Aus dem Institut für Medizinische Psychologie der

Ludwig-Maximilians-Universität München

Lehrstuhl: Medizinische Psychologie

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Long-term Effects of Preterm Birth on large-scale Brain Organization: Evidence from Structural and Functional Magnetic Resonance Imaging

Dissertation zum Erwerb des Doktorgrades der Humanbiologie

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

Vorgelegt von

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aus München

2017

Mit Genehmigung der Medizinischen Fakultät

der Universität München

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Tag der mündlichen Prüfung:	08.02.2017

“If the brain were simple enough for us to understand it, we would be too simple to understand it.” – Ken Hill*

***** as cited in Buzsáki (2006, p.8)

Contents

1. Abstract & Deutsche Zusammenfassung

1.1 Abstract

Being born preterm (< 37 weeks of gestation) increases the risk for several psychiatric disorders, cognitive impairments, and academic underachievement. It is hypothesized that this is due to perinatal brain injury and subsequent alterations in brain development. Structural and functional magnetic resonance imaging allows the identification of such brain abnormalities in-vivo. Accordingly, previous MRI studies have shown that preterm born infants, children and adolescents demonstrate both structural and functional alterations when compared to their term born peers. However, it is unclear whether such changes persist into adulthood. Therefore, the present doctoral thesis aimed to investigate the long-term effects of preterm birth on large-scale brain organization. Study I: in 95 preterm and 83 full-term born adults, structural and functional magnetic resonance imaging at-rest was used to analyze both voxel-based morphometry and spatial patterns of intrinsic functional connectivity (iFC) in ongoing blood oxygenation level–dependent activity. We found widespread iFC differences that overlapped and correlated with aberrant regional gray matter volume in subcortical and temporal areas. Overlapping changes were predicted by the degree of prematurity and neonatal medical complications. The second study investigated functional brain organization in 73 adults born very preterm and/or with very low birth weight (VP/VLBW), and 73 term-born controls, while participants were involved in a verbal N-Back paradigm with varying workload. Although behavioral performance was comparable between groups, VP/VLBW adults showed significantly stronger deactivations of posterior default mode network regions during the most demanding 2-back condition. Our results suggest long-term effects of preterm birth on both structural and functional brain organization and imply compensatory brain activity as a mechanism to help overcome functional deficits.

1.2 Deutsche Zusammenfassung

Eine Frühgeburt (d.h. Geburt vor der 37. Schwangerschaftswoche) erhöht das Risiko für psychiatrische Erkrankungen, kognitive Defizite und schwächere akademische Leistungen. Es wird vermutet, dass dies auf perinatale Hirnschädigungen und nachfolgende Veränderungen in der Gehirnentwicklung zurückzuführen ist. Die strukturelle und funktionelle Magnetresonanztomographie ermöglicht es solche Gehirnveränderungen in-vivo darzustellen. Frühere MRT-Studien haben gezeigt, dass frühgeborene Säuglinge, Kinder und Jugendliche sowohl strukturelle als auch funktionelle Unterschiede im Vergleich zu reifgeborenen Gleichaltrigen aufweisen. Jedoch ist unklar, ob solche Veränderungen bis ins Erwachsenenalter bestehen. Das Ziel der vorliegenden Doktorarbeit war es daher, die langfristigen Auswirkungen einer Frühgeburt auf die Gehirnorganisation im Erwachsenenalter zu untersuchen. Zu diesem Zweck wurden in der ersten Studie strukturelle und Ruhe-fMRT Daten von 95 frühgeborenen und 83 reifgeborenen Erwachsen erhoben und mittels Voxel-basierter Morphometrie und „Independent Component Analysis“ analysiert. Bei frühgeborenen Erwachsenen zeigten sich ausgedehnte Veränderungen in der funktionellen Konnektivität intrinsischer Hirnnetzwerke, die mit subkortikalen und temporalen Veränderungen im Volumen der grauen Substanz überlappten und korrelierten. Überlappende Veränderungen wurden durch den Grad der Frühgeburtlichkeit und das Ausmaß an perinatalen medizinischen Komplikationen vorhergesagt. Die zweite Studie untersuchte die funktionelle Gehirnorganisation von 73 Erwachsenen, die sehr frühgeboren und/oder ein sehr geringes Geburtsgewicht (SF/SGG) hatten, und 73 reifgeborenen Kontrollen, während diese ein verbales N-Back Paradigma mit variierendem Schwierigkeitsgrad absolvierten. Beide Gruppen meisterten die Aufgabe gleich gut. Jedoch zeigten die SF/SGG Erwachsenen während der schwierigsten 2-back Bedingung eine signifikant stärkere Deaktivierung von Regionen, die zum posterioren „default mode“ Netzwerk gezählt werden. Unsere Ergebnisse lassen langfristige Effekte einer Frühgeburt auf die strukturelle und funktionelle Gehirnorganisation im Erwachsenenalter vermuten und

