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TIME RESOLVED FUNCTIONAL BRAIN NETWORKS

- A NOVEL METHOD AND DEVELOPMENTAL PERSPECTIVE

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Time resolved functional brain networks – a novel method and developmental perspective

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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ABSTRACT

Functional neuroimaging has helped elucidating the complexity of brain function in ever more detail during the last 30 years. In this time the concepts used to understand how the brain works has also developed from a focus on regional activation to a network based whole brain perspective (Deco et al., 2015). The understanding that the brain is not just merely responding to external demands but is itself a co-creator of its perceived reality is now the default perspective (Buzsáki and Fernández-Ruiz, 2019). This means that the brain is never resting and its intrinsic architecture is the basis for any task related modulation (Cole et al., 2014). As often in science, understanding and technological advances go hand in hand. For the advancement of the functional neuroimaging field during the last decade, methods that are able to track, capture and model time resolved connectivity changes has been essential (Lurie et al., 2020). This development is an ongoing process. Part of the work presented in this thesis is a small contribution to this collective endeavor.

The first theme in the thesis is time resolved connectivity of functional brain networks. This theme is present in Study I which presents a novel method for analysis of time resolved connectivity using BOLD fMRI data. With this method, subnetworks in the brain are defined dynamically. It allows for connectivity changes to be tracked from time point to time point while respecting the temporal ordering of the data. It also provides relational properties in terms of differences in phase coherence between simultaneously integrated networks and their gradual change. The method can be used see how whole brain connectivity configurations recure in quasi-cyclic patterns. Finally, the method is able to estimate flexibility and modularity of individual brain areas. The method is applied in Study III in order to understand how premature birth effects flexibility and modularity of intrinsic functional brain networks.

Beyond the purely scientific endeavor to understand how the brain creates cognition, consciousness, perception and supports motor function, neuroimaging research has also been helpful in elucidating normal brain development and neurodevelopmental disorders. The second theme in this thesis is brain development in extremely preterm born children at school age. This theme is the focus of Study II & III. Study II investigates the prevalence of discrete white matter abnormalities at school age in children born extremely preterm and the relationship to neuro-motor outcome. The prevalence of white matter abnormalities was high but there was no relationship to an unfavorable outcome. Also, a longitudinal association to neonatal white matter injury was seen. While discrete white matter abnormalities were not correlated to

quantitative measures of white matter volume and white matter integrity, neonatal white matter injury was associated with lower volume and integrity at age 8– 11 years. Moreover, neonatal white matter injury was associated with lower processing speed at 12 years.

The third and final study investigated flexibility and modularity as well as lateralization of intrinsic networks in children born extremely preterm at age 8–11 years. No significant differences in either flexibility or modularity was seen for any intrinsic network after correcting for multiple comparisons. However, at the level of individual brain areas, preterm children showed decreased flexibility in both the basal ganglia and thalamus. Also, children born extremely preterm had a decreased level of lateralization in most networks.

LIST OF SCIENTIFIC PAPERS

I. **Strindberg M.**, Fransson P., Cabral J., Ådén U. (2021) ”Spatiotemporally flexible subnetworks reveal the quasi–cyclic nature of integration and segregation in the human brain.” Neuroimage 236, 11287

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II. Nosko D*., **Strindberg M.***, Svoboda J., Kvanta H., Broström L., Padilla N., Mårtensson G., Örtqvist M., Canto Moreira N., Ådén U. (2021)” Discrete white matter abnormalities at age 8–11 years in children born extremely preterm are not associated with negative or cognitive outcome. ” Acta Paediatrica 2021; 00:1–10.

**These authors contributed equally to this work*

III. **Strindberg M**, Fransson P, Ådén U. (In preparation). ”Reduced flexibility in functional brain networks in children born extremely preterm”

CONTENTS

LIST OF ABBREVIATIONS

BOLD–signal	Blood–oxygen–level–dependent signal
CAP	Co–activation pattern
dFC	Dynamic functional connectivity
DTI	Diffusion tensor imaging
EEG	Electroencephalography
FA	Fractional anisotropy
FC	Functional connectivity
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
GA	Gestational age
ICA	Independent component analysis
IPSA	Instantaneous phase synchrony analysis
LPF	Local field potential
MEG	Magnetoencephalography
MN	Meta–network
RSN	Resting state network
SN	Subnetwork
SNC	Subnetwork component
TEA	Term equivalent age
TFM	Temporal functional mode
TR	Repetition time
WMA	White matter alteration
WMI	White matter injury

1 INTRODUCTION

To a large extent the work in this thesis will be presented separately under headlines Study I, Study II, Study III. The rationale behind this is the rather separate character of the three studies. However, there is a common theme joining them. Or rather, there are two combined themes. The first theme is *time resolved functional connectivity*, the second theme is *preterm brain development*. The first theme is found in Study I & III. The second theme is found in Study II & III. Study I describe a novel method for time resolved analysis of functional brain network connectivity. In Study III, the method is applied to extremely preterm brain development in relation to normal brain development at school age. This study therefore is a bridge joining the two themes. Study II focuses on the prevalence of white matter alterations in extremely preterm born children at school age and any relation to motor development and cognitive outcome. It also explores the longitudinal relationship to neonatal white matter alterations and injury.

2 LITERATURE REVIEW

2.1 THE BOLD SIGNAL

In functional MRI (fMRI) research, the blood–oxygen–level–dependent (BOLD) signal is leveraged as a proxy marker for neuronal activity to map the functional organization of the brain (Huettel et al., 2009). The BOLD–signal results from the difference in magnetic properties of oxygenated and deoxygenated hemoglobin. In gradient echo pulse sequences sensitive to T_2 weighted contrast, the paramagnetic effect of deoxyhemoglobin causes local distortion of the magnetic field which leads to a weakening of the signal (Ogawa et al., 1990). According to the neurovascular coupling explanatory model on which all fMRI research is based, areas with increased neuronal activation are flushed with oxygenated blood (Raichle, 2010). Since the increase in oxygen extraction from the capillaries is much smaller than the extra amount made available, the fraction of deoxyhemoglobin in the venous portion of the capillary bed and venules increases. This in turn results in a local increase in the BOLD signal

(Huettel et al., 2009). Even though arteries and arterioles can dilate substantially as a response to neuronal activation, the BOLD signal itself mainly reflects the venous side since that is where the most marked changes in the proportion of oxygenated and deoxyhemoglobin is seen. The response is therefore delayed relative to the hemodynamic response function of the arterial side and potentially biased medially due to the draining pattern (Hillman, 2014). The exact mechanisms underlying the neurovascular coupling are not known (Huettel et al., 2009). However, the evidence for a link between the BOLD signal and neuronal activity is supported by studies using a range of different and complimentary approaches. For example, compelling evidence comes from optogenetics showing that stimulation of specific neurons resulted in a local BOLD–response (Lee et al., 2010). In a study using transcranial magnetic stimulation (TMS), a concomitant neuronal and hemodynamic response was seen (Allen et al., 2007). Other important studies have focused on correlating the BOLD signal with local field potentials (LPFs). LFPs are invasive recordings of the extracellular voltage (<500Hz) and is thought to reflect the sum of current generated by synaptic input on the dendrites and cell bodies of the neuronal populations in its field of reach (Herreras, 2016). This means that LFPs do not only reflect the activity originating in close proximity to the recording site but also from a distance. Moreover, several factors influence the contribution of the different sources such as local geometry, the frequencies generated and electrical conductivity of the extracellular medium. The timing of the contributions from the different sources cannot be disentangled. LFP interpretation is therefore non–trivial and LFPs share the problem of source localization with electroencephalography (EEG) / magnetoencephalography (MEG) (Herreras, 2016; Lindén et al., 2011). Despite these challenges, clear correlations between LPF power time courses and the BOLD signal can be seen (Schölvinck et al., 2010). Also studies using EEG and MEG have provided important evidence for the link between neuronal activity and the BOLD signal (Baker et al., 2014; Gohel and Biswal, 2015; Grooms et al., 2017; Keilholz, 2014). While questions about the exact mechanisms of the BOLD signal remain, the statement that the BOLD signal is indeed coupled to neuronal activity is uncontroversial.

