Using Neuro-Cognitive Modelling to Link Attention Deficits to Structural and Functional Brain Changes

Dissertation der

Graduate School of Systemic Neurosciences der

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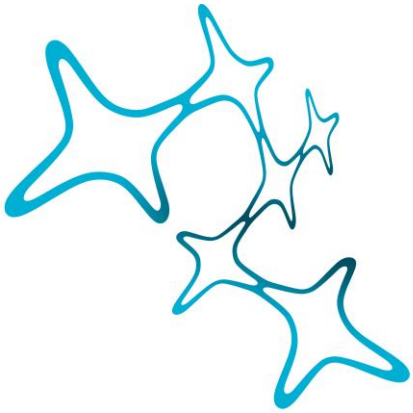

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Munich, 28 February 2017

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ABSTRACT

‘Visual attention’ is an emerging property of interconnected neural networks, in which the interconnections are biased to promote targets over distracting stimuli. It has been shown that efficiency of the attention system is lost after many kinds of brain damage, with each presumably effecting different aspects of basic visual attention functions. Yet, our understanding of these processes is limited by the methodological shortcomings of classical neuropsychological assessment. The overarching goal of the current thesis was to overcome these constrains and thereby extend the link between attention deficits and underlying brain changes. The here used approach incorporates parametric measurement of visual attention derived from the computational Theory of Visual Attention (TVA, Bundesen, 1990) and modern magnetic resonance imaging techniques.

Project 1 of the current thesis applied a combined TVA–neuroimaging analysis in a neurodevelopmental model (preterm birth) to relate attention deficits with changes in functional connectivity networks. We found that pre- versus full-term born adults show a selective reduction of visual short-term memory capacity. The remarkable changes we observed in attention-related large-scale brain networks of the occipital and posterior parietal cortices were most pronounced in those preterm born individuals with the most preserved attention functions. This finding was interpreted as evidence for a compensatory reorganization of functional connectivity in order to ameliorate the advert consequences of preterm birth on visual short-term memory.

Project 2 of this thesis applied a combined TVA-neuroimaging analysis in a neurodegenerative model (posterior cortical atrophy) to relate attention deficits with structural changes in grey and white matter morphometry. Compared to healthy control participants, patients with posterior cortical atrophy suffered from a selective disturbance of visual processing speed. The individual rate of processing speed slowing was a valid predictor for the severity of simultanagnosia, the core symptom in this clinical condition. We further found wide-spread atrophy in occipital as well as parietal and to a smaller degree in temporal brain areas. White matter degeneration in the superior parietal lobe, rather than atrophy of any grey matter cluster, was significantly associated with patients’ impaired processing

speed. Based on these results we propose that disruption of white matter pathways especially within the superior parietal lobe leads to reduced processing speed which then results in the overt clinical symptoms of simultanagnosia.

Altogether, projects of the current thesis expanded the link between specific attention deficits and underlying brain damage by using neuro-cognitive modelling. We demonstrated that parametric measurements of attention facilitate, in the role of intermediate cognitive constructs, the mapping between etiological factors and behavioral outcomes. Identifying predictable behavior-brain relationships in attention disorders may offer new perspectives for diagnosis and treatment. The clinical application of an integrated TVA-neuroimaging analysis could additionally compliment insights from healthy participants toward understanding the principles of normal visual attention as well as identifying their neuronal basis.

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1.

General Introduction: Visual Attention, Deficits and the Brain

In complex visual scenes, attention is required to select what is relevant and disregard irrelevant information. The need for selectivity arises from the human brain's severe capacity limits: we can only process and use a small portion of stimuli available on our retina at any given moment (Lennie, 2003). Hence, all objects in the visual environment compete for limited resources, whereby attention biases this competition in favor of the most relevant object (core reviews are Beck & Kastner, 2009; Desimone & Duncan, 1995; Reynolds & Chelazzi, 2004). Most modern research conforms to the view that visual attention is the working of a few specific mechanisms to resolve biased competition (Bundesen, 1990). Clearly, visual attention is critical for almost every daily life activity, and influences more general capabilities as well, for example maths skills, reading or academic achievements (McClelland *et al.,* 2013). Visual attention is realized by organized activity across a wide-spread network of thalamo-cortical and cortico-cortical feedback loops which are mainly situated within the posterior brain (for a review see Hopf *et al.,* 2009). Given the dependence on tightly-coupled network communication, deficits of visual attention arise from various kinds of neuropathology throughout the life span. Although excellent models of visual attention have been developed over the last decades (for an extensive review see Carrasco, 2011), clinical studies often lack an explicit conceptualization when measuring attention deficits. A key limitation is that assessment tools are used which are based on clinical routine and hence do not allow to differentiate disturbances of distinct attentional functions. Such specificity is, however, crucial for the establishment of behavior-brain relationships, and ultimately necessary for developing targeted therapeutic interventions. In brief, the two projects of the current thesis aimed to overcome this shortcoming by applying the prominent and computationally explicit Theory of Visual Attention (TVA, Bundesen, 1990) in an early developmental example (preterm birth), and a late neurodegenerative example (posterior cortical atrophy) of, yet unspecified, impairments of visual attention. In contrast to conventional clinical tests, this

parametric, model-based assessment tool reveals independent and "process-pure" measures of basic attentional functions. The projects furthermore used modern structural and functional magnetic resonance imaging techniques to identify large-scale brain changes that underlie the observed attention deficits. The General Introduction is divided into four parts. The first part describes normal visual attention on the basis of TVA's core principles and their neuronal interpretation. The second part focuses on disturbances of visual attention, thereby focusing on the limitations of conventional neuropsychological tests and how they can be resolved by TVA-based measurement of visual attention. The third part introduces the two clinical example groups and reviews related work on visual attention deficits and potentially associated brain changes. Finally, the fourth part summaries the aim and specific research questions of this thesis.

1.1. Theoretical Framework: Theory of Visual Attention

The Theory of Visual Attention (TVA; Bundesen, 1990) reduces the vast number of attentional phenomena to a few principle computations that can be expressed in a small set of mathematical equations and importantly estimated from performance in two simple letter recognition experiments. In order to present the theoretical framework of this thesis, the current section describes: a) the biased competition hypothesis; b) the central assumptions; and c) the neuronal interpretation of TVA.

1.1.1. Biased Competition

TVA strongly builds on the mechanistic principles of biased competition, but as we will see later, rephrased them to fit an explicative computational model. Biased competition is one of the most prevalent theories of visual attention. Its assumptions are fundamentally based on electrophysiological studies and the critical observation that smaller receptive fields of sensory neurons at lower hierarchical levels compete to drive larger higher level receptive fields (Desimone & Duncan, 1995). Clearly, larger receptive fields cover a greater angle of a visual scene, but can only represent, i.e. respond to, one object at a time. When multiple objects fall within a cell's receptive field, they are assumed to compete for the limited processing resources. Single-cell recordings in monkeys confirmed that objects compete in this mutually suppressive matter in higher visual cortices, such as in areas V2 and V4, but not in

primary visual cortex, where receptive fields are smaller and unlikely represent multiple competing objects (e.g. Luck *et al.,* 1997; Reynolds, Chelazzi & Desimone, 1999). In the human brain, evidence for neuronal competition have been found using functional magnetic resonance imaging (fMRI) (e.g. Beck & Kastner, 2005; Kastner *et al.,* 1998; Kastner *et al.,* 2001). The probability by which an object is represented depends on two distinct kinds of bias signals. Bottom-up biases result from the properties of an object, e.g. its perceptual saliency or novelty, while top-down biases reflect requirements of the task, e.g. to attend to a certain spatial location. Taken together, biased completion theories hold the assumption that attention is an emerging property of competition between all objects in the visual field which is biased by characteristics of the objects and task requirements, or in other words by bottom-up and top-down influences.

1.1.2. Core Principles and Equations of TVA

The core idea of TVA holds that attentional selection means to make a perceptual categorization following the form 'element *x* belongs to category *i*'. An object is said to be selected or categorized as soon as the categorization enters the visual short-term memory (STM) store. In this sense selection and categorization are no longer thought to occur after each other (cf Deutsch & Deutsch, 1963; Treisman & Gelade, 1980), but happen simultaneously. The visual STM store has limited capacity such that only a very few objects can be maintained at a time. The way in which multiple objects strive towards the visual STM store is described as a parallel race which is governed by the mechanisms of biased competition. According to TVA, each object in the visual field is assigned with an attentional weight reflecting the importance of that element according to either reflexive bottom-up bias signals that separate figure from background or goal-driven top down bias signals. The following weight equation determines the computation of the weight values:

$$w_x = \sum_{j \in R} \eta(x, j)\pi_j$$

where the weight of an object is given by the sensory evidence η that element x belongs to category i of response set R, and the pertinence value π of category i. The rate equation below gives full account of the moment-to-moment probability that a categorization 'x belongs to i' will be encoded into the visual STM store

$$\nu(x, i) = \eta(x, i)\beta_i \frac{w_x}{\sum_{z \in S} w_z}$$

where the rate of categorizing $\nu(x,i)$ is a function of the sensory evidence η that element x belongs to category i, the perceptual decision bias β associated with this category i and the weight w_x of one object relative to the summed weights $\underline{w_z}$ of all the other objects in the stimulus set S. Provided with a sensory system that informs about the strength of sensory evidence and given completed computation of pertinence values and attentional weights, the attention system performs visual selection according to the rate equation. Visual attention is assumed to be determined by five latent parameters which reflect aspects of the system's general capacity (visual threshold, visual STM storage capacity, processing speed) and specific (task-related and spatial) attentional weighting. The TVA framework provides simple assessment and model-fitting procedures on which basis these four parameters can be mathematically estimated (Duncan *et al.,* 1999). This is an essential advantage to which will be returned in later sections. Importantly, TVA's principles seem to not only work in theory, but represent a valid description of how humans select visual information. Bundesen (1990) used TVA's quantitative precision to model a large proportion of empirical findings on human performance in classical visual recognition and attention tasks.

1.1.3. Anatomy of the Visual Attention System

A general neurobiological interpretation of the given equations was proposed at the level of single cells. The Neuronal Theory of Visual Attention (NTVA, Bundesen, Habekost & Kyllingsbæk, 2005) holds that visual attention is realized in a distributed network of cortical and subcortical areas, in which the posterior cortex is roughly regarded as the target site where attentional modulation takes effect. Visual information from the eyes is transmitted via the lateral geniculate nucleus (LGN) to striate and extrastriate cortical areas which compute the strength of perceptual evidence. These η values are multiplied by the pertinence values π that had been earlier generated in higher-level brain regions probably outside the visual system. Subcortical areas, in particular the pulvinar nucleus of the thalamus, hold the basic topographical map of attentional weights (i.e. the priority map). Resulting weighting signals (w values) are transmitted back to the visual cortex to initiate a second selective wave of processing. When the race starts, all categorizations of an

object strive towards the visual STM store, while their speed (v value) depends on the product of η and β values. The visual STM map of spatial locations is probably situated in the thalamic reticular nucleus. From there, information about the winners of the race is back projected to the LGN and thereby sustains neuronal activity related to the winners by positive feedback.

In summary, TVA provides a computational framework of normal visual attention, thereby integrating the problem of visual recognition and attentional selection into a unified theory. Its central assumptions are formulated in basic algebra given by the weight and rate equation. Recently, TVA's principles had been interpreted at the level of thalamo-cortical and cortico-cortical circuits of the posterior brain. Given the dependence on intact functions of a large network, visual attention is frequently targeted by various clinical conditions.

1.2. Methodological Basis: Assessment of Visual Attention Deficits

Disturbances of visual attention are observed after many different kinds of brain damage and neuropathology, covering neurodevelopmental disorders, acquired brain injury or neurodegenerative diseases. As a consequence, research on visual attention deficits is a broad and inconsistent field. To overcome this heterogeneity and progress in the understanding, diagnosis and treatment of attention deficits, it is crucial to elucidate how certain types of brain damage affect visual attention functions. Yet, a major drawback towards this goal are the methodological issues of many clinical studies, particularly related to the week and unspecific conceptualization and measurement of attention deficits. This section outlines a) the limitations of conventional assessment tools; b) how they can be overcome by TVA-based measurement; and c) the here applied approach of combining TVA-neuroimaging analysis.

1.2.1. Conventional Measurements

To be useful, a neuropsychological test score should reflect a relatively pure measure of a specific aspect of the patient's cognitive abilities. The most critical constraint of conventional assessment of visual attention is that often several abilities are necessary in order to perform well, and a low score hence reflects a quite nonspecific finding. Many classical tests are confounded by motor functions.

For instance, reaction time tasks or other types of speeded responses are conventionally used to determine processing speed deficits. A prominent example is the digit symbol substitution test (Wechsler, 1997), where digits and symbols are paired and patients should write down as fast as possible under each newly given digit the corresponding symbol. The number of correct symbols within the allowed time is measured. Besides the pure processing of visual information, this tasks incorporate complex motor components (e.g. the patient has to manually write symbols) that very likely contribute to response latency scores. More fundamentally, test performance cannot be easily related to a basic component of visual attention. Instead, test scores are bound to the complex task used for the assessment. Visual STM deficits are traditionally measured by immediate memory span tasks. For example, in the Corsi block-tapping test (Corsi, 1973) patients are asked to observe a sequence of blocks being tapped by the examiner, and then repeat the sequence. The number of blocks increasingly grows, whereby the sequence length which can be correctly reproduced is assessed. A serious constrain of the Corsi and many other attention span tasks is that the serial and relatively long presentation of stimuli allows verbal recoding. The use of rehearsal strategies critically impedes the pure measurement of the visual (non-strategic) attention span. To state it more generally, conventional measurements of visual attention are influenced by quite complex motor and cognitive abilities preventing a clear interpretation of the test scores. These main limitations, poor specificity and validity, can be primarily traced back to conventional tests' foundation in the clinical routine. The designs of such tests are often determined by practicability rather than conceptual considerations. Lacking a theoretical background is also one reason why classical tests fall short on other important quality characteristics such as sensitivity and reliability.

1.2.2. Parametric Measurements

A potential way to resolve these limitations is offered by parametric measurements of visual attention adopted form TVA. Within this framework, five central attention parameters can be estimated based on individual performance in two simple whole and partial report experiments. The basic test design is as follows. In the whole report, an array of briefly flashed objects (usually letters) is presented on the screen, while participants maintain central fixation and the task is to identify and verbally

report as many objects as possible. Presentation times are set in a way that they cover the whole range from an individual's perception threshold up to near-ceiling performance. This design allows to quantify three general capacity factors of visual attention: 1) *t0*, visual threshold, 2) *K*, visual STM storage capacity and 3) *C*, visual processing speed. In the partial report, participants are required to identify and verbally report only a subset of stimuli specified by an a priori given criterion (usually color). This design reveals values for two selective factors of visual attention: 4) α, efficiency of top-down control and 5) w_λ, spatial distribution of visual attention. A more detailed description of the test and model fitting procedures can be found elsewhere (Duncan *et al.,* 1999).

The main advantage of TVA-based measurement is the method's high specificity. Due to the mathematically independent fitting procedures, attentional parameters can be quantified separately from each other and with high precision. They are furthermore not confounded by motor slowing, since non-speeded verbal responses are used. Unlike many other neuropsychological tests, the method rests upon a theoretical framework that explains a wide range of the empirical effects in the literature on normal visual attention (Bundesen, 1990). Consequently, the estimated attention parameters can be interpreted as basic elements of visual attention that have been identified in the general theory. Other main strengths of the TVA method are its high sensitivity to detect attention deficits which went unnoticed by using other neuropsychological tests (e.g. Habekost & Rostrup, 2006) and its reliability which has been approved in healthy participants and patients (Finke *et al.,* 2005; Habekost, Petersen & Vangkilde, 2014; Habekost & Rostrup, 2006).

From a practical viewpoint, it is convenient that all parameters are derived in one integrated test set-up including simple instructions and minor response requirements. Using the same set of stimuli and response formats results in highly consistent measures of lateralized and non-lateralized aspects of visual attention. The fact that the experiments can be tailored to different research interests and clinical groups (e.g. by changing layout and the stimuli of the display) as well as to the individual performance level (by adopting the exposure duration) ensures maximal flexibility for many types of studies. Another important quality is that TVA's computational principles had been already specified at the single-cell level,

and recent neuroimaging studies expand our knowledge of their neuroanatomical correlates within the healthy brain (e.g. Gillebert *et al.,* 2012).

Owing to its many advantages compared to conventional neuropsychological tests, about 30 investigations have used TVA-based assessment today to study visual attention deficits in patients with neglect (Duncan *et al.,* 1999; Duncan *et al.,* 2003), parietal versus frontal stroke (Bublak *et al.,* 2005; Peers *et al.,* 2005), Alzheimer's disease (Bublak *et al.,* 2011; Redel *et al.,* 2012), Huntington's disease (Finke *et al.*, 2006; Finke *et al.*, 2007), pure alexia (Starrfelt, Habekost & Leff, 2009; Habekost *et al.,* 2014), and attention deficit/hyperactivity disorder (ADHD) (Finke *et al.,* 2011; McAvinue *et al.,* 2012).

1.2.3. Integrating Parametric Measurements with Neuroimaging

The cognitive specificity and neuronal description of TVA offers a comprehensive basement to more precisely identify the effect of brain damage on specific attention functions. Yet large portions of the TVA literature does not incorporate brain imaging (e.g. Bogon *et al.,* 2014; Bublak *et al.,* 2011; Redel *et al.,* 2012; Starrfelt, Habekost & Leff, 2009) or use a rather subjective and non-automated evaluation of lesion anatomy (e.g. Duncan *et al.,* 1999; Habekost & Rostrup, 2007, 2006; Peers *et al.,* 2005). In addition, a few earlier conclusions are based on case reports and should be interpreted with some caution (e.g. Duncan *et al.,* 2003; Habekost & Bundesen, 2003). To explore its usability we applied an integrated TVA-neuroimaging approach in two exemplary clinical groups with either a neurodevelopmental (preterm birth) or a neurodegenerative condition (posterior cortical atrophy). Both of them are known for experiencing visual attention deficits and showing brain changes in attention-related brain areas and networks. Additionally, those examples were chosen to be quite dissimilar in terms of age and neuropathology for illustrating that the drawn conclusions are not restricted to a certain context. Thus, studying those clinical groups allowed us to systematically investigate the relationship between TVA parameters, supposedly reflecting very basic aspects of the visual attention system, and pathological brain changes. If close behavior-brain relationships can be demonstrated, this may have broader implications for a) extending the combined TVA-neuroimaging approach to other patient groups, b) developing or improving diagnoses and therapeutic interventions,

together with appropriate evaluation criteria, and for c) the validation of the principles of TVA and their neuronal interpretation. We will return to these points in the General Discussion section.

Taken together, disturbances of visual attention follow from various kinds of brain damage. Our understanding of these processes is, however, largely constrained by the nonspecific measurement of visual attention based on conventional neuropsychological assessment. In contrast, whole and partial report experiments combined with TVA model-fitting procedures allow to estimate basic attentional functions in "process-pure" and mathematically independent measures. Combined TVA-neuroimaging approaches may offer a promising tool to elucidate the neuronal correlates of attention deficits, an idea which we tested in two clinical examples.

1.3. Clinical Examples of Visual Attention Deficits

Two clinical groups were chosen in which attention deficits exist, but which had never been investigated with TVA-based assessment. Preterm birth as well as PCA represent clinical conditions with diffusely distributed pathology affecting large-scale brain networks relevant for attention. The current section introduces the two study groups by reviewing the related literature on a) attention deficits as well as b) brain changes and c) proposes how they may be linked with each other.

1.3.1. Example 1: Early Developmental Disturbances

Current progress in neonatal intensive care results in sharply increased survival rates of very immature infants. In 2010, estimates of preterm birth rates showed that 14.9 million infants had been born preterm which are 11.1 percent of all livebirths worldwide (Blencowe *et al.,* 2012). Hence, long-term consequences of preterm birth become a major concern with clear socioeconomic relevance (Moster, Lie & Markestad, 2008).

Attention Deficits

Especially deficits of visual attention have been described as one of the most pronounced sequelae following prematurity which may be responsible for many other cognitive disadvantages (major reviews are Anderson, 2014; Jong, Verhoeven & van Baar, 2012; Mulder *et al.,* 2009; van de Weijer-Bergsma, Wijnroks &

Jongmans, 2008). Numerous investigations on premature infants and pre-schoolers found less efficient performance across all attention domains compared to term controls: they are less efficient to orient their attention to objects or events in their environment, they shift their attention more slowly and have problems to maintain anticipatory attention (van de Weijer-Bergsma, Wijnroks & Jongmans, 2008). More recent large-scale studies replicated those findings in 8-year-old children (Anderson *et al.,* 2011; Jaekel, Wolke & Bartmann, 2013) and adolescents (Wilson-Ching *et al.,* 2013) born prematurely.

During recent years, data on the neuro-cognitive outcome of preterm birth in young adulthood have become available due to several longitudinal cohort studies and from large-scale Scandinavian national databases (for an extensive review see Saigal, 2014). However, a key limitation for interpreting available findings is that the measures different studies used varies remarkably and are most of the time rather unspecific. Many studies compared global measures, from which can be assumed that they rely, at least partially, on efficient attentional processing. For instance, most reports indicate that preterm born young adults still have lower full-scale IQ scores compared to those born at term. Moreover, rates of educational achievement, employment and independent living seem to be slightly diminished in preterm individuals (major reviews are Doyle & Anderson, 2010; Hack *et al.,* 2002; Hack, 2009; Jong, Verhoeven & van Baar, 2012; Saigal & Doyle, 2008; for a meta-analysis see Kormos *et al.,* 2014). More direct indications for long-lasting attention deficits come from data showing that elevated problems of ADHD reported in childhood still exist in preterm born young adults (Lund *et al.,* 2011; Sonja Strang-Karlsson *et al.,* 2008; van Lieshout *et al.,* 2015). In addition, some studies examined executive functions, comprising tests of visual selectivity and attention as well (e.g. measure by the Visual Search and Attention Test), and generally found that preterm born adults perform more poorly relative to their term born peers (Hille *et al.,* 2007; Nosarti *et al.,* 2007; Pyhälä *et al.,* 2011; Skranes & Løhaugen, 2016; Strang-Karlsson *et al.,* 2010). Due to the lack of more specific follow-up investigations, it is still unclear whether or not attention abilities of preterm adults catch up with those of full-terms at comparable age. Yet, it seems likely that some basic attentional functions are still less efficient, which may explain the global cognitive deficits observed more than two decades after preterm birth.

