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Title page

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 inverted. 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 **1. Introduction**

2 Preterm birth is associated with an increased risk for lasting impairments in both brain structure and
3 cognitive functions (Baron and Rey-Casserly, 2010; D'Onofrio et al., 2013). Among cognitive functions,
4 attention is particularly affected, as evidenced by pronounced attentional impairments along childhood
5 following preterm delivery (Anderson and Doyle, 2003; Atkinson and Braddick, 2007). Concerning brain
6 structure, white matter integrity is particularly affected, as demonstrated by widespread changes (e.g., in
7 posterior thalamic radiations, corpus callosum, and superior longitudinal fasciculus) in fractional
8 anisotropy (FA) from infancy (Ball et al., 2012, 2013b) to adulthood (Vangberg et al., 2006; Skranes et al.,
9 2007; Constable et al., 2008; Eikenes et al., 2011; Mullen et al., 2011; Meng et al., 2015; for review see
10 Ment et al., 2009; Pandit et al., 2013).

11 As concerns lasting impairments in attention and their relation with lasting brain changes after preterm
12 delivery, a recent study has linked selective attentional deficits in preterm-born adults to functional
13 connectivity changes of intrinsic posterior brain networks (Finke et al., 2015). Attention parameters were
14 estimated based on the computational Theory of Visual Attention (TVA; Bundesen, 1990). In TVA, visual
15 processing is conceived as a parallel-competitive race of visual objects towards selection, that is,
16 representation in a capacity-limited visual short-term memory (vSTM) store. Bottom-up and top-down
17 biases determine the relative 'attentional weights' for objects. The probability of selection is determined
18 by an object's processing rate v , which depends on its attentional weight (w), sensory effectiveness, and
19 the capacity of the vSTM store (if the store is filled, the selection process terminates). By means of TVA
20 model- based fitting of performance accuracy in simple psychophysical tasks (requiring verbal report of
21 briefly presented letter arrays), separable, independent latent parameters underlying an individual's
22 performance can be extracted. Finke et al. (2015) showed that specifically parameter vSTM capacity K ,
23 which reflects the number of items that can be categorized in parallel and transferred to vSTM (Cowan,
24 2001; Luck and Vogel, 1997), was reduced in preterm- compared to term-born adults, while other
25 parameters, such as visual processing speed C and attentional selectivity measures, were preserved. Of
26 note, in the preterm group, vSTM capacity was linked with brain changes in intrinsic networks in a
27 compensatory way: the more pronounced the functional connectivity changes of bilateral posterior brain
28 networks (e.g., dorsal attention network), the higher the individual's vSTM capacity. Similar evidence for
29 compensatory activation following preterm birth comes from a number of other studies (Gimenez et al.,
30 2005; Peterson et al., 2002; Nosarti et al., 2006). For example, Froudust-Walsh and colleagues (2015)

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

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

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

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

71 Based on (i) such complex and permanent patterns of brain re-organization, (ii) on the altered
72 relationship between vSTM capacity and functional connectivity in the posterior brain (Finke et al.,
73 2015), and (iii) on the fact that functional connectivity depends on underlying structural connectivity
74 (e.g. Honey et al., 2009), we hypothesized that the linkage of microstructure of posterior brain circuits
75 with vSTM capacity might be changed, too, in preterm-, as compared to full-term-, born adults.
76 Furthermore, we assumed that the way these relationships are changed might differ between cortico-
77 thalamic fibers microstructure on the one hand and cortico-cortical fibers on the other. Specifically, (i)
78 with respect to cortico-thalamic tracts microstructure in full-term-born adults, based on the NTVA
79 thalamo-visual cortex vSTM loop model, we expected greater integrity of tracts connecting thalamus and
80 posterior cortex, that is, of the posterior thalamic radiations, to be associated with higher vSTM capacity.
81 Accordingly, we used the posterior thalamic radiations as a proxy for cortico-thalamic structural
82 connectivity. Given profound changes of cortico-thalamic connectivity in preterm-born adults (Meng et
83 al., 2015), this relationship could be changed in the preterm group. (ii) Based on findings of changes in CC
84 connectivity in preterm-born infants (Ball et al., 2014) and compensatory functional connectivity changes
85 in bilateral posterior intrinsic networks in preterm-born adults (Finke et al., 2015), we hypothesized that
86 the role of cortico-cortical structural connectivity for vSTM capacity might also be changed (i.e., be
87 potentially enhanced) for preterm- as compared to term-born adults. We analyzed FA in a main cortico-
88 cortical fiber tract, the splenium of the corpus callosum, as a simple proxy for cortico-cortical
89 connectivity. The corpus callosum is classically regarded as important for compensatory functional
90 recovery following brain damage, as it provides an interhemispheric connection to contralateral
91 homologous brain systems (Bartolomeo and Thiebaut de Schotten, 2016). We focused on the splenium
92 of the corpus callosum as it supports interactions between bilateral posterior visual intrinsic networks.
93 Parallel activation of homologous vSTM systems has been shown to improve vSTM storage in healthy

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

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

108 **2. Material and methods**

109 **2.1. Participants**

110 *2.1.1. Sample description*

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

127

128 *2.1.2. Measure of Prematurity*

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

132

133 *2.1.3. Cognitive evaluation*

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

137

138 **2.2. Theoretical TVA framework and TVA-based behavioural assessment of vSTM capacity**