deuten an, dass kompensatorische Gehirnaktivität ein möglicher Mechanismus ist, um funktionelle Defizite auszugleichen.

2. Introduction

A major goal of clinical neuroscience is to identify predisposing factors associated with an increased prevalence of psychiatric disorders, cognitive impairments and academic underachievement. One such risk factor appears to be preterm birth (Hack et al. 2002; Taylor et al. 2004; Johnson et al. 2009; Litt et al. 2012; Nosarti et al. 2012). Every year, an estimated 15 million infants are born preterm, i.e. before the completion of 37 weeks of gestation (Blencowe et al. 2013). Despite advancing knowledge of risk factors and mechanisms related to preterm labor, this number is rising in many industrialized countries (Goldenberg and Rouse 1998; Goldenberg et al. 2008). With the establishment of neonatal intensive care units (NICUs) in the 1960s and the emergence of sophisticated medical interventions, such as mechanical ventilation, surfactant therapy and administration of glucocorticoids, survival rates of ever lower gestation infants have dramatically increased (Wyatt 2010). However, cognitive problems, which are a major sequela of preterm birth, have remained substantially stable (Moore et al. 2012), particularly those involved with language and executive functions (Salmaso et al. 2014). When more preterm born children survive while rates of cognitive problems remain the same, the percentage of children in the community with cognitive problems increases (Jaekel et al. 2013). Moreover, studies that have followed preterm born children longitudinally report these neurodevelopmental deficits to be persistent throughout childhood, adolescence and adulthood (Allin et al. 2008; Pyhälä 2012; Breeman et al. 2015). It is hypothesized that the increased risk of neurocognitive impairments in this population is due to perinatal brain injury and subsequent alterations in brain development (Volpe 2009a; Back and Miller 2014; Salmaso et al. 2014). A better understanding of the primary destructive mechanisms at micro-scale and the secondary maturational differences at macro-scale is necessary to develop potential treatments on the long-run.

3. The encephalopathy of prematurity: Microscopic perspective

3.1 Etiology of perinatal brain injury

Preterm born infants are at increased risk of perinatal brain injury due to hypoxia-ischemia, infections, inflammatory processes and/or drug exposure (Deng 2010; Penn et al. 2015). This has been attributed to the fact, that premature infants are born at a time when many body systems (e.g. the respiratory system, the cardiovascular system, the immune system, and the central nervous system), are not fully developed.

For instance, fetal lungs lack pulmonary surfactant, a conglomeration of surface-active lipids and proteins that reduce the surface tension of the fluid that lines the alveolar cells (Jobe and Ikegami 1987; Willson et al. 2005; Roberts and Dalziel 2006). In a surfactant deficient lung air-spaces are collapsed, often resulting in infant respiratory distress syndrome (Jobe and Bancalari 2001). Despite ongoing progress in neonatal medicine, hypoxia-ischemia continues to be a major problem of preterm born infants in modern neonatal intensive care units (Sweet et al. 2013; Penn et al. 2015). A second type of injury involves intraventricular hemorrhage (IVH) induced by disturbances in cerebral blood flow and poorly vascularized germinal matrix vessels (Ballabh 2010). IVH is particularly prominent in extremely premature infants with an incidence of 45% (Ballabh 2010). Furthermore, at least 40% of preterm births involve intrauterine infections (Agrawal and Hirsch 2012). Associated immune responses induce a proinflammatory cascade involving cytokines and other effector molecules (Agrawal and Hirsch 2012). Finally, fundamental neurodevelopmental processes (e.g. neural migration, axon and dendritic sprouting, glial cell proliferation, synapse formation) that start to evolve in the second and third trimester of pregnancy coincide with the high-risk period for perinatal brain injury (de Graaf-Peters and Hadders-Algra 2006). Consequently, the developing brain is extremely vulnerable to adverse perinatal events as observed in the context of preterm birth (Volpe 2009a; Salmaso et al. 2014).