Brain Changes

Preterm neonates are at high risk of brain injury. The major type of brain lesions are focal white matter (WM) injuries, i.e. periventricular leukomalacia. Modern MRI techniques show that even in the absence of focal lesions, preterm birth is often accompanied by diffuse neuronal, axonal and glial damage extending to deep grey matter (thalamus), cortical and cerebellar areas (major reviews are Deng, 2010; Volpe, 2009; Ment, Hirtz & Hüppi, 2009; Salmaso *et al.,* 2014). The unique vulnerability of the premature brain has to be considered in front of the major changes it undergoes during the late second and third trimester of gestation including: differentiation of the foetal subplate zone, alignment and layering of cortical neurons, expansion of axons and dendrites, as well as selective pruning of synapses and glia cells (Miller & Ferriero, 2009). Major neurobiological models of early brain injury propose that initially destructive processes (e.g. loss of oligodendrocytes due to perinatal insults, such as ischemia or inflammation) are followed by secondary maturational disturbances (Deng, 2010; Volpe, 2009). Microstructural damage during the perinatal period, particularly disruptions in a) the formation of structural connectivity between thalamo-cortical and cortico-cortical regions (Kostović & Judaš, 2010; McQuillen & Ferriero, 2005), and b) the emergence of synchronous brain signaling (Bartos, Vida & Jonas, 2007), has been associated with a large-scale reorganization of the preterm brain's intrinsic network architecture (Doria *et al.,* 2010).

Intrinsic functional connectivity (iFC) is characterized by temporally and spatially coherent patterns of low-frequent (< 0.1 Hz) fluctuations of the blood oxygenation level-dependent (BOLD) signal measured by fMRI (Biswal *et al.,* 1995). These patterns correspond to known neuroanatomical systems (Smith *et al.,* 2009), and are consistent across individuals (Damoiseaux *et al.,* 2006), different states of consciousness (Horovitz *et al.,* 2008), and even species (Vincent *et al.,* 2007). Thus, intrinsic brain networks (IBN) are thought to represent a principle, functionally relevant organization of the mammalian brain. The emergence of IBN has been placed mainly within the last trimester of gestation (Fransson *et al.,* 2007; Smyser *et al.,* 2010). In a longitudinal investigation, Smyser et al. tracked the development of IBN from fragmented but recognizable elements at 30 weeks of gestation to an adult-like repertoire at term (40 weeks). Moreover, the authors report that very

preterm infants (< 26 weeks) exhibit less mature and abnormally formed IBN at term age (see also Fuchino *et al.,* 2013). Changes of iFC seem to be only partially caused by WM lesions (Smyser *et al.,* 2013), but even exist without evident structural injury (Smyser *et al.,* 2014). These findings suggest that the functional network architecture of preterm and full-term infants follow diverging developmental trajectories during the perinatal period, because of distinct experiences, physiological and structural development. Differences still persist into childhood (Damaraju *et al.,* 2010), and as recent data from our group shows have not disappeared by adulthood. Instead, we observed wide-spread patterns of decreased and increased iFC in the pre- versus full-term adult brain (Bäuml *et al.,* 2014; see also White *et al.,* 2014). Rather than a delay in maturation, these results indicate a systematic and long-lasting reorganization of the cerebral functional architecture in association with preterm birth.

Linking Attention Deficits and Brain Changes

Critically, thalamic, visual and dorsal attention IBN – brain systems which are essential for visual attention – are among those networks showing long-term effects of preterm birth. It is likely that observed re-modelling of iFC in attention-related IBN plays a role in the attention deficits experienced by preterm born individuals. There is strong support for the idea that attention operates on low-frequent (< 1 Hz) spontaneous oscillations to control neuronal excitability via cross-frequency coupling (evidences in rabbits Bishop, 1932, monkeys Lakatos *et al.,* 2008 and humans Besle *et al.,* 2011, for a review see Schroeder & Lakatos, 2009). Following this notion, the dynamic organization of the brain in large-scale, yet flexible, networks allows tuning the ongoing fluctuations of neuronal excitability (mediated by slow cortical potentials, He *et al.,* 2008) to the temporal stream of task-relevant events (for reviews on the relevant cellular processes see Vaishnavi *et al.,* 2010). The resting-state BOLD signal clearly represents a focused (frequency-limited) view on these events. Still, it provides a unique window for the non-invasive investigation of task-relevant neuronal processes which are intrinsically realized in the rhythmic, ongoing activity of the human brain (Raichle, 2010, 2011; Zhang & Raichle, 2010).

Integrated investigations of resting-state and event-related fMRI showed that ongoing fluctuations in the BOLD signal significantly contributes to the trial-by-

trial variability in task-evoked signals (Fox *et al.,* 2006) and variability in the related behavior (Fox *et al.,* 2007). Regarding visual attention, iFC have already been linked to individual differences of attentional performances in healthy participants (Sali, Courtney & Yantis, 2016), and to attention deficits in patients with ADHD (Hoekzema *et al.,* 2014; Sripada, Kessler & Angstadt, 2014, for a review see Parks & Madden, 2013). To date no study has examined whether and how altered iFC in attention-related IBN are linked to the adverse development of visual attention in preterm born individuals. Two different hypotheses exist. First, changes in iFC may express an impaired functional organization of the preterm adult brain, whereby stronger iFC alterations lead to more severe attention deficits. Or alternatively, changed iFC may constitute a compensatory mechanism to mitigate harmful consequence of preterm birth, such that stronger iFC alterations lead to less severe attention deficits.

1.3.2. Example 2: Late Neurodegenerative Disturbances

We now move to the last decades of the life span, where the risk of developing dementia increasingly grows. The most common form of dementia arises from Alzheimer's disease (AD) and is primarily associated with memory deficits. However, in very rare cases, neuropathology is largely restricted to primary visual and visual association cortices (Hof *et al.,* 1997; Renner *et al.,* 2004; Tang-Wai *et al.,* 2004). This neurodegenerative syndrome is known as posterior cortical atrophy (PCA).

Attention Deficit

According to the atrophy pattern, patients with PCA show a fairly selective deficit of visual attention and other higher visual and visuospatial skills. Salient features of PCA include Balint's syndrome (simultanagnosia, optic ataxia and ocular apraxia) and Gerstman's syndrome (agraphia, acalculia and finger agnosia) (Benson, Davis & Snyder, 1988). Full presentations of Balint's and/or Gerstman's syndrome are rare. Instead, patients commonly show single components of either syndrome. The most widely observed symptom, affecting 82-92% of PCA patients, is simultanagnosia (Kas *et al.,* 2011; Tang-Wai *et al.,* 2004). It refers to the impaired awareness of more than one visual object at a time (Bálint, 1909). By definition, simultanagnosia is not caused by restricted vision, eye or head movements what is

evidenced by patients' ability to name single items of a visual scene. Instead, they are no longer able to integrate individual elements to form a meaningful whole (Wolpert, 1924), a condition which is tremendously disturbing for daily life functioning. For example, a very typical disabling impairment are reading difficulties (Beh *et al.,* 2014). Simultanagnosia has been grossly characterized as a deficit of visual attention (e.g. Rizzo & Robin, 1990), though the specific underlying impairment has not been fully elucidated.

Two alternative accounts of simultanagnosia had been proposed. The first approach dates back to a single case report of a patient whose STM memory capacity seemed to be so much decreased that he could only perceive one object at a time. Speed of perceptual processing for a single item, on the other hand, occurred to be normal (Coslett & Saffran, 1991b; see also Pavese *et al.,* 2002). In a large review article, Rizzo and Vecera (2002) proposed that the investigation of STM capacity deficits might be especially fruitful for our understanding of the specific defects causing simultanagnosia. More recent studies were able to more systematically investigate the independent contribution of impaired STM capacity and processing speed to symptom occurrence. By using TVA-based assessment, Duncan et al. (2003) demonstrated that two patients with simultanagnosia following stroke suffered from extremely reduced rates of visual processing speed. The authors argue that in complex scenes where multiple objects compete for processing resources, a severe slowing of processing speed might cause perceptual failure for all but the most salient object. Consistently, Finke and colleagues (2007) revealed a significant correlation between slowed visual processing speed and severity of simultanagnosia in patients with Huntington's disease. The controversy of whether reduced STM storage capacity or visual processing speed leads to simultanagnosia has not been reconciled yet. This is mainly because the literature is, despite of some more recent group studies (Finke *et al.*, 2007), still dominated by single case reports and non-uniform conceptualization and assessment of visual attention (Rizzo & Vecera, 2002).

Brain Changes

Although the most common underlying cause is AD, other kinds of neuropathology have been reported to result in PCA, including corticobasal degeneration, dementia with Lewy bodies, and prion disease (Renner *et al.,* 2004; Tang-Wai *et al.,* 2004).

Only cases with underlying AD will be considered here. Histopathological examinations evidence that PCA is characterized by a focal accumulation of senile plaques and neurofibrillary tangles in parietal, occipital and posterior temporal brain regions, particularly in Brodmann areas 17 and 18 (Hof *et al.,* 1997; Tang-Wai *et al.,* 2004). Investigations of Lehmann and colleagues in relatively large patient groups extensively broadened our understanding of the neuroimaging profile of PCA. The authors used voxel-based morphometry (VBM) to quantify and localize patterns of atrophy based on anatomical MRI scans in an objective and fully-automated manner. Compared to healthy control participants, the researchers found enormous volume loss within the cerebral posterior hemisphere, whereby the occipital and parietal lobe showed the greatest reductions, with superior parietal cortex being on average 20% smaller in patients, followed by areas in the temporal lobe (Lehmann *et al.,* 2011; Lehmann *et al.,* 2012). This atrophy pattern is syndrome-specific as a direct comparison between PCA and patients with the amnestic AD or logopenic AD variant reveals (Lehmann *et al.,* 2011; Lehmann *et al.,* 2012; Lehmann *et al.,* 2013b; Caso *et al.,* 2015, for a review see Alves *et al.,* 2013). VBM analyses of white matter (WM) volume show extensive atrophy within posterior brain regions in PCA patients relative to healthy controls. Specific volume loss compared to other AD variants, was observed in bilateral dorsal occipito-parietal and ventral occipito-temporal regions along the major visual pathways (Migliaccio *et al.,* 2012a). Results from diffusion tensor imaging (DTI) confirm bilateral microstructural changes in the major association bundles, e.g. inferior fronto-occipital, superior and inferior longitudinal fasciculus, as well as in the splenium and thalamic radiations (Caso *et al.,* 2015; Cerami *et al.,* 2015). Beyond structural grey matter (GM) and WM changes, PCA had been reported to affect many different characteristics of the posterior brain, including large-scale functional connectivity (Lehmann *et al.,* 2013b; Migliaccio *et al.,* 2016), glucose metabolism (Lehmann *et al.,* 2013a; Nestor *et al.,* 2003), and brain perfusion (Kas *et al.,* 2011).

Linking Attention Deficits to Brain Changes

Relatively little work has been done to systematically associate PCA patients' brain lesions with their deficits of visual attention. No study has been carried out with regard to simultanagnosia. The most influential work on the neuroanatomical

underpinnings of simultanagnosia comes from the stroke literature. Chechlacz et al. (2012) compared lesion patters between stroke patients with symptoms of simultanagnosia versus unilateral visuospatial attention deficits (neglect, extinction). Lesion subtraction and VBM analyses revealed that damage to both GM and WM areas is linked to simultanagnosia. In more details, symptoms of simultanagnosia were related to GM lesions within large portions of the occipital (bilateral calcarine, cuneus and parieto-occipital fissure, left middle and superior occipital gyrus) and parietal cortex (right intraparietal sulcus, bilateral postcentral and superior parietal gyri). Regarding WM damage associated with simultanagnosia, the bilateral occipital and parieto-occipital lesions found here indicate a critical role for damage within long association pathways. A further characterization of WM lesions by DTI tractography confirms that especially bilateral microstructural impairments within the main projection fibers of the visuospatial attention system underlie deficits of simultaneous perception. Preliminary evidences from a DTI study of two PCA patients support the idea that disruptions of the superior and inferior longitudinal fasciculus as well as the inferior fronto-occipital fasciculus are necessary for the occurrence of simultanagnosia (Migliaccio *et al.,* 2012b). Following the notion of Duncan et al. (2003), Chechlacz and colleagues proposed that the observed reduction of structural connectivity might have led to a slowing of processing speed and by that caused simultanagnosia. Yet, this speculative neuro-cognitive model of simultanagnosia has never been tested empirically.

In summary, while previous work in both clinical groups points towards substantial disturbances of visual attention, no investigation to date has systemically assessed the effect of preterm birth or posterior cortical atrophy on basic visual attention functions by means of TVA-based assessment. From earlier studies we know that both groups show changes in attention-related brain areas or networks. Yet, the relationship between these neuronal changes and attention deficits is not sufficiently understood.

1.4. Aims of This Thesis

The overarching goal of the current thesis was to use neuro-cognitive modelling to systematically link deficits of visual attention and underlying brain changes. To this

end, the computational Theory of Visual Attention (TVA) combined with modern structural and functional MRI techniques were applied in a neurodevelopmental (preterm birth) and neurodegenerative (posterior cortical atrophy (PCA)) condition with attention deficits. We aimed to utilize the specificity of model-based assessments of latent, "process-pure" and independent parameters of visual attention in order to establish robust behavior-brain relationships. With regard to preterm birth, attention problems are the most prominent sequelae which may even persist into adulthood. Long-lasting alterations of intrinsic functional connectivity (iFC) in attention-related brain networks seem to be a potentially underlying mechanism. However, previous studies have not yet identified which specific attention process is impaired and how it is linked to changes of iFC in preterm bon adults. The first project of the current thesis assessed the specific long-term effect of preterm birth on basic attentional functions and the nature of the relationship to alterations of intrinsic brain networks. With regard to PCA, perception of simultaneously presented object is often severely impaired (simultanagnosia) due to degenerative processes within the visuospatial attention system. However, controversies exist about which attention deficit underlies simultanagnosia and how it is related to grey matter (GM) and white matter (WM) atrophy. The second project of the current thesis systematically investigated the cognitive and neuroanatomical features of simultanagnosia in a relatively large group of patients with PCA.

To broaden our understanding of the relationship between attention deficits and changes of the large-scale structural and functional architecture of the human brain, the current thesis focuses on the following research questions:

Project 1

a) Besides the observed attention deficits in childhood, does preterm birth have specific long-lasting effects on the attention system's general capacity (perceptual threshold, short-term memory (STM) capacity, visual processing speed) or selective (spatial, task-related) weighting? To answer this question, we compared TVA-based attention parameters between formally preterm and term born adults who took part in the prospective Bavarian Longitudinal Study.

b) Are impaired attention parameters linked to changes of iFC in the thalamic, visual and dorsal attention network, and does the nature of this relationship reflect a detrimental or compensatory mechanism? For each preterm adult, we correlated attentional performance scores with the strength of iFC within clusters showing a significantly altered functional organization between pre- versus full-term born participants.

Project 2

a) Do deficits of STM capacity or visual processing speed contribute to the occurrence of simultanagnosia? To answer this question, we compared independent estimates of STM capacity and visual processing speed between patients with PCA and healthy control participants and tested, in a regression analysis, which one of both attentional parameters significantly predicts patients' simultanagnosia symptoms.
b) Does GM or WM atrophy predict impairments of visual attention parameters? Volumetric changes of GM and WM were assessed by voxel-based morphometry and compared between study groups. We subsequently related, in a voxel-wise regression analysis, patterns of GM and WM atrophy to patients' deficits in visual attention functions.

2.

Project 1: Visual Attention in Preterm Born Adults: Specifically Impaired Attentional Sub-mechanisms that Link with Altered Intrinsic Brain Networks in a Compensation-like Mode

The current chapter includes a research article entitled "Visual attention in preterm born adults: Specifically impaired attentional sub-mechanisms that link with altered intrinsic brain networks in a compensation-like mode". This article showed for the first time that short-term memory storage capacity is selectively impaired in preterm born adults, and cortical changes in intrinsic functional connectivity seem to compensate for these adverse consequences of prematurity on visual attention development. The manuscript was published in NeuroImage in 2015.

Contributions:

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The author of this thesis is the shared first author of this manuscript together with K.F. J.N., K.F. and C.S. conceived the experiment. B.B., N.B. and P.B. recruited participants. J.N. and P.R. conducted behavioral data acquisition and J.B., C.M., M.D. and L.S. conducted fMRI data acquisition. J.N. analyzed behavioral and imaging data, under the supervision of C.S. J.N. and K.F. wrote the manuscript, which was commented on and reviewed by J.J., P.B., H.B., H.J.M, T.H., A.W., D.W. and C.S.

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Visual attention in preterm born adults: Specifically impaired attentional sub-mechanisms that link with altered intrinsic brain networks in a compensation-like mode

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ABSTRACT

Although pronounced and lasting deficits in selective attention have been observed for preterm born individuals it is unknown which specific attentional sub-mechanisms are affected and how they relate to brain networks. We used the computationally specified 'Theory of Visual Attention' together with whole- and partial-report paradigms to compare attentional sub-mechanisms of pre- (n = 33) and full-term (n = 32) born adults. Resting-state fMRI was used to evaluate both between-group differences and inter-individual variance in changed functional connectivity of intrinsic brain networks relevant for visual attention.

In preterm born adults, we found specific impairments of visual short-term memory (vSTM) storage capacity while other sub-mechanisms such as processing speed or attentional weighting were unchanged. Furthermore, changed functional connectivity was found in unimodal visual and supramodal attention-related intrinsic networks. Among preterm born adults, the individual pattern of changed connectivity in occipital and parietal cortices was systematically associated with vSTM in such a way that the more distinct the connectivity differences, the better the preterm adults' storage capacity.

These findings provide first evidence for selectively changed attentional sub-mechanisms in preterm born adults and their relation to altered intrinsic brain networks. In particular, data suggest that cortical changes in intrinsic functional connectivity may compensate adverse developmental consequences of prematurity on visual short-term storage capacity.

Introduction

Preterm birth (<37 weeks of gestation) is a substantial risk factor for suboptimal neurocognitive development with disadvantages persisting into adulthood (Baron and Rey-Casserly, 2010; D'Onofrio et al., 2013; Wolke and Meyer, 1999). Due to improvements in medicine and demographic changes preterm birth and survival rates are increasing with a global prevalence of about 10% (Blencowe et al., 2012). In order to identify specific neurocognitive targets for potential intervention, it is important to scrutinize the long-term cognitive and neuronal changes following preterm birth.

Specific functional weakness in preterm born individuals, which persists into early adulthood and is not explained by global cognitive deficit, has been observed for visual attention (Anderson and Doyle, 2003; Atkinson and Braddick, 2007, 2012; Mulder et al., 2009; Shum

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et al., 2008; Strang-Karlsson et al., 2010; van de Weijer-Bergsma et al., 2008). Attention deficits and their long-term stability are documented, for example, by changed eye movement at infancy (Atkinson and Braddick, 2012; van de Weijer-Bergsma et al., 2008), by deficits in neuropsychological tests at school age (Anderson and Doyle, 2003; Atkinson and Braddick, 2007; Johnson, 2007; Luciana et al., 1999; Shum et al., 2008; Taylor et al., 2004), and by slower reaction times in perceptive–attentional tests in early adulthood (Strang-Karlsson et al., 2010). However, the specific cognitive mechanisms underlying such observable behavior are unknown.

The major forms of brain injury after preterm birth are subcortical white and gray matter lesions together with impaired structural connectivity (Ball et al., 2012; Eikenes et al., 2011; Ment et al., 2009; Nosarti et al., 2008; Padilla et al., 2014; Pierson et al., 2007; Srinivasan et al., 2007; Salmaso et al., 2014; Volpe, 1998, 2009). These initially rather localized lesions are assumed to lead to widespread and functionally relevant long-term consequences (Hack and Taylor, 2000; Volpe, 2009), particularly in intrinsic brain networks (Bäuml et al., 2014; White et al., 2014). Such networks organize brain activity (Fox and Raichle, 2007) and are relevant for specific cognitive functions (Laird et al., 2011; Smith et al., 2009).

In the current study, we wanted to specify sub-mechanisms of visual attention affected in adults born preterm on the basis of the "Theory of Visual Attention" (TVA) framework. Furthermore, we aimed to integrate potential cognitive changes in visual attention with changes in intrinsic functional connectivity (iFC) of intrinsic brain networks in preterm born adults.

TVA, attentional sub-mechanisms, and its neural correlates

TVA is a mathematically formulated model of selective attention (Bundesen, 1990; Bundesen et al., 2005). In TVA, visual processing is conceived of as a parallel-competitive race. Visual objects in a given display are supposed to compete for selection, i.e., conscious representation, into the capacity-limited visual short-term memory (vSTM) store. Bottom-up and top-down generated bias signals determine 'attentional weights' for objects. Depending on their relative weights, some objects are thus favored for selection. The probability of selection is determined by an object's processing rate v, which depends on the attentional weight (w) that it receives, on sensory effectiveness, and the capacity of the vSTM store (if the store is filled, the selection process terminates). In TVA, the processing speed, C, for a display is defined as the sum of all v values in the display and, thus, characterizes the visual information processing rate of a given participant. Methods that have been previously used to disentangle impaired and preserved parameters of visual attention and short-term memory in neurodevelopmental disorders such as dyslexia, ADHD and spina bifida myelomeningocele (Bogon et al., 2014; Caspersen and Habekost, 2013; Finke et al., 2011; McAvinue et al., 2012; Stenneken et al., 2011) are simple psychophysical tests of whole and partial report of briefly presented letter arrays. Integrated within the TVA framework these tests permit different parameters of visual attention in a given participant to be extracted and quantified independently, and in measurements that are not confounded by, for example, cognitive or motor slowing. Such cognitive specificity is the optimal basis for relating quantified basic parameters of visual attention performance to underlying neural networks in healthy and patient populations (Gillebert et al., 2012; Peers et al., 2005; Sorg et al., 2012; Wiegand et al., 2013). We used the TVA based approach in order to collect estimates of visual perceptual processing speed (parameter C), vSTM storage capacity (parameter K), top-down control (parameter α), and spatial laterality of attention (parameter w_λ).

With respect to normally developed brains, the neural interpretation of TVA (NTVA) (Bundesen et al., 2005) specifies that posterior visual perceptual areas are governed by bias signals generated in frontoparietal areas and by a salience map putatively located in the pulvinar (Corbetta and Shulman, 2002; Kanwisher and Wojciulik, 2000; Kastner and Ungerleider, 2000). Visual perception is assumed to rely on a parallel race of visual objects that compete for access to the limited vSTM store (Bundesen, 1990). Thalamo-cortical feedback loops are suggested to (re)-activate the same visual neurons in posterior parts of the cortex coding and maintaining the winner objects (Gillebert et al., 2012; Magen et al., 2009; Todd and Marois, 2004; Xu and Chun, 2006). Due to their reliance on widespread interconnected brain areas the TVA parameters, and particularly vSTM storage capacity, are vulnerable to interruptions or connectivity changes within large-scale brain networks (Habekost and Rostrup, 2007). Based on these areas relevant for TVA-related mechanisms, we focused our analysis on intrinsic brain networks of the posterior brain that might be a brain base for impaired attentional sub-mechanisms in preterm born adults.

