclusively in preterm-born subjects, indicative of a specific compensatory re-organization of the vSTM loop system.

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Tables

Table 1: Sample characteristics

	Preterm group *n* = 26			Full-term group *n* = 21			Statistical comparison
	M	*SD*	*Range*	*M*	*SD*	*Range*	
gender (f/m)	14/12			10/11			p = .67
age (years)	26.6	±0.53	25.8-27.6	26.7	±0.54	25.9-27.9	p = .64
GA (weeks)	30.6	±2.43	27-36	39.6	±0.95	38-42	**p < .01**
IQ	93.8	±9.62	72-117	101	±11.3	77-117	**p = .03**
t0	7.31	±15.2	0-53.8	1.49	±2.85	0-9.42	p = .10
C	26.3	±190.1	9.8-53.3	27.1	±8.11	17.2-47.5	p = .76
μ	98.3	±40.8	49-220	99.8	±32.1	36-194	p = .89
K	2.76	±0.35	1.98-3.83	3	±0.43	2.47-3.89	**p = .02**

Abbreviations:

m: male, f: female; GA: gestational age; IQ: Wechsler Intelligence Test for Adults at 26 years of age, t0: visual threshold in ms, μ: duration of iconic memory in ms, *C*: visual processing speed, *K*: visual short-term memory storage capacity. Statistical comparisons: gender: chi-squared statistics; age, IQ: t-tests; *K*, *C*, *t0*, μ: permutation tests; GA: nonparametric Mann-Whitney-U-test.

Figures

Figure 1: Regions of interest (ROI) for visual short term memory capacity.

Coronal, axial, and sagittal views illustrating the localization of posterior thalamic radiations and the splenium of the corpus callosum superimposed on the T1-weighted brain image of MNI152 structural standard template and group-generated white matter skeleton. Brown color indicates the common skeleton over preterm- and full-term born and groups. Blue color shows bilateral posterior thalamic radiations and green represents the splenium of the corpus callosum.

Figure 2: Prematurity modulates the association between vSTM capacity and FA in posterior thalamic radiation.

a) In the upper panel, coronal, axial, and sagittal views illustrate a significant interaction between prematurity and vSTM capacity *K* on fractional anisotropy (FA). Blue color shows the posterior thalamic radiations. Red color indicates where prematurity and *K* significantly interacted on FA (permutation test, $P < 0.05$, FWE corrected). MNI coordinates were provided near the sagittal view. **b)** (Axial view representing the significant interaction between prematurity and *K* on FA. The same color code as in a) is used). Same illustration of the interaction between prematurity and *K* on FA as in a). Additionally, yellow shows the significant voxels where prematurity and K interact on FA when controlling for IQ (permutation test, $P < 0.05$, FWE corrected). **c)** For visualization of the direction of association in each group separately vSTM capacity *K* and averaged FA of significant voxels in a) were illustrated in a scatter plot.

Figure 3. Prematurity modulates the association between vSTM capacity and FA in the splenium of the corpus callosum.

a) In the upper panel, coronal, axial, and sagittal views illustrate a significant interaction between prematurity and vSTM capacity *K* on fractional anisotropy (FA). Green color indicates the splenium of the corpus callosum, red color indicates where prematurity and K significantly interacted on FA (permutation test, $P < 0.05$, FWE corrected). MNI coordinates were provided near the sagittal view. **b)(** axial view representing the significant interaction between prematurity and *K* on FA. The same color code as in a) is used). Same illustration of the interaction between prematurity and *K* on FA as in a). Additionally, yellow shows the significant voxels where prematurity and *K* interact on FA controlling for IQ

(permutation test, $P < 0.05$, FWE corrected). **c)** For visualization of the direction of association in each group separately, vSTM capacity *K* and averaged FA of significant voxels in a) were illustrated in a scatter plot.