2.2 RESTING STATE FMRI

While the field of task fMRI research has been prolific since the discovery of the BOLD signal in the early 1990's, the field of resting state–fMRI is more recent and has had a slow start (Raichle and Mintun, 2006). In task fMRI, a subject is instructed to perform

some kind of task which can be purely cognitive or engage the sensory motor system. The mean activity is considered as background noise and averaged out from the analysis. However, in a study in 1995, researchers noted the presence of slow spontaneous fluctuations bilaterally in the motor cortex which showed strong temporal correlation without external stimulation (Biswal et al., 1995). Around the same time using positron emission tomography (PET), it was seen that brain activity at wakeful rest is not random but constrained by intrinsic activity patterns (Raichle, 2010). In fact, the extra energy expenditure of cognitive task load compared to intrinsic, or resting, activity rarely exceed 5% (Raichle, 2010). Clearly, these experimental results confirm the subjective experience of a non-idle brain even when not engaged in a specific task. Since then, using fMRI in the task free condition, the presence of distinct and highly reproducible patterns of co-activations have been widely corroborated (Raichle, 2010). These patterns can be reproduced by simply correlating regional time-series of a full acquisition which is typically 10 min long. Importantly, areas that tend to activate together are believed to work together as a network. Due to the dichotomy between task and non-task (aka "rest") conditions, that is used in neuroimaging research , the intrinsic functional networks in the human brain are commonly referred to as resting state networks (RSNs) (Smith et al., 2009). Broadly speaking, the RSNs encompass primary sensory-motor networks (visual (VIS), somato-motor (SOM)) and higher-order association networks (default mode (DMN), fronto-parietal control (FPN), dorsal attention (DAN), ventral attention (VAN)) (Thomas Yeo et al., 2011). Alternative partitions of the association networks include the salience (SA) network, language/auditory network (Lang/Aud), the cingulo-opercular network (CO), central executive (CEN) (Menon, 2015). Due to the ease of acquisition and reliability of network identification across MR scanner protocols and image data pre- and post-processing pipelines, rs-fMRI have become an important non-invasive method to better understand functional architecture of the healthy human brain. It has also been used to map changes in brain network connectivity due to disease affecting the brain such as Alzheimer's, intractable epilepsy and depression (Fornito et al., 2015) as well as developmental disorders including autism and ADHD. The method has also been used to study brain reorganization secondary to acquired brain injury and preterm birth (Cao et al., 2016) as well as altered states of consciousness, such as coma, sleep, anesthesia (Heine et al., 2012) and psychoactive drugs (Müller et al., 2018).

While connectivity within and between RSNs (Resting-State Networks) has been shown to be altered in a number of health conditions affecting the brain, examples of integration of the RSN-methodology into clinical practice to aid diagnosis is scarce (O'Connor and Zeffiro, 2019). To date, the clinical use is limited to presurgical planning prior to removal of brain tumors and to locate epileptogenic foci (Boerwinkle et al., 2017). The reasons for

the lack of clinical applications are many. One important factor is the diversity of pre-processing protocols and variability in analysis methodology which leads to inconsistent results across studies (O'Connor and Zeffiro, 2019). Perhaps the most serious limitation for use of rs-fMRI in clinical practice is a lack of robust network measures in individual subjects (O'Connor and Zeffiro, 2019).

2.2.1 Developmental perspective

Using fetal imaging, precursors to RSNs have been identified in fetuses at least as early as 21 weeks gestational age (GA) (Jakab et al., 2014). From the end of the second trimester up to birth, interhemispheric connectivity and cortical-subcortical connectivity increases as a function of gestational age. Connectivity between the hemispheres first develops between homotropic midline structures as the callosal fibers connect (Thomason et al., 2013). The development then gradually includes more lateral regions. The temporal cortices which are separated by most distance are last to develop bilateral connectivity (Keunen et al., 2017a). In the first study examining RSNs in healthy full term neonates, primary sensorimotor were identified together with precursors to the cognitive control networks (Fransson et al., 2007). Subsequent studies have largely corroborated these findings. Primary somato-sensory networks mature earlier and show adult like connectivity and topography at birth. In contrast, higher order association networks exist as less well-connected precursors at birth and mature later. Interestingly, the most significant part of the maturation process of these networks happens already within the first year (Gao et al., 2015). This coincides with a period of remarkable psycho-motor development. Functional hubs in healthy neonates are mainly found in primary sensory-motor areas, precuneus, cingulate cortex, medial prefrontal cortex (mPFC), posterior cingulate cortex(PCC) but also in subcortical-limbic-paralimbic regions (De Asis-Cruz et al., 2015; Fransson et al., 2011; Gao et al., 2011). The newly born brain already exhibit a small world topology, i.e. short average path lengths (resembling a random network) and high clustering coefficient (resembling a grid network) (Fransson et al., 2011). After one year, anti-correlation between DMN and DAN are present and becomes more apparent by 2 years (Gao et al., 2013). With development local short range connectivity decrease (networks become more locally focused/specialized) and long-range connections increase (networks become more integrated). Segregation between networks increase with age (Fair et al., 2009; Gao et al., 2015).

2.2.2 Effect of prematurity on functional brain network development

The presence of primary RSNs have been demonstrated in premature born babies as early as 26 weeks GA (Smyser et al., 2010). The DMN together with some other higher order RSNs has been identified at 30 weeks GA (Doria et al., 2010). While the functional network topology largely seem to be preserved in preterm born babies at term equivalent age (TEA) (Fransson et al., 2011), connectivity is generally stronger in the term population with the exception for the visual network with show stronger connectivity in the preterm group (Bouyssi–Kobar et al., 2019; Eyre et al., 2021a; Smyser et al., 2010; Van Den Heuvel et al., 2015). When compared at TEA, preterm born children have weaker long–range connectivity and spatially smaller networks (fewer voxels with strong connections) compared to controls. Perhaps the most salient finding is altered functional connectivity between cortex and the thalamus and basal ganglia in preterm neonates (Ball et al., 2016; Cai et al., 2017; Smyser et al., 2010; Toulmin et al., 2015). For example, in a study applying a vector based classification approach, half of the network edges that had discriminatory power between term and preterm subject were connections between the cortex and basal ganglia (Ball et al., 2016). Another study found that strength in connectivity between the medial sensorimotor cortex and thalamus at TEA in preterm infants predicted motor outcome at 2 years (Toulmin et al., 2021). Alterations in cortical–subcortical connectivity is in line with the timing of preterm birth and the establishment of cortical–subcortical connectivity (Kostović and Jovanov–Milošević, 2006).

2.3 THE BRAIN AS A NETWORK

Important advances in the understanding of the brain have come from viewing the brain as a network. In any science involving networks, be it a brain or some other complex system, a fundamental aim is to find meaningful structure in order to understand the fundamental properties of organization and information flow. Graph theory is the branch of mathematics that is dedicated to characterizes and understand network properties. The fundamental building blocks of a network are the nodes and the connections between them, i.e. the edges (Bullmore and Sporns, 2009). Network measures can be global (characterizes the network as a whole) or local (characteristics of a single node or sets of nodes). Perhaps the most basic measure of connectivity within a network is the concept of degree. Degree simply means the number of edges associated with a node, i.e. how many direct connections it has with other nodes.

Other commonly used measures are betweenness (the proportion of shortest paths that includes the node) and closeness (short path length to a large subset of other nodes gives rise to high closeness score) (van den Heuvel and Sporns, 2013). These are all measures of centrality that quantifies how important nodes are in the central information flow in the brain. High centrality scores generally implies that the node is important in the global communication within the network. Brain areas that score high on centrality measures, either an isolated measure such as degree or a combination of measures, are often referred to as hubs (Hagmann et al., 2008). Hubs are central to integrating information from segregated regions. However, in a scenario where information flow is decentralized, hubs can in effect contribute to information detours leading to less effective communication (Avena–Koenigsberger et al., 2018). The clustering coefficient is another important measure. It quantifies the degree to which the nodes that are connected to a specific node are also directly connected to each other. A high clustering coefficient are seen within communities. A community is a set of nodes that are highly interconnected while they share relatively few edges, i.e. connections, with the rest of the network. Communities are also referred to as modules. It has repeatedly been shown that the brain at rest, in contrast to a random network, has a core organization that is highly modular (Sporns and Betzel, 2016). In the functional connectome these modules correspond to the RSNs. Within the network theoretical framework, the functionality of nodes is in essence a consequence of how they are connected (Avena–Koenigsberger et al., 2018). In this perspective, nodes gain their importance from being part of a larger highly interdependent context. Importantly, information flow in the brain seems to take place through the dynamics of multiple parallel pathways. In contrast to connectionism, the new field of network neuroscience stresses that the computations believed to take place in the brain are inherently linked to the topology of the network. In this context, computation mean some level of signal transformation (Avena–Koenigsberger et al., 2015). The modes of communications within the brain is likely heterogenous possibly spanning the full spectrum from diffusion to routing (Avena–Koenigsberger et al., 2018).

2.4 THE FLEXIBLE BRAIN

Importantly, the brain is not a static entity. The brain is a highly nested systems that simultaneously functions on multiple time scales spanning from milliseconds to years and spatial scales ranging from sub molecular level to the macroscopic systems level (Buzsaki, 2006).