Intrinsic brain networks after preterm birth and its potential link with altered attention

Large-scale intrinsic functional connectivity is organized in intrinsic brain networks, which are defined by synchronous ongoing activity (i.e. iFC) in the frequency range of 0.01–0.1 Hz (Fox and Raichle, 2007). Intrinsic networks are consistent across individuals (Damoiseaux et al., 2006), development (Fransson et al., 2007), different behavioral states (Horovitz et al., 2008), and even species (Vincent et al., 2007), and possibly represent a basic organization principle of the mammalian brain. They are functional networks i.e. their areas commonly co-activate during both non-task and task states, suggesting intrinsic networks to implement specific aspects of cognition and behavior (Laird et al., 2011; Smith et al., 2009). One possible explanation for this functional specificity is that functional connectivity at rest reflects the history of correlated activity changes during goal-directed behavior (Berkes et al., 2011; Lewis et al., 2009; Riedl et al., 2011). By the use of resting-state functional resonance imaging (rs-fMRI), precursors of intrinsic brain networks are already detectable in newborns (Fransson et al., 2009) and even preterm born infants (Doria et al., 2010), with the latter showing subtle alterations in network connectivity (Damaraju et al., 2010; Smyser et al., 2010). Recently, changed intrinsic networks have been demonstrated for preterm born adults (Bäuml et al., 2014; White et al., 2014; Wilke et al., 2013), indicating distinct developmental trajectories for intrinsic networks after preterm delivery.

Given the functional–cognitive relevance of intrinsic networks, it seems reasonable to expect that impaired mechanisms of visual attention might be related to changes of intrinsic networks, which cover posterior areas of the brain relevant for visual attention, i.e. thalamic, visual, and dorsal attention networks. In principle, two types of relationship are possible: (i) the more attention is impaired the more intrinsic connectivity is changed from that of healthy controls, reflecting detrimental effects of preterm birth; (ii) the less attention is impaired the more intrinsic connectivity is changed from that of healthy controls, reflecting compensatory response on effects of preterm birth. Beyond the pattern of altered attentional sub-mechanisms in preterm born adults, the present study investigates the nature of the relationship between altered visual attentional mechanisms and intrinsic networks of the posterior brain.

Materials and methods

Participants

Participants were recruited as part of the prospective Bavarian Longitudinal Study (BLS) (Riegel et al., 1995; Wolke and Meyer, 1999), a geographically defined whole-population sample of preterm born children and full-term controls. Of the initial sample, 33 preterm adults and 32 healthy term controls (all aged 25 to 27 years)

Table 1
Sample characteristics.

	Preterm group $n = 33$			Full-term group $n = 32$			Statistical comparison
	M	SD	Range	M	SD	Range	
Sex (f/m)	17/16			14/18			$p = 0.45$
Age (years)	26.5	±0.53	25.7–27.6	26.6	±0.54	25.7–27.9	$p = 0.68$
GA (weeks)	30.5	±2.20	27–36	39.6	±1.1	37–42	$p < 0.01$
BW (gram)	1268.8	±274.3	800–1850	3368.4	±469.3	2250–4200	$p < 0.01$
OPTI score	4.8	±1.40	1–8	2.3	±1.6	0–6	$p < 0.01$
Acuity *r*	96.88	±8.96	60–120	95.33	±9.37	60–100	$p = 0.50$
Acuity l	98.13	±6.45	80–120	97.33	±5.21	80–100	$p = 0.58$
SES	2.0	±0.80	1–3	2.0	±0.8	1–3	$p = 0.99$
Maternal age	30.3	±3.70	22–38	29.3	±6.3	18–42	$p = 0.44$
Education	5.53	±2.46	1–9	7.0	±2.21	2–9	$p = 0.04$
IQ	93.76	±10.12	72–117	99.84	±11.46	77–128	$p = 0.03$
BDI	3.06	±4.25	0–8	3.50	±5.47	0–10	$p = 0.96$
C	26.28	±10.23	9.8–53.3	25.78	±7.24	14.8–47.5	$p = 0.32$
K	2.77	±0.37	1.98–3.83	3.03	±0.47	2.47–3.89	$p = 0.03$
α	0.51	±0.22	0.09–1.22	0.52	±0.27	0.16–0.87	$p = 0.95$
w_λ	0.50	±0.06	0.35–0.60	0.49	±0.06	0.38–0.62	$p = 0.65$

Abbreviations: m: male, f: female; GA: gestation age; BW: birth weight; OPTI: optimality score of perinatal conditions; Acuity l: visual acuity of left eye at 6 years of age, Acuity *r*: visual acuity of right eye at 6 years of age; SES: socioeconomic status at birth; maternal age: maternal age at birth; education: school performance at 13 years of age; IQ: Wechsler Intelligence Test for Adults at 26 years of age; BDI: Beck Depression Inventory at 26 years of age, *C*: processing speed, *K*: visual short-term memory storage capacity, α: top-down control of attention, w_λ: spatial distribution of attention. Statistical comparisons: sex: chi-squared statistics; age, GA, BW, IQ: t-tests; OPTI, acuity *r* and *r*, SES, education, BDI: nonparametric Mann–Whitney-U-tests, *C*, *K*, α, w_λ: ANCOVAs with IQ as a covariate.

participated in TVA-based attention assessment and magnetic resonance imaging including rsfMRI. Relevant biographical and clinical data are listed in Table 1. Groups were matched in terms of sex, age, visual acuity, socioeconomic background, maternal age, and depressive symptom scores. Education level and IQ were significantly lower in the preterm group. The local ethics committee of the Klinikum rechts der Isar approved the study. All study participants gave written informed consent and received travel expenses and payment for attendance. Before participants were asked to attend examinations, each subject was carefully screened for MR-related contraindications (e.g. pregnancy, pacemaker implants). The additional 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.

Measures of prematurity, demography, and cognitive performance

Gestational age was estimated from maternal reports of the last menstrual period and serial ultrasounds during pregnancy at birth. When the two measures differed by more than two weeks, a clinical assessment with the Dubowitz method was applied (Dubowitz et al., 1970). Maternal age and birth weight were obtained from obstetric records. Perinatal medical complications were assessed with a standardized optimality scoring system (OPTI) including 15 items (e.g. amnion infectious syndrome; pathologic CTG) (Prechtl, 1967). Items were coded as 1 (non-optimal) or 0 (optimal) and summed into an index score with the higher value indicating more complications. The family socio-economic background was collected through structured parental interviews within 10 days of the child's birth. It was computed as a weighted composite score based on the profession of the self-identified head of family together with the highest educational qualification held by either parent (Bauer, 1988). Prior to attention and MRI examination, subjects were asked to take part in an assessment of 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) allowing computation of Full Scale IQ.

Behavioral assessment of TVA parameters of attention

Computational TVA framework

Briefly, in TVA-based measurement of individual attentional functions of a given participant, two parameters determine general capacity aspects: Visual perceptual processing speed *C* is the number of visual elements that can be processed by a given participant per second; vSTM storage capacity *K* quantifies the number of items that can be categorized and selected in parallel and transferred into a vSTM store (Cowan, 2001; Habekost and Starrfelt, 2009; Luck and Vogel, 1997; Sperling, 1960). Two other parameters describe specific attentional weighting processes. One is the efficiency of top-down control α and the other the laterality of the spatial distribution of attention w_λ. These weighting parameters determine how a person distributes the amount of attentional resources available when presented with multiple, alternative inputs, that is: when selective attention needs to be allocated. All TVA parameters are derived from two experimental tests, namely, whole and partial report tasks with high similarity in terms of stimulus material and response requirements, and thus of perceptual and motor skill requirements. For formal TVA descriptions and equations, maximum likelihood model fitting and software, see Kyllingsbæk (2006).

General assessment procedure

Participants underwent TVA-based assessment and fMRI scanning on the same day. Stimuli were presented on a 17-inch monitor (1024 by 1280-pixel resolution, 60-Hz refresh rate), in a dimly lit room. A chin rest was used to keep viewing distance at 50 cm. Each participant completed the whole- and partial-report, each lasting ~0.5 h, within one testing session. Task order was balanced across participants. In both experiments, first, the participants were instructed to fixate on 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. Individual exposure durations were determined in a practice session to meet a criterion value. 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 or unmasked. In unmasked conditions, the effective exposure durations were prolonged

by several hundred milliseconds due to 'iconic' memory buffering. The verbal report of individual letters was performed in arbitrary order and without stress on response speed. The experimenter entered the responses on the keyboard. The total number of trials was 288 in the partial- and 192 in the whole-report experiment, separated into blocks of 48 trials each. Within each block, the different trial types were presented equally often in randomized order.

Whole report

In the whole-report task participants were briefly presented with multiple stimuli and had to identify as many of them as possible (see Fig. 1A). On each trial, a column of five equidistant red or green letters was presented 2.5° of visual angle to the left or the right of the fixation. All letters were either red or green. The participants' task was to identify and report as many letters as possible.

In a pretest (24 trials), the individual exposure duration was determined at which the participant could report, on average, one letter correctly. In the whole report, this value was then used as the 'intermediate', together with a shorter (half as long) and a longer (twice as long) exposure duration. The preterm group's average exposure durations were 45.64 (SD = 7.83), 88.79 (SD = 19.57), and 174.48 (SD = 39.08) ms, and did not differ significantly from those of the full-term group, that were 45.17 (SD = 7.0), 82.23 (SD = 17.26), and 164.90 (SD = 33.40). Letter displays were presented either masked or unmasked. This resulted in six 'effective' exposure durations because, in unmasked displays, storage of visual information in iconic memory leads to prolonged information processing. Twelve different conditions were obtained (2 hemifields, 3 exposure durations, 2 masking conditions), each with 16 trials. Performance (i.e. the number of letters reported correctly) was measured as a function of exposure duration.

Based on accuracy in the different effective exposure duration conditions, parameters reflecting processing efficiency were modeled. In TVA the processing race depends on the dynamics of the processing system. This is expressed in an exponentially increasing probability for an object to be selected with increasing exposure duration. By the use of six effective exposure durations we aimed to measure a broad

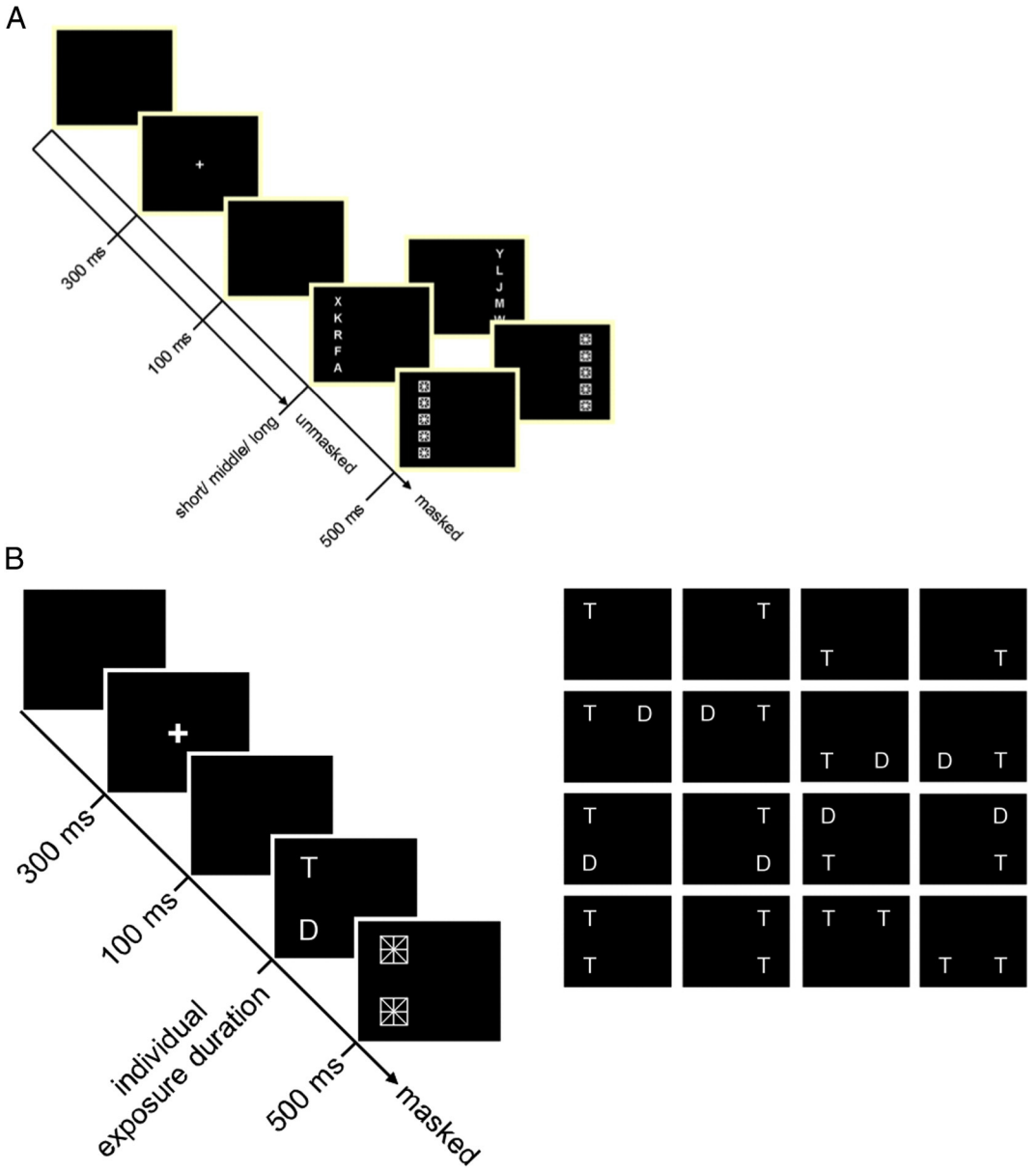

Fig. 1. Schematic illustration of the TVA tasks. (A) Whole-report paradigm: different trial types with presentation of five equidistant letters (either red or green, respectively) in columns on the left or the right of the fixation cross are shown. (B) Partial-report paradigm (left) with 16 trial types (right): 4 single target (depicted as 'T', always red), 8 target with distractor (depicted as 'D', always green) and 4 dual target conditions. (For interpretation of the references to colors in this figure legend, the reader is referred to the web version of this article.)

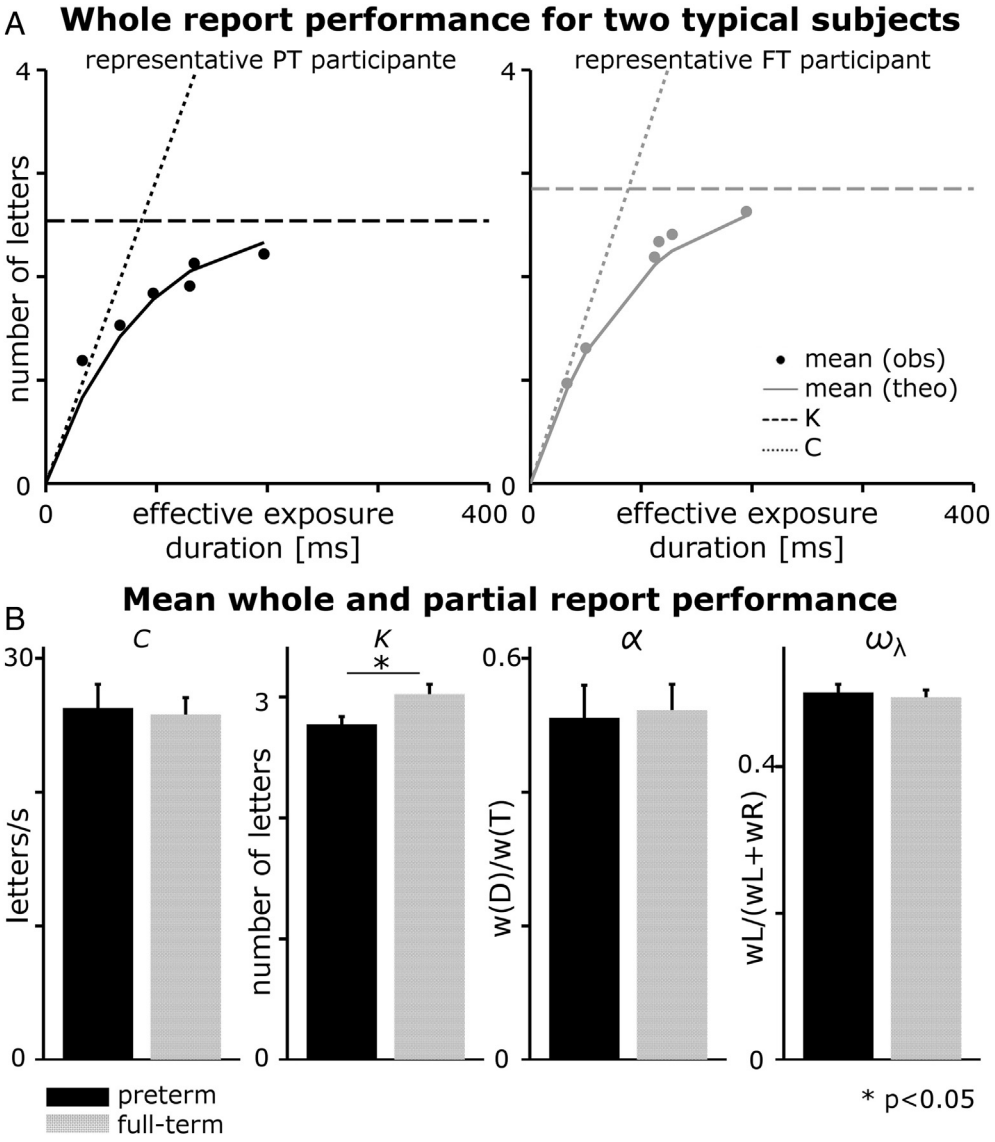

Fig. 2. (A) Representative whole report results for two subjects. Whole-report performance for a representative preterm group participant and a representative full-term group participant. Mean number of correctly reported letters as a function of effective exposure duration. Solid curves represent the best fits from the TVA to the observations. The estimate of visual short-term storage capacity *K* and processing speed *C* is marked by dashed lines. (B) Whole and partial report results. Average estimates and standard errors for parameter *K*, *C*, α (i.e. efficiency of top-down control), and w_λ (i.e. spatial laterality of attention). Analyses of covariance were used for group comparisons ($p < 0.05$).

range of performance spectrum that reflects the early as well as the late section of the participant's whole report functions, thereby allowing a reliable model fit of the data. The probability of identification was modeled by an exponential growth function in which the growth parameter reflects the rate at which objects can be processed (processing speed *C*: number of element/s) and the asymptote indicates the maximum number of objects that can be represented within vSTM (vSTM storage capacity *K*) (for illustration see Fig. 2A, left panel). Note that two additional parameters, minimum effective exposure duration ($t0$) and effective additional exposure duration in unmasked displays ($m\mu$) were also determined (and did not differ significantly between groups). Here, they mainly served the valid estimation of parameters *C* and *K*.[2]

Partial report

In the partial-report task participants had to report pre-specified (i.e., with respect to color) targets only, while ignoring distractors. In each trial either a single target (letter) or a target plus distractor (letter) or two targets appeared at the corners of an imaginary square with an edge length of 5° centered on the midpoint of the screen (see Fig. 1B). Two stimuli were presented either horizontally or vertically. Sixteen conditions (4 single target, 8 target + distracter, 4 dual target conditions) resulted. All stimuli were masked. Participants were asked to identify and report all red targets and ignore the green distracters. In a pretest (32 trials), the individual exposure duration was determined at which the participant could report single targets with 80% accuracy. In the partial report, 6 blocks, each with 48 trials, were presented. The average exposure duration determined for the preterm group was 90.21 ms (SD = 24.69); that of the full-term group was 91.5 ms (SD = 23.42).

From the probabilities of target identification, separate attentional weights were derived for left and right hemifields (w_L and w_R, respectively) and for targets (w_T) and distractors (w_D). The distribution of attentional weights across hemifields and that across target and

[2] For whole report fitting, we set up a model for variable exposure durations and fixed display size. We thresholded the maximum score to the individual highest score of the participants and, when a small number of high scores occurred (in <5% of trials), the threshold was set 1 item below the maximum. The *K* range was limited to values between this maximum score and 1 item below. Its initial score was set at the average of these two values. By setting limits to v-values (information uptake at each stimulus location), the range of *C*-estimates was 0–100. The minimum of parameters $t0$ and $m\mu$ were set to 0 and the initial values at 10 ms and 100 ms, respectively.

distractors was used for estimates of the attentional–selectivity parameters: spatial distribution of attention and top-down control. The parameter spatial distribution of attention w_λ is defined as the ratio $w_L/(w_L + w_R)$. Hence, a value of $w_\lambda = 0.5$ indicates balanced weighting, and values of $w_\lambda > 0.5$ indicate a leftward and values of $w_\lambda < 0.5$ a rightward spatial bias. Parameter top-down control α indicates the relative attentional weights of distracters compared to targets (w_D/w_T). Targets receive more weight than distracters if $\alpha < 1$. Accordingly, the lower the α-value, the more efficient the top-down control. Note that 4 additional parameters, sensory effectiveness values A, for the four display locations were fitted additionally. These again served the reliable estimation of weighting parameters and did not differ between participant groups.[3]

Analysis of behavioral data

For each participant, TVA-based model fitting yielded individual estimates for (1) C, processing speed in objects per second (2) K, vSTM storage capacity in number of objects (3) α, efficiency of top-control (4) w_λ, spatial distribution of attention. TVA performance was compared between groups by means of analysis of covariance (ANCOVA). To be independent of effects of general intelligence on potential group differences between pre- and full-term born participants, we entered IQ as a covariate in the ANCOVA model.

Functional MRI

Image acquisition

Imaging was performed on a 3 T MR scanner (Achieva TX, Philips, Netherlands) with an 8-channel phased-array head coil. Resting-state data was collected for 10 min and 52 s from a gradient-echo echo-planar sequence (TE = 35 ms, TR = 2608 ms, flip angle = 90°, FOV = 230 mm^2, matrix size = 64 × 63, 41 slices, thickness 3.58 mm and 0 mm interslice gap, reconstructed voxel size = 3.59 × 3.59 × 3.59 mm^3) resulting in 250 volumes of BOLD fMRI data per subject. T1-weighted anatomical data were gained using magnetization-prepared rapid acquisition gradient echo sequence (MPRAGE: TE = 3.93 ms, TR = 7.71 ms, flip angle = 15°, FOV = 256 mm^2, matrix = 256 × 256, 180 slices, voxel size = 1 × 1 × 1 mm^3). Immediately before undergoing the resting-state sequence, subjects were instructed to keep their eyes closed and to restrain from falling asleep. We verified that subjects stayed awake by interrogating via intercom immediately after the rsfMRI scan.