Hypoxia-ischemia, infections, inflammatory processes and intraventricular bleedings can occur in isolation or coexist and their effects may be amplified by subject-inherent features (e.g. gender, genetics, hypoglycemia, socio-economic status, maternal smoking) and

exogenous factors (e.g. drug exposure) (Penn et al. 2015). The main downstream mechanisms that eventually cause injury to the developing brain are thus excitotoxicity, oxidative stress and inflammation and entail activated microglia, astrogliosis and neuronal and/or axonal damage (Deng 2010; Back and Rosenberg 2014).

3.2 Consequences of perinatal brain injury on the developing brain

Most of what we know about the deleterious effects of premature birth on the brain at micro-scale comes from post-mortem human studies and from animal models of preterm birth (Rice et al. 1981; Marín-Padilla 1997, 1999; Elovitz and Mrinalini 2004; Back et al. 2012). Those studies have shown that the encephalopathy of prematurity comprises both primary destructive and secondary developmental disturbances (Volpe 2009a). For instance, primary injurious events (e.g. hypoxia-ischemia) may subsequently interrupt endogenous developmental events in the brain thereby compromising postnatal developmental programs and their normal timing (Penn et al. 2015). Although, the factors triggering neonatal brain injury may be quite heterogeneous (see above), the observed injury pattern is characterized well.

3.2.1 Oligodendrocytes

Injury to developing oligodendrocytes is the most common cause of preterm brain injury and a major source of chronic neurological impairments including cerebral palsy (Volpe 2009a; Back and Rosenberg 2014). Oligodendrocytes develop from oligodendrocyte progenitor cells during the last trimester of pregnancy (Cameron-Curry and Le Douarin 1995). Thus, the timing of oligodendrocyte progenitor cell proliferation and migration coincides with the high-risk period for periventricular white matter injury (Back et al. 2001). This makes developing oligodendrocytes highly vulnerable to injurious events associated with preterm birth, such as systemic inflammations (Rousset et al. 2006; Favrais et al. 2011; Verney et al. 2012), hypoxia-ischemia (Back and Rosenberg 2014), as well as neonatal pain and stress (Brummelte et al. 2012). The consequences include hypomyelination due to disruptions in

the developmental program of oligodendrocyte lineage cells, acute death of premyelinating late oligodendrocyte progenitors (Back and Miller 2014), arrest of late oligodendrocyte progenitor differentiation and astrogliosis (Buser et al. 2012; Back and Rosenberg 2014).

Due to considerable improvements in neonatal management, cystic, necrotic white matter lesions, characteristic of periventricular leucomalacia and common epiphenomena in former preterm cohorts, are now rarely observed (Woodward et al. 2006; Volpe 2009b). Instead, diffuse, non-necrotic alterations in white matter are now predominant (Counsell et al. 2003; Hamrick et al. 2004). Yet, both necrotic and non-necrotic forms of white matter injury lead to changes in white matter volume and myelination disturbances (Penn et al. 2015).

Premyelinating oligodendrocyte injury may also cause deficient axonal development and degeneration as oligodendrocytes have a trophic function for axonal development and function (Volpe 2009a). However, axonal injury has only been observed in association with periventricular white matter necrosis (Buser et al. 2012), but not in non-necrotic forms of WMI (Riddle et al. 2012).

3.2.2 Neurons

3.2.2.1 Cortical and subcortical neurons

While injury to developing oligodendrocytes has long been acknowledged as a major sequela of preterm birth, the recognition of neuronal abnormalities is relatively recent (Penn et al. 2015). Developing neurons and glia cells tend to show disparate responses to early deleterious events. Although immature neurons appear to be more resilient to hypoxic-ischemic cell death than immature oligodendrocytes, they display significant reductions in the complexity of their dendritic arbors and in synaptic density (Dean et al. 2013). Significant neuronal loss has been shown to occur particularly in association with necrotic forms of white matter injury (Pierson et al. 2007; Ligam et al. 2009). Neuropathological studies in preterm infants with periventricular leucomalacia showed that neuronal loss was most common in the thalamus (Pierson et al. 2007; Ligam et al. 2009), the caudate and putamen (Pierson et al. 2007). Yet overall, preterm birth appears to be rather characterized by gray matter

abnormalities than injuries (Back and Miller 2014). For instance, mice reared under hypoxia demonstrated a 25-30% decrease in cortical parvalbumin and somatostatin expressing GABAergic interneurons in adulthood (Komitova et al. 2013). However, there was no evidence of hypoxia-induced GABA interneuron cell death which implies that the decrease rather results from a delay in maturation of these cells.

