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# 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.

## 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 pro-

*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; BLS, bavarian longitudinal study; IQ, intelligence quotient

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nounced 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 et al. (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; Xu 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 et al. (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 reorganization, (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 cortico-cortical 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 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