Data preprocessing

For each participant, the first five functional scans of each resting-state fMRI-session were discarded due to magnetization effects. Data were then preprocessed according to an automated in-house pipeline (Meng et al., 2013) using SPM8 (Wellcome Trust Centre for Neuroimaging, University College London, UK: http://www.fil.ion.ucl.ac.uk/spm [date last accessed 24 October 2014]). Functional volumes were realigned to correct for head motion and coregistered to the structural T1-image. Subsequently the T1-weighted image was segmented into its different departments using Unified Segmentation (Ashburner and Friston, 2005). To transform the individual images into common MNI (Montreal Neurological Institute) space, segmentation-based normalization parameters were applied to the coregistered structural and functional data. Normalized rsfMRI images were smoothed using a Gaussian kernel with a full-width at half-maximum of 6 mm to increase signal-to-noise ratio. In a final step, preprocessed functional time-series for each voxel were de-spiked using AFNI. Excessive head motion (cumulative motion translation or rotation >5 mm or 3° and mean point-to-point translation or rotation >0.15 mm or 0.1°) was applied as an exclusion criterion for movement artifacts. No subject had to be excluded. To ensure data quality, particularly concerning motion-induced artifacts, temporal signal-to-noise ratio (tSNR) and point-to-point head motion were estimated for each subject (Murphy et al., 2007; Van Dijk et al., 2012). Point-to-point motion was defined as the absolute displacement of each brain volume compared to its previous volume. Two-sample t-tests yielded no significant differences between groups regarding mean point-to-point translation or rotation of any direction ($p > 0.20$) as well as tSNR ($p > 0.35$).

Group independent component analysis

Preprocessed data from both groups was entered into a group ICA framework as implemented in the GIFT toolbox (GIFT v1.3h; http://icatb.sourceforge.net). Before performing ICA, a two-step data reduction approach was conducted using principal component analysis (PCA). First, PCA was done on the single subject level retaining 100 principal components. Large numbers of subject-specific principal components preserve most of the individual variance and have been shown to stabilize subsequent back-reconstruction (Erhardt et al., 2011). We chose a high model order ICA (number of independent components [ICs] = 75; Allen et al., 2011), since such models decompose rsfMRI data into components that are in best agreement with known anatomical and functional networks (Kiviniemi et al., 2009). In a second step, each of the subject's reduced data was concatenated in time to perform a second PCA on the group level followed by independent component analysis with the Infomax algorithm. ICs were depicted as spatial maps and corresponding IC time courses. To estimate the reliability of the decomposition, ICA was repeated 20 times by using the Icasso-toolbox (http://research.ics.aalto.fi/ica/icasso/). Reliability was quantified using the Icasso cluster quality index Iq, ranging from 0 to 1. The group ICA framework in GIFT results in a set of average group components, which are then back reconstructed into single subject space using the GICA3 back-reconstruction method. Each back-reconstructed component consists of a spatial z-map reflecting component's functional connectivity pattern across space and an associated time course reflecting component's activity across time. Spatial z-maps were used as surrogates of networks' intrinsic functional connectivity (iFC) and analyzed further.

Selection of intrinsic brain networks

To automatically select independent components reflecting intrinsic networks involved in visual attention, we conducted multiple spatial regressions on 75 independent components' spatial maps using T-maps of selected intrinsic connectivity networks as described in Allen and colleagues (Allen et al., 2011). These T-maps (Fig. 4 in Allen et al., 2011) were based on 603 healthy adolescents and adults and were made available online by the Medical Image Analysis Lab (MIALAB, http://mialab.mrn.org/data/). For each network, the independent component with the largest correlation coefficient was chosen. Networks of interest were networks covering thalamus, unimodal visual occipital cortex, and multimodal parietal cortex. These choices are based on networks' theoretical and empirical relation with the TVA framework locating networks that perform TVA-relevant operations particularly in the posterior human brain (see the Introduction section) (Bundesen et al., 2005; Finke et al., 2006; Gillebert et al., 2012; Peers et al., 2005; Sorg et al., 2012). Visual networks were represented by Allen's ICs 46, 64, and 67 (in Fig. 4 of Allen et al., 2011), multimodal parietal networks included two dorsal attention networks with IC numbers 52 and 72 in Allen et al. (2011)). Since Allen et al. did not report an explicit thalamus network, a visual inspection by two independent raters revealed such network (Kim et al., 2013). This network fulfilled the criteria of stability (ICASSO > 0.95) and was located in the gray matter thus it was used for further analysis.

[3] For partial report fitting, a model was set up with fixed display durations and variable display size. The fitting produced 4 values for target weights and 4 values for distractor weights at different exposure durations with a range of 0–1, with initial values of 1 and of 0.5, respectively. Initial values of all A parameters were 1, with a range of 1–20.

Statistical analysis of intrinsic networks across subjects

To statistically evaluate spatial maps of selected independent components, we calculated voxel-wise one-sample t-tests on participants' reconstructed spatial z-maps for all subjects, using SPM 8 ($p < 0.05$ family wise error corrected for cluster level (FWE-cluster), height threshold $p < 0.005$). Based on the resulting t-maps of one-sample t-tests we generated masks including all voxels with a value of $p < 0.001$ uncorrected. These masks were then used to restrict the search space in the subsequent two-sample t-test. The two sample t-tests for z-maps were controlled for the effects of gender and IQ as covariates of no interest ($p < 0.05$ FWE-cluster, height threshold $p < 0.005$, Bonferroni-corrected for multiple testing of 12 tests i.e. testing for 6 networks and two contrasts, respectively).

Analysis of relationship between attentional parameter and intrinsic connectivity changes

In order to link increased connectivity in intrinsic networks to attentional parameter changes, we extracted mean iFC scores for each preterm participant in those attention-related intrinsic networks, which showed significantly increased connectivity in the preterm compared to the full-term group. These mean iFC scores were correlated with TVA parameters that differed significantly between groups. In order to link decreased connectivity to attentional changes, we similarly extracted iFC scores in networks with decreased connectivity and correlated them to the critical TVA parameters. In both cases, we used partial correlation analyses controlling for variables of preterm birth (gestational age, birth weight and OPTI score) and general cognitive performance measured by Full Scale IQ. Control for prematurity-related variables in the group of preterm born adults ensures that a potential relationship between altered intrinsic connectivity and vSTM capacity is independent from specific aspects of preterm birth. Control for general cognitive performance ensures that a potential link between intrinsic connectivity and vSTM capacity is independent from severity of general cognitive impairments. Partial correlation analyses for increased and decreased iFC across networks, respectively, are thresholded at significance level $p < 0.05$ and corrected for multiple testing via Bonferroni correction.

Results

Behavioral results: reduced visual short-term memory capacity in preterm born adults

Whole report results: short-term memory capacity and processing speed

In Fig. 2A the mean number of correctly reported letters as a function of the (effective) exposure duration is presented for a representative participant from each group. The scores predicted by TVA-model fits (represented by solid curves) and the observed scores were in close correspondence. Goodness-of-fit measures averaged across all participants showed that 85% (SD = 7.32) of variance in the observed scores of the preterm group and 81% (SD = 10.14) in the full-term group was accounted for by the maximum likelihood fits. Visual processing speed C estimates were comparable between the two groups (see Fig. 2B; $F(1) = 1.05, p = .31$). Accordingly, in Fig. 2A both representative participants have similar initial slopes that approximately reflect the rate of information uptake in objects per second (high processing speed is indicated by a steep increase). vSTM storage capacity estimates were significantly lower in the preterm compared to the full-term group (see Fig. 2B; $F(1) = 5.31$, $p = 0.03$). Furthermore, we did not find any interaction effect between vSTM storage capacity and IQ ($F(1) = 0.00$, $p = 0.97$). Fig. 2A shows that with prolonged exposure duration, an asymptotic level of reported letters is reached (indicated by the dashed horizontal line), which is an approximation of vSTM storage capacity. The full-term born participant reached a maximum of around three objects; by contrast, the preterm-born participant's asymptote is lower, indicative of a reduced number of letters that can be represented.

Partial report results: top-down and spatial attentional weighting

Theoretically and empirically obtained mean scores showed a reasonably close correspondence. That is, 62% (SD = 19.33) of the variance of performance in the preterm group and 61% (SD = 18.90) in the full-term group was explained by the maximum likelihood fit measures. Top-down control α: Fig. 2B shows that average parameter estimates and standard errors were comparable across groups ($F(1) = 0.01$, $p = 0.94$). Values of parameter α at around 0.5 indicated that both groups, on average, were able to allocate twice as much relative attentional weight to targets compared with distractors and were thus able to prioritize relevant over irrelevant information. *Spatial distribution of attentional weighting* w_λ: Fig. 2B also shows that groups had comparable spatial attentional weighting values ($F(1) = 0.22$, $p = 0.64$), which are generally centered around the optimum value of 0.5 and, thus, do not indicate any spatial bias.

fMRI results: changes in visual and attention-related intrinsic networks in preterm born adults

ICA of rs-fMRI data revealed uni-modal visual, multi-modal attention-related and thalamic intrinsic networks for full- and preterm born adults that have been described previously (one-sample t-test, $p < 0.05$ FWE-cluster; Fig. 3A; Table 2; e.g. Allen et al., 2011; Damoiseaux et al., 2008; Kim et al., 2013). The three uni-modal visual networks covered mainly lingual and calcarine gyri (Allen et al., 2011). The multi-modal attention-related networks included two dorsal attention networks, which cover frontal cortices like frontal eye fields and parietal cortices such as superior parietal lobe (Allen et al., 2011; Corbetta and Shulman, 2002). The identified thalamus network is centered on bilateral thalamus (Damoiseaux et al., 2008; Kim et al., 2013).

Preterm born adults demonstrated altered spatial patterns of functional connectivity in unimodal visual and multimodal attention-related networks ($p < 0.05$, FWE cluster-corrected and Bonferroni-corrected; Fig. 3A, Table 3) including areas showing increased and areas showing decreased connectivity compared to the full-term group. Increased iFC was found in the calcarine and lingual gyri of visual networks as well as in the superior parietal lobe of dorsal attention networks. Decreased iFC was found in lingual gyri of two visual networks and in the superior parietal lobe of dorsal attention networks. Taken together, these data demonstrate substantial re-organization of functional connectivity in intrinsic networks that overlap with regions critical for visual attention.

Compensation-like relationship between changes in intrinsic networks and vSTM performance in preterm born adults

For each preterm born adult, we extracted averaged iFC scores of clusters with increased connectivity and related them with corresponding vSTM capacity scores via partial correlation analyses controlled for gestational age, birth weight, OPTI, and IQ (Fig. 3B). For these clusters of increased iFC in the preterm group (indicated by the red color in Fig. 3B), we found positive correlations between iFC and vSTM capacity in two visual networks and one dorsal attention network, i.e. the higher the intrinsic connectivity in selected clusters of these networks the higher the vSTM capacity of preterm born adults (*visual network I*: $r = 0.35$, $p = 0.05$; *dorsal attention network II* $r = 0.47$, $p = 0.01$). Notably, only the correlation with the dorsal attention network was significant at a level that survived correction for multiple comparisons (Bonferroni correction), critical alpha = 0.01: visual I (FT > PT) versus visual II (FT > PT) versus dAtt I (FT > PT) versus dAtt II (FT > PT). We also extracted average iFC scores of clusters of decreased connectivity in the visual and dorsal attention networks (indicated by the blue color in Fig. 3B). When correlating these with corresponding vSTM

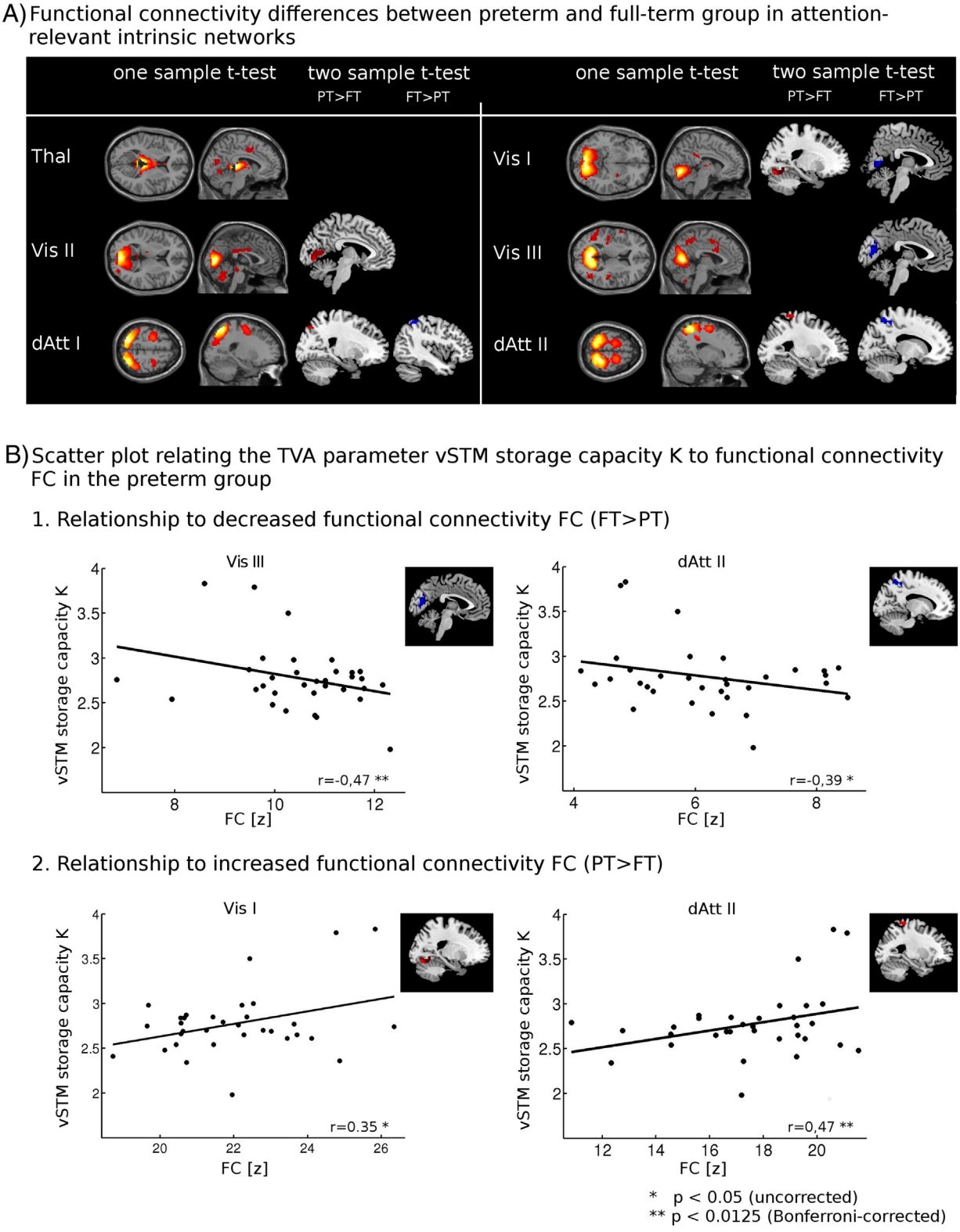

Fig. 3. (A) Resting-state functional MRI data of subjects were decomposed by independent component analysis (ICA). Resulting subject-specific ICs include both spatial z-maps reflecting component's functional connectivity pattern across space and time courses reflecting component's activity across time. Spatial maps were analyzed via one-sample t-tests across all subjects ($p < 0.05$ FWE-cluster) and via two-sample t-tests across groups of pre- and full-term (PT, FT) born adults ($p < 0.05$ FWE cluster-corrected and corrected for multiple comparison using Bonferroni procedure; blue: PT < FT; red: PT > FT). (B) Partial correlations between averaged between-group different aberrant functional connectivity FC and vSTM storage capacity *K* in the preterm group including additional variables of gestational age, birth weight, perinatal medical complications ($p < 0.05$, Bonferroni corrected for multiple testing). Vis I–III: visual networks I–III; Thal: Thalamus network; dAtt I, II: dorsal Attention networks I and II.

capacity scores, we found negative correlations between iFC and vSTM i.e. the lower the intrinsic connectivity the higher the vSTM capacity (*visual network III*: $r = -0.47$, $p = 0.01$; *dorsal attention network II*: $r = -0.39$, $p = 0.04$). Only the correlation between vSTM capacity and iFC of visual II network survived Bonferroni correction (critical alpha = 0.01: visual I (PT > FT) versus visual III (PT > FT) versus dAtt I

Table 2
Intrinsic networks related with visual attention in full- and preterm born adults.

Network	Region	k_E	t_{max}	Peak coordinates		
Full-term participants						
Thalamus	L thalamus	602	27.19	−6	−28	10
Visual I	Bi lingual gyrus	1828	26.44	6	−73	−5
	R precuneus	109	6.68	21	−82	34
	Bi cingulate cortex	54	3.88	3	−40	28
Visual II	Bi lingual gyrus	1161	31.78	0	−79	4
Visual III	Bi calcarine gyrus	2428	33.17	−6	−64	10
dAtt I	R superior parietal lobe	1835	20.05	21	−67	58
	L inferior frontal gyrus	260	5.63	−45	41	4
	L frontal superior lobe	258	9.07	−24	−7	61
	R precuneus	240	6.60	3	−55	22
	L anterior cingulate	179	4.66	−6	29	22
dAtt II	R superior parietal lobe	3243	27.71	21	−46	64
	L superior parietal lobe	1985	23.60	−30	−46	64
	R middle frontal gyrus	266	6.34	45	20	34
	L inferior frontal gyrus	150	7.98	−57	17	16
	Bi anterior cingulate	148	7.47	0	41	10
	R superior frontal gyrus	105	4.71	9	65	1
	L superior frontal gyrus	89	6.36	−30	50	28
	L precuneus	73	6.86	−12	−52	13
Pre-term participants						
Thalamus	L thalamus	576	29.45	−6	31	7
Visual I	Bi lingual gyrus	1583	25.03	6	−76	−8
Visual II	Bi lingual gyrus	1186	34.21	−3	−79	1
Visual III	Bi lingual gyrus	2272	28.01	9	−64	7
dAtt I	L superior parietal	1765	20.51	−24	−64	55
	L middle frontal gyrus	232	6.64	−27	−10	58
	R posterior cingulum	134	6.91	3	−40	25
	R middle frontal gyrus	68	4.41	24	−7	46
	R middle temporal gyrus	54	6.58	54	−52	−11
dAtt II	R postcentral gyrus	984	19.39	27	−40	64
	L postcentral gyrus	846	24.61	−18	−52	67
	R inferior parietal lobe	138	8.42	54	−31	31
	R superior frontal gyrus	95	6.70	18	−4	67
	L inferior parietal lobe	69	5.34	−54	−31	22
	L middle frontal gyrus	52	5.75	−15	−10	64

For each group of full- and preterm born adults: one-sample t-tests for spatial z-maps derived from independent component analysis of resting-sate fMRI data: $p < 0.05$ family wise error corrected at cluster level, height threshold $p < 0.005$. Abbreviations: k_E: cluster extent, L: left, R: right, dAtt: dorsal attention network, visual: visual network.

(PT > FT) versus dAtt II (PT > FT)). Taken together these results indicate a consistent pattern of inter-related vSTM performance and intrinsic connectivity distribution: the more the intrinsic connectivity of preterm adults differ from that of healthy term adults, the better the vSTM capacity. This pattern suggests a redistribution of intrinsic connectivity as a beneficial compensatory mechanism following early brain damage.

Table 3
Group differences between full- and preterm adults for intrinsic networks related with visual attention.

Network	Region	k_E	t_{max}	Peak coordinates			$p_{FWE\text{-}corr}$
Full-term > Preterm							
Visual I	L lingual gyrus	120	6.56	3	−64	4	<0.001
Visual III	L lingual gyrus	267	6.02	−3	−76	16	<0.001
dAtt I	L inferior parietal lobe	96	6.24	−42	−49	55	0.001
dAtt II	R precuneus	87	4.74	−15	−55	58	0.001
Preterm > full-term							
Visual I	L lingual gyrus	103	8.17	−21	−76	−14	<0.001
Visual II	L lingual gyrus	299	6.04	−6	−79	−8	<0.001
dAtt I	R precuneus	71	5.51	21	−76	46	0.002
dAtt II	L postcentral gyrus	72	4.85	−27	−48	70	0.003

Group comparison between full- and preterm born adults: two-sample t-tests for spatial z-maps derived from independent component analysis of resting-state fMRI data: significance level $p < 0.05$ family-wise error corrected at cluster level and corrected for multiple comparisons using Bonferroni procedure. Abbreviations: k_E: cluster extent, L: left, R: right, dAtt: dorsal attention network, visual: visual network.

Discussion

The objective of the present study was to assess the specific long-term effect of preterm birth on sub-mechanisms of selective attention and how potential changes link with alterations in intrinsic brain networks. Using the computational Theory of Visual Attention and whole and partial-report paradigms in preterm and full-term born adults, we found reduced vSTM storage capacity in preterm born adults. The remaining attentional sub-mechanisms, i.e. visual processing speed, top-down control and spatial attention, were unaffected. Using resting-state fMRI we found changes in visual and multimodal attention-relevant intrinsic networks in preterm born adults. Among these preterm born adults, the individual pattern of changed intrinsic connectivity in occipital and parietal cortices was systematically associated with vSTM in a way that the more distinct the connectivity differences the better the preterm adults' storage capacity. Our results go beyond previous indications of lasting visual attention deficits in preterm born individuals as they provide first evidence for specifically impaired vSTM storage capacity in visual attention. Furthermore data suggest that functional reorganization of intrinsic connectivity in visual and dorsal attention networks may serve as compensatory mechanisms of the early-lesioned brain, which may protect from vSTM malfunction.

The nature of long-term impairments in visual attention following preterm birth

Using the TVA-based procedure, we found vSTM storage capacity specifically reduced in preterm born adults during visual attention whole-report performance, indicating that the number of elements that preterm born persons can maintain in a given moment is limited compared to full-term born adults (Fig. 2). Other attentional sub-mechanisms, i.e. visual processing speed, top-down control, and spatial attention, were not changed (Fig. 2). vSTM storage capacity is known to explain individual variance in a range of cognitive tasks (Cowan et al., 2005; St Clair-Thompson and Gathercole, 2006). Thus, low vSTM storage capacity may be a relevant underlying cause of various attention and cognitive deficits reported after preterm birth (e.g. Aylward, 2002; Bhutta et al., 2002). Furthermore, low vSTM storage capacity is associated with academic underachievement (Bull et al., 2008; Gathercole and Pickering, 2000; Jarvis and Gathercole, 2003), and thus provides a possible explanation for suboptimal career development documented in preterm-born individuals (Hack et al., 2002; Olsen et al., 1994; Saigal and Doyle, 2008).

