

Aus dem Institut für Medizinische Psychologie der
Ludwig-Maximilians-Universität München
Lehrstuhl: Medizinische Psychologie
Vorstand: Prof. Martha Merrow, PhD

**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
Josef Bäuml
aus München

2017

Mit Genehmigung der Medizinischen Fakultät
der Universität München

Berichterstatter: Prof. Dr. Dr. h.c. Ernst Pöppel

Mitberichterstatter: Prof. Dr. Kolja Schiltz
Prof. Dr. Michael Ewers
Honorarprof. Dr. Franz Joseph Freisleder

Mitbetreuung durch: Dr. med. Christian Sorg; Klinikum rechts der Isar,
Technische Universität München

Dekan: Prof. Dr. med. dent. Reinhard Hickel

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	6
1.1 Abstract	6
1.2 Deutsche Zusammenfassung	7
2. Introduction	9
3. The encephalopathy of prematurity: microscopic perspective	10
3.1 Etiology of perinatal brain injury	10
3.2 Consequences on the developing brain	11
3.2.1 Oligodendrocytes	11
3.2.2 Neurons	12
3.2.2.1 Cortical and subcortical neurons	12
3.2.2.2 Subplate neurons	13
3.2.3 Conclusion and Caveats	14
4. The encephalopathy of prematurity: macroscopic perspective	14
4.1 Large-scale structural brain organization	15
4.2 Large-scale functional brain organization	16
4.2.1 Resting-state fMRI	17
4.2.2 Task-fMRI	19
5. Questions and Hypotheses: long-term effects of preterm birth on macroscopic brain organization	20
6. Contribution statement	21
7. Published scientific work	23
7.1 Correspondence Between Aberrant Intrinsic Network Connectivity and Gray-Matter Volume in the Ventral Brain of Preterm Born Adults	23
7.2 Working Memory in Preterm-Born Adults: Load-Dependent Compensatory Activity of the Posterior Default Mode Network	24
8. References	25
9. Danksagung	39

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 Erwachsenen 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 epiphrenomena 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 and 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

8. References

Agrawal V, Hirsch E. 2012. Intrauterine infection and preterm labor. *Semin Fetal Neonatal Med.* 17:12-19.

Allen EA, Erhardt EB, Damaraju E, Gruner W, Segall JM, Silva RF, et al. 2011. A baseline for the multivariate comparison of resting-state networks. *Front Syst Neurosci.* 5:2. doi:10.3389/fnsys.2011.00002.

Allendoerfer KL, Shatz CJ. 1994. The subplate, a transient neocortical structure: its role in the development of connections between thalamus and cortex. *Annu Rev Neurosci.* 17:185-218.

Allin M, Walshe M, Fern A, Nosarti C, Cuddy M, Rifkin L, Murray R, Rushe T, Wyatt J. 2008. Cognitive maturation in preterm and term born adolescents. *J Neurol Neurosurg Psychiatry.* 79:381-386.

Angevine J, Sidman RL. 1961. Autoradiographic study of cell migration during histogenesis of cerebral cortex in the mouse. *Nature.* 192:766-768.

Ashburner J, Friston KJ. 2000. Voxel-based morphometry--the methods. *Neuroimage.* 11:805-821.

Assaf M, Jagannathan K, Calhoun VD, Miller L, Stevens MC, Sahl R, O'Boyle JG, Schultz RT, Pearlson GD. 2010. Abnormal functional connectivity of default mode subnetworks in autism spectrum disorder patients. *Neuroimage.* 53:247-256.

Back SA, Luo NL, Borenstein NS, Levine JM, Volpe JJ, Kinney HC. 2001. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. *The Journal of Neuroscience.* 21:1302-1312.

Back SA, Riddle A, Dean J, Hohimer AR. 2012. The instrumented fetal sheep as a model of cerebral white matter injury in the premature infant. *Neurotherapeutics.* 9:359-370.

Back SA, Miller SP. 2014. Brain injury in premature neonates: a primary cerebral dysmaturation disorder? *Ann Neurol.* 75:469-486.

Back SA, Rosenberg PA. 2014. Pathophysiology of glia in perinatal white matter injury. *Glia.* 62:1790-1815.

Baddeley AD, Hitch GJ. 1994. Developments in the concept of working memory. *Neuropsychology*. 8:485-493.