From the perspective of a dynamical system, the brain is modeled as a set of highly coupled ensembles which interactions are commonly described by a set of non–linear equations. Central to this view is the whole brain perspective where information transfer is propagated through phase synchronization. Due to the complexity and non–linearity of the dynamical models, downstream effects to perturbations of the systems can be hard to predict (Deco and Kringelbach, 2016). Synchrony or near synchrony corresponds to connectivity in the graph theoretical models. However, it also provides a mechanistic account where phase coupling is a mode of information transfer within and across levels in the system. Importantly, the phase coupling does have to be perfect in–phase synchrony to integrate information flow (Deco and Kringelbach, 2016; Fries, 2005). Moreover, metastability provides an additional principle for the global ebb and flow of phase synchronization seen in the brain. It means that a system is not in equilibrium and moves between of quasi attractors representative of specific states. In a metastable framework, the duration of coupling between any two ensembles is linked to the strength of the coupling such that stronger phase coupling leads to longer duration of synchronization (Tognoli and Kelso, 2014).

In both the context of network theory and dynamical systems, intrinsic brain organization has been seen to shift between states of segregation (high modularity) and more integrated states (Ponce–Alvarez et al., 2015; Sporns, 2013). Also, functional organization adapts to shifting task demands. Tasks can either further emphasize the segregation seen at rest or promote network integration (Cohen and D'Esposito, 2016). While this includes a certain degree of network reorganization, task engagement does not induce a complete reorganization of the intrinsic functional structure at rest but rather modulates it (Cole et al., 2014). To understand both intrinsic fluctuations inherent to the brain at rest as well as the extent of reorganization to resolve specific cognitive sensorimotor tasks, measures that track connectivity in a time resolved fashion are necessary.

2.4.1 Measures of time resolved connectivity

For the first step, i.e. the measure of time resolved connectivity itself, the level of granularity is bounded by the time resolution of the acquisition. The most commonly used method to get a measure of time varying connectivity is the sliding window approach that exists in many variations (Allen et al., 2014; Lurie et al., 2020). Most often, the basic measure in this approach is Pearson's correlation. Instead of correlating entire time series, correlation is done over shorter segments. The window is then moved, usually by one time point at a time, such that it partly overlaps with the previous window to calculate the correlation for the next time point. The windowed

correlations are summarized in a functional connectivity (FC) matrix representing each time point. The sliding window correlation approach has worked very well to show that connectivity between pairwise networks and areas indeed change with time (Allen et al., 2014; Zalesky et al., 2014). Importantly, not all pairwise relationships show equal levels of fluctuations in connectivity. The most dynamic relationships seem to be connections between the canonical RSNs while connections within RSNs are typically exhibit less time variation (Zalesky et al., 2014). This also means that homologous areas show the least degree of variability in connectivity over time (Gonzalez-Castillo et al., 2012). One of the main critiques of sliding window approach is that it entails a choice of window length. If a too short window consisting only a handful of time points is used, the correlation or covariance measures will not be robust from a statistical perspective. In contrast, if the window is too long, meaningful variability will be lost. Common window lengths in the literature span 30–60s (Hutchison et al., 2013). With the windowed approach there is also a risk of aliasing of frequencies (high and low) that do not fall within the window. One of the first measures employed to show time varying connectivity in BOLD data is the use of time-frequency coherence analysis in the form of the wavelet transform (Chang and Glover, 2010). With time-frequency analysis, the one-dimensional time-series (frequency domain) is broken down into a two-dimensional time-frequency map. An important advantage of time-frequency analysis is it can be used on time series with non-stationary power including a wide range of frequencies (Torrence and Compo, 1998). Like the windowed correlation approach, time-frequency analysis is done over snippets of time series. The wavelet transform has also been used to identify changing community structure across time (Bassett et al., 2011). In contrast, in the multivariate co-activation patterns (CAP) approach each volume is analyzed separately (Liu et al., 2018; Liu and Duyn, 2013). Initially the method was based on seed regions analysis but was subsequently developed into a whole brain data driven approach. In the data driven approach the spatial correlations maps of each volume and each participant were vectorized. K-means clustering was applied on the vectors to maximize correlation between vectors within the same group and minimize it between vectors of separate groups. Each cluster group was then average and normalized resulting in a CAP. Occurrence rate (how frequently a CAP occurred), similarity (how similar the volumes contribution to a cap were) and polarity (if the CAP was dominated by positive or negative correlations)(Liu et al., 2013). When comparing the CAPs to temporal functional modes (TMFs)(Smith et al., 2012), a method based on spatial ICA followed by temporal ICA, only a few of the spatial maps showed similar spatial distributions. Instantaneous phase synchrony analysis (IPSA) is another method for time resolved analysis that is less frequently used but is gaining more attention recently (Cabral et al., 2017b; Glerean et al., 2012a; Ponce-Alvarez et al., 2015). In IPSA, the instantaneous phase of a signal is leveraged using the Hilbert transform

(See section 4.1.4 for details). By taking the cosine of the instantaneous phase between two signals, a measure of phase coherence spanning the range [–1,1] is gained where 1 is perfect in phase coherence and –1 is perfect anti–phase coherence. The range of the measure is therefore the same as for for Pearson's r correlation. An important advantage of IPSA is that instantaneous frequency is not sensitive to amplitude fluctuations in the signal. This can be important since it increased levels of drowsiness has been shown to increase amplitudes an might in certain circumstances induce false positive correlations (Hutchison et al., 2013). The methods mentioned here are far from an exhaustive list. Additional methods exists and the numbers are growing as outlined in several excellent review articles (Hutchison et al., 2013; Keilholz et al., 2017; Lurie et al., 2020; Preti et al., 2017)

Among the methods mentioned above, IPSA and CAP are truly time resolved in that they treat each volume separately while sliding window and time frequency analysis relay on several time points to derive a time resolved estimate. However, it is not only the time resolved measure itself that matter in the analysis. The combined set of methodological choices are of importance. Temporal ordering is a central aspect. IPSA, sliding–window and time–frequency analysis all respect the temporal order while the CAP method does not. However, when clustering is applied to summarize FC matrixes into representative patterns such as FC states (Cabral et al., 2017b; "Tracking whole–brain connectivity dynamics in the resting state," 2014), the temporal order is ignored in the sense that non–continuous time points are clustered together. An important drawback with clustering is therefore a loss of time point to time–point resolution. Community detection has been used as an alternative approaches to identify time resolved network structure (Bassett et al., 2011).

2.5 PRETERM BIRTH AND BRAIN DEVELOPMENT

An estimated 15 million babies are born prematurely (< 37 + 0 weeks GA) in the world each year (WHO, 2012). Among these, the most premature are those born < 28 + 0 weeks GA, also called extremely premature (EPT). Sweden belongs to the countries with the lowest incidence of preterm birth. Still, approximately 340 children in Sweden each year are born EPT. The majority of the Swedish born EPT neonates now survive beyond the first year while the prognosis is much grimmer for those born in low and middle income countries (Norman et al., 2019; WHO, 2012). It is well established that extremely preterm (EPT) neonates are at increased risk for adverse neurodevelopmental outcomes. This includes impaired motor function, cognitive and

attention deficits, anxiety, depression and autism with negative impact on school performance and life quality (Brydges et al., 2018; Gire et al., 2019; Johnson and Marlow, 2011; Serenius et al., 2016). Even in the absence of overt brain injury, medical complications and environmental stressors in the NICU have a negative impact on the very immature brain (Joseph J. Volpe, 2009).