Intrinsic connectivity changes in cortical large-scale brain networks compensate for vSTM storage capacity deficits

The remarkable changes that we found in various intrinsic networks relevant for visual attention functions in preterm adults (i.e. visual and dorsal attention networks; Fig. 3) correspond to previous findings in infants (Doria et al., 2010; Smyser et al., 2010), children (Damaraju et al., 2010), and adults (Bäuml et al., 2014; Wilke et al., 2013). Since we found both areas of increased and decreased intrinsic connectivity, data suggest complex re-organization of intrinsic functional connectivity. Notably, all intrinsic connectivity changes affect areas that are specified as contributors to visual attention and particularly vSTM functions in the NTVA model: both bilateral occipital visual perceptual areas and frontoparietal areas of the dorsal visual stream are assumed to be relevant for visual attentional selection and maintenance in vSTM storage feedback loops (Bundesen et al., 2005; Crick, 1984; McAlonan et al., 2008). In line with this correspondence, individual vSTM storage capacity in preterm born adults was associated with an individual degree of connectivity changes (Fig. 3B): in those visual areas with (on average) lower intrinsic connectivity in the preterm group compared to the full-term group, *lower* connectivity was associated with *relatively high* vSTM storage capacity in the preterm group. In areas of the dorsal

attention network that showed higher average intrinsic connectivity in the preterm compared to the full-term group, *higher* connectivity was related to *relatively high* performance. These relationships remained significant even after controlling for potentially confounding factors such as birth weight, gestation age, perinatal complications, and IQ. These data – particularly their consistent pattern across networks and regions – indicate that more pronounced cortical connectivity changes were present in those participants with higher behavioral performance. Dynamic adaptive reorganization of cortical intrinsic connectivity networks may represent a compensatory mechanism that ameliorates the development of preterm birth induced vSTM deficits and the individual degree of such reorganization might serve as a biomarker of adaptive neural plasticity. Following the demonstration of compensatory changes in *functional* connectivity, it would be interesting to explore whether other brain changes, e.g. those in *structural* connectivity, might be related to a vSTM performance drop.

Previous views on neuro-cognitive plasticity following preterm birth were mixed. While Pavlova and Krageloh-Mann (2013) suggested that the typically symmetric bilateral damage in preterm born infants reduces the degree of neural plasticity as it is found in other developmental disorders, other authors interpreted the finding as preterm-born individuals activating a broad bilateral neuronal network during language processing as evidence for compensatory neural processing (Gozzo et al., 2009; Mullen et al., 2011; Myers et al., 2010; Schafer et al., 2009). Complementary to our findings, a recent resting-state fMRI study demonstrates positive associations between altered iFC in the cerebellum and language skills in a preterm born sample of young adults suggesting involvement of alternative cerebellar pathways for language in preterm born subjects (Constable et al., 2013). Critically, to the best of our knowledge, such changes of iFC have never been linked to mechanisms of visual attention. We provide direct evidence for the existence and the functional relevance of residual compensatory capabilities for vSTM storage capacity within the developing brain affected by preterm birth. In preterm adults, functionally reorganized brain networks relevant for attention may contribute to the amelioration of functional deficits in vSTM induced by early developmental disturbances. Further research is needed to test whether such compensatory reorganization can be stimulated.

Methodological issues and limitations

Participants

The sample of the current study consisted of preterm born adults with lower neonatal complications and higher IQ. Persons with more complications or severe impairments 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 declined to participate in MRI scanning. Thus observed results are conservative estimates of the true differences in attentional sub-mechanisms and their intrinsic network correlates in preterm born adults. Severely impaired preterm born individuals might not have the same compensatory mechanisms or such mechanisms might be disrupted. Further studies on subgroups are necessary. Furthermore, it is relevant for the development of treatment strategies to know the trajectory of specific attention sub-mechanisms and their compensation after preterm birth. Here longitudinal studies are necessary.

ICA

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

Conclusion

Our study provides first evidence for selectively disrupted attention sub-mechanisms in preterm born adults that are associated with potentially compensatory changes of functional connectivity in intrinsic brain networks. These findings may contribute to our search for specific neuro-cognitive targets for the treatment of the long-term effects of preterm birth on cognition.

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Conflict of interest

All authors report no biomedical financial interests or potential conflicts of interest.

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3.

Project 2: Neuro-cognitive Mechanisms of Simultanagnosia in Patients with Posterior Cortical Atrophy

The current chapter includes a research article entitled "Neuro-cognitive mechanisms of simultanagnosia in patients with posterior cortical atrophy". This article showed for the first time in a relatively large group of PCA patients that white matter disconnections within the superior parietal lobe lead to slowing of visual processing speed, which underlies the overt clinical symptoms of simultanagnosia. The manuscript was published in BRAIN in 2016.

Contributions:

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The author of this thesis is the shared first author of the manuscript together with M.O. J.N., C.S. and K.F. conceived the experiment. M.O. and P.B. recruited participants. J.N. and P.R. conducted behavioral data acquisition and I.Y., A.D. and C.P. conducted clinical MRI data acquisition. J.N. analyzed behavioral and imaging data, with some help from M.H. J.N. wrote the manuscript, supervised by K.F., and the manuscript was commented on and reviewed by P.B., T.G., M.O. and C.S.

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Neuro-cognitive mechanisms of simultanagnosia in patients with posterior cortical atrophy

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Posterior cortical atrophy is dominated by progressive degradation of parieto-occipital grey and white matter, and represents in most cases a variant of Alzheimer's disease. Patients with posterior cortical atrophy are characterized by increasing higher visual and visuo-spatial impairments. In particular, a key symptom of posterior cortical atrophy is simultanagnosia i.e. the inability to perceive multiple visual objects at the same time. Two neuro-cognitive mechanisms have been suggested to underlie simultanagnosia, either reduced visual short-term memory capacity or decreased visual processing speed possibly resulting from white matter impairments over and above damage to cortical brain areas. To test these distinct hypotheses, we investigated a group of 12 patients suffering from posterior cortical atrophy with homogenous lesion sides in parieto-occipital cortices and varying severity of grey and white matter loss. More specifically, we (i) tested whether impaired short-term memory capacity or processing speed underlie symptoms of simultanagnosia; (ii) assessed the link to grey and white matter damage; and (iii) integrated those findings into a neuro-cognitive model of simultanagnosia in patients with posterior cortical atrophy. To this end, simultaneous perception of multiple visual objects was tested in patients with posterior cortical atrophy mostly with positive Alzheimer's disease biomarkers and healthy age-matched controls. Critical outcome measures were identification of overlapping relative to non-overlapping figures and visuo-spatial performance in tests sensitive to simultanagnosia. Using whole report of briefly presented letter arrays based on the mathematically formulated 'Theory of Visual Attention', we furthermore quantified parameters of visual short-term memory capacity and visual processing speed. Grey and white matter atrophy was assessed by voxel-based morphometry analyses of structural magnetic resonance data. All patients showed severe deficits of simultaneous perception. Compared to controls, we observed a specific slowing of visual processing speed, while visual short-term memory capacity was preserved. In a regression analysis, processing speed was identified as the only significant predictor of simultaneous perception deficits that explained a high degree of variance (70–82%) across simultanagnosia tasks. More severe slowing was also indicative for more severe impairments in reading and scene comprehension. Voxel-based morphometry yielded extensive reductions of grey and white matter in parieto-occipital and thalamic brain areas. Importantly, the degree of individual atrophy of white matter in left superior parietal lobe, but not of any grey matter region, was associated with processing speed. Based on these findings, we propose that atrophy of white matter commonly observed in posterior cortical atrophy leads to slowing of visual processing speed, which underlies the overt clinical symptoms of simultanagnosia.

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Abbreviations: BORB = Birmingham Object Recognition Battery; PCA = posterior cortical atrophy; SPT = simultaneous-perception task; STM = short term memory; TVA = Theory of Visual Attention; VBM = voxel-based morphometry; VOSP = Visual Object and Space Perception Battery

Introduction

Posterior cortical atrophy (PCA) is a neurodegenerative syndrome dominated by extensive grey and white matter loss in parietal, occipital and occipito-temporal brain regions. It mostly arises from Alzheimer's disease neuropathology (Hof *et al.*, 1997; Renner *et al.*, 2004; Tang-Wai *et al.*, 2004). However, neurofibrillary tangles are most pronounced in primary visual and visual association cortices (especially in Brodmann areas 17 and 18) and significantly less in the hippocampus. Accordingly, patients with PCA show a fairly selective, progressive decline of higher visual and visuospatial skills, while at least initially memory is relatively spared. The cardinal visual symptom, affecting 82–92% of patients, is simultanagnosia (Tang-Wai *et al.*, 2004; Kas *et al.*, 2011), the inability to recognize more than one visual object at a time (Bálint, 1909). While patients can describe individual elements of a visual scene, they cannot integrate them into a coherent meaningful whole (Wolpert, 1924), leading to severely impaired daily life activities. Although simultanagnosia is generally characterized as an attention deficit and linked to damage of the visuospatial attention system, the precise neuro-cognitive mechanism remains elusive. Here, we tested two alternative hypotheses about the functional and neuroanatomical substrates of simultanagnosia in a group of 12 patients with PCA.

There are two basic accounts for simultanagnosia. An early single case report of a patient who showed a normal processing rate for single objects, but was unable to name any additional objects suggested a reduced visual short term memory (STM) storage capacity (Coslett and Saffran, 1991; see also Pavese *et al.*, 2002). However, descriptions of patients with significantly slowed single object processing supported a processing speed account (Bálint, 1909; Luria, 1959). Recent studies based on the integrated mathematical framework of the Theory of Visual Attention (TVA; Bundesen, 1990) were able to formalize and test these two alternatives. Duncan *et al.* (2003) showed that two simultanagnostic stroke patients suffered from slowed processing speed, rather than reduced visual STM capacity. Congruently, Finke *et al.* (2007) found Huntington's disease patients with more severe deficits in simultaneous perception to suffer from more reduced processing speed.

Analyses of the neuronal substrates of simultanagnosia have long been limited to case reports (Bálint, 1909; Naccache *et al.*, 2000; Rizzo and Vecera, 2002; Himmelbach *et al.*, 2009; Thomas *et al.*, 2012). The first systematic evaluation presented by Chechlacz *et al.* (2012) compared the lesion patterns between seven patients with simultanagnosia and patients with unilateral visuospatial deficits. Voxel-based morphometry (VBM) analyses showed that simultanagnosia was related to grey matter lesions of bilateral parieto-occipital cortices and right intraparietal sulcus, together with extensive white matter lesions of long association pathways. Diffusion-tensor imaging (DTI) analyses confirmed that bilateral superior longitudinal, inferior fronto-occipital, and inferior longitudinal fasciculus disconnections are necessary for simultanagnosia (Migliaccio *et al.*, 2012*b*). Thus, both grey and white matter damage within the visuospatial attention network seem to contribute to simultanagnosia. Like Duncan *et al.* (2003), the authors proposed extensive white matter disconnections to result in slowed visual processing speed and impaired simultaneous object perception. Yet, this interpretation remains speculative, as reduction of visual STM capacity and visual processing speed have never been systematically contrasted with respect to their linkage to grey and/or white matter damage.

The present study aims to systematically investigate the relationship between the functional and neuroanatomical features of simultanagnosia by (i) determining whether changes of visual STM capacity or processing speed underlie symptom occurrence; (ii) assessing the link between the critical mechanism underlying simultanagnosia, and grey and white matter abnormalities; and (iii) integrating these findings into a neuro-cognitive model of simultanagnosia in patients with PCA. We investigated 12 patients with PCA who mostly had positive biomarkers for Alzheimer's

Table 1 Sample characteristics

	TVA		Statistical comparison (*P*)	MRI		Statistical comparison (*P*)
	PCA	HC1		PCA	HC2	
N	12	12		10	12	
Gender, male/female	7/5	6/6	0.682	5/5	5/7	>0.999
Age [years], mean (SD)	64.2 (7.5)	64.9 (2.5)	0.737	64.7 (7.5)	64.8 (5.7)	>0.956
Education [years], mean (SD)	10.4 (1.4)	10.4 (1.7)	>0.999	10.2 (1.3)	10.7 (1.8)	0.499
Handedness, right/left	12/0	12/0	>0.999	10/0	10/2	0.481
MMSE, mean (SD)	19.3 (3.4)	28.8 (0.8)	<0.001	19.4 (379)	28.9 (1.1)	<0.001

HC = healthy control participants; MMSE = Mini-Mental State Examination.
Statistical comparisons: gender, handedness: chi-squared statistics; age, education and MMSE: non-parametric Mann-Whitney tests.

disease confirmed either by ^{11}C-Pittsburgh compound-B-PET (PiB-PET) imaging or CSF amyloid-β_{42}. This patient group enabled us to study the consequences of homologous lesion sites in parieto-occipital brain regions and of varying degree of grey and white matter atrophies in a relatively large cohort.

Severity of simultanagnosia was assessed by ratios and test scores known to be sensitive for the syndrome. Object perception deficits were assessed with ratios comparing identification accuracy for multiple overlapping and embedded against adjacent objects. Typical visuo-spatial deficits were assessed by dot counting and position discrimination. In six patients we assessed daily-life symptoms in reading and scene perception.

By using TVA-based (Bundesen, 1990) whole report of brief letter arrays, we quantified mathematically independent parameter estimates of visual STM capacity (*K*) and visual processing speed (*C*). In contrast to conventional clinical tests, this parametric measurement is established to reveal process-pure and independent measures (Finke *et al.*, 2005; Habekost, 2015). Thus, valid assessment of visual STM capacity is possible even in patients with reduced processing speed (and vice versa). To date, the methodology was successful in >30 patient studies (Habekost, 2015), including neurodegenerative diseases (Bublak *et al.*, 2006, 2011; Finke *et al.*, 2006, 2007). Furthermore, dissociations between processing speed and visual STM were documented in different patient groups (Finke *et al.*, 2011; Stenneken *et al.*, 2012), in distinct EEG correlates (Wiegand *et al.*, 2012, 2014) and in different cueing and pharmacological effects (Matthias *et al.*, 2009; Finke *et al.*, 2012; Vangkilde *et al.*, 2013; Sørensen *et al.*, 2015). We used this cognitive specificity to test, in a regression analysis, whether visual STM capacity or visual processing speed significantly predicted the simultanagnosia symptoms. Control analyses on figure naming and memory tasks tested the possibility that stronger impairments in TVA parameters simply reflect that a patient with PCA is generally performing more poorly in visuo-cognitive or even all cognitive tasks.

Such cognitive specificity is optimal to relate basic attentional deficits to patterns of neuropathology in patient populations (Sorg *et al.*, 2012). The integrity of grey and white matter was measured by whole-brain VBM analysis of high-resolution structural MRI.

Materials and methods

Participants

Twelve patients with PCA [mean age ± standard deviation (SD) 64.0 ± 7.18, five females] were included in the study (for demographical and clinical data see Tables 1 and 2). Patients were recruited from the Department of Psychiatry ($n = 10$), Klinikum rechts der Isar, Technische Universität München (TUM), Munich, Germany or the Hans-Berger Department of Neurology ($n = 2$), University Hospital Jena, Germany. Diagnosis of PCA was based on published criteria (Mendez *et al.*, 2002). Ten patients were positive for Alzheimer's disease biomarkers based on amyloid-PET and CSF amyloid-β_{42} levels. PiB-PET images were visually assessed by experienced raters and evaluated as positive if there was cortical binding in one or more brain regions (Rabinovici *et al.*, 2010). For CSF amyloid-β_{42}, we used a threshold of <640 ng/l that corresponds highly with global PiB PET binding (Zwan *et al.*, 2014). Clinical diagnoses were established by a multidisciplinary team consensus. Exclusion criteria were subcortical vascular pathology indicated by severe white matter hyperintensities, other major neurological conditions, such as other types of dementia, other neurodegenerative diseases, stroke, brain tumours, severe systemic diseases, and psychiatric disorders. For MRI data analysis, only the 12 Munich subjects were included to avoid scanner confounds. Twelve participants with visual attention assessment (HC1) and 12 subjects with MRI (HC2) formed two healthy control groups matched for age, gender, and education. All control participants lacked any history of neurological or psychiatric disorders. All participants had normal or corrected-to-normal visual acuity (for demographical data see Tables 1 and 2). All participants provided written informed consent before participating in the study, which was approved by the

Table 2 Single case demographical and test data of patients and group-level data of patients and controls

	Assessments			Demographics			Clinical			TVA			Simultanagnosia						
Patient	TVA	SA	MR	Age	Sex	Edu	MMSE	CDR	Onset	TIV	C	K	BORB over:adjac	SPT embed:adjac	SPT over:adjac	VOSP dot	VOSP position	Reading	Scene
SK	x	x	x	52	F	10	19	1.0	1	1.38	5.82	1.94	0.90	0.76	0.58	70.0	60.0	155	p
GK	x	x	x	69	M	12	23	0.5	1	1.47	19.68	2.00	0.99	1.00	0.98	80.0	100.0	-	-
MTP	x	x	x	68	F	10	16	0.5	5	1.40	2.37	1.95	0.75	0.87	0.52	30.0	60.0	n.a.	p
FR	x	x	x	73	M	13	19	1.0	2	1.60	13.26	1.87	0.79	0.96	0.72	50.0	80.0	52	p
WZ	x	x	x	55	F	10	12	2.0	3	1.39	3.19	3.00	0.85	0.75	0.31	40.0	70.0	83	p
GC	x	x	x	57	F	9	19	-	3	1.39	1.61	2.50	0.84	0.75	0.27	20.0	70.0	-	-
SR	x	x	x	61	F	10	25	1.0	1	1.31	22.83	1.95	0.95	1.04	0.75	90.0	80.0	-	-
RD	x	x	-	55	M	10	19	1.0	4	-	17.31	3.00	1.03	0.98	0.84	90.0	95.0	138	h
HG	x	x	-	68	M	13	19	1.0	3	-	2.38	2.88	0.81	0.91	0.17	40.0	60.0	n.a.	p
AN	x	-	x	73	M	9	20	1.0	2	1.42	4.49	2.85	-	-	-	-	-	-	-
WW	x	-	x	66	M	10	18	1.0	1	1.46	22.33	2.90	-	-	-	-	-	-	-
JW	x	-	x	69	M	9	23	0.5	6	1.47	2.94	2.53	-	-	-	-	-	-	-
Patients, mean (SD)										1.43 (0.08)	9.85 (8.55)	2.45 (0.47)	0.88 (0.09)	0.89 (0.12)	0.57 (0.28)	57.00 (25.00)	75.00 (15.00)	107.00 (47.8)	
Controls, mean (SD)										1.39 (0.16)	17.03 (4.90)	2.76 (0.17)	1.00 (0.00)	1.00 (0.01)	0.99 (0.03)	95.33 (7.43)	98.33 (4.08)	38.11 (2.37)	
P-value										0.506	<0.05	0.248	<0.005	<0.05	<0.001	<0.05	<0.001	<0.01	

SA = simultanagnosia assessment; MR = structural magnetic resonance imaging; f = female; m = male; Edu = education in number of years; MMSE = Mini-Mental State Examination total score; CDR = clinical dementia rating score (global); onset = duration from estimated symptom onset until examination in years; TIV = total intracranial volume in litres; *C* = visual processing speed; *K* = visual STM storage capacity; $BORB_{over:adjac}$ = ratio of accuracy in overlapping-figure condition divided by accuracy in adjacent-figures condition; $SPT_{embed:adjac}$ = ratio of accuracy in embedded- divided by overlapping stimuli condition; $SPT_{over:adjac}$ = ratio of accuracy in overlapping-divided by adjacent-stimuli condition; $VOSP_{dot}$ = Visual Object and Space Perception battery, dot counting test; $VOSP_{position}$ = VOSP position discrimination test; % correct; Reading = text B of 'Saarbrücker Lesetexte' reading test, number of seconds; Scene = description of the meaning of the Boston cookie theft picture; p = piecemeal; h = holistic; n.a. = not able to perform the task.
Statistical comparisons: non-parametric Mann-Whitney tests.

Committees of Human Research at the LMU, TUM and Jena University.

Behavioural assessment of Theory of Visual Attention parameters of attention at time-limited presentation

Computational Theory of Visual Attention framework

According to TVA, two distinct parameters determine the individual processing capacity of a given participant: Visual perceptual processing speed *C* is the number of visual elements that can be processed per second; visual STM storage capacity *K* quantifies the number of items that can be categorized and selected in parallel and transferred into a visual STM store (Sperling, 1960; Luck and Vogel 1997; Cowan, 2001; Habekost *et al.*, 2009). These TVA parameters are derived from a whole report of briefly presented letter arrays. For formal TVA descriptions and equations, maximum likelihood model fitting and software, see Kyllingsbæk (2006).

Theory of Visual Attention whole report procedure

Figure 1B illustrates the applied whole report procedure, described previously (Bublak *et al.*, 2006, 2011; Finke *et al.*, 2006, 2007; Redel *et al.*, 2012). In short, participants are presented with a briefly displayed letter column, and asked to report as many letters as possible. As it is now standard in experimental research on visual STM and visual working memory capacity (Luck and Vogel, 1997), visual stimuli are presented simultaneously to ensure not only that the representation is acquired through the visual modality, but also that it is visual in nature. This is important since a verbal or amodal conceptual representation, which could arise via verbal recoding during serial presentations of the sensory input, cannot be considered as visual STM (Luck and Vogel, 2013).

Letters can be reported in any arbitrary order and without time limits. Individual exposure durations are determined in a preceding practice session. Three different exposure durations (short, medium, and long) are used. In the present study, patients' average exposure durations were 317.1 ms (SD = 163.9), 658.7 ms (SD = 323.3), and 1301.7 ms (SD = 679.8). Healthy controls' average exposure duration were 126.5 ms (SD = 13.4), 254.7 ms (SD = 19.4), and 512.7 ms (SD = 45.7). In half of the trials the letter stimuli were followed by a mask. This resulted in six effective exposure durations, because, in unmasked trials, storage of visual information in iconic memory leads to prolonged information processing. Viewing distance was 50 cm as stabilized by a chin rest. The examination lasted 45–60 min. Performance (i.e. the number of letters reported correctly) was measured as a function of exposure duration.

Based on accuracy in the different effective exposure duration conditions, parameters reflecting processing efficiency were modelled. In TVA, the processing rate depends on the dynamics of the processing system. This is expressed as an exponentially rising probability for an object to be selected with increasing exposure duration. By the use of six effective exposure durations we aimed to measure a broad range of the performance spectrum that reflects the early as well as the late

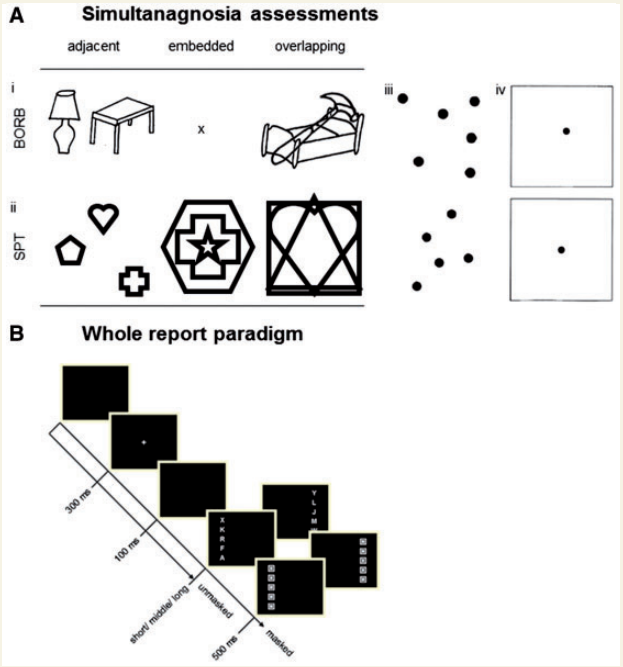

Figure 1 Schematic illustration of the simultanagnosia tests and the TVA-based whole report paradigm. (**A, i**) Stimuli of the overlapping-figures test of the BORB for each presentation conditions (adjacent and overlapping); (**ii**) stimuli of the simultaneous-perception task (Finke *et al.*, 2007) for each presentation condition (adjacent, embedded, overlapping); (**iii**) dot counting task of the VOSP; (**iv**) position discrimination task of the VOSP. (**B**) Whole report paradigm: different trial types with presentation of five equidistant letters (either red or green, respectively) in columns on the left or the right of the fixation cross are shown.

section of a participant's whole report function, thereby allowing a reliable model fit of the individual data. Note that, due to adjusted exposure, absolute report accuracy is not of significance. The probability of identification was modelled by an exponential growth function in which the growth parameter reflects the rate at which objects can be processed (processing speed *C*: number of letters/s) and the asymptote indicates the maximum number of objects that can be represented within visual STM (visual STM storage capacity *K*) (Fig. 2A).