Ball G, Pazderova L, Chew A, Tusor N, Merchant N, Arichi T, Allsop JM, Cowan FM, Edwards AD, Counsell SJ. 2015. Thalamocortical connectivity predicts cognition in children born preterm. *Cerebral cortex*. 25:4310-4318.

Ballabh P. 2010. Intraventricular hemorrhage in premature infants: mechanism of disease. *Pediatr Res*. 67:1-8.

Baron IS, Kerns KA, Müller U, Ahronovich MD, Litman FR. 2012. Executive functions in extremely low birth weight and late-preterm preschoolers: effects on working memory and response inhibition. *Child Neuropsychology*. 18:586-599.

Berger H. 1929. Ueber das elektroenkephalogramm des menschen. *Archiv für Psychiatrie und Nervenkrankheiten*. 87:527-570.

Biswal B, Yetkin FZ, Haughton VM, Hyde JS. 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med*. 34:537-541.

Bjuland KJ, Løhaugen GCC, Martinussen M, Skranes J. 2013. Cortical thickness and cognition in very-low-birth-weight late teenagers. *Early Hum Dev*. 89:371-380.

Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller A-B, Kinney M, Lawn J. 2013. Born too soon: the global epidemiology of 15 million preterm births. *Reproductive health*. 10:1.

Boardman JP, Counsell SJ, Rueckert D, Kapellou O, Bhatia KK, Aljabar P, Hajnal J, Allsop JM, Rutherford MA, Edwards AD. 2006. Abnormal deep grey matter development following preterm birth detected using deformation-based morphometry. *Neuroimage*. 32:70-78.

Boddaert N, Chabane N, Gervais H, Good C, Bourgeois M, Plumet M, Barthelemy C, Mouren M, Artiges E, Samson Y. 2004. Superior temporal sulcus anatomical abnormalities in childhood autism: a voxel-based morphometry MRI study. *Neuroimage*. 23:364-369.

Bora E, Fornito A, Pantelis C, Yücel M. 2012. Gray matter abnormalities in major depressive disorder: a meta-analysis of voxel based morphometry studies. *Journal of affective disorders.* 138:9-18.

Boynton GM, Engel SA, Glover GH, Heeger DJ. 1996. Linear systems analysis of functional magnetic resonance imaging in human V1. *The Journal of Neuroscience.* 16:4207-4221.

Breeman L, Jaekel J, Baumann N, Bartmann P, Wolke D. 2015. Preterm Cognitive Function into Adulthood. *Pediatrics.* 136. Doi: 10.1542/peds.2015-0608.

Bressler SL, Menon V. 2010. Large-scale brain networks in cognition: emerging methods and principles. *Trends Cogn Sci.* 14:277-290.

Brummelte S, Grunau RE, Chau V, Poskitt KJ, Brant R, Vinall J, Gover A, Synnes AR, Miller SP. 2012. Procedural pain and brain development in premature newborns. *Ann Neurol.* 71:385-396.

Burnett AC, Scratch SE, Anderson PJ. 2013. Executive function outcome in preterm adolescents. *Early Hum Dev.* 89:215-220.

Buser JR, Maire J, Riddle A, Gong X, Nguyen T, Nelson K, Luo NL, Ren J, Struve J, Sherman LS. 2012. Arrested preoligodendrocyte maturation contributes to myelination failure in premature infants. *Ann Neurol.* 71:93-109.

Buzsaki G. 2006. *Rhythms of the Brain.* New York: Oxford University Press.

Cameron-Curry P, Le Douarin NM. 1995. Oligodendrocyte precursors originate from both the dorsal and the ventral parts of the spinal cord. *Neuron.* 15:1299-1310.

Cole MW, Bassett DS, Power JD, Braver TS, Petersen SE. 2014. Intrinsic and task-evoked network architectures of the human brain. *Neuron.* 83:238-251.

Counsell SJ, Allsop JM, Harrison MC, Larkman DJ, Kennea NL, Kapellou O, Cowan FM, Hajnal JV, Edwards AD, Rutherford MA. 2003. Diffusion-weighted imaging of the brain in preterm infants with focal and diffuse white matter abnormality. *Pediatrics.* 112:1-7.