139 *2.2.1. Computational TVA framework*

140 In TVA, visual processing is conceived as a race: objects are processed in parallel and compete for being
141 selected, that is, represented in vSTM for conscious report. VSTM capacity K quantifies the number of
142 items that can be categorized and selected in parallel and transferred into the vSTM store (Cowan, 2001;
143 Habekost and Starrfelt, 2009; Luck and Vogel, 1997; Sperling, 1960). Note that three additional
144 parameters, visual processing speed C , minimum effective exposure duration (visual threshold) t_0 , and
145 effective additional exposure duration in unmasked displays μ , were also determined. While not being in
146 the focus of the present study, these parameters play a role for valid estimation of parameter vSTM
147 capacity K . All parameters are obtained from the fitting of the accuracy of letter report across the
148 different conditions of a so-called whole-report task. For a formal description of TVA and the TVA
149 equations, maximum likelihood model fitting and software, see Kyllingsbæk (2006).

150

151 2.2.2. *Assessment Procedure*

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

169

170 2.2.3. *Statistical analysis*

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

174

175 **2.3. Diffusion imaging and data analysis.**

176 *2.3.1. Image Acquisition*

177 Both T1 and diffusion tensor imaging were obtained using a 3 T Philips scanner with an 8-channel
178 phased-array head coil. A whole-head, high-resolution T1-weighted image was acquired using a
179 magnetization-prepared rapid acquisition gradient echo sequence with the following parameters: echo
180 time (TE) = 3.9 ms, repetition time (TR) = 7.7 ms, flip angle = 15° , field of view = $256 \times 256 \text{ mm}^2$, matrix =
181 256×256 , 180 sagittal slices, slice thickness = 1 mm, and 0 mm inter-slice gap, voxel size = $1 \times 1 \times 1 \text{ mm}^3$.
182 Diffusion images were acquired using a single-shot spin-echo echo-planar imaging sequence, resulting in
183 one non-diffusion weighted image ($b = 0 \text{ s/mm}^2$) and 32 diffusion weighted images ($b = 1000 \text{ s/mm}^2$, 32
184 non-collinear gradient directions) covering whole brain with: echo time (TE) = 47 ms, repetition time (TR)
185 = 20,150 ms, flip angle = 90° , field of view = $224 \times 224 \text{ mm}^2$, matrix = 112×112 , 75 transverse slices, slice
186 thickness = 2 mm, and 0 mm inter-slice gap, voxel size = $2 \times 2 \times 2 \text{ mm}^3$

187

188 *2.3.2. Quality Check*

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

197

198 *2.3.3. Preprocessing*

199 Diffusion data preprocessing was performed using FMRIB Diffusion Toolbox in the FSL software
200 (www.fmrib.ox.ac.uk/fsl) after converting data from DICOM to niftii format by using dcm2nii as
201 described in previous work (Meng et al., 2015). All diffusion-weighted images were first corrected for
202 eddy current and head motion by registration to b_0 image. Using the Brain Extraction Tool (BET), skull

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

205

206 *2.3.4. Skeletonized FA generation*

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

213

214 *2.3.5. Region of interest (ROI) generation*

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

222

223 *2.3.6. Statistical analysis*

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

235 separately using Matlab (MathWorks). Group differences in mean FA were analysed by ANCOVA
236 including Full-scale IQ as additional co-variate using SPSS statistics package version 21 (IBM).
237

238 **3. Results**

239

240 **3.1. vSTM capacity is reduced in preterm-born adults**

241 As previously reported by Finke and colleagues (2015), vSTM capacity K was significantly lower in the
242 preterm- compared to the full-term-born group ($p = 0.023$) (see Table 1). Also in line with Finke et al.
243 (2015), visual processing speed (C) and minimum effective exposure duration (t_0) did not differ
244 significantly between the two groups. There was also no difference for the parameter of no interest,
245 effective additional exposure duration in unmasked displays (μ).

246

247 **3.2. Preterm birth modulates the relationship between vSTM capacity and FA in posterior thalamic**
248 **radiation**

249 To investigate whether there was a distinct association between vSTM capacity K and cortico-thalamic
250 fibers' integrity in preterm- and full-term-born adults, we performed a voxel-wise analysis of the
251 interaction between prematurity (preterm-born group, term-born group) and vSTM capacity K on
252 posterior thalamic radiation FA values by means of ANCOVA modeling and permutation testing (Fig. 2).
253 We found a significant interaction between prematurity and vSTM capacity K on FA in a cluster of voxels
254 (264 voxels) in the posterior part of the right posterior thalamic radiation (Fig. 2a, $P_{FWE} < 0.05$ TFCE
255 corrected).

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

269 **3.3. Preterm birth modulates the relationship between vSTM capacity and FA in the splenium of the**
270 **corpus callosum**

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

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

290 **4. Discussion**

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

307

308 **4.1 Prematurity modulates the relationship between vSTM capacity and posterior thalamic radiation**
309 **microstructure**

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

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

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

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

348

349 **4.2 Prematurity modulates the relationship between vSTM capacity and the splenium of the corpus** 350 **callosum microstructure**

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

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

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

402

403 **4.3. Methodological issues and limitations.**

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

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

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

431

432 **4.4. Conclusion**

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

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Tables

Table 1: Sample characteristics

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