Minimal effective exposure duration *t0*, i.e. sensory threshold (minimum presentation time) beneath which nothing is perceived and prolongation of effective exposure duration (duration of iconic memory μ, were additionally determined from TVA-based model fitting). Parameter *t0* and μ mainly served the valid fitting of the main parameters of interest.

Assessment of simultanagnosia symptoms at unlimited presentation

Overlapping figures task

In the overlapping figures task [Fig. 1A(i)] of the Birmingham Object Recognition Battery (BORB; Riddoch and Humphreys, 1993) identification performance on overlapping objects was assessed relative to non-overlapping objects. More specifically, the participants' task was to name line-drawings of common objects that are shown in three different presentation conditions. In each of the conditions, objects were presented under time-unlimited viewing conditions. That is, participants viewed and processed the objects as long as they wished and stopped the report when they regarded it to be complete. There were three conditions, each containing 40 objects. The first two were control conditions where patients suffering from simultanagnosia, but not from a general visual agnosia, should perform relatively well. (i) In the single-figure condition one object was shown at a time and it was tested whether all patients were generally able to name the objects presented in the test. Note that all participants passed this control assessment with a maximal amount of one error. (ii) In the non-overlapping-figures (adjacent) condition two objects were shown simultaneously side by side without overlap. This condition was introduced as a baseline condition. (iii) Finally, the overlapping-figures condition was the critical condition where patients with simultanagnosia should have difficulties as the objects were presented in a superimposing manner (Riddoch and Humphreys, 2004). The critical outcome measure that specifically reflects the degree of simultaneous perception deficits was the ratio of the mean accuracy in the overlapping condition to the mean accuracy in the adjacent condition. Values approximating 1 indicate that accuracy in the overlapping condition equals that in the non-overlapping condition, while values approximating 0 indicate severe impairment of simultaneous perception. We expected lower ratio scores in the PCA patient compared to the control group.

Simultaneous-perception task

The computerized simultaneous-perception task (SPT) [Fig. 1A(ii)] used in a previous study in patients with Huntington's disease (Finke *et al.*, 2007) was applied. Participants had to name black outline shapes displayed on a white background: triangle, square, pentagon, hexagon, heart, crescent, cross, star, and circle. (i) In a single-stimulus condition all shapes were presented one at a time. No patient committed more than one error. (ii) In the adjacent-stimuli condition, stimuli were shown side by side without overlap. (iii) In the embedded-stimuli condition, smaller stimuli were enclosed by the lines of the next larger one and so forth, with the largest stimulus forming the outer boundary. (iv) In the overlapping-stimuli condition, shapes were presented superimposed. In the adjacent-, embedded- and overlapping-stimuli condition, set sizes varied between two and five items.

Performance in a given trial was rated as correct if participants reported all figures correctly. Each presentation condition included 16 trials. In analogy to the BORB, we computed two ratio scores, by dividing mean accuracy in the embedded-stimuli condition and in the overlapping-stimuli condition, respectively, by mean accuracy in the adjacent-stimuli condition. Critically, simultanagnosia should be reflected by deficits of naming multiple objects that are occupying overlapping locations. That is, we expected particular low ratio scores in patients with PCA for the overlapping-stimuli condition, while the ratio score for the embedded-stimuli condition should also be somewhat affected. In contrast, no considerable problems were expected to occur in the healthy control group resulting in ratio scores approximating 1.

Visuospatial abilities

Two subtests of the Visual Object and Space Perception Battery (VOSP; Warrington and James, 1991) known to be sensitive for simultanagnosia, were used. In the dot counting task [Fig. 1A(iii)] 10 stimulus arrays of five up to nine black dots on a white background are shown and participants have to count the dots without using their fingers. In the position discrimination task [Fig. 1A(iv)] 20 stimulus cards, each showing two identical squares, are presented. Each square contains a black dot and participants have to identify the square where the dot is located exactly in the centre. Stimuli are shown with unlimited presentation time.

Assessment of symptoms in daily-life activities

Reading abilities

Patients' reading performance was assessed by the standardized German text B of the 'Saarbrücker Lesetexte' reading test (Kerkhoff *et al.*, 2012). The instruction was to read the 180-word-long text as accurately and fast as possible. It was assessed whether a patient was at all able to read the text and, if so, reading time was measured in seconds.

Comprehension of thematic complex scenes

To assess holistic scene interpretation, we asked the patients to describe what is happening in the complex scene displayed on the Boston cookie theft picture (Goodglass *et al.*, 1983). We assessed whether scene comprehension was at all possible. It was classified as not possible when a patient took a piecemeal approach characterized by reporting individual objects without being able to comprehend the meaning of the picture within a maximum time of 2 min. If the patient was able to figure out the global meaning of the scene, the time needed for this interpretation was measured.

Analysis of behavioural data

For each participant, TVA-based model fitting yielded individual estimates for (i) parameter visual processing speed C; and (ii) visual STM storage capacity K. Attentional parameters were compared between the two study groups by means of Mann-Whitney tests. In addition, we compared the five distinct measures of simultaneous perception to that of healthy controls using separate Mann-Whitney tests.

Analysis of the relationship between symptoms of simultanagnosia and attentional parameters

To test which changes in attentional parameters are predictive for the occurrence of simultanagnosia symptoms, regression analyses were performed for each of the five measures of simultanagnosia with TVA parameters C and K as predicting variables.

MRI

Image acquisition

MRI assessment was performed on a 3 T integrated Siemens Biograph MR-PET scanner using a 12-channel phase-array head coil. Magnetization prepared rapid acquisition gradient echo (MP-RAGE) T_1-weighted anatomical images were acquired using the following scanning parameters: echo time = 2.98 ms, repetition time = 2.300 ms, inversion time = 900 ms, flip angle = 9°, 160 slices (gap 0.5 mm), covering the whole brain: field of view = 256 mm, matrix size = 256 × 256, voxel size = 1.0 × 1.0 × 1.0 mm^3.

Voxel-based morphometry

VBM was performed using SPM12 (Statistical Parametric Mapping, Version 12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12), and executed in Matlab R2014a (Mathworks, Sherborn, Massachusetts). First, scans were segmented into grey matter, white matter and CSF using unified segmentation (Ashburner *et al.*, 2005). Default values were used for bias regularization (0.0001) and full-width at half-maximum cut-off (60 mm). Then, grey and white matter segments of all subjects were imported to generate a custom template using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL, Ashburner, 2007). This method iteratively registered the grey and white matter segments to an emerging estimation of their group-wise average by refining the parameters that are required to warp each subject's images into a common space. During the template creation, flow fields were calculated for each participant. In the final step, grey and white matter images were normalized using the DARTEL deformations, modulated to consider local volume changes and smoothed with an 8 mm full-width at half-maximum Gaussian kernel.

To evaluate the VBM results statistically, separate two-sample t-tests were calculated for comparing grey and white matter volumes between study groups using SPM12. Both analyses were controlled for the effect of age, gender and total intracranial volume. Total intracranial volume was estimated by first computing and then adding up the totals (in litres) of the warped, modulated and smoothed grey matter, white matter, and CSF segments with the in-built SPM Tissue Volumes Utility (Malone *et al.*, 2015). Explicit grey and white matter masks were applied to only include voxels for which the intensity was at least 0.1 in at least 70% of the images (Ridgway *et al.*, 2009). We only report results that showed significant effects at $P < 0.05$ family-wise error (FWE) corrected at cluster level with a height threshold of $P < 0.001$ uncorrected. The brain coordinates are presented in standard Montreal Neurological Institute (MNI) space. The anatomical localization of volumetric group-differences in grey matter was based on the Automated Anatomical Labelling (AAL) toolbox (Tzourio-Mazoyer *et al.*, 2002). The JHU white matter tractography atlas was used for localizing volumetric group-differences in white matter (Hua *et al.*, 2008). Resulting t-maps are displayed as overlays on a standard T_1 template in MRIcron (Chris Rorden, Georgia Tech, Atlanta, GA).

Analysis of the relationship between attentional parameters and atrophy patterns

To test whether atrophy patterns can predict changes in visual attention parameters, we performed a voxel-wise multiple regression analysis within the patient group. The normalized and smoothed grey and white matter images were used as independent variables. The dependent critical TVA parameter that differed significantly between the study groups was inserted as the dependent variable. We inserted age, gender, and total intracranial volume as covariates of no interest. Moreover, the regression analysis was restricted to voxels that were significantly atrophied in patients versus healthy controls by using an explicit mask based on the results of the preceding two-sample *t*-tests (PCA < HC2). Results of the regression analyses are reported at a significance level of $P < 0.05$ FWE corrected at cluster level and $P < 0.005$ height threshold.

Results

Behavioural results: reduced visual processing speed explains simultanagnosia

In Fig. 2A the mean number of correctly reported letters in the TVA-based whole report task is displayed as a function of exposure duration for a representative PCA patient and control participant, respectively. The scores predicted by TVA model fit (reflected by the solid curves) and observed scores were in close correspondence: mean goodness-of-fit measures showed that 84.92% of variance in the PCA and 88.67% in the HC1 group was accounted for by the maximum likelihood fits. The initial slope of the curve, which approximately reflects the information uptake in objects/s, is less steep for the PCA patient than for the control participant (Fig. 2A). A Mann-Whitney test accordingly revealed that visual processing speed *C* in patients with PCA (mean = 10 objects/s) was significantly reduced compared to controls (mean = 17 objects/s) ($U = 38, z = -1.966$, $P < 0.05$, Fig. 2B). Furthermore, with increasing exposure, the PCA patient's and the control participant's curves reach a comparable asymptote level that indicates the maximum number of letters that can be maintained in visual STM and, hence, reported. In line with this, estimates of *K* were not significantly different between groups ($U = 52$, $z = -1.155$, $P = 0.248$).

Comparisons on all simultanagnosia indices revealed significantly lower performance in patients with PCA compared to controls (Table 2), and were, thus, indicative of a pronounced deficit of simultaneous perception. The majority of patients obtained ratio scores <1 in the two indices reflecting a decline in identification accuracy for multiple overlapping relative to non-overlapping figures ($BORB_{over:adjac}$ and $SPT_{over:adjac}$). A somewhat less dramatic decline was also found for multiple embedded figures ($SPT_{embed:adjac}$). Moreover, patients' accuracy in the position discrimination task was <80% and even lower in the dot counting task of the VOSP while the control group made almost no errors. Only one patient (Patient GK) performed within the range of the healthy participants in the BORB and SPT, but showed noticeable difficulties in dot counting.

We tested whether visual processing speed and/or visual STM storage capacity reductions can predict patients with PCA' simultanagnosia, using five separate regression analyses (for each simultaneous perception measure). Each of these yielded the same correlation pattern: the lower visual processing speed the more severe the impairment in simultaneous perception. As can be seen in Table 3, only visual

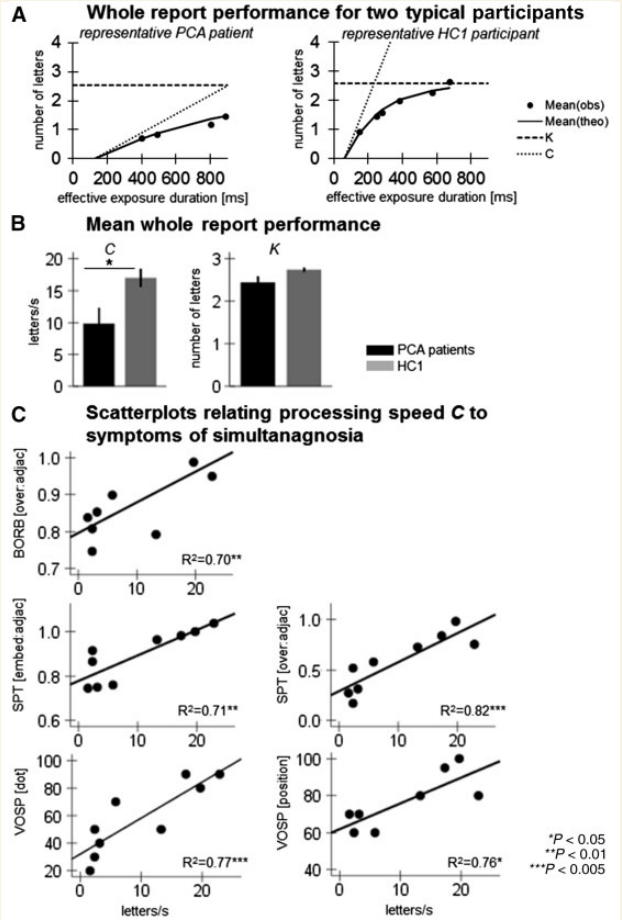

Figure 2 Visual processing speed is slowed in PCA and predicts simultanagnosia symptoms. (**A**) Whole-report performance for a representative PCA patient and a representative control participant: mean number of correctly reported letters as a function of effective exposure duration. Solid curves represent the best fits from the TVA to the observations. The estimate of visual processing speed *C* and visual STM storage capacity *K* is marked by dashed lines. (**B**) Whole report results: average estimates and standard errors for parameters *C* and *K*. Non-parametric Mann-Whitney tests were used for group comparisons ($P < 0.05$). (**C**) Regression analyses: relationship between processing speed *C* and five distinct measures of simultanagnosia in PCA patients ($P < 0.05$).

Table 3 Results of separate regression analyses for each simultanagnosia score in patients with PCA with visual processing speed *C* and visual STM *K* as predictors

Simultanagnosia test	R^2	Processing speed, *C*			Visual STM capacity, *K*		
		β	t	*P*	β	t	*P*
$BORB_{over:adjac}$	0.704	0.87	3.72	<0.01	0.41	1.76	0.128
$SPT_{embed:adjac}$	0.711	0.85	3.69	<0.01	0.02	0.09	0.928
$SPT_{over:adjac}$	0.815	0.81	4.37	<0.005	−0.23	−1.24	0.262
$VOSP_{dot}$	0.765	0.91	4.28	<0.005	0.17	0.79	0.459
$VOSP_{positon}$	0.759	0.87	3.88	<0.05	0.36	1.57	0.176

$BORB_{over:adjac}$ = ratio of accuracy in overlapping-figure condition divided by accuracy in adjacent-figures condition; $SPT_{embed:adjac}$ = ratio of accuracy in embedded- divided by overlapping-stimuli condition; $SPT_{over:adjac}$ = ratio of accuracy in overlapping- divided by adjacent-stimuli condition; $VOSP_{dot}$ = VOSP, dot counting test; $VOSP_{position}$ = VOSP position discrimination test; R^2 = explained variance; β = standardized regression coefficient; t = *t*-value for eight degrees of freedom; *P* = significance level.

processing speed *C*, but not visual STM capacity *K*, was a valid predictor for simultanagnosia symptoms (Fig. 2C).

We qualitatively elucidated the impact of processing speed reductions on the daily life activities reading and scene comprehension in a subgroup of six patients. Those patients with the slowest processing speed (Patients MTW and HG) were no longer able to read, while the other participants could read albeit with marked difficulties (mean reading time, patients: 107.0 s; controls: 38.1 s) (Table 2). Moreover, all patients were unable to comprehend the global meaning of a complex visual scene, except of one patient (Patient RD) whose processing speed was least impaired in this subgroup.

To test the validity of the current results several control analyses were performed. Details about the results can be found in the Supplementary material. First, we computed the same regression tests without the patient who presented with only slight deficits of simultaneous perception (Patient GK). The relationship between reduced processing speed and all measures of simultanagnosia still remained significant demonstrating that it was not driven by a single, only mildly impaired patient. Additionally, we computed identical regression analyses for the absolute number of errors in the overlapping conditions of the BORB and SPT instead of using ratio scores. The results revealed a comparable correlation pattern: the lower visual processing speed the more errors occurred. To ensure that the obtained group differences in processing speed *C* were not a side effect of fatigue induced in the patient group by the relatively long whole report procedure, we re-estimated parameter *C* based on the report performance in the first experimental block (of 48 trials). For both groups the average processing speed values were highly similar to those obtained from the full task and those of patients with PCA were significantly reduced compared to controls (patients: 7.42 letters/s; controls: 18.87 letters/s; $U = 19$, $z = -3.061$, $P < 0.01$). Significant and high correlations were found for patients' estimates of *C* based on the first block with those based on the full task ($r_S = 0.909$, $P < 0.001$). Thus, reduced processing speed in patients is a general phenomenon that is found from the beginning of the whole report task and not only found in conditions where patients suffer from enhanced fatigue. Complementary to our main analyses, we also investigated group-differences in minimal effective exposure duration *t0*, i.e. sensory threshold (minimum presentation time) beneath which nothing is perceived and prolongation of effective exposure duration (duration of iconic memory μ). The results demonstrated significantly increased *t0* values ($U = 88.0$, $z = 3.45$, $P < 0.001$) and decreased μ-values ($U = 29.0$, $z = 2.05$, $P < 0.05$) in the patient compared to the control group. We subsequently tested whether these changes were predictive of patients' simultanagnosia symptoms. To this end, regression analyses for each measure of simultaneous perception were performed with *C*, and additionally *t0* or μ as predictors. None of them yielded a consistent association between *t0* or μ and simultanagnosia.

To examine whether poorer processing speed might simply reflect that a patient is performing less well in any visuo-cognitive task, or even in any cognitive task sensitive for more advanced dementia, we ran regression analyses on significant control indicators. First, to test whether processing speed has an impact also on control visuo-cognitive tasks not assumed to rely on simultaneous object perception, we examined whether processing speed is a significant predictor of performance in the adjacent condition of the BORB and SPT and in the Boston naming subtest of the CERAD (Consortium to Establish a Registry for Alzheimer's Disease). Second, we tested whether it might predict performance in the memory subtests of the CERAD. We did not find evidence for a significant contribution of processing speed to the variance of performance in these control tasks (see Supplementary material for more details). Taken together, these results indicate that a slowing of information uptake is a decisive mechanism underlying specifically the overt simultanagnosia symptoms in patients with PCA.

Imaging results for global grey and white matter atrophy in patients with posterior cortical atrophy

VBM results were subjected to two separate two-sample *t*-tests for comparing grey and white matter volume

Table 4 Group differences between patients and controls for grey matter and white matter and relationship to processing speed *C*

Analysis	Cluster region	Cluster size	Peak region	Peak coordinates			t_{max}	$P_{FWE-cor}$
VBM: grey matter								
	Occipital, parietal, temporal lobe	63 499	R postcentral gyrus	45	−33	48	9.37	<0.001
	Thalamus	5684	L thalamus	−20	−22	9	10.12	<0.001
	Insula	1687	R insula	40	12	6	4.17	<0.001
	Frontal lobe	1282	L inferior frontal gyrus	−42	2	30	4.47	<0.005
	Temporal lobe	812	L hippocampus	−28	−6	−24	4.02	<0.05
VBM: white matter								
	Occipital, parietal lobe	5061	L precuneus	−9	−48	48	7.98	<0.001
	Temporal lobe	1088	L medial temporal lobe	−60	−33	−6	8.28	<0.05
	Occipital, parietal lobe	1009	R precuneus	18	−33	50	4.99	<0.05
	Temporal lobe	976	L hippocampus	−27	−21	−15	5.44	<0.05
	Parietal lobe	462	L superior parietal	−26	−56	57	8.06	<0.05
Multiple regression: white matter atrophy −C								
	Parietal lobe	462	L superior parietal	−26	−56	57	8.06	<0.05

To identify atrophy patterns in patients with PCA, modulated and smoothed structural magnetic resonance data was subjected to separate two-sample *t*-tests comparing grey and white matter volume at each voxel (VBM analysis) between the patient and control group: $P < 0.05$ family-wise error (FWE) corrected at cluster level, height threshold $P < 0.001$. Then, multiple regression analysis was performed to link structural changes and TVA parameter processing speed *C* in the PCA group: $P < 0.05$ FWE corrected at cluster level, height threshold $P < 0.005$. L = left; R = right.

between the study groups. Both comparisons were controlled for age, gender and total intracranial volume. The results of the statistical analyses together with the peak coordinates can be found in Table 4. The analysis of grey matter atrophy indicated global tissue loss in the PCA versus the control group (Fig. 3A). The most significant atrophy clusters were found within bilateral thalamus, occipital, parietal and inferior temporal lobes, spanning the dorsal and ventral visual streams, with some additional tissue loss in the frontal lobe.

The analysis of white matter volume changes revealed wide-spread atrophy clusters in bilateral precuneus and superior parietal lobes indicative of severe degeneration of the superior longitudinal fasciculus (parietal section) (Fig. 3B). Extensive white matter atrophy was also found in the posterior cingulum, spanning into the parahippocampal area. Restricted to the left hemisphere, we also found a large white matter atrophy cluster adjacent to the temporal-occipital fusiform cortex extending laterally to the middle temporal gyrus suggesting tissue loss within the left inferior longitudinal fasciculus and superior longitudinal fasciculus (temporal section). No significant volume differences were found in the reverse grey and white matter contrasts (PCA > HC2).

Atrophy of white matter is linked to low visual processing speed

Voxel-wise multiple regression analysis, controlled for age, gender and total intracranial volume, was performed to relate each patient's grey and white matter volume changes to the corresponding estimates of visual processing speed. We found a significant association between the individual degrees of white matter atrophy in the left superior parietal lobe and the rate of information uptake (Fig. 3C and Table 4). This suggests that atrophy within the superior longitudinal fasciculus affects visual processing speed in patients with PCA. We did not find a significant correlation between grey matter atrophy and processing speed.

Discussion

Using a TVA-based whole report paradigm, we revealed a visual processing speed impairment in PCA, while visual STM capacity was unaffected. Critically, impaired processing speed was a valid predictor for individual severity of simultaneous perception deficits. Volumetric analyses yielded extensive grey matter and white matter loss in bilateral occipito-parietal brain areas in patients compared to controls. Voxel-wise regression analyses showed the degree of atrophy of white matter in the superior parietal lobe to predict processing speed slowing. These findings converge to a coherent neuro-cognitive model of simultanagnosia with progressive white matter lesions in the posterior brain leading to impaired visual processing speed and consequently to impaired simultaneous perception.