Curristin SM, Cao A, Stewart WB, Zhang H, Madri JA, Morrow JS, Ment LR. 2002. Disrupted synaptic development in the hypoxic newborn brain. *Proceedings of the National Academy of Sciences*. 99:15729-15734.

Damaraju E, Phillips JR, Lowe JR, Ohls R, Calhoun VD, Caprihan A. 2010. Resting-state functional connectivity differences in premature children. *Front Syst Neurosci*. 4. Doi: 10.3389/fnsys.2010.00023.

Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF. 2006. Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A*. 103:13848-13853.

de Graaf-Peters VB, Hadders-Algra M. 2006. Ontogeny of the human central nervous system: what is happening when? *Early Hum Dev*. 82:257-266.

Dean JM, McClendon E, Hansen K, Azimi-Zonooz A, Chen K, Riddle A, Gong X, Sharifnia E, Hagen M, Ahmad T. 2013. Prenatal cerebral ischemia disrupts MRI-defined cortical microstructure through disturbances in neuronal arborization. *Science translational medicine*. 5:168ra167-168ra167.

Deng W. 2010. Neurobiology of injury to the developing brain. *Nat Rev Neurol*. 6:328-336.

Di X, Gohel S, Kim EH, Biswal BB. 2013. Task vs. rest—different network configurations between the coactivation and the resting-state brain networks. *Front Hum Neurosci*. 7. Doi: 10.3389/fnhum.2013.00493.

Diamond A. 2013. Executive functions. *Annu Rev Psychol*. 64:135.

Doria V, Beckmann CF, Arichi T, Merchant N, Groppo M, Turkheimer FE, Counsell SJ, Murgasova M, Aljabar P, Nunes RG, Larkman DJ, Rees G, Edwards AD. 2010. Emergence of resting state networks in the preterm human brain. *Proc Natl Acad Sci U S A*. 107:20015-20020.

Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. 2004. Neuroplasticity: changes in grey matter induced by training. *Nature*. 427:311-312.

Elovitz MA, Mrinalini C. 2004. Animal models of preterm birth. *Trends in Endocrinology & Metabolism*. 15:479-487.

Eryigit Madzwamuse S, Baumann N, Jaekel J, Bartmann P, Wolke D. 2014. Neuro-cognitive performance of very preterm or very low birth weight adults at 26 years. *Journal of Child Psychology and Psychiatry*. 56:857-864.

Fair DA, Dosenbach NU, Church JA, Cohen AL, Brahmbhatt S, Miezin FM, Barch DM, Raichle ME, Petersen SE, Schlaggar BL. 2007. Development of distinct control networks through segregation and integration. *Proceedings of the National Academy of Sciences*. 104:13507-13512.

Favrais G, Van De Looij Y, Fleiss B, Ramanantsoa N, Bonnin P, Stoltenburg-Didinger G, Lacaud A, Saliba E, Dammann O, Gallego J. 2011. Systemic inflammation disrupts the developmental program of white matter. *Ann Neurol*. 70:550-565.

Fransson P, Sköld B, Horsch S, Nordell A, Blennow M, Lagercrantz H, Aden U. 2007. Resting-state networks in the infant brain. *Proc Natl Acad Sci U S A*. 104:15531-15536.

Fries P. 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn Sci*. 9:474-480.

Friston K, Frith C, Frackowiak R. 1993. Time-dependent changes in effective connectivity measured with PET. *Hum Brain Mapp*. 1:69-79.

Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RS. 1994. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp*. 2:189-210.

Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. 1999. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci*. 2:861-863.

Goldenberg RL, Rouse DJ. 1998. Prevention of premature birth. *New England Journal of Medicine*. 339:313-320.

Goldenberg RL, Culhane JF, Iams JD, Romero R. 2008. Epidemiology and causes of preterm birth. *The Lancet*. 371:75-84.

Goldman-Rakic PS. 1982. Neuronal development and plasticity of association cortex in primates. *Neurosciences Research Program bulletin*. 20:520-532.

Griffiths ST, Gundersen H, Neto E, Elgen I, Markestad T, Aukland SM, Hugdahl K. 2013. fMRI: blood oxygen level-dependent activation during a working memory-selective attention task in children born extremely preterm. *Pediatr Res*. 74:196-205.

Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N. 2002. Outcomes in young adulthood for very-low-birth-weight infants. *N Engl J Med*. 346:149-157.