The brain, like the rest of the body, develops according to a sophisticated and sequential program which takes the form of self–assembly where each step is a response to local ques (Hiesinger, 2021). However, in contrast to most other organs which have established their core architecture already during the first trimester, the intricate architecture of the brain continues to develop in the third trimester (Kostović and Jovanov–Milošević, 2006). In fact, EPT babies are born during a period when the brain is in a very rapid and sensitive phase of development. At 22 weeks GA the brain weighs only on average 75g which is less than a fifth of the weight of a term born baby brain (Guihard–Costa and Larrocheb, 1990). Only the lateral and sagittal sulci are present (Raybaud et al., 2013). The intricate cortical folding process which coincides with synaptogenesis and is the result of a combination of genetic, cellular and mechanic factors has not yet started (Llinares–Benadero and Borrell, 2019). At this time most pyramidal neurons have migrated to the cortex but interneurons originating in the germinal matrix are still migrating. The sub plate that emerged at 10 weeks is several orders thicker than the cortex and act as a waiting station for incoming sensory projections from thalamus which are the first to enter the subplate (Joseph J Volpe, 2009). They are followed by callosal fibers and lastly projections from other interhemispheric cortical regions (Kostović and Judas, 2010; Rados et al., 2006). Cortico–thalamic connectivity starts in the sensory–motor regions at approximately 22 weeks and is directly followed by formation of primary sulci in the same region. The sulci–gyrification progresses happens simultaneously as the establishment of tangential cortical expansion which has been proposed to be tightly linked (Llinares–Benadero and Borrell, 2019; Raybaud et al., 2013). The vasculature is also still developing in the preterm brain. It is sparse and lack autoregulation. This leaves the extremely preterm brain very vulnerable to blood pressure changes that can lead to hemorrhages notably in the germinal matrix which can lead to disruption in the competition of migration of interneurons. Blood pressure changes can also cause under perfusion resulting in diffuse hypoxia–ischemia. The oligodendroglia precursors are among the most exposed and vulnerable to hypoxia, especially at the watershed areas next to the ventricles (Raybaud et al., 2013; Joseph J Volpe, 2009). The oligodendrocytes will later be responsible for axonal myelination. Varying degrees of injury to the white matter is therefore commonly seen in EPT neonates. They range from mild white matter alterations (WMA) to severe forms of white matter injury (WMI) in the form of cystic

periventricular leukomalacia (PVL) (Joseph J Volpe, 2009). Due to improvements in neonatal care during the last decades, milder forms of WMA/WMI are now dominating and severe forms are becoming increasingly rare. However, also milder forms of injury to the white matter can also have important negative consequences. Secondary widespread trophic and maturational alterations affecting axonal and neuronal growth in cortex, cerebellum, subcortical nuclei and brainstem has more recently been identified. Together these dysmaturational changes are called encephalopathy of prematurity (Joseph J Volpe, 2009). At term equivalent age, very preterm born children show cortical alterations most pronounced in the temporal lobe, insula and pre- and postcentral sulci (Engelhardt et al., 2015). Widespread gray and with matter volume alterations (mostly reductions) remains into adulthood (Nosarti, 2002).

2.5.1 Brain development beyond the neonatal period

During the first years of life the brain continues to grow and develop in a remarkable way. It is during this time it is at its highest levels of plasticity which enables the baby to begin the journey to acquire language and social skill and develop its motor capabilities (Gao et al., 2017). During the first year the subplate disappears completely and by the end of the first year the brain has doubled in volume. The majority of the volume increase during this time is due to synapse and dendritic growth in the gray matter and growth of the cerebellum (Knickmeyer et al., 2008) . During the second year, brain volume increases another 15%. At 6 years, the brain has reached >90% of its adult size. Postnatally synaptic density rapidly increases to reach its maximum level around 2 years where it is 50% larger than in the adult brain (Lenroot and Giedd, 2006). The pruning of synaptic connection is region specific according to the same gradient that seems to be true for many other maturing events in the brain i.e. primary sensory–motor regions mature before association cortices. Synaptic density hence reaches its maximum in the primary visual cortex at 4 months of age but not until 4 years in prefrontal cortex (Lenroot and Giedd, 2006). Myelination is complete by 2 years but continues in practice to mature and develop well beyond adolescence into the mid-twenties and possibly beyond (Barkovich et al., 1988). Glial progenitor cells continue to migrate, proliferate and differentiate in the preschool years. Even though the majority of programmed neuronal cell death takes place before birth it continues until the 2nd year (Lenroot and Giedd, 2006). Cortical thickness steadily declines from 2 years to adulthood while cortical surface area shows a peak around 10–12 years. However, variability in cortical surface area between individuals at any given age is larger than the variability over development (Brown, 2017). This is true for many other measures of the brain including total volume (Brown et al., 2012; Brown and Jernigan,

2012). A multicenter cross–sectional study of 885 children aged 3–20 combined measures from T1–, T2– and diffusion weighted MRI sequences into a model that was able to explained 92% of the variance in age. Mean prediction error was 1 year. Taken together, despite large variability between individual children there seem to be a strong general multimodal pattern of chronological structural brain maturation (Brown, 2017; Brown et al., 2012).

3 RESEARCH AIMS

3.1 STUDY I

The general aim of the first study was to gain a better understanding of time resolved network dynamics in the brain using BOLD fMRI data. This meant developing a novel method with the capacity to capture the gradual processes of functional network integration and segregation in the brain on a time point to time point basis respecting the temporal ordering. This involves formation and subsequent disintegration of transient networks reflecting the flexible aspect of intrinsic connectivity. The project was motivated by a lack of methods that use the full granularity of the time series and also respects the temporal ordering in order to track connectivity changes on a time point to time point basis, allowing for network definitions to change dynamically (Hutchison et al., 2013; Lurie et al., 2020).

The intention was subsequently to use the method to answer specific questions pertaining to the functional brain development in children born extremely preterm. A secondary aim was to provide a novel tool that could be applied broadly both in clinical and basic fMRI–based neuroscience.

3.2 STUDY II

The second study aimed to investigate the prevalence of subtle macroscopic white matter alterations in children born extremely preterm and its potential relationship to neurocognitive and motor outcomes at 12 years as well as to quantitative measures indicative of white matter injury. Macroscopic means that the alterations could be identified based on visual inspection. Consensus classification systems for white matter injuries and alterations exist in the literature for the neonatal period but not beyond (Woodward et al., 2006). Since mild white matter alterations (WMA) and injury are common in extremely preterm neonates, we hypothesized that discrete alterations would be common at 8–11 years. We defined a new lowest level of WMA based on visual inspection of the shape of the lateral ventricles in the absence of signs other of injury. We hypothesized that discrete WMA, if present, would be related to reduction in global FA and white matter volume. We also hypothesized that there would be a longitudinal association between a diagnosis of any grade of WMI in the neonatal period and signs of WMA/WMI at 8–11 years. The clinical relevance of a finding of discrete WMA was evaluated in relation to cognitive and motor performance at 12 years.

3.3 STUDY III

In the third study the aim was to apply the method developed in Study I to explore changes in brain network flexibility and modularity as a result of extremely preterm birth. We hypothesized to see a global reduction in RSN flexibility and increase in modularity at twelve years. For this purpose, novel measures of RSN flexibility and modularity were introduced. A secondary aim was to investigate the degree of time resolved intrinsic network lateralization. This poorly investigated in the literature and its potential role in development is unknown. Given the strong connectivity between homotropic areas in the two hemispheres, deviations in the level of uncoupling could potentially be meaningful. Homotropic bilateral connectivity is established early in development and seen in fetal imaging and the preterm neonates (Keunen et al., 2017b). Since time resolved lateralization has been so sparsely studied (if at all), this investigation was exploratory and not associated with a specific hypothesis.

4 MATERIALS AND METHODS

4.1 STUDY I

4.1.1 Participants

From a cohort of 100 young adults from the Human Connectome Project (HCP) (www.humanconnectome.org/study/hcp-young-adult), sixty-one subjects that had low motion scores on both the left-right (LR) and right-left (RL) resting state scans were included. The definition of low motion was a maximum peak in FDRMS (framewise displacement root mean square) time series < 1 mm combined with a mean FDRMS < 0.1 mm. Since this was openly available data no additional ethical clearance was necessary beyond what had been obtained by the HCP prior to data acquisition.

4.1.2 Resting state fMRI acquisition and parcellation.

The preprocessed LR resting state acquisition was used for analysis. No additional preprocessing was conducted. The standard time repetition (TR) in many resting state studies is 2 second. This means that a BOLD contrast image is acquired every other second. However, the HCP data is acquired using a faster protocol which results in an images every 0.72 seconds. Since each images equals a time point in a time series the faster acquisition results in more densely sampled time series.

Static parcellations scheme are commonly used in rs-fMRI studies. A number of different options exist as well as levels of granularity ranging from less than 100 parcels to over 1000. The scope of the parcellations can be limited to the cortex or include subcortical regions and/or cerebellum as well. Some are volume based while others are based on cortical surface. Another important difference is whether the parcellation sorts regions into RSN or not (Lawrence et al., 2021; Schaefer et al., 2018). Common for all parcellations is that they entail dimensionality reduction. With the use of a parcellation, only a few hundred time series are analyzed instead tens of thousands of voxel time-series. This is important not least since the temporal resolution in most cases consist of much fewer time points ranging from a few hundred to little over a thousand. This mismatch in spatial and temporal resolution would lead to a rank deficient matrix. With the use of a parcellation this problem is resolved. It also makes sense to use a parcellation since there is an inherent covariation between many voxels in the brain which is reflected in the parcellations. Here we used the version of the

Schaefer parcellation which divides the cortex into two hundred distinct areas grouped by 7 canonical RSNs (Schaefer et al., 2018). Since the cortex is highly integrated with the subcortical nuclei, we used the subcortical portion of a different parcellation to in order to include the thalamus, basal ganglia, amygdala and hippocampi (Fan et al., 2016a). Therefore, a total of 9 RSNs were include in the combined parcellation.