Simultanagnosia follows from reduced processing speed

Previous attempts to answer the question whether simultanagnosia results from reduced visual STM storage capacity and/or processing speed led to conflicting results. While

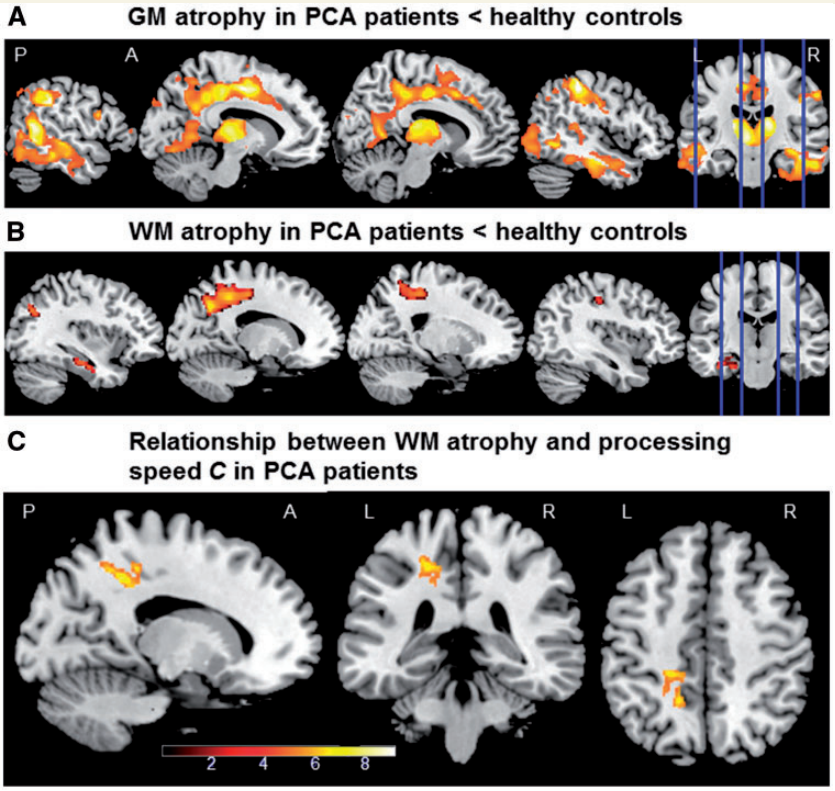

Figure 3 Volume reduction in PCA patients as compared to controls. (**A**) grey matter and (**B**) white matter ($P < 0.05$ FWE-corrected at cluster level, height threshold $P < 0.001$). Shown are sagittal slices from left to right. (**C**) Voxel-wise multiple regression analysis for between-group different white matter volume and visual processing speed *C* in the PCA group. Scale bars represent *t*-values, with warmer colours representing statistically greater correlations between white matter volume and processing speed. GM = grey matter; WM = white matter; L = left; R = right; P = posterior; A = anterior.

some evidence suggested that simultanagnosia patients suffer from a reduction of visual STM capacity close to one single item (Coslett and Saffran, 1991; Pavese *et al.*, 2002), other authors have argued against visual STM capacity as the primary deficit (Huberle and Karnath, 2006). By using a TVA-based approach, we directly contrasted both accounts and were able to clearly decide between these two alternatives: we found a substantial reduction of visual processing speed in a group of patients with PCA suffering from simultanagnosia, while visual STM capacity was comparable to that of control participants (Fig. 2A and B). Moreover, the individual severity of the reduction in processing speed, but not in visual STM capacity, predicted the severity of simultanagnosia symptoms to high degree, i.e. 70–82% of variance was explained for several simultaneous perception tasks (Fig. 2C and Table 3). Therefore, while a visual STM reduction might be present in some patients suffering from simultanagnosia, it is clearly not necessary for the occurrence of these symptoms. Furthermore, in control regression analyses, we did not find evidence that processing speed was a significant predictor of variance in visuo-cognitive tasks not assumed to rely on simultaneous object perception or in memory measures. Thus, we can conclude that slower processing speed does not simply reflect that a patient is performing poorer on any visuo-cognitive task or, even more generally, across all tasks sensitive for more advanced dementia symptoms. Rather, it seems to specifically underlie simultanagnosia symptoms. Our findings are consistent with previous TVA-based studies on patients suffering from simultaneous perception deficits but with other syndromes than PCA. Patients with Bálint's syndrome following stroke showed severely reduced processing speed *C*, but no comparable reductions in visual STM storage capacity (Duncan *et al.*, 2003). Finke *et al.* (2007) observed more severe deficits of simultaneous perception in Huntington's disease patients with more pronounced processing speed slowing, as assessed by TVA. Based on these complementary and congruent results, we conclude that a severe slowing of visual information uptake is the most plausible and common functional cause of impairments in the simultaneous perception of objects across patients with diverse aetiologies. The deficit in this elementary attentional parameter presumably contributes to the characteristic impairments encountered in daily life activities, such as reading (Kas *et al.*, 2011; for the relevance of visual processing speed in reading see Starrfelt *et al.*, 2009; Dubois *et al.*, 2010). We found support for this assumption in a subgroup of six

patients who additionally underwent a reading and a thematic scene comprehension task. Among these, the two patients with most pronounced processing speed slowing were unable to read. While the others also showed significant difficulties, they were in principle still able to read. Furthermore, only the patient with the highest processing speed value could extract the meaning of a complex visual scene within a time frame of 2 min.

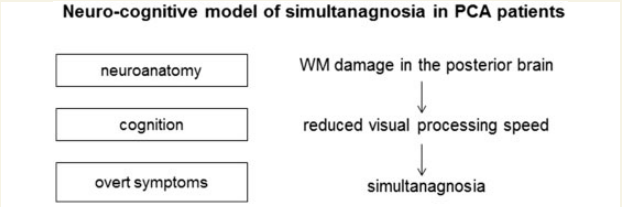

Figure 4 Neuro-cognitive model of simultanagnosia in patients with PCA. WM = white matter.

White matter atrophy leads to reduced processing speed

Corresponding to previous VBM studies (Whitwell *et al.*, 2007; Lehmann *et al.*, 2011; Migliaccio *et al.*, 2012*a*, *b*; Alves *et al.*, 2013), we observed extensive decreases of occipital, parietal and posterior temporal grey and white matter volumes in patients with PCA compared to healthy controls (Fig. 3A and B). Furthermore, atrophy of white matter as the independent variable in a regression analysis significantly explained variance in PCA patients' visual processing speed parameter values while no significant relationship was found for atrophy of grey matter (Fig. 3C and Table 4). Especially reduced structural integrity of the left superior parietal lobe predicted lower processing speed in patients with PCA. The critical white matter cluster showing this relationship was located in the superior longitudinal fasciculus connecting occipito-parietal cortices with frontal brain regions (Umarova *et al.*, 2009). In line with the present results, previous studies have linked the degree of structural integrity of white matter (Rabbitt *et al.*, 2007; Penke *et al.*, 2010; Espeseth *et al.*, 2014; Arvanitakis *et al.*, 2015; Johnson *et al.*, 2015; Kuznetsova *et al.*, 2015) and in particular that of the superior longitudinal fasciculus (Turken *et al.*, 2008; Thiebaut de Schotten *et al.*, 2011; Kerchner *et al.*, 2012) to individual differences in visual information uptake of healthy young and elderly participants. Very recently, a TVA-based study demonstrated that higher speed of visual information processing was linked with higher microstructural integrity of the right superior longitudinal fasciculus as well as of the inferior fronto-occipital fasciculus (Chechlacz *et al.*, 2015). Studies of neurological patients have additionally highlighted the close relationship between white matter deterioration and deficits in tasks demanding fast processing of visual material (Burton *et al.*, 2004; Turken *et al.*, 2008). For example, Turken *et al.* (2008) found that processing speed of stroke patients, measured by the Digit-Symbol subtest of the Wechsler Adult Intelligence Scale, was associated with white matter damage of the left posterior parietal lobe. The large left-sided white matter atrophy cluster and the correlation with processing speed would be in line with the suggestion that patients with PCA show an unexpectedly high frequency of right-sided visual hemi-neglect compared to stroke patients (Andrade *et al.*, 2010, 2012, 2013, but see Silveri *et al.*, 2011), as it was also found in patients with early Alzheimer's disease (Redel *et al.*, 2012; Sorg *et al.*, 2012). These findings might indicate that some damage to the right hemisphere is necessary for right neglect signs to appear. Thus, future studies should test whether patients with PCA show a lateralization in the TVA-based partial report which provides a spatial laterality index (Redel *et al.*, 2012).

This study, for the first time, links the neuronal and cognitive mechanisms underlying simultanagnosia in a group of patients with PCA. Based on our results, we propose the following neuro-cognitive model of simultanagnosia in patients with PCA (Fig. 4): extensive white matter damage particularly within the superior parietal lobe leads to a severe slowing of visual processing speed resulting in the overt deficits of simultaneous perception. While Chechlacz *et al.* (2012) had already proposed that white matter lesions might be linked to simultanagnosia via a slowing of visual information uptake, the present study provides direct lesion-based causal evidence for this model.

Clinical implications

PCA is often recognized only at relatively late stages of the disease as patients do not show the typical memory loss in standard dementia screenings (Crutch *et al.*, 2012, 2013). As visual processing speed explains simultanagnosia symptoms this parameter might be of valuable help for earlier diagnosis. This would lend a time resource to early-state patients that could be used for developing coping strategies for upcoming deficiencies. Importantly, only as long as memory, insight and judgement are spared in patients with PCA, they benefit from compensatory procedures and functional adaptations to reduce errors in visual tasks. For example, they can successfully learn to use visual cues in their home environment or to reduce the number of relevant objects in typical daily tasks. This can improve confidence, self-esteem and coping abilities (Perez *et al.*, 1996; Roca *et al.*, 2010).

Identifying processing speed as the deficient mechanism in simultanagnosia also implies that targeted intervention procedures, known to enhance processing speed, could offer effective treatment options for patients with PCA. Computerized speed of processing trainings were repeatedly shown to improve age-related declines in healthy populations with transfer to everyday abilities, self-rated healthy and quality of life (Ball *et al.*, 2007; Wolinsky *et al.*, 2010). Importantly, healthy individuals with low baseline speed

seem to benefit most (Edwards *et al.*, 2005; Ball *et al.*, 2007) and also patients with Parkinson's disease (Edwards *et al.*, 2013) and with visual impairments (Elliott *et al.*, 2014) show similar benefits. Thus, such training might lend resilience against simultanagnosia induced by increasing white matter degeneration.

Parameter processing speed *C* might serve as a specific and sensitive indicator for the evaluation of both, the individual progression of the disease and the effectiveness of potential therapeutic treatments. Finally, given the clear-cut relationship between superior parietal white matter degeneration and visual processing speed slowing, these could serve as neural and cognitive biomarkers of decline in longitudinal studies. Their joint analysis might reveal decisive information that helps to improve the understanding of the progression of PCA.

Limitations

Processing speed could be slowed in other dementia types and it remains to be tested whether changes of multiple object perception are present in these populations. Comparable correlations were already found in patients with Huntington's disease (Finke *et al.*, 2006, 2007). In amnestic forms of Alzheimer's disease, more subtly reduced attentional capacity (Bublak *et al.*, 2011) might also lead to some difficulties in simultaneous perception. Rather than implying a specific processing speed – simultanagnosia relationship only in patients with PCA we suggest that more generally, patients suffering from severe processing speed reductions will show symptoms of simultanagnosia.

Conclusion

Simultanagnosia reflects impairment of visual processing speed rather than of visual STM capacity. While we observed extensive grey and white matter volume reductions across the entire occipito-parietal lobes, only white matter atrophy within the left association fibre pathway of the visuospatial system was associated with reduced processing speed. Thus, we propose that such white matter disconnections impair the speed of visual information uptake which results in the overt symptoms of simultanagnosia in patients with PCA.

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Supplementary material

Supplementary material is available at *Brain* online.

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4.

General Discussion: Linking Attention Deficits to Structural and Functional Brain Changes

The current thesis aimed to systematically link disturbances of visual attention and underlying brain changes by using neuro-cognitive modelling in two clinical examples of attention deficits. The General Discussion provides an overview of these investigations, their findings and conclusions that can be drawn from them. The first part of this section summarizes and discusses the key findings, separately touching on both clinical examples. To offer a comprehensive account of the main results, the second part of the section provides a unified evaluation of the wider implications across both projects. The third part includes a critical analysis of methodological issues, while the fourth part offers suggestions for future research. The section finishes with a conclusion.

4.1. Main Findings of Each Project

To address the aims of the current thesis two projects were conducted, resulting in two original, peer-reviewed articles: 1) Visual attention in preterm born adults: Specifically impaired attentional sub-mechanisms that link with altered intrinsic brain networks in a compensation-like mode (Finke, Neitzel *et al.*, 2015); and 2) Neuro-cognitive mechanisms of simultanagnosia in patients with posterior cortical atrophy (Neitzel *et al.*, 2016). On the basis of parametric assessment of visual attention deficits derived from the Theory of Visual Attention (TVA, Bundesen, 1990), project 1 extends the link to functional brain changes in a neurodevelopmental model, while project 2 expands the link to structural brain changes in a neurodegenerative model. This section includes a summary of the key findings and how they relate to the current state of research.

4.1.1. Linking Attention Deficits to Functional Network Connectivity

Numerous investigations document profound, yet vaguely defined, deficits of visual attention in preterm born (< 37 weeks of gestation) infants and children, which may even remain into adulthood (Anderson, 2014; Jong, Verhoeven & van Baar, 2012; Mulder *et al.,* 2009; van de Weijer-Bergsma, Wijnroks & Jongmans, 2008). Long-lasting effects of preterm birth have been observed within the adult brain's functional network architecture (e.g. Bäuml *et al.,* 2014; Smyser *et al.,* 2010). Given their functional relevance, attention deficits may be related to altered intrinsic brain networks (IBN) covering posterior brain areas that are relevant for visual attention. With the aim of systematically linking attention deficits and functional brain changes, project 1 applied a combined analysis of parametric measurements of visual attention and functional network connectivity in a well-defined cohort of preterm born adults taken from the Bavarian Longitudinal Study.

Project 1 Finke, Neitzel et al. (2015) set out to quantify and compare attentional functions in formerly preterm (n = 33) and full-term (n = 32) born participants at 26 years of age by means of the TVA-based methodology (Duncan *et al.,* 1999). To this end, all participants completed whole and partial report experiments and observed performance was mathematically modelled in order to yield individual estimates for general and selective capacity factors of the visual attention system. In addition, all participants underwent resting-state functional magnetic resonance imaging (fMRI) in order to extract and compare intrinsic functional connectivity (iFC) within attention-related networks. These consisted of (1) uni-model visual networks centered on the lingual and calcarine gyrus (2) multi-modal dorsal attention networks covering superior parietal cortices and frontal eye fields and (3) a thalamic network which included the bilateral thalamus.

Results showed that estimates of visual short-term memory (STM) capacity *K* were significantly lower in pre- versus full-term individuals, while all other attention parameters (visual threshold, processing speed, task-related and spatial weighting) were comparable between study groups. Group-differences did not change after correcting for general intelligence. Regarding the current literature, there is no earlier work in which long-term consequences of preterm birth have been examined in association with specific attentional functions. It seems reasonable to assume that a selective impairment of visual STM capacity could be an explanation for the more

global disadvantages experienced by preterm born adults which had been previously observed, such as poorer intelligence scores, academic underachievement or increased risk of attention-deficit/hyperactivity disorder (ADHD) (Hack, 2009; Saigal, 2014; van Lieshout *et al.,* 2015). A very recent investigation form our colleagues in the full cohort of the Bavarian Longitudinal Study supports this notion (Breeman *et al.,* 2016). By comparing parent ratings, expert behaviour observations, and clinical DSM-IV diagnose of ADHD, Breeman et al. found that preterm adults experience significantly more attention problems, show a shorter attention span and are more frequently diagnosed with ADHD than term born controls.

Furthermore, we found remarkable changes in various IBN, including significantly increased and decreased iFC, consistent with earlier findings in children (Doria *et al.,* 2010; Smyser *et al.,* 2010) and adults (Bäuml *et al.,* 2014; White *et al.,* 2014). There was a consistent relationship between preterm adults' alterations of iFC and individual estimates of visual STM capacity in a way that the more iFC in visual and dorsal attention networks diverged from that of the full-term born control group, the better visual STM capacity. Note that observed associations remained even after controlling for potential confounding factors such as gestational age, birth weight, perinatal complications and IQ. Thus, these findings point towards an adaptive reorganization of IBN to compensate for the adverse consequences of preterm birth on visual STM capacity. Complementary findings come from task-based (Gozzo *et al.,* 2009; Myers *et al.,* 2010) and resting-state (Constable *et al.,* 2013; Schafer *et al.,* 2009) fMRI studies in the domain of language processing, where it has been shown that preterm born individuals recruit alternative neuronal networks than term controls both at school age and in adulthood. This observation has been very recently extended to emotional processing (Papini *et al.,* 2016). Our collaborators conducted a working memory fMRI investigation in almost the same group of preterm born adults and found, strongly supporting our results, load-dependent compensatory activity in posterior brain regions (Daamen *et al.,* 2015).

Altogether, project 1 is the first study which identified a compensatory link between visual attention deficits and functional brain changes following preterm birth.

4.1.2. Linking Attention Deficits to Grey and White Matter Volume

Posterior cortical atrophy (PCA) is a rare focal variant of Alzheimer's disease (AD) which is characterized by higher visuospatial deficits. One of the core symptoms is simultanagnosia, i.e. the inability to perceive multiple objects at the same time (e.g. Tang-Wai *et al.,* 2004). Two alternative attention deficits had been proposed to underlie simultanagnosia, which are reduced STM capacity (Coslett & Saffran, 1991; Pavese *et al.,* 2002) or slowed visual processing speed (Duncan *et al.,* 2003; Finke *et al.*, 2007) the latter potentially resulting from WM atrophy (Chechlacz *et al.,* 2012). With the aim of systematically linking attention deficits and volumetric brain changes, project 2 applied a combined analysis of parametric measurements of visual attention and grey matter (GM) and white matter (WM) morphometry in a relatively large group of PCA patients.

Project 2 Neitzel *et al.* (2016) assessed simultaneous perception based on four separate tests in twelve PCA patients mostly with positive biomarkers for AD and twelve demographically matched healthy control participants. By using the whole report paradigm together with TVA-based model fitting, visual STM storage capacity and visual processing speed were independently estimated. Additionally, voxel-based morphometry (VBM) was performed based on high-resolution anatomical MR images to quantify GM and WM volume in both study groups.

Our findings demonstrated profound symptoms of simultanagnosia across all measures in the patient group, while healthy participants performed almost without any errors. Moreover, visual processing speed, but not STM capacity was significantly decreased in PCA patients. Separate regression analyses with parameter *K* and *C* as predictors and simultanagnosia test scores as dependent variables evidenced that only visual processing speed could validly predict symptom severity. Interestingly, slowed processing speed seemed to be also associated with patients' daily life difficulties in reading and scene perception. We ensured that this slowing was not an unspecific reflection of dementia state by proving that no correlation existed to patients' ability of identifying single objects or retrieving objects from memory. Consistent with other TVA-based approaches, we clearly demonstrated that reduced visual processing speed rather than visual STM capacity is the underlying attention deficit of simultanagnosia (Duncan *et al.*, 2003; Finke *et al.*, 2007).

In addition, we found global tissue loss in PCA patients compared to healthy control participants. Particularly affected was patients' GM volume in bilateral thalamus, occipital, parietal and inferior temporal lobes, spanning the dorsal and ventral visual streams. Regarding WM, larges volume reduction was observed in bilateral precuneus and superior parietal lobes, together with a large atrophy cluster in the intersection between the occipital and temporal lobe. Voxel-wise regression analysis among patients yielded a significant association between the individual degree of WM loss in the superior parietal lobe covering the superior longitudinal fasciculus and speed of information uptake. No such association was observed for any GM cluster. This result is in large agreement with multiple studies in healthy young and old populations which found that structural WM integrity explains inter-individual differences in processing speed (e.g. Johnson, Diaz & Madden, 2015; Penke *et al.,* 2010; Schotten *et al.,* 2011, for TVA-based evidences see Chechlacz *et al.,* 2015). An investigation in neurological patients furthermore found an association between lesions of posterior parietal WM and processing speed (Turken *et al.,* 2008).

In summary, project 2 revealed for the first time the following neuro-cognitive model of simultanagnosia: WM atrophy within the dorsal part of the visuospatial attention system leads to slowed visual processing what underlies the overt clinical symptoms of simultanagnosia.

4.2. Key Implications Across Projects

Since Duncan et al.'s (1999) seminal work, about 30 studies have used TVA-based assessment to examine attention deficits in various neurological and psychiatric conditions. Yet, only a very few investigations systematically linked impaired attention parameters to biological disease measures. To fill this gap, both projects of the current thesis applied an integrated TVA-neuroimaging approach in two clinical examples. Taken together the current findings could be informative for the wider field of visual attention research. This section discusses major implications across projects, focusing on 1) the selectivity of attention deficits after brain damage; 2) the specificity of the obtained behavior-brain relationships; 3) potential targets for diagnosis and treatment; and 4) the validation and potential extension of TVA's principles and their neuronal interpretation.

4.2.1. Selective Attention Deficits

Both studies demonstrate that brain damage leads to selective deficits of attentional functions. Project 1 showed that preterm born adults suffer from a specific reduction of visual STM storage capacity, while visual processing speed was spared. As project 2 evidenced, the reverse is true for PCA patients who displayed a profound slowing of visual processing speed, but no impairment of visual STM capacity. Though certain methodological limitations should be considered (see section 4.3.2), together these findings should lead us away from the simple idea that brain damage results in "impaired attention". Instead, results of both projects emphasize the importance to differentiate disturbances of distinct attentional functions. Parametric measures adopted from the TVA framework are one promising way to distinguish a set of separate attention components in clinical populations. On this way, attentional difficulties can be characterized by well-defined parameter profiles going far beyond conventional assessment approaches. In addition, project 1 approves the high sensitivity of TVA-based assessment by detecting a selective reduction of visual STM capacity many years after preterm birth. Using less sensitive markers might explain why earlier studies found no disturbances of visual attention in preterm born adolescents and adults tested with different versions of the digit span test (Pyhälä *et al.,* 2011; Rushe *et al.,* 2001; Tideman, 2000; but see Løhaugen *et al.,* 2010).

It is important to notice that earlier TVA-based patient studies (for a recent review see Habekost, 2015) show high degrees of overlap between the parameter profiles of many, quite distinct clinical conditions (e.g. reduced visual STM capacity and processing speed was observed in neglect (Duncan *et al.,* 1999), pure alexia (Starrfelt, Habekost & Leff, 2009), and Huntington's disease (Finke *et al.,* 2006). Taking the broader literature into account, TVA parameters seem to be less stringently related to the symptom-based descriptions of clinical entities and thus the selective and differential findings across both projects should not be misinterpreted as being diagnostic. They rather point to disturbances of more basic cognitive functions which could be impaired in different clinical conditions. Following this idea, it might be more insightful to examine associations with underlying brain changes rather than diagnostic categories.