Hallin AL, Hellström-Westas L, Stjernqvist K. 2010. Follow-up of adolescents born extremely preterm: cognitive function and health at 18 years of age. *Acta Paediatrica*. 99:1401-1406.

Hämäläinen A, Pihlajamäki M, Tanila H, Hänninen T, Niskanen E, Tervo S, Karjalainen PA, Vanninen RL, Soininen H. 2007. Increased fMRI responses during encoding in mild cognitive impairment. *Neurobiology of aging*. 28:1889-1903.

Hamrick SE, Miller SP, Leonard C, Glidden DV, Goldstein R, Ramaswamy V, Piecuch R, Ferriero DM. 2004. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: the role of cystic periventricular leukomalacia. *J Pediatr*. 145:593-599.

Harvey P-O, Fossati P, Pochon J-B, Levy R, LeBastard G, Lehéricy S, Allilaire J-F, Dubois B. 2005. Cognitive control and brain resources in major depression: an fMRI study using the n-back task. *Neuroimage*. 26:860-869.

Hoerder-Suabedissen A, Molnár Z. 2015. Development, evolution and pathology of neocortical subplate neurons. *Nature Reviews Neuroscience*. 16:133-146.

Hölzel BK, Carmody J, Vangel M, Congleton C, Yerramsetti SM, Gard T, Lazar SW. 2011. Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Research: Neuroimaging*. 191:36-43.

Honea R, Crow TJ, Passingham D, Mackay CE. 2005. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *American Journal of Psychiatry*. 162:2233-2245.

Horovitz SG, Fukunaga M, de Zwart JA, van Gelderen P, Fulton SC, Balkin TJ, Duyn JH. 2008. Low frequency BOLD fluctuations during resting wakefulness and light sleep: a simultaneous EEG-fMRI study. *Hum Brain Mapp.* 29:671-682.

Hughes SW, Lőrincz ML, Parri HR, Crunelli V. 2011. Infra-slow (< 0.1 Hz) oscillations in thalamic relay nuclei: basic mechanisms and significance to health and disease states. *Prog Brain Res.* 193:145.

Jaekel J, Baumann N, Wolke D. 2013. Effects of gestational age at birth on cognitive performance: a function of cognitive workload demands. *PLoS One.* 8:e65219.

Jobe A, Ikegami M. 1987. Surfactant for the treatment of respiratory distress syndrome. *American Review of Respiratory Disease.* 136:1256-1275.

Jobe AH, Bancalari E. 2001. Bronchopulmonary dysplasia. *American journal of respiratory and critical care medicine.* 163:1723-1729.

Johnson S, Hennessy E, Smith R, Trikic R, Wolke D, Marlow N. 2009. Academic attainment and special educational needs in extremely preterm children at 11 years of age: the EPICure study. *Arch Dis Child Fetal Neonatal Ed.* 94:F283-289.

Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ. 2007. Functional and anatomical cortical underconnectivity in autism: evidence from an fMRI study of an executive function task and corpus callosum morphometry. *Cerebral cortex.* 17:951-961.

Kanold PO, Kara P, Reid RC, Shatz CJ. 2003. Role of subplate neurons in functional maturation of visual cortical columns. *Science.* 301:521-525.

Karlsgodt KH, Glahn DC, van Erp TG, Therman S, Huttunen M, Manninen M, Kaprio J, Cohen MS, Lönnqvist J, Cannon TD. 2007. The relationship between performance and fMRI signal during working memory in patients with schizophrenia, unaffected co-twins, and control subjects. *Schizophrenia research.* 89:191-197.

Komitova M, Xenos D, Salmaso N, Tran KM, Brand T, Schwartz ML, Ment L, Vaccarino FM. 2013. Hypoxia-induced developmental delays of inhibitory interneurons are reversed by environmental enrichment in the postnatal mouse forebrain. *The Journal of Neuroscience.* 33:13375-13387.

Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R. 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences*. 89:5675-5679.

Lauterbur PC. 1973. Image formation by induced local interactions: examples employing nuclear magnetic resonance. *Nature*. 242:190-191.

Ligam P, Haynes RL, Folkerth RD, Liu L, Yang M, Volpe JJ, Kinney HC. 2009. Thalamic damage in periventricular leukomalacia: novel pathologic observations relevant to cognitive deficits in survivors of prematurity. *Pediatr Res*. 65:524-529.