4.1.3 EMD - Empirical mode decomposition

Band pass filtering is commonly used to limit the frequencies of interest in rs–fMRI studies. One of the main motives is to exclude higher frequency ranges contaminated by aliasing from heart rate and respiration. Another motivation might be that one sometimes has a hypothesis about a specific frequency range as being more tightly coupled to neuronal activity than others. Regardless of the motivation, with band pass filtering a choice has to be made of what frequency range to focus on. If phase synchrony analysis is used, the band pass filtering must be narrow enough to eliminate riding waves which leads to contradictory instantaneous phase information. However, a narrow filter also smooths the amplitude fluctuations in the signal. Since amplitude fluctuations likely have a biological significance, this is suboptimal. An alternative that was used in this study is the empirical mode decomposition (EMD) (Huang et al., 1998). The EMD is a heuristic sifting algorithm. This means that it breaks down a signal into a finite set of oscillatory components. These are called intrinsic mode functions (IMF). The first IMF always contains the highest frequencies. Subsequent IMFs contain increasingly lower frequency ranges. The number of IMFs resulting from the sifting process is dependent on the frequency range of the signal: a wider frequency range will produce more IMFs. When applied to fMRI data, it has been shown that IMFs produce similar results as the corresponding band pass filtered signals when used in analysis of specific RSNs (Niazy et al., 2011). In contrast to band pass filtering, the IMFs contain more variability in amplitude fluctuations.

4.1.4 IPSA – Instantaneous phase synchrony analysis

Instantaneous phase synchrony analysis (IPSA) has been widely used in the analysis of electrophysiological data (Yoshinaga et al., 2020). More recently it has also been applied to rs–fMRI data (Cabral et al., 2017a; Glerean et al., 2012b; Ponce–Alvarez et al., 2015). With IPSA, phase coherence is used as a measure of the functional relationships between regions in the brain. In contrast to measures that rely on using a window of time points to estimate a time resolved measure (Allen et al., 2014), instantaneous phase is measured directly at each time point. IPSA therefor provides a solid basis for

time point to time point analysis. The instantaneous phase of a signal is harnessed through the Hilbert transformation which transforms the real signal *s* to is analytical form. Expressed in polar coordinates:

$$s(t) = A(t) \times e^{i\phi(t)}$$

where t = time, A = instantaneous amplitude (envelope), ϕ = instantaneous phase.

Using IPSA, at each time point t, the phase coherence matrix (dPC) that reflects the functional relationship between all areas in the parcellation can be calculated. If N are all areas in the parcellation and $n, m \in N$, then the phase coherence between n and m at time point t is calculated as:

$$dPC_{t,n,m} = cos(\Delta\phi_{t,n,m}) \ .$$

Therefore, phase coherence as calculated above range from 1 (perfect in–phase) to –1 (prefect anti–phase).

4.1.5 Community detection

Many methods exist to find patterns in complex data where there is no a priori knowledge of the inherent structure, if any. In graph theory, modularity maximization is a common approach to finding community structure in networks (Newman, 2006). Modularity is a measure of the density of the connections within and between sets of nodes in relation to what is expected by chance. High modularity scores mean a more modular organization, i.e clearly separable groups of (nonoverlapping) nodes with a large number of connections between themselves and relatively few connections with other groups can be identified. The Louvain algorithm is one of the most commonly used algorithms for community detection (Blondel et al., 2008). It was used to find time resolved community structure in the dPC matrix. It was chosen since it accepts both positive and negative entries which is necessary in order to capture both the negative and positive phase coherence relationships in the dPC matrix.

4.1.6 q_{int} – a novel measure of temporal coupling strength

Finding community structure in the dPC matrix resulted in that each area was assigned to a community at each time point. Based on the range and distribution of the dPC values it was hypothesized that same community assignment would equal positive phase coherence between areas. Separate community assignment would in the same way imply a negative of orthogonal phase coherence. Moreover, frequent assignment to the same community would therefore translate as strong phase coherence across

time. With these considerations, the q_{int} measure was defined as the relative number of time points of same community assignment in comparison to the total duration of the resting–state fMRI experiment. A high value of q_{int} would therefore mean strong phase coherence.

4.1.7 Modeling time resolved networks

Time resolved changes in connectivity were modeled using dynamically defined networks. This meant that the topology of a given network would be allowed to change across time within some spatial limits. In time–resolved analysis, flexible remodeling is contrasted to the main modular tendencies of static network analysis. Flexibility is harder to capture and hence less explored than modularity.

With the q_{int} measure as a basis, the strength of functional relationships beyond the pair wise level was calculated. The dynamic representation of subnetworks (SNs) was created through combination of smaller units, i.e. subnetwork components (SNC). The SNCs consisted of unique combination of eight areas with their own time course. They were derived in an iterative fashion from seeds of pairwise areas. The seed were the each of the areas in the parcellation together with the area with which it was most frequently integrated. Given the size of the parcellation and the approximation of the probability distributions of sets of areas from $n = 4$ to $n = 12$, the SNC size was set to $n = 8$. SNCs where then grouped into SNs. It was done such that the SNCs belonging to the same SN were guaranteed to be assigned to the same community at times of integration. Finally, to represent the general trend of SN integration and segregation, SNs with a strong tendency to integrate were collectively represented as a meta–network (MN). The MNs were derived using a thresholded hierarchical clustering approach.

4.1.8 Flexibility and modularity

The approach taken in this study was to build flexible subnetworks using combinations of smaller components. This also allowed for a novel way to estimate flexibility and modularity of individual brain areas. Flexibility and modularity were defined by combining information on temporal representation and spatial diversity. Temporal representation was defined as the relative frequency that an area was represented as part of at least one SNC. Spatial diversity was defined as the proportion of total areas that an area shared an SNC with. An area with low temporal representation but high spatial diversity would be classified as high in flexibility. In contrast, an area with high temporal representation but low spatial diversity would be classified as modular. The

reasoning behind these definitions is that areas that are characterized as high in modularity tend to frequent integrate with the same set of areas. Flexible areas instead integrate during short time spans with a large set of other areas. The large number of SNCs that the participate in are therefore not always represented by the model leading to lower temporal representation.

4.1.9 Statistical analysis

For statistical analysis, two–sided permutation t–test were used in most instances. The resulting p values where, when appropriate, corrected for multiple comparison using false discovery rate (FDR). Pearson's correlation and a Mantel test was also used to compare matrices.

4.1.10 Software and computational resources

All code was written in MATLAB. Some imaging rendering was done using python. For large computations resources at KI as well as Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) were used. The resources at UPPMAX are provided by Swedish National Infrastructure for Computing (SNIC) and partially funded by the Swedish Research Council through grant agreement no. 2018–05973.

4.2 STUDY II

4.2.1 Ethical consideration

The local ethics board at the county council of Stockholm approved the study.

4.2.2 Participants and MRI acquisition

The study was part of a regional arm (Stockholm County) of a national longitudinal follow up study of children born EPT, the Extremely Preterm Infants in Sweden Study (EXPRESS). In total 68 children born < 27 weeks gestation participated as well as 45 term born controls matched for residential area, sex and date of birth. In total 112 children (median age 10.3 years, 56 girls) participated. All children were born in Stockholm, Sweden, between 1 January 2004 and 31 March 2007. Children with cerebral palsy, aneuploidy, acquired brain damaged after the neonatal period and those with a

ventriculoperitoneal shunt were excluded from the study. The control group was included in order to estimate the specificity of the performance of the visual inspection method since they were not expected to have white matter injury.

MRI of the brain at age 8–11 years was performed without sedation and in the presence of a parent. All children were scanned at MR–Centrum Karolinska University Hospital using a Sigma 3.0–T MR scanner (GE Healthcare, Wisconsin, USA). The neonatal scans (a subset of the preterm children only) were done at Karolinska university hospital pediatric radiology department using a Philips Intera 1.5–T MRI system (Philips International, Amsterdam, The Netherlands). Anatomical scans and DTI sequences were acquired at both time points.

4.2.3 Diffusion tensor imaging - DTI

The integrity of white matter in the brain can be assessed using diffusion tension imaging (DTI). DTI take advantage of the speed and directionality of water diffusion in white matter to assess its integrity. Different measures of diffusivity exist where fractional anisotropy (FA) is the most common (O´Donnell and Westin, 2011). High FA indicates that diffusion is restricted in mainly one direction which is a sign high integrity of the white matter. The use of DTI ranges from simple voxel–vise analyses of FA to advanced reconstruction of white matter tracts i.e. tractography (Jeurissen et al., 2019). A common way to analyze DTI data is tract–based spatial statistics (TBSS) (Bach et al., 2014). It is a voxel–based method that uses the FA map in order to reconstruct major white matter tracts. Compared to the more advanced tractography methods, tract–based spatial statistics is not able to discern the orientation of the fibers which is particularly problematic at points of fiber crossings.