Changes in cortical gray matter microstructure may thus be due to maturational delay (Dean et al. 2013), abnormal subcortical growth causing subsequent anomalies in cortical development (McQuillen and Ferriero 2005), or altered gene expression causing loss of coordination of developmentally regulated processes (Curristin et al. 2002).

3.2.2.2 Subplate neurons

A subtype of neurons, known as subplate neurons, has further been shown to be vulnerable to the consequences of preterm birth. During ontogeny subplate neurons are among the first neurons to be generated and to form transient functional circuits with thalamic and cortical neurons (Angevine andi Sidman 1961; Rakic 1974). They are located at the junction of white and gray matter and play a crucial role in the establishment of intra-cortical and thalamo-cortical connections (Goldman-Rakic 1982; Allendoerfer and Shatz 1994). This process occurs relatively late in human fetal development (15-35 post-conception weeks (Hoerder-Suabedissen and Molnár 2015)) and might thus be particularly vulnerable to adverse perinatal events. For instance, subplate neurons appear to be selectively vulnerable to perinatal hypoxia-ischemia (McQuillen et al. 2003). Depending on the timing of the insult, subplate neuron damage results in deficient cortical morphogenesis (Kanold et al. 2003), in a failure of thalamo-cortical innervation or interferes with the refinement of thalamo-cortical connections into mature circuits (McQuillen and Ferriero 2005). Some authors even proposed subplate neuron damage to be the missing link in understanding preterm brain injury (Volpe 1996).

3.2.3 Conclusion and caveats

The distinct and complex responses of neurons, subplate neurons and premyelinating oligodendrocytes to prematurity-related adverse perinatal events result in large numbers of cells that fail to fully mature during a critical window in development of neural circuitry (Back and Miller 2014). Animal models of preterm birth as well as post-mortem human studies greatly contributed to our understanding of the neuropathological mechanisms and consequences of preterm birth. Their findings imply an impaired brain development and aberrant brain connectivity in preterm born subjects. However, such studies also have major downsides. For instance, access to human autopsy brains is very limited allowing only for small sample sizes. Moreover, human histological studies often report findings of cerebral alterations restricted to the short-term while information about the long-term effects of preterm birth remains sparse.

In contrast, animal models of preterm birth help to explain the exact pathological mechanisms that lead to perinatal brain injury. However, experimental animal approaches are invariably reductionistic and typically focus on a single insult (e.g. hypoxia-ischemia, infection, etc), although there may be several factors involved (Penn et al. 2015). Furthermore, most animal studies rely upon rodent brains although there are significant differences from human brains with respect to anatomy, physiology, postnatal development and composition of major neural cell types (Back et al. 2012). Thus, the one-to-one transferability of findings from animal models to human brains remains questionable. Structural (sMRI) and functional magnetic resonance imaging (fMRI) studies in humans offer an alternative approach to study the effects of preterm birth on the brain and will be described in the next paragraphs.

4. The encephalopathy of prematurity: Macroscopic perspective

In contrast to histological studies, magnetic resonance imaging (MRI) is non-invasive and can be performed in living human subjects. It allows to in-vivo map the human brain and to identify structural and functional abnormalities that cannot be detected otherwise. MRI makes

use of the fact that hydrogen atoms, which are abundant in biological tissues, emit a detectable radio-frequency signal when placed in an external magnetic field and stimulated with pulses of radio waves (Lauterbur 1973). The relaxation properties of hydrogen atoms (and hence the emitted signal) vary in different biological tissue (e.g. bone, water, fat), thereby offering a natural contrast mechanism. Some pulse sequences (e.g. BOLD-fMRI) are further sensitive for transient signal dropouts associated with regional changes in tissue composition (e.g. the blood oxygen level) (Ogawa et al. 1990; Kwong et al. 1992). Such signal changes can be used to investigate human brain function. With the advent of sophisticated structural and functional MRI techniques in recent years we have started to understand the complex pattern of brain alterations associated with preterm birth.