Litt JS, Gerry Taylor H, Margevicius S, Schluchter M, Andreias L, Hack M. 2012. Academic achievement of adolescents born with extremely low birth weight. *Acta Paediatrica*. 101:1240-1245.

Lowel S, Singer W. 1992. Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. *Science*. 255:209-212.

Luo C, Li Q, Lai Y, Xia Y, Qin Y, Liao W, Li S, Zhou D, Yao D, Gong Q. 2011. Altered functional connectivity in default mode network in absence epilepsy: a resting-state fMRI study. *Hum Brain Mapp*. 32:438-449.

Manoach DS, Press DZ, Thangaraj V, Searl MM, Goff DC, Halpern E, Saper CB, Warach S. 1999. Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. *Biol Psychiatry*. 45:1128-1137.

Marín-Padilla M. 1997. Developmental neuropathology and impact of perinatal brain damage. II: white matter lesions of the neocortex. *Journal of Neuropathology & Experimental Neurology*. 56:219-235.

Marín-Padilla M. 1999. Developmental neuropathology and impact of perinatal brain damage. III: gray matter lesions of the neocortex. *Journal of Neuropathology & Experimental Neurology*. 58:407-429.

McQuillen PS, Sheldon RA, Shatz CJ, Ferriero DM. 2003. Selective vulnerability of subplate neurons after early neonatal hypoxia-ischemia. *J Neurosci*. 23:3308-3315.

McQuillen PS, Ferriero DM. 2005. Perinatal subplate neuron injury: implications for cortical development and plasticity. *Brain Pathol.* 15:250-260.

Mechelli A, Price CJ, Friston KJ, Ashburner J. 2005. Voxel-based morphometry of the human brain: methods and applications. *Current Medical Imaging Reviews.* 1:105-113.

Meng C, Brandl F, Tahmasian M, Shao J, Manoliu A, Scherr M, Schwerthoffer D, Bauml J, Forstl H, Zimmer C, Wohlschlager AM, Riedl V, Sorg C. 2013. Aberrant topology of striatum's connectivity is associated with the number of episodes in depression. *Brain.* 137:598-609.

Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL, Marlow N. 2012. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. *Bmj.* 345:e7961.

Mulder H, Pitchford NJ, Hagger MS, Marlow N. 2009. Development of executive function and attention in preterm children: a systematic review. *Dev Neuropsychol.* 34:393-421.

Mulder H, Pitchford NJ, Marlow N. 2010. Processing speed and working memory underlie academic attainment in very preterm children. *Arch Dis Child Fetal Neonatal Ed.* Doi:10.1136/adc.2009.167965.

Mummery CJ, Patterson K, Price C, Ashburner J, Frackowiak R, Hodges JR. 2000. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. *Ann Neurol.* 47:36-45.

Nagy Z, Ashburner J, Andersson J, Jbabdi S, Draganski B, Skare S, Bohm B, Smedler AC, Forssberg H, Lagercrantz H. 2009. Structural correlates of preterm birth in the adolescent brain. *Pediatrics.* 124:e964-972.

Nosarti C, Giouroukou E, Micali N, Rifkin L, Morris RG, Murray RM. 2007. Impaired executive functioning in young adults born very preterm. *Journal of the International Neuropsychological Society.* 13:571-581.

Nosarti C, Giouroukou E, Healy E, Rifkin L, Walshe M, Reichenberg A, Chitnis X, Williams SC, Murray RM. 2008. Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome. *Brain.* 131:205-217.

Nosarti C, Reichenberg A, Murray RM, Cnattingius S, Lambe MP, Yin L, MacCabe J, Rifkin L, Hultman CM. 2012. Preterm birth and psychiatric disorders in young adult life. *Arch Gen Psychiatry*. 69:E1-8.

Ogawa S, Lee T-M, Kay AR, Tank DW. 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences*. 87:9868-9872.

Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K. 1992. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Sciences*. 89:5951-5955.

Padilla N, Alexandrou G, Blennow M, Lagercrantz H, Aden U. 2014. Brain Growth Gains and Losses in Extremely Preterm Infants at Term. *Cereb Cortex*. Doi: 10.1093/cercor/bht431.