4.2.4 Neuroradiological assessment of discrete WMA

Standardized scoring of PVL and WMA/WMI exist for the neonatal period but not for older children (Woodward et al., 2006). For the assessment of discrete WMA at age 8–11 years, a modified scoring based on previously published data was used (Flodmark et al., 1989; Imamura et al., 2013) . In addition, a new lowest level of WMA was introduced based on the shape of the shape of the lateral ventricles. A squared form of the trigonum of the lateral ventricles was classified as discrete WMA if no other abnormalities were present. It was hypothesized that it would potentially reflect a minimal focal loss of white matter in the peri–trigonum following ischemic insults in the neonatal period. The scoring of WMA/WMI at 8–11 years therefore was: grade I,

discrete WMA, i.e. squared margins of the lateral wall of the ventricles; grade II, periventricular signal changes; grade III, periventricular signal changes plus volume loss; grade IV, cysts, extensive changes. A majority of the EPT children had neonatal scans (61/68). The standardized neonatal WMI scoring is based on five parameters: WM signal abnormality, reduction in WM volume, cysts, ventriculomegaly (Woodward et al., 2006).

4.2.5 Cognitive and motor tests

Cognitive and motor function was assessed at 12 years. The Weschler Intelligence Scale for Children (Fifth Edition) was used for cognitive testing. It encompasses five primary index scores: verbal comprehension, visual spatial, fluid reasoning, working memory, processing speed. Combined, they provide a full–scale intelligence index (mean = 100, SD = 15). Movement Assessment Battery for Children – Second Edition. (MABC–2), was used for the assessment of motor function. MABC assesses gross and fine motor function using three scales: manual dexterity, ball skills and balance. Total test score and percentiles are given for each scale. Test scores at or below the 5th percentile indicates abnormal motor function, scores between the 5th and the 15th percentile indicate borderline motor problems.

4.2.6 Statistical analysis

Statistical analyses were preformed using SPSS and MATLAB.

4.3 STUDY III

4.3.1 Ethical considerations

As for study II, this study was approved by the local ethics board at the county council of Stockholm.

4.3.2 Participants

The subjects in this study were drawn from the same cohort as Study II. Head motion is a serious confound in fMRI and particular rs-fMRI studies (Power et al., 2012). Therefore, the criteria for inclusion in this study was based on strict criteria for head-motion which was the same as were used in Study I. Different measures of head motion exists. Here, the FDRMS (framewise displacement root mean square) was used. Children with otherwise high-quality scans and a maximum peak in FDRMS time series < 1 mm and a mean FDRMS < 0.1 mm were included in the study. In total 41 children were included of which 20 were born EPT and 21 were controls. For comparison, in the young adult HCP study, 61 out of 100 subjects met the same criteria. Mean GA at birth for the EPT born children was 25 w + 6 d (SD = 6 d, range [23 w + 6 d, 26 w + 6 d]) and 40 w + 0 d (SD = 8 d, range [37 w + 3 d, 41 w + 5 d]) for the control group.

4.3.3 Data and removal of noise

The rs-fMRI sequence was acquired with a TR = 2 s during 10 min resulting in 300 volumes. Most image preprocessing was done using the FMRIB Software Library (FSL) v 5.0.9 (Jenkinson et al., 2012). Details of the pre-processing and acquisition are available in the manuscript. To clean the data from additional noise, independent component decomposition (ICA) using FSL MELODIC 3.0 was utilized. Automatic algorithms such as AROMA and FIX exists for this purpose (Pruim et al., 2015; Salimi-Khorshidi et al., 2014) . However, after trying AROMA with unsatisfying results, manual removal was done. Noise components (scanner related and head motion) were identified based on published data (Griffanti et al., 2017). The cleaning process was conducted in an iterative fashion (3–4 times). The classification decision was reviewed once after initial assessment. Mean FDRMS prior to removal of noise components was 0.061mm (SD = 0.025 mm) and 0.013 mm (SD = 0.003 mm) after. Hence, this cleaning strategy seems to be highly efficient in removing noise from the data compared to other ICA-based cleaning strategies (Dipasquale et al., 2017).

4.3.4 Parcellation

The same parcellation was used as in Study I, that is the Schaefer 200 areas 7 RSN parcellation together with the subcortical portion of the Brainnetome atlas (Fan et al., 2016b; Schaefer et al., 2018). This yielded a total of 9 RSNs, where the thalamus and basal ganglia were additional network partitions added to the 7 cortical RSNs in the Schaefer 7 parcellation. In the same way as for Study I, amygdala and hippocampal areas were grouped with the limbic network.

4.3.5 Flexible vs modular RSNs in the time resolved domain

The method developed in Study I was used to understand the long-term development of flexibility and modularity of functional brain networks in children born extremely preterm. However, a slightly different approach was taken in that subnetworks (SNs) and meta-networks were not calculated. Instead, subnetworks components (SNCs) were used to assess flexibility and modularity of RSNs as defined by the static parcellation. Novel measure of flexibility and modularity was therefore introduced. The idea behind these measures was to estimate how frequently the areas of a predefined RSN were integrated in the same community, what proportion of total areas were integrated and how frequently an RSN was integrated simultaneous in two different communities (i.e. segregated). With the definitions introduced in this work, an RSN which seldom segregate and where a large proportion of its areas are frequently integrated in the same community score high on modularity. Conversely, an RSN which frequently segregate and where only a small proportion of its areas, if at all, on average integrate in the same community score high on flexibility (Figure 1).

To test for significance in differences in flexibility and modularity for each of the nine RSNs permutation t-test with 10000 iterations was used. Resulting p-values were subsequently corrected for multiple comparisons using the Benjamini-Hoschberg procedure for false discovery rate (FDR) (Benjamini and Yekuti, 2001).

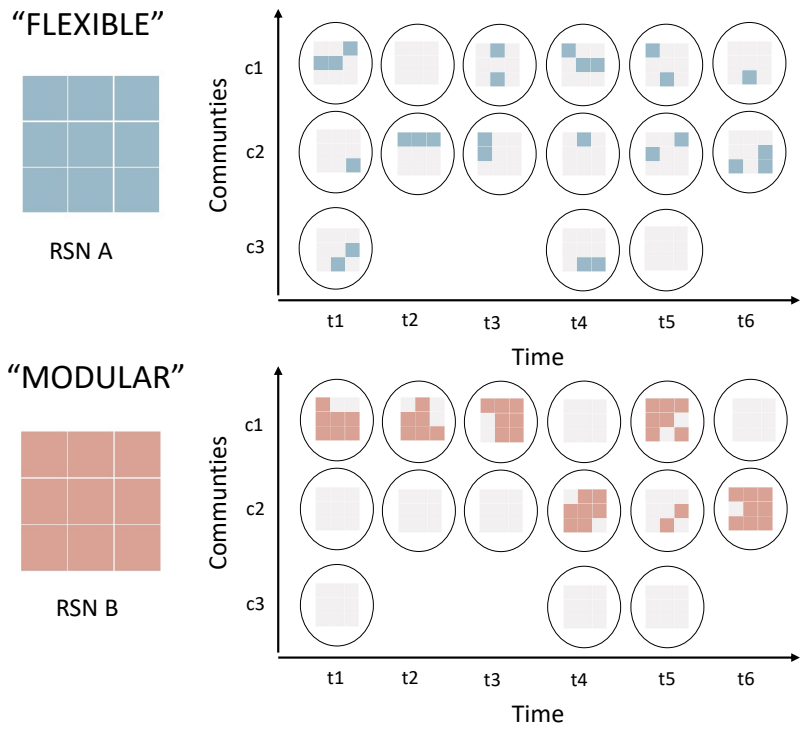

Figure 1. Schematic illustration of a flexible (first row, blue) and modular (second row, red) RSN. Flexible RSNs are frequently segregated, i.e. its areas are split on multiple communities. Only a small proportion of the total areas of the RSN is integrated in the same community at any given time. In contrast, a large proportion of total areas belonging to the modular RSN most of the time integrate in only one community.

4.3.6 Time resolved RSN lateralization

Static RSNs are typically bilaterally symmetric engaging homotropic areas from the two hemispheres. It is also well known that homotropic areas are the first to show co–activation during early brain development and continue to exhibit the strongest connectivity into adulthood (Keunen et al., 2017b). Few studies have explored the time resolved RNS lateralization. In other words, how frequently RSN areas from only one hemisphere integrate as a temporary network. Since aberrant functional connectivity within networks could potentially be seen as deviations in the frequency of lateralized integration, we investigated potential differences in lateralization between the two groups for all 9 RSNs. Here, we count instances of lateralization defined as time points where RSN areas from only one hemisphere are integrated. Left– and right–sided lateralization are counted separately for each RSN. Permutation t–test are used to test for statistical significance. Multiple comparisons are corrected for using false discovery rate (FDR).