4.1 Large-scale structural brain organization

One way to investigate brain organization at the large-scale level involves structural magnetic resonance imaging. SMRI uses T1-weighted MR images to examine the anatomy and pathology of the brain. For instance, voxel-based morphometry (VBM) applied to preprocessed gray matter images encompasses a voxel-wise comparison of gray matter volume (GMV) between two groups of subjects (Ashburner and Friston 2000). Gray matter is a major component of the central nervous system and comprises both neuronal cell bodies, dendrites, synapses and astroglia among others. Thus, GMV, as measured with VBM, may represent an indirect measure of neuron density in a certain region (Mechelli et al. 2005) and provide valuable information about the structural integrity of the brain.

Although a measure of structural integrity, GMV has a dynamic component. It varies as a function of development and is amenable to learning induced plasticity (Draganski et al. 2004; Hölzel et al. 2011). Across life, it has been shown to follow an inverted U-shaped curve with a preadolescent increase followed by a postadolescent decrease (Giedd et al. 1999). Moreover, previous studies have demonstrated that interindividual variance in regional GMV predicts cognitive performance differences (Mummery et al. 2000; Vasic et al. 2008). Notably, VBM has been shown to be sensitive for regional alterations in GMV associated

with different neurological and psychiatric diseases such as multiple sclerosis (Sepulcre et al. 2006), schizophrenia (Honea et al. 2005), autism (Boddaert et al. 2004), as well as major depressive disorder (Bora et al. 2012). Thus, VBM may also have the potential to identify cerebral alterations associated with preterm birth which is a risk factor for several psychiatric disorders (Nosarti et al. 2012). Of particular interest is the question whether VBM studies in preterm born individuals can mimic the structural alterations in gray matter that have been described in histological studies at micro-scale.

Accordingly, numerous studies investigated the effect of preterm birth on regional GMV in infancy (Boardman et al. 2006; Padilla et al. 2014), childhood (Zubiaurre-Elorza et al. 2011) and adolescence (Nosarti et al. 2008; Spencer et al. 2008; Nagy et al. 2009). Although there is some variation with respect to the reported findings, there is some consistency across all age groups: preterm born subjects show regional GMV reductions in bilateral superior and middle temporal gyri, as well as in the thalamus and striatum. These findings are consistent with neuropathological post-mortem studies (Pierson et al. 2007; Ligam et al. 2009). Additionally, some studies also report preterm born subjects to show GMV increases in the visual and frontal cortices (Padilla et al. 2014) as well as in cingulate areas (Nosarti et al. 2008). However, it is unclear whether these changes persist into adulthood. Thus, in the first study we investigated regional GMV in preterm born individuals that have reached adulthood.

4.2 Large-scale functional brain organization

A complementary method to investigate brain organization at the large-scale level is functional magnetic resonance imaging. FMRI takes into account that the brain is a highly dynamic system that exhibits high degrees of intrinsic activity and responds adaptively to external stimulation. As mentioned above, BOLD-fMRI is sensitive for transient signal dropouts associated with regional changes in the blood oxygenation level. Such changes in the amount of oxyhemoglobin are the result of a phenomenon called hemodynamic response where the amount of oxygenated blood flowing through an area is increased in response to augmented neuronal activity (Ogawa et al. 1992). Regional changes in neuronal activity are

thus accompanied by uniform alterations in the BOLD signal (Boynton et al. 1996). Hence, BOLD-fMRI provides an indirect measure of macro-level brain activity.

With the advent of BOLD-fMRI in the early 1990s (Ogawa et al. 1990; Kwong et al. 1992), the in-vivo investigation of brain function both under rest ('resting-state fMRI') and while the participant is involved in a specific cognitive task ('task-fMRI') became possible. While GMV provides a measure of structural brain organization, resting-state or intrinsic functional connectivity (iFC) and task-related functional coactivation are measures of large-scale functional brain organization. Previous studies have shown that spontaneous brain activity is organized in so called intrinsic brain networks (IBNs) and that these networks significantly overlap with the so called task-state network architecture (Di et al. 2013; Cole et al. 2014). Results suggest that there is a "standard" architecture of functional brain organization that is primarily driven by intrinsic brain activity, and secondarily by task-general and task-specific network changes. IFC and task-related coactivation in the context of preterm birth will be introduced in the following paragraphs.