Palva JM, Palva S. 2012. Infra-slow fluctuations in electrophysiological recordings, blood-oxygenation-level-dependent signals, and psychophysical time series. *Neuroimage*. 62:2201-2211.

Penn AA, Gressens P, Fleiss B, Back SA, Gallo V. 2015. Controversies in preterm brain injury. *Neurobiology of disease*. 92:90-101.

Pierson CR, Folkerth RD, Billiards SS, Trachtenberg FL, Drinkwater ME, Volpe JJ, Kinney HC. 2007. Gray matter injury associated with periventricular leukomalacia in the premature infant. *Acta Neuropathol*. 114:619-631.

Poldrack RA, Mumford JA, Nichols TE. 2011. *Handbook of functional MRI data analysis*. Cambridge: Cambridge University Press.

Pyhälä R. 2012. Psychological and psychophysiological functioning of young adults born preterm: The Helsinki Study of Very Low Birth Weight Adults [Dissertation]. University of Helsinki.

Rakic P. 1974. Neurons in rhesus monkey visual cortex: systematic relation between time of origin and eventual disposition. *Science*. 183:425-427.

Rice JE, Vannucci RC, Brierley JB. 1981. The influence of immaturity on hypoxic-ischemic brain damage in the rat. *Ann Neurol.* 9:131-141.

Riddle A, Maire J, Gong X, Chen KX, Kroenke CD, Hohimer AR, Back SA. 2012. Differential susceptibility to axonopathy in necrotic and non-necrotic perinatal white matter injury. *Stroke.* 43:178-184.

Roberts D, Dalziel S. 2006. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review). *Cochrane Database Syst Rev.* 19:CD004454.

Rocca M, Valsasina P, Absinta M, Riccitelli G, Rodegher M, Misci P, Rossi P, Falini A, Comi G, Filippi M. 2010. Default-mode network dysfunction and cognitive impairment in progressive MS. *Neurology.* 74:1252-1259.

Rousset CI, Chalon S, Cantagrel S, Bodard S, Andres C, Gressens P, Saliba E. 2006. Maternal exposure to LPS induces hypomyelination in the internal capsule and programmed cell death in the deep gray matter in newborn rats. *Pediatr Res.* 59:428-433.

Salmaso N, Jablonska B, Scafidi J, Vaccarino FM, Gallo V. 2014. Neurobiology of premature brain injury. *Nat Neurosci.* 17:341-346.

Schnitzler A, Gross J. 2005. Normal and pathological oscillatory communication in the brain. *Nature Reviews Neuroscience.* 6:285-296.

Sepulcre J, Sastre-Garriga J, Cercignani M, Ingle GT, Miller DH, Thompson AJ. 2006. Regional gray matter atrophy in early primary progressive multiple sclerosis: a voxel-based morphometry study. *Arch Neurol.* 63:1175-1180.

Sepulcre J, Liu H, Talukdar T, Martincorena I, Yeo BT, Buckner RL. 2010. The organization of local and distant functional connectivity in the human brain. *PLoS Comput Biol.* 6:e1000808.

Singer W. 1993. Synchronization of cortical activity and its putative role in information processing and learning. *Annual review of physiology.* 55:349-374.

Smyser CD, Inder TE, Shimony JS, Hill JE, Degnan AJ, Snyder AZ, Neil JJ. 2010. Longitudinal analysis of neural network development in preterm infants. *Cereb Cortex*. 20:2852-2862.

Smyser CD, Snyder AZ, Shimony JS, Blazey TM, Inder TE, Neil JJ. 2013. Effects of white matter injury on resting state fMRI measures in prematurely born infants. *PLoS One*. 8:e68098.

Smyser CD, Snyder AZ, Shimony JS, Mitra A, Inder TE, Neil JJ. 2014. Resting-state network complexity and magnitude are reduced in prematurely born infants. *Cerebral Cortex*. Doi: 10.1093/cercor/bhu251.

Sorg C, Riedl V, Muhlau M, Calhoun VD, Eichele T, Laer L, Drzezga A, Forstl H, Kurz A, Zimmer C, Wohlschlager AM. 2007. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. *Proc Natl Acad Sci U S A*. 104:18760-18765.