4.2.2. Specific Behavior-Brain Relationships

Based on the application of a combined TVA-neuroimaging analysis both projects uncovered very specific behavior-brain relationships. To provide a better overview, the main results of project 1 and 2 are reconstructed on top of one standard brain, but the different methodological approaches should be kept in mind. Figure 1 illustrates that among preterm born adults individual patterns of changed functional connectivity in occipital and posterior parietal cortices were related to visual STM capacity in a compensatory-like mode (depicted in blue). Although previous functional and diffusion tensor imaging work repeatedly empathized that preterm born individuals rely on additional brain systems for cognitive (working memory, language, emotion recognition) tasks, they failed to link these alterations with any behavioral advantages (Daamen *et al.,* 2015; Gozzo *et al.,* 2009; Mullen *et al.,* 2011; Myers *et al.,* 2010; Papini *et al.,* 2016; Schafer *et al.,* 2009; but see Constable *et al.,* 2013). In project 2, disturbances of more basic attentional functions served as intermediate cognitive constructs which could clarify that neurodegeneration of distinct WM pathways, rather than atrophy of any GM area, was associated with the behavioral manifestation of simultanagnosia (depicted in green). In contrast, Chechlacz et al. (2012) tried to directly link brain changes with overt clinical symptoms and by that were not able to clearly distinguish the role of GM and WM damage for simultanagnosia. Future studies are certainly required to examine the specificity of the here reported neuro-cognitive relationships by applying complementary methods or studying different patient groups (see 4.4.1 and 4.4.2, respectively).

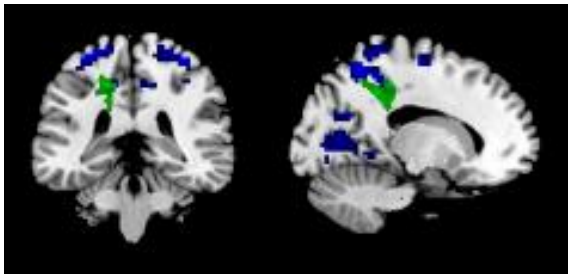

Figure 1 Overlap of the contrast pre-versus full-term born participants which was correlated with visual STM capacity in the preterm group (in blue) and the contrast PCA < controls which was correlated with visual processing speed in the patient group (in green). The original statistical thresholds were used.

In large agreement with our findings, previous TVA-based patient studies demonstrate that damage of the parietal cortex constitutes the most critical lesion (outside of the striatal visual system) for impairments of both visual STM capacity and processing speed (e.g. Peers *et al.,* 2005). The vital role of WM damage for reduced attentional capacity has also been mentioned previously (Habekost & Rostrup, 2007). Apart from MR imaging, a few researchers started to utilize TVA's cognitive specificity for linking attention deficits with other biological disease markers. These include glucose hypometabolism in amnestic AD (Sorg *et al.,* 2012) and gene mutation in Huntington's disease (Finke *et al.,* 2006). In addition, electroencephalography components have been systematically associated with age-dependent declines of attention functions in healthy elderly participants (Wiegand *et al.,* 2014). Together with the current projects, these studies illustrate how intermediate constructs (e.g. attention parameters) help to link etiological factors (e.g. neuronal or genetic abnormalities) with the resulting usually complex behavioral consequences (e.g. simultanagnosia). Establishing specific behavior-brain relationships not only enriches our knowledge about visual attention deficits, but may also help to improve diagnosis and treatment.

4.2.3. Precise Targets for Diagnosis and Therapy

By uncovering differential deficits of visual attention and their specific neurological correlates, both projects have clinical implications. Each finding points towards a very precise neuro-cognitive target – visual STM capacity / iFC of visual and dorsal attention networks in preterm born individuals and visual processing speed / WM atrophy of superior parietal lobe in patients with PCA – which could inform diagnostics and be tackled by tailored intervention programs. Generally speaking, both projects foreshadow the potential of TVA-neuroimaging results to guide the clinical practice away from the focus on specific symptoms (e.g. simultanagnosia) towards approaches that consider the underlying impaired mechanism (e.g. reduced processing speed, superior parietal WM degeneration). These cognitive and neuroimaging markers could moreover support the monitoring of disease progression and the evaluation of treatment outcome. They may further help to develop more precise model systems for animal research or computational modelling. The present results also have several distinct implications, especially with regard to therapeutic success.

By identifying the preterm brain's potential to compensate for the adverse developmental consequences of prematurity, project 1 raises optimistic expectations about therapy outcome. Training programs for enhancing visual STM capacity could be one promising option. Based on the present data, one would hypothesize that cognitive training may stimulate functional connectivity changes in STM-related brain networks, thereby possibly triggering compensatory processes. This in turn may exert a beneficial (long-term) effect on the development of visual STM (see also 4.4.3). It might be even possible to facilitate behavioral and neuronal plasticity more directly by using pharmacological therapy or transcranial magnetic stimulation. The functional relevance of compensatory reorganization within specific IBN, as illustrated in project 1, might offer a hint towards which brain regions or mechanisms to tackle.

In contrast, therapeutic interventions seem generally less promising in PCA in light of the detrimental effect of WM atrophy observed in project 2, and given the progressive nature of the disease. In order to be successful, interventions have to be applied as early as possible, when memory and insight are not affected yet. However, PCA is often recognized only at a late stage, because disturbances of visual attention tend to be confused with ophthalmic diseases. Importantly, as visual processing speed explains simultanagnosia this parameter may facilitate earlier diagnoses. This additional time could then be used to set-up training programs known to enhance processing speed, combined with psychoeducation and copying strategies for the upcoming deficiencies. The current findings may also inform caregivers how to arrange the environment of and interact with PCA patients, e.g. slow down the pace of daily life activities.

4.2.4. Validating the Principles of TVA and Their Neuronal Interpretation

Although parameter *K* and *C* are theoretically defined and mathematically estimated as independent measures in the TVA model, empirical findings in healthy young participants point to some degree of dependency (r = 0.40) (Finke *et al.,* 2005). Similarly positive correlations had been reported in a clinical study of neglect patients (Habekost & Rostrup, 2006). However, we found no relationship between *K* and *C* in pre- (r = 0.30) or full-term born adults (r = 0.19) or PCA patients (r = -0.04), solely the healthy elderly control group of project 2 showed a significant

correlation (r = 0.77). A more fundamental proof of concept is that we found dissociable effects of brain damage impairing one parameter but not the other and vice versa. Thus, the current data lends support for the conceptual idea of rather separate attentional components. Related to this point, Habekost and Starrfelt (2009) reported that preliminary data from their lab suggests a noteworthy correlation between *K* and *C* values and scores of general intelligence. Parameter *K* and intelligence were also weekly related in the study by Finke et al, while parameter *C* seemed to be IQ-independent. We reanalyzed the data of project 1 and found no correlation between either parameter *K* or *C* and intelligence in pre- (r = 0.32 / 0.29) or full-term born adults (r = 0.19 / 0.16). No measure of general intelligence was available in the PCA study. When considering the Mini Mental Status Examination as a marker of dementia state, we found no significant association with *K* (r = 0.16) or *C* (r = 0.35). Thus, our findings validate TVA's conceptualization of pure parameters of visual attention that are not markedly confounded by general cognitive abilities or their decline.

In addition, both projects concern damage to particular either functional or structural properties of neuronal systems and therefore bear on the question of the anatomical basis of visual attention. Due to several methodological issues outlined below (see 4.3.3) the following interpretations should be treated with caution. The current findings document in line with the neuronal interpretation of TVA (NTVA) that the two capacity limits of visual attention depend on large-scale networks of the posterior brain. These fairly general assumptions of NTVA could be further extended. Whereas NTVA specifies how basic attentional principles (rate and weight equation) may be realized by single-cell properties studied in non-human primates, the current findings hint at particular networks of the human brain that seem to be essential for each attention parameter. These are intrinsic networks of the occipital and posterior parietal cortex for visual STM capacity and volume of superior parietal WM pathways for visual processing speed (see Figure 1). Support for these ideas come from multiple imaging studies in healthy participants documenting that visual STM capacity depends on regions of the parietal cortex, particularly the inferior parietal sulcus (Gillebert *et al.,* 2012). Variability of global WM (Espeseth *et al.,* 2014) and especially of the superior longitudinal fasciculus (Chechlacz *et al.,* 2015) has been linked to individual differences in speed of

information uptake. Taken together, clinical TVA-neuroimaging approaches seem to compliment evidences from healthy participants and may inspire hypotheses that can inform further investigations on the neuronal basis of visual attention.

4.3. Methodological Considerations

Considering that both projects included in this thesis employed an integrated TVA-neuroimaging analysis, some methodological issues should be noted. The current section outlines the most relevant considerations and provides suggestions for future improvements. It addresses a) practical aspects of TVA-based assessment; b) reasons why severity of attention deficits might have been underestimated; and c) the limitation that brain changes we examined here may be rather necessary than sufficient for the appearance of associated attention deficits.

4.3.1. Practicability of TVA-based Assessment

Several practical aspects should be taken into considerations when applying TVA-based assessment in patient groups. It is clearly not a bedside test. In general, the examination has to be carried out under appropriate conditions. For example, it is essential to take care of suitable ambient light and a computer set-up that allows to control presentation times at the level of milliseconds. An obstacle particularly for testing patients could be the relative long time of testing. It usually takes at least 30 minutes to obtain a reasonable number of trials which is needed to reliably estimate TVA parameters (~1h for whole and partial report, plus about ten minutes for the practice trials). Patients who are no longer able to focus for this amount of time (e.g. due to fatigue), cannot be examined or may need many breaks. Because the test duration was indeed quite long in the PCA patient group, we tested whether reported effects might have been stemmed from tiredness. This alternative explanation could be ruled out, since a substantial reduction of parameter *C* was evident from the very beginning of the experiment. The recently developed CombiTVA (Vangkilde, Bundesen & Coull, 2011) addresses this issue. It combines whole and partial report, thereby reducing the total time to 45 minutes. Whether the new paradigm meets the critical quality criteria awaits further research. TVA-based assessment additionally relies on verbal responses such that aphasic patients can usually not been tested. Patients with serious visual impairments may have to be

excluded as well. Especially when assessing patients it is crucial to ensure before testing that all test requirements are fulfilled what was the case in our two samples.

4.3.2. Underestimated Severity of Attention Deficits

It should be noted that attention difficulties caused by preterm birth or PCA might have been underestimated in the current projects. One underlying reason could have been that we examined a rather exclusive group of healthy preterm adults. A drop-out analysis of childhood data confirming that our preterm sample showed less neonatal complications and higher IQ. Preterm born adults with more severe impairments were more likely excluded during the screening for fMRI or TVA-based assessment. This positive selection bias seems to be not only an issue of our study, but has been observed in other study cohorts that followed premature populations into adulthood (e.g. Nosarti *et al.,* 2007). Future studies could consider different subgroups of varying neonatal adversities and cognitive impairments. One critical question would be whether more affected preterm born individuals present with quantitatively or qualitatively different compensatory reorganization and hence broader attention deficits. Yet our results are consistent with former TVA-based investigations in another neurodevelopmental conditions which likewise found selective attention deficits, for example in ADHD (Finke *et al.,* 2011) or dyslexia patients (Stenneken *et al.,* 2011). Of particular interest here is that adults with ADHD also suffer from a selective reduction of visual STM capacity (Finke *et al.,* 2011). This fits nicely with the increased risk of developing ADHD observed in preterm born populations.

The attention deficits of PCA patients might have been underestimated as well. Due to practical reasons it was not possible to apply the whole and partial report task in one test session. However, the latter would have been needed for estimating parameters of task-related and spatial weighting. That PCA may lead to a spatial bias of visual attention is indicated by the lateralization of GM and WM atrophy we found towards the left hemisphere. Previous observations of neglect symptoms in PCA (e.g. Andrade *et al.,* 2013) and in amnestic AD patients (e.g. Redel *et al.,* 2012; Sorg *et al.,* 2012) support this idea. Additionally, task-related weighting might have been also impaired in the PCA group. An argument in favor comes from an investigation in patients with mild cognitive impairment due to AD revealing

that parameter α is already affected at this early stage (Redel *et al.,* 2012). The neuronal basis of task-related selectivity is thought to rely on frontoparietal networks (e.g. Corbetta & Shulman, 2002). Since at least the parietal part of this network is strikingly atrophied in PCA, it seems quite likely that efficiency of task-related weighting is reduced in those patients. Further studies could address these hypotheses (see 4.4.1)

4.3.3. Necessary but not Sufficient Brain Changes

Though our findings provide new insights about which brain changes are necessary for certain attention deficits to occur, they might not be sufficient. It is likely that the neuroimaging data used here were not able to capture all brain changes that contributed to the study groups' attentional disturbances. In project 1 we focused on the role of altered functional connectivity for the development of visual STM after preterm birth. Although functional connectivity frequently occurs between regions without direct anatomical linkage, its variability is nevertheless constrained by the brain's structural architecture (Honey *et al.,* 2009). Earlier investigations found that prematurity significantly affects the establishment of thalamo-cortical and cortico-cortical connectivity (Ball *et al.,* 2012). Thus, it can be assumed that besides functional also structural reorganization influences STM functions in preterm born individuals. We confirmed this hypothesis in a follow-up diffusion tensor imaging (DTI) investigation revealing a compensatory involvement of the splenium of the corpus callosum (Menegaux *et al.*, 2017; for more details see 4.4.1). A further follow-up study could disentangle the respective roles of functional and structural brain changes for the development of visual STM after preterm birth.

Project 2 concentrated on the cognitive consequences of GM and WM loss in PCA. Occipito-parietal hypometabolism is another frequently observed phenomenon in those patients, even at early disease stages (Lehmann *et al.,* 2013a; Nestor *et al.,* 2003). Hence metabolic defects may also play a role in the detrimental slowing of visual processing speed and thereby contribute to symptoms of simultanagnosia. A single photon emission computed tomography study by Kas and colleagues (2011) addresses this question. The authors found a robust correlation between impaired perfusion within higher associative areas of the visual occipital system and simultaneous perception scores. In contrast to our findings, this correlation pattern

suggests no significant involvement of parietal areas in simultanagnosia. Two methodological discrepancies should be noted however. First, Kas et al. did not consider the underlying attention deficits in the simultanagnosia-hypometabolism correlation analysis and second their results were not corrected for multiple testing. It would be interesting for future research to test whether metabolic disturbances besides WM atrophy exert a unique effect on processing speed slowing.

4.4. Future Directions

Both projects offer a foundation for numerous future studies that could lend additional support for the relationships we found between attention deficits and functional and structural brain changes and extend these links further. This section presents three future directions that build on the projects of this thesis by either a) employing different neuroimaging methods, b) distinct patient groups, or c) combining TVA-neuroimaging analyses with cognitive training programs.

4.4.1. Other Neuroimaging Measures

Since neuroimaging approaches are inherently correlative, the current implications should be further tested using different methods. DTI is a powerful tool to study WM structural connectivity in-vivo. Identifying a compensatory role of changed functional connectivity following preterm birth in project 1, raises the question whether and how underlying structural WM integrity is linked to visual STM capacity. A follow up investigation by Menegaux *et al.,* (2017) used fractional anisotropy obtained by DTI tractography to explore cortico-thalamic and cortico-cortical connections in the same groups of pre- and full-term born adults. The authors found for the first time that prematurity modulates the relationship between structural connectivity and visual STM. For cortico-thalamic fibers, full-term born adults with higher integrity of the posterior thalamic radiation showed higher visual STM capacity, whereas a significant negative correlation was found in the preterm born group. These findings evidence, consistent with the NTVA model, the involvement of recurrent cortical-thalamic loops for visual STM which appear to be compromised after preterm birth. For cortico-cortical fibers, higher integrity of the splenium of the corpus callosum was associated with higher visual STM capacity in preterm born adults. Together with the data of project 1, it seems that

particularly preterm born individuals with relatively preserved visual STM capacity employ a compensatory bilateral posterior network that may at least partially rely on structural connectivity via the splenium.

Results of project 2 also raise several research questions that could be tackled in a DTI follow-up study. We showed that superior parietal WM atrophy is associated with visual processing speed in PCA patients. The critical WM cluster was located in the left superior longitudinal fasciculus, though voxel-based morphometry is not ideal to make claims on distinct WM pathways. The proposed study would incorporate TVA-based assessment of visual processing speed and DTI tractography in PCA patients and healthy control participants. The analysis of group differences in WM integrity would focus primarily on pathways crossing the superior parietal lobe (see project 2), but could additionally consider other critical pathways of the visual attention system (see Chechlacz *et al.,* 2012). This proposed TVA-DTI investigation could provide complementary information about the anatomical underpinnings of the processing speed slowing caused by PCA. A second question derived from project 2 refers to the large left-sided WM atrophy we found that might indicate an atypically frequent occurrence of right-sided visual hemi-neglect in patients with PCA relative to stroke patients. This idea has been likewise suggested by other authors (for evidences in PCA see Andrade *et al.*, 2013; for amnestic AD see Redel *et al.*, 2012; Sorg *et al.,* 2012). The before proposed DTI project could be extended to also employ TVA-based measures of spatial weighting (parameter w_i) derived from the partial report task. We would first test the hypothesis that PCA patients show a significant lateralization of attentional resources relative to control participants. With the help of DTI tractography, the project would additionally explore the link to lateralized degeneration of WM pathways. On this way obtained results could enrich our understanding of the neglect syndrome and may refine the widely-accepted idea that lesions to the right-sided arousal system are critical for its chronic manifestation (e.g. Robertson, 1993).

4.4.2. Different Clinical Groups

Future studies are necessary to test the specificity of the behavior-brain relationship which we have reported in each project of the current thesis. Specificity in this

context does not mean that only a specific patient group shows these relationships. Instead we suggest more generally that the same attention deficits in other patients will be related to similar patterns of brain changes. In order to test this idea the analysis pursued in project 1 could be in particular transferred to ADHD which has been also associated with reduced visual STM capacity in adulthood (Finke *et al.,* 2011). ADHD leads similarly to changes in functional connectivity of attention-related networks, whereby both hypo- and hyper-connectivity have been documented (see Pereira, Castro-Manglano & Esperon, 2016 for a review). It is yet unclear whether and how these network changes relate to deficits of visual STM. The proposed project would carry out TVA-based assessment of visual attention and resting-state fMRI in individuals with ADHD and healthy control participants. By analyses of group differences we would firstly aim to reproduce earlier findings that ADHD lead to a selective impairment of visual STM capacity as well as significant connectivity changes within networks project 1 showed to be relevant for visual STM. Among ADHD patients, we would then test whether the individual degree of changes in intrinsic networks and visual STM capacity are reliably associated. The proposed project would further expand the link between visual STM deficits and underlying functional brain changes and may add to the endophenotypes research in ADHD (e.g. Castellanos & Tannock, 2002).

Like PCA patients, adults with developmental dyslexia (or at least a subgroup of them) seem to exhibit a selective deficit in visual processing speed (Stenneken *et al.,* 2011). Previous work on brain abnormalities have provided conflicting and spatially distributed results, likely because of the diffuse nature of the pathology (see Richlan, Kronbichler & Wimmer, 2013 for a meta-analysis). Interestingly, a previous VBM–DTI study found a significant correlation between WM integrity of the inferior and superior longitudinal fasciculus, but not of any GM cluster, and speed of pseudoword reading (Steinbrink *et al.,* 2008). It could be insightful to use a similar analysis as carried out in project 2, in order to test whether slowing of visual processing speed is the underlying impairment that links reading difficulties and changed WM morphometry. The proposed project would involve written language assessments, TVA-based measurement of visual processing speed and structural MR imaging in dyslexic and non-dyslexic individuals. Two main hypotheses should be tested: (i) is impaired processing speed a valid predictor for

reading performance of dyslexic participants and (ii) is there a clear-cut relationship between individual WM volume of the parietal lobe and processing speed scores. Using a distinct patient group, the study would expand the link between processing speed deficits and structural brain changes and could potentially specify the underlying mechanisms of reading difficulties in developmental dyslexia.

4.4.3. Cognitive Training Programs

As we have argued above, the individual parameter profiles identified in each project hint at precise cognitive targets for treatment. One critical question concerns inasmuch basic attention functions can be enhanced by cognitive training. Because treatment success is more likely in preterm born individuals compared to PCA patients, we focused our research proposal on preterm birth. Based on the data of project 1, it would be interesting to examine whether preterm born children profit from training programs known to enhance visual STM. A combined training-fMRI approach could further clarify the role of altered functional connectivity for STM development. To this end, STM training together with a pre- and post-training assessment of visual STM capacity and resting state brain imaging should be applied at early stages of development (Wass, 2015). A promising training approach for children is to use eye tracking stimuli that change contingently with gaze direction, such that the program can be applied before the development of fine motor skills (see e.g. Wass, Porayska-Pomsta & Johnson, 2011). However, it has to be noted that TVA-based assessment has never been used in children before the age of 10 years (Bogon *et al.,* 2014). Two main hypotheses should be tested. First, parameter *K* is expected to be higher after the training program. Second, the training should have stimulated significant differences in the functional connectivity of STM-related brain networks identified in project 1, following the idea that these alterations support STM performance. Non-trained STM tasks (e.g. the Visual Memory Span from the WMS-R) as well as far-transfer tasks (e.g. arithmetic) should be employed to test the generalizability of training effects. Follow-up investigations would be necessary to demonstrate that visual STM training has long-term effects and thereby outperforms earlier training programs (Melby-Lervåg, Redick & Hulme, 2016; Orton *et al.,* 2009; Spittle *et al.,* 2007). The proposed project may present one way of how insights gained from TVA-neuroimaging studies could be transferred into clinical application.

4.5. Conclusion

The current thesis complements and enriches our understanding of visual attention deficits and their underlying brain changes by using neuro-cognitive modelling. It provides original findings showing a significant association between the individual degree of structural or functional disturbances within large-scale brain networks and basic attention functions. Altogether, the current thesis took a small but relevant step towards the discovery of predictable behavior-brain relationships in the context of visual attention deficits. These findings could serve as neuro-cognitive targets for diagnosis and treatment and may inform us about the principles and neuronal correlates of normal visual attention. By successfully applying a combined TVA-neuroimaging analysis in two clinical examples, this thesis offers a promising approach for future studies exploring the neuro-cognitive mechanisms underlying attention deficits.

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LIST OF PUBLICATIONS

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Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation ‘Linking attention deficits to structural and functional brain changes’ selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation ‘Linking attention deficits to structural and functional brain changes’ is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

Munich, 28 February 2017 Julia Neitzel

DECLARATION OF AUTHOR CONTRIBUTIONS

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The author of this thesis is the shared first author of this manuscript together with K.F. **J.N.**, K.F. and C.S. conceived the experiment. B.B and N.B. and P.B. recruited participants. **J.N.** and P.R. conducted behavioral data acquisition and J.B., C.M., M.D. and L.S. conducted fMRI data acquisition. **J.N.** analyzed behavioral and imaging data, under the supervision of C.S. **J.N.** and K.F. wrote the manuscript, which was commented on and reviewed by J.J., P.B., H.B., H.J.M, T.H., A.W., D.W. and C.S.

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