4.2.1 Resting-state fMRI

In 1995, Barat Biswal made a simple but striking observation: spontaneous brain activity (i.e. activity that is not induced by an external task) as measured with resting-state fMRI fluctuates in a spatiotemporally organized manner (Biswal et al. 1995). Until then, spontaneous BOLD oscillations were considered as undesired noise and removed from the data by filtering or averaging techniques. In contrast, Biswal's study suggested spontaneous BOLD fluctuations – particularly in the low-frequency range (< 0.1 Hz) – to reflect physiologically meaningful signals. Ever since, numerous studies have been published that evaluated the spatial and temporal organization of such spontaneous brain activity across development (Fransson et al. 2007), different states of consciousness (Horovitz et al. 2008), and even species (Vincent et al. 2007). The huge scientific interest in intrinsic BOLD fluctuations is attributed to the early 20th century discovery that oscillatory neuronal activity is an essential component of the mammalian brain (Berger 1929). Particularly, synchronous

oscillations across distinct temporal and spatial scales are thought to be the basis for neuronal communication and information processing (Singer 1993; Fries 2005; Schnitzler and Gross 2005). Although the neuronal mechanism of synchronous infra-slow BOLD oscillations is not completely understood (Hughes et al. 2011; Palva and Palva 2012), previous studies suggest slow oscillations to modulate faster local events by regulating large-scale neuronal network excitability (Vanhatalo et al. 2004). As such, perturbations occurring at slow frequencies may cause a cascade of energy dissipation at higher frequencies (Buzsaki 2006).

At the large-scale brain level, techniques to investigate synchronized neuronal activity with a sufficient spatial resolution were lacking for a long time. With the advent of resting-state fMRI this problem was fixed and many micro-level measures were transferred to the macro-level. For instance, this resulted in the concept of intrinsic functional connectivity, which is defined as the temporal correlation between spatially remote neurophysiological events (Friston et al. 1993). IFC is widely used in resting-state fMRI studies and relies on the Hebbian principle, which can be roughly summarized as: “neurons that fire together, wire together” (Lowel and Singer 1992). As such, synchronous low-frequency oscillations in the BOLD signal may reflect the history of coactivation between large populations of neurons (Fair et al. 2007).

Brain regions whose activity levels fluctuate synchronously over time (and thus display a high iFC) are arranged in intrinsic brain networks. IBNs represent a basic form of large-scale functional brain organization (Biswal et al. 1995; Vincent et al. 2007; Bressler and Menon 2010; Sepulcre et al. 2010). They correspond to known neuroanatomical systems and are consistent across different study populations and even species (Damoiseaux et al. 2006; Vincent et al. 2007; Allen et al. 2011). Aberrant iFC of such IBNs has been associated with a variety of psychiatric (Sorg et al. 2007; Assaf et al. 2010; Meng et al. 2013; Sorg et al. 2013) and neurological disorders (Rocca et al. 2010; Luo et al. 2011), as well as with cognitive decline (Wang et al. 2011). This raises the question whether aberrant iFC is also present in subjects at increased risk for psychiatric disorders, and cognitive impairments, such as preterm born individuals.

IBNs emerge during the last trimester of gestation and are thus particularly vulnerable to adverse perinatal events (Fransson et al. 2007; Doria et al. 2010). Accordingly, several rs-fMRI studies evaluated the short-term effect of preterm birth on the large-scale organization of IBNs. These studies report preterm born infants to show reduced internetwork (Damaraju et al. 2010), inter-hemispheric (Smyser et al. 2013), and subcortical-cortical iFC (Smyser et al. 2010; Ball et al. 2015; Toulmin et al. 2015), as well as reduced network complexity and magnitude (Smyser et al. 2014). Moreover, they imply such alterations to become even more pronounced with increasing age (Damaraju et al. 2010). However, it is unknown, whether aberrant iFC persists into adulthood. Therefore, in our first study we investigated the long-term effects of preterm birth on IBN's intrinsic functional connectivity.

4.2.2 Task fMRI

In contrast to resting-state fMRI, task-fMRI aims to identify brain regions that commonly co-activate in response to a specific external stimulation. In its simplest and original form, episodes of stimulation (e.g. visual stimulation) were contrasted to episodes of non-stimulation ('baseline') by simply subtracting the average activation during one task from activation during another (Kwong et al. 1992; Poldrack et al. 2011). However, more recent approaches model the functional time series (i.e. the BOLD signal) using a general linear model (GLM) (Friston et al. 1994). Thus, complementary to rs-fMRI, task-fMRI measures activity-induced changes in the BOLD signal associated with a very specific task. It enables the investigation of task-specific functional brain organization at the large-scale level.

As resting-state fMRI, task-fMRI has been shown to be sensitive for abnormal brain activation patterns associated with psychiatric disorders and cognitive impairments (Manoach et al. 1999; Harvey et al. 2005; Hämäläinen et al. 2007; Just et al. 2007; Karlsgodt et al. 2007). This is of particular interest with respect to preterm born individuals who are at increased risk for several psychiatric disorders and cognitive impairments. Apart from lower general cognitive abilities (Eryigit Madzwamuse et al. 2014; Breeman et al. 2015), preterm born individuals show specific deficits in executive functions (Nosarti et al. 2007; Mulder et al.

2009; Burnett et al. 2013). One key aspect of executive functions is working memory (Diamond 2013). Working memory refers to the capacity limited cognitive system that is involved in the transient maintaining, processing and manipulation of information (Baddeley and Hitch 1994; Diamond 2013). It is an essential requirement for the successful mastering of everyday challenges, such as scholar attainments (Griffiths et al. 2013). Previous studies reported impaired working memory functions in preterm born children (Mulder et al. 2010; Baron et al. 2012), adolescents (Bjuland et al. 2013), and young adults (Hallin et al. 2010). However, these findings are less consistent than for other executive functions, such as attentional control and cognitive flexibility (Burnett et al. 2013). This may either indicate that working memory processes are more robust to prematurity-related brain alterations or reflect compensatory mechanisms that help preterm born individuals overcome existing brain dysfunctions. Hence, the aim of our second study was to test whether preterm born adults show working memory impairments or exhibit signs of compensatory brain activity that helps overcome functional deficits.

5. Questions and Hypotheses: long-term effects of preterm birth on macroscopic brain organization

Study I. Bäuml et al. 2015:

As previous studies suggest observed brain alterations in preterm individuals to be persistent throughout childhood and adolescence (Nosarti et al. 2008; Back and Miller 2014), we hypothesized that:

1. preterm born adults showed widespread regional alterations in GMV,
2. preterm born adults showed widespread alterations in the intrinsic functional connectivity of intrinsic brain networks,
3. that structural and functional changes were specifically associated,
4. that in regions of correspondent changes, alterations in both brain structure and connectivity were predicted by the degree of prematurity or associated neonatal medical complications

Study II. Daamen et al. 2015:

Previous studies have shown that preterm born infants performing N-back paradigms activate working memory related brain networks less effectively than their term born peers (Taylor et al. 2012; Griffiths et al. 2013). However, it is unclear whether this translates into adulthood, or whether preterm born adults develop compensatory mechanisms during later brain maturation. Thus, in our second study, we used a verbal N-Back paradigm with varying workload (0-back, 1-back, 2-back) to address these questions. We hypothesized that:

1. if preterm born adults showed weaker working memory performance, it would be restricted to the most demanding 2-back task,
2. compensatory activation preferentially emerged with higher task demands (i.e. particularly in the 2-back task),
3. aberrant working memory related activations in preterm born adults were predicted by the degree of prematurity or perinatal risk factors.

6. Contribution statement

Both studies were conducted as part of a BMBF funded multi-center project initiated by Prof. Bartmann (University of Bonn) and Prof. Wolke (University of Warwick). The project ("The Bavarian Longitudinal Study") involved a behavioral follow-up examination of a geographically defined whole-population sample of former very preterm and/or very low birth weight born adults together with structural and functional magnetic resonance imaging. MRI data acquisition was carried out in Munich by Josef Bäuml (Principal investigators: Dr. Christian Sorg, Dr. Afra Wohlschläger) and in Bonn by Marcel Daamen (Principal investigator: Prof. Dr. Henning Boecker).