Sorg C, Manoliu A, Neufang S, Myers N, Peters H, Schwerthoffer D, Scherr M, Muhlau M, Zimmer C, Drzezga A, Forstl H, Baum J, Eichele T, Wohlschlager AM, Riedl V. 2013. Increased intrinsic brain activity in the striatum reflects symptom dimensions in schizophrenia. *Schizophr Bull*. 39:387-395.

Spencer MD, Moorhead TW, Gibson RJ, McIntosh AM, Sussmann JE, Owens DG, Lawrie SM, Johnstone EC. 2008. Low birthweight and preterm birth in young people with special educational needs: a magnetic resonance imaging analysis. *BMC Med*. 6:1. Doi: 10.1186/1741-7015-6-1.

Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Vento M. 2013. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants-2013 update. *Neonatology*. 103:353-368.

Taylor HG, Minich N, Bangert B, Filipek PA, Hack M. 2004. Long-term neuropsychological outcomes of very low birth weight: associations with early risks for periventricular brain insults. *J Int Neuropsychol Soc*. 10:987-1004.

Taylor M, Donner E, Pang E. 2012. fMRI and MEG in the study of typical and atypical cognitive development. *Neurophysiologie Clinique/Clinical Neurophysiology*. 42:19-25.

Toulmin H, Beckmann CF, O'Muircheartaigh J, Ball G, Nongena P, Makropoulos A, Ederies A, Counsell SJ, Kennea N, Arichi T. 2015. Specialization and integration of functional thalamocortical connectivity in the human infant. *Proceedings of the National Academy of Sciences*. 112:6485-6490.

Vanhatalo S, Palva JM, Holmes M, Miller J, Voipio J, Kaila K. 2004. Infraslow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. *Proc Natl Acad Sci U S A*. 101:5053-5057.

Vasic N, Walter H, Höse A, Wolf RC. 2008. Gray matter reduction associated with psychopathology and cognitive dysfunction in unipolar depression: a voxel-based morphometry study. *Journal of affective disorders*. 109:107-116.

Verney C, Pogledic I, Biran V, Adle-Biassette H, Fallet-Bianco C, Gressens P. 2012. Microglial reaction in axonal crossroads is a hallmark of noncystic periventricular white matter injury in very preterm infants. *Journal of Neuropathology & Experimental Neurology*. 71:251-264.

Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, Van Essen DC, Zempel JM, Snyder LH, Corbetta M, Raichle ME. 2007. Intrinsic functional architecture in the anaesthetized monkey brain. *Nature*. 447:83-86.

Volpe JJ. 1996. Subplate neurons-missing link in brain injury of the premature infant? *Pediatrics*. 97:112-113.

Volpe JJ. 2009a. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol*. 8:110-124.

Volpe JJ. 2009b. The Encephalopathy of Prematurity—Brain Injury and Impaired Brain Development Inextricably Intertwined. *Semin Pediatr Neurol*. 16:167-178.

Wang Z, Yan C, Zhao C, Qi Z, Zhou W, Lu J, He Y, Li K. 2011. Spatial patterns of intrinsic brain activity in mild cognitive impairment and alzheimer's disease: A resting-state functional MRI study. *Hum Brain Mapp.* 32:1720-1740.

Willson DF, Thomas NJ, Markovitz BP, Bauman LA, DiCarlo JV, Pon S, Jacobs BR, Jefferson LS, Conaway MR, Egan EA. 2005. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. *Jama.* 293:470-476.

Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. 2006. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *New England Journal of Medicine.* 355:685-694.

Wyatt J.(2010). The changing face of intensive care for preterm newborns. In Nosarti C, Murray R, Hack M (Ed.), *Neurodevelopmental outcomes of preterm birth* (pp. 17-29). Cambridge: Cambridge University Press.

Zubiaurre-Elorza L, Soria-Pastor S, Junque C, Segarra D, Bargallo N, Mayolas N, Romano-Berindoague C, Macaya A. 2011. Gray matter volume decrements in preterm children with periventricular leukomalacia. *Pediatr Res.* 69:554-560.

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.

Eidesstattliche Versicherung

Name, Vorname

Ich erkläre hiermit an Eides statt,
dass ich die vorliegende Dissertation mit dem Thema

selbständig verfasst, 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.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

Ort, Datum

Unterschrift Doktorandin/Doktorand