5 RESULTS

5.1 STUDY I

5.1.1 Integration and segregation

As hypothesized, we could show that assignment of areas to the same community meant positive phase coherence between the areas at that time point. Same community assignment was therefore definition as integration. Similarly, it was shown that assignment of areas to different communities most of the time equaled orthogonal (i.e. phase difference close to zero) or negative phase coherence relationships. Assignment to different communities was defined as segregation. It was also shown that the phase coherence matrixes at all time points were divided into either two or three communities. This meant that some level of segregation was always present in the brain. Integration and segregation were therefore noted to be simultaneous events, not consecutive as has previously been suggested (Shine et al., 2016). However, these results do not preclude that some time-points are characterized by higher levels of segregation than others.

5.1.2 Measures of temporal coupling

The method resulted in novel measures of temporal coupling between areas in the brain. These were 1) frequency of instances of integration, 2) duration of integration 3) strength of the phase coherence during integration. The first two were summarized in a common measure denoted q_{int} (the subscript is short for integration). These measures of temporal coupling are applicable to all levels of network granularity used in the study: pairwise areas, SNCs, SNs and MNs.

5.1.3 Levels of spatial network granularity

Four levels of temporal networks granularity were examined in the study: 1) pairwise areas, 2) subnetwork components (SNCs), 3) Subnetworks (SNs) and 4) Meta-Networks (MNs).

1) At the first level, pair wise areas, the q_{int} measure was shown to yield a very similar results as Pearson's correlation between areas.

2) At the second level, an iterative search to find the most common combinations of brain areas that were frequently integrated across subject was conducted. The top pairs of each brain area was used as initiaing seeds in the search. The search resulted in 31976 SNCs representing all brain areas in the parcellation. Together they formed a sparse representation of the of the strongest spatiotemporal couplings in the brain.

3) At the third level, the SNCs were combined into SNs. Each SNC consisted of a unique combination of eight areas with its own time course. Therefore, the SN representation in time and space resulted from the combination of its SNCs that were integrated. The code was written to assure that all SNCs belong to an SNs were always integrated in the same community at all time points and for all subjects, i.e. "no–split".

4) At the final level, SNs were combined into MNs. The reason for this step was the large number of similar and spatially partly overlapping SNs. The MNs were an attempt to summarize the main tendencies for SN integration and segregation. At this level, the "no–split" condition implemented at the level of SNs could not be kept since it would result in that only a small number of SNs could be combined into MNs. Therefor, threshold och mean and minimun frequency of community split for MNs were implemented. A final number of 71 MNs resulted (also see Errata). The first MNs were very similar to known RSNs or combinations of them (Figure 2). MNs were named according to the classical RSNs that contributed most weight in terms of frequency of area participation. The MN maps are probablistic representations of frequency of participation of specific areas in each MN.

5.1.3.1 Errata

After publication, an error was found in the part of the code that selects seed pairs for that initiate the search for the SNCs. The result of the bug was that a subset of the seeds was incorrectly selected. This meant that it was not the top pair for some of the areas that were selected but a pair with lower q_{int} than the top pair. It led to a larger number of SNCs compared with the correct code ($n = 31976$ vs $n = 26755$). The reason is the lower degree of convergence between iteration levels with the random pairs. It results in a subset of SNCs with lower q_{int} and somewhat more diversity in constituting areas. The downstream consequence was a larger number of SNs (240 vs 216) and MNs (71 vs 47).

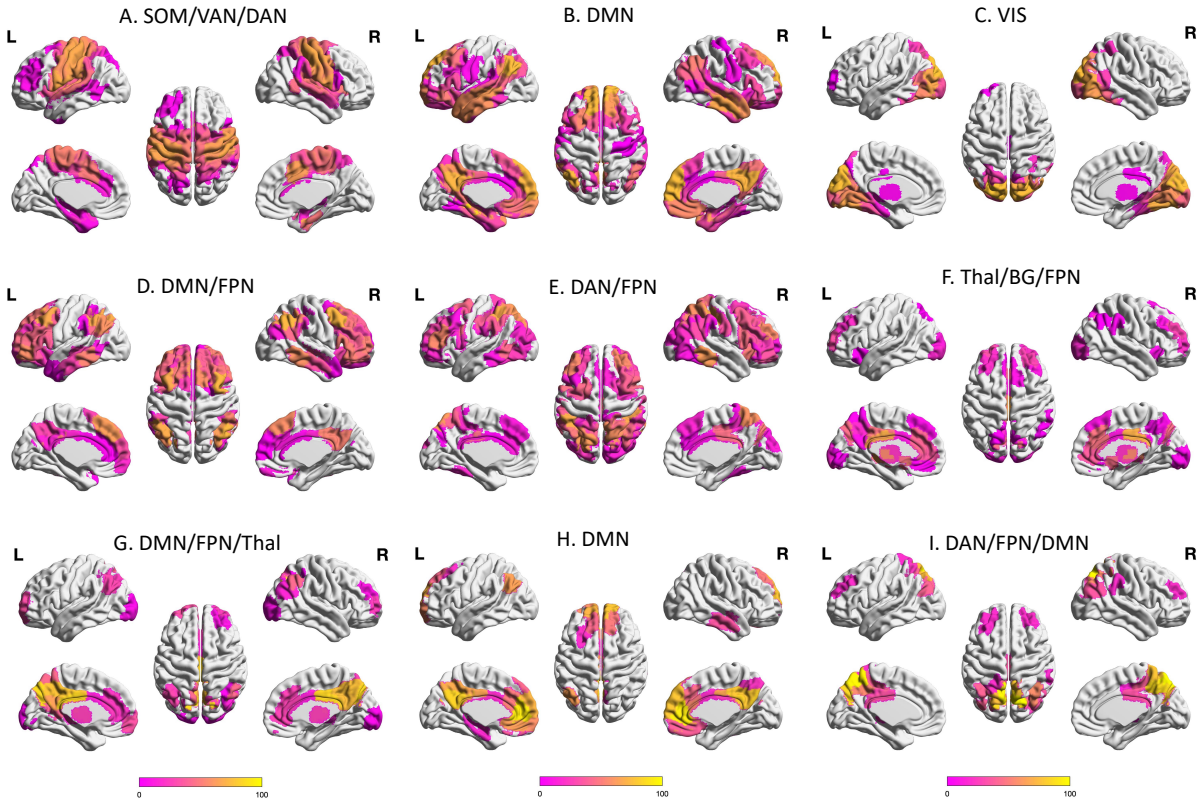

Figure 2 – Top 9 MNs resulting from the corrected code (see Errata 5.1.3.1). A. DMN/VAN/DAN (mean $q_{int} = 0.96$), B. DMN (mean $q_{int} = 0.95$), C. VIS (mean $q_{int} = 0.85$), D. DMN/FPN (mean $q_{int} = 0.84$), E. DAN/FPN (mean $q_{int} = 0.84$), F. Thal/BG/FPN (mean $q_{int} = 0.71$), G. DMN/FPN/Thal (mean $q_{int} = 0.35$), H. DMN (mean $q_{int} = 0.28$), I. DAN/FPN/DMN (mean $q_{int} = 0.19$)

5.1.4 Global state

In order to capture the larger picture of integration and segregation and to see if any pattern across time was visible, time resolved state vectors were constructed. State vectors were simply the mean activation, i.e. IMF amplitude, of each of the SNs an MNs at each time point combined into a vector. A third set of state vectors were based on the IMF amplitude of the individual areas in the parcellation. By simple Pearson's correlation of all state vectors in each of the three sets, a recurrence plot was constructed. At the levels of SNs and MNs, it revealed a quasi–cyclic pattern of recurrence of patterns of integration and segregation that was similar to the pattern seen at the basic level of areas. It was therefore concluded that SNs and MNs were adequate coarse–graining's of the amplitude fluctuations of the areas. If they had failed

as course–graining strategies, no amplitude fluctuations would have been seen in the SNs or MNs and also no quasi–recurrent patterns. When taking the average across subjects, no patterns of recurrence was seen. This was expected since each subject during a resting state acquisition has their own internal time course unrelated to external cues.

5.1.5 Flexibility vs modularity

A novel measure of flexibility was introduced in the paper. This measure reflected the relative propensity for each area to either synchronize repeatedly with the same set of areas (i.e. modularity) or frequently but during short periods integrate in varied constellations (i.e. flexibility). Relative here means relative to the other areas. As can be seen in Figure 3, the highest levels of flexibility were exhibited by areas belonging to the basal ganglia, thalamus and limbic networks (upper left quadrant). In contrast, part of the visual network score highest on modularity (lower left quadrant).

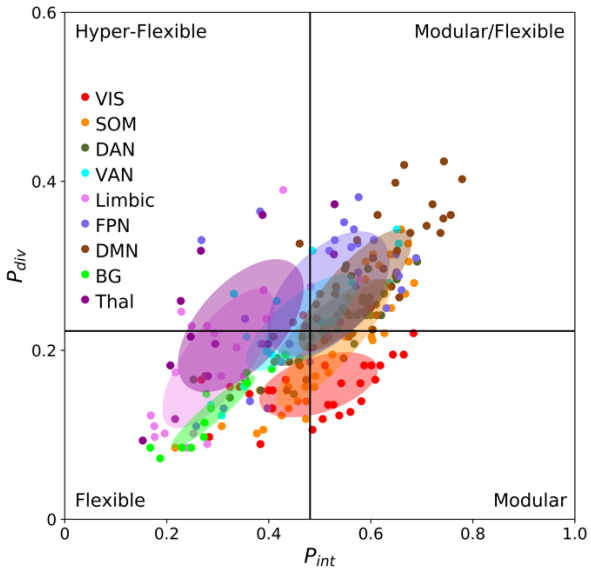

Figure 3. Flexibility and modularity of brain areas grouped by RSN belonging. P_{div} = spatial diversity. P_{int} = temporal representation. The ovals are centered at the mean P_{div} and P_{int} for each RSN. The tilt of the ovals is the co-variance. The width and length correspond to 1 SD. This is the same image as in the publication except the changes in SD giving the oval with and length.

5.2 STUDY II

In Study II, the prevalence of discrete WMA alterations in EPT born school children was investigated. The focus was to explore any potential relationship between cognitive and neuromotor outcomes as well as quantitative measures of white matter volume and white matter diffusivity. The longitudinal relationship between neonatal

WMI and WMA/WMI at school age was also analyzed. The main results are summarized below.

5.2.1 Neuromotor outcome

Of the children with no WMA or discrete WMA at 12 years, a majority (47 out of 56) had also completed MABC–2 at 12 years. Of these, 36% had test results at or below the 15th percentile. This is a test result that either indicates problems or potential problems with motor function. The assessment of minor neurological dysfunction (Touwen) indicated difficulties in 43% of children. A majority of children also completed the WISC–V assessment at 12 years (46 out of 56). Of these, 30% had a full–scale index < 85 indicating potential intellectual challenges. Similarly, difficulties with visuo–spatial processing were seen in 31% of children.

5.2.2 Prevalence of discrete WMA and neuromotor outcome

As expected, the prevalence of discrete WMA in the EPT group at 8–11 years was 52%. Furthermore, 2% had grade II, 0% had grade III, 2% had grade IV, 7% could be explained by other diseases. In the control group, 12 % were classified as having discrete WMA (grade I). Contrary to what was hypothesized, discrete WMA was not related to neuromotor, cognitive or visuo–motor integration outcomes either before or after adjusting for the mother's education level.

The prevalence of WMI in the subgroup of EPT children that had neonatal scans was: 51% no WMI, 44% mild WMI, 3% moderate WMI and 2% severe WMI. There was a significantly better processing speed index ($p=0.017$) at 12 years in the group of children born EPT without mild WMI at TEA, compared with those who had mild WMI. No other significant differences between groups were seen.

5.2.3 WMA/WMI in relation to quantitative measures

No cross–sectional association was seen between WMA/WMI and WM volumes at 8–11 years. Nor was there any significant relationship between WMA/WMI and mean diffusivity or diffusivity of major white matter tracts. There was however a positive relationship between WMI at TEA and WMA/WMI 8–11 years. Moreover, after adjusting for total brain volume, there was a positive relationship between WMI at TEA and both lower WM volume and lower global diffusivity.

5.3 STUDY III

In Study III, we investigated how extremely preterm birth influences modular and flexible aspects of time resolved functional brain networks. The method developed in Study I was employed for this purpose. A relatively small sample of children born extremely preterm (< 27 weeks GA) (N = 20) and a control group of children born after a normal pregnancy (N = 21) was analyzed. This is a subsample of the cohort used in Study II. Inclusion criteria was high quality MR acquisition with low head motion on the resting state sequence.

5.3.1 Modularity and flexibility in the preterm brain

For both groups, there was a distinct pattern for flexibility/modularity for all RSNs. The visual, basal ganglia and thalamic networks scored higher on modularity than flexibility, while the somatosensory network had similar scores for flexibility and modularity. For the remaining RSNs, flexibility was higher than modularity (Figure 4). There were no significant differences between extremely preterm born children in either flexibility or modularity for any of the RSNs after FDR correction. However, prior to correction for multiple comparisons several differences were seen. In the preterm group compared to the controls, three RSNs showed significantly decreased flexibility: SOM (effect size = –0.75, p= 0.022), DAN (effect size = –0.86, p = 0.007) and BG (effect size = –0.69, p = 0.034). The Limbic network showed increased flexibility in the preterm group (effect size = 0.79, p = 0.017). Increased modularity was seen in the preterm group for SOM (effect size = 0.94, p = 0.005), DAN (effect size = 0.74, p = 0.019) and BG networks(effect size = 0.81, p = 0.015).

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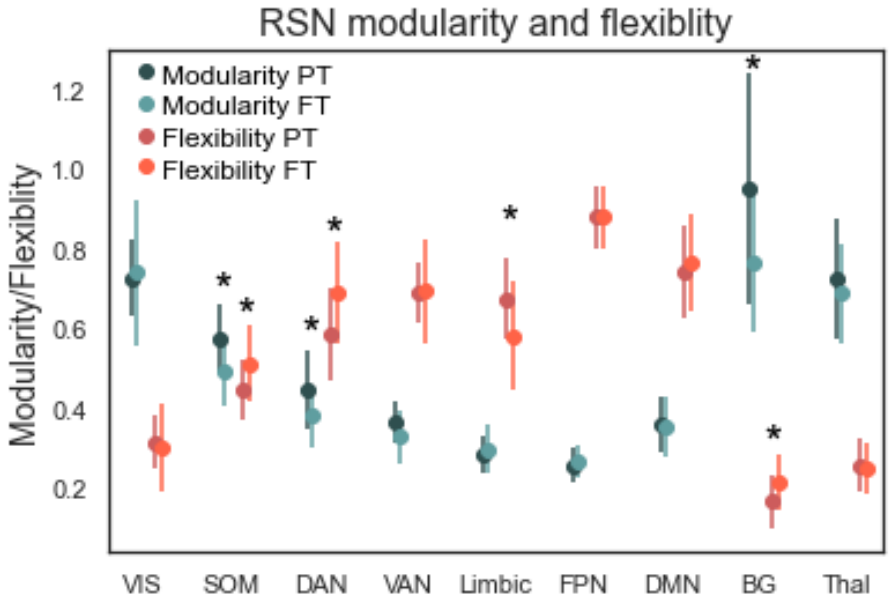

Figure 4. Modularity and flexibility estimated for RSNs for both groups. PT = extremely preterm, FT = Full term, Dark green = Modularity PT, Light green = Modularity FT, Dark orange = Modularity PT, Light orange = Modularity FT. In both groups, the visual, basal ganglia and thalamic networks all scored higher on modularity than flexibility. In the preterm group the somato–sensory (SOM), dorsal–attention (DAN) and basal ganglia (BG) networks had higher scores on modularity in the preterm group compared to the control group. In contrast, higher scores on flexibility in the preterm group was seen for the limbic network and lower scores for SOM, DAN and BG networks. * = significant differences between groups before correction for multiple comparison (permutation t–tests, 10000 iterations). After correction for multiple comparison, none remained significant.

5.3.2 Time resolved RSN lateralization

The statical representation of RSNs typically includes homotropic areas of the two hemispheres. Little is known to what extent time resolved connectivity is lateralized and its potential role in normal and aberrant development. In this group of EPT children and controls, significant differences in frequency of lateralization, i.e. instances of unique unilateral integration, were seen for multiple RSNs.

The preterm group showed decreased lateralization for several RSNs compared to controls (left visual, right somato–motor, right dorsal attention, right limbic, left fronto–parietal, right default mode, left and right basal ganglia and left thalamus). Only left portion of the limbic network showed increased lateralization in the EPT group. The largest differences were seen for the left thalamic and bilateral basal ganglia networks.

Interestingly, the FPN which is sometimes represented as a separate left and right network (Smith et al., 2009), did not score high on lateralization (Figure 5).