Study I: Josef Bäuml and Christian Sorg conceptualized the study. Josef Bäuml and Marcel Daamen reviewed existing literature. Control of data quality and data analysis (i.e. preprocessing of structural and functional MR images, independent component analysis of resting-state fMRI data, voxel-based morphometry of structural MRI data, statistical parametric mapping, analysis of brain-behavior relationship) were done by Josef Bäuml with

initial support from co-author Chun Meng. Josef Bäuml wrote the manuscript with critical revision by Christian Sorg. Other co-authors contributed to the manuscript by giving their feedback.

Study II: Marcel Daamen, Lukas Scheef, and Henning Boecker conceptualized the study. Marcel Daamen and Josef Bäuml reviewed existing literature. M.D. performed data quality checking and analyzed fMRI data of participants that had been scanned in Bonn, while Josef Bäuml did the very same thing for participants that had been scanned in Munich. Marcel Daamen wrote the manuscript with critical revision by Josef Bäuml and Henning Boecker. Other co-authors contributed to the manuscript by giving their feedback.

As both Josef Bäuml and Marcel Daamen were involved in the whole process of participant recruitment, data quality checking and data acquisition, principal investigators in Bonn and Munich a priori decided that J.B. and M.D shared first-authorships in the first two publications.

7. Published scientific works

7.1 Correspondence Between Aberrant Intrinsic Network Connectivity and Gray-Matter Volume in the Ventral Brain of Preterm Born Adults.

Cerebral Cortex, 2015

DOI: 10.1093/cercor/bhu133.

Published in print: Volume 25, Issue 11, pp. 4135-4145.

First published online: 06/16/2014

7.2 Working memory in preterm-born adults: Load-dependent compensatory activity of the posterior default mode network.

Human Brain Mapping, 2015

DOI: 10.1002/hbm.22691

Published in print: Volume 36, Issue 3, pp.1121-1137.

First published online: 11/21/2014

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9. Danksagung

Ein sehr ereignisreiches und spannendes Kapitel meines Lebens neigt sich dem Ende zu. Diese Gelegenheit möchte ich nutzen, um einigen zentralen Personen zu danken, die mich in dieser Zeit begleitet haben.

An vorderster Stelle bedanke ich mich bei meinem Doktorvater, Prof. Ernst Pöppel, der es mir erst ermöglichte, mein großes Interesse an Wissenschaft und Forschung unter strukturierter Anleitung ‚auszuleben'. Sein schier unendlicher Wissensreichtum, der den Bereich der Neurowissenschaften bei weitem übersteigt, hat mich sehr beeindruckt und außerordentlich motiviert!

Herrn Prof. Claus Zimmer möchte ich dafür danken, dass die zeitaufwendigen Messungen und Analysen in den Räumlichkeiten seiner Klinik durchgeführt werden konnten. Dabei durfte ich einige seiner hochqualifizierten Mitarbeiter und den hohen wissenschaftlichen Standard seines Hauses kennenlernen.

Mein ganz besonderer Dank gebührt Herrn Dr. Christian Sorg, der mich mit großer Geduld an die hochkomplexe Thematik heranführte. Seine eigene Leidenschaft und Faszination für das menschliche Gehirn haben mich dabei unglaublich inspiriert. Von ihm konnte ich außerordentlich viel über die funktionelle Organisation intrinsischer Hirnnetzwerke lernen. An dieser Stelle sei auch an die äußerst intensiven, wöchentlichen Meetings über die Anatomie und Physiologie des kortiko-striato-thalamo-kortikalen Regelkreises erinnert, die meine Sicht auf das Gehirn nachhaltig geprägt haben.

Bedanken möchte ich mich auch bei meinen langjährigen Kollegen Dr. Chun Meng und Dr. Marcel Daamen, die mir vor allem zu Beginn meines Doktorats geduldig mit Rat und Tat zur Seite standen.

Des Weiteren möchte ich mich bei den Studienleitern der Bayerischen Entwicklungsstudie, Prof. Peter Bartmann und Prof. Dieter Wolke, bedanken, die mich trotz der großen räumlichen Distanz durchgehend gefördert haben.

Ich danke auch allen StudienteilnehmerInnen der Bayerischen Entwicklungsstudie, ohne die die hier gewonnenen Erkenntnisse gar nicht möglich gewesen wären.

Zu guter Letzt möchte ich mich ganz herzlich bei meiner Familie bedanken, die mich in allen Phasen meines Doktorats mit großem Wohlwollen fürsorglich unterstützt, ermutigt und begleitet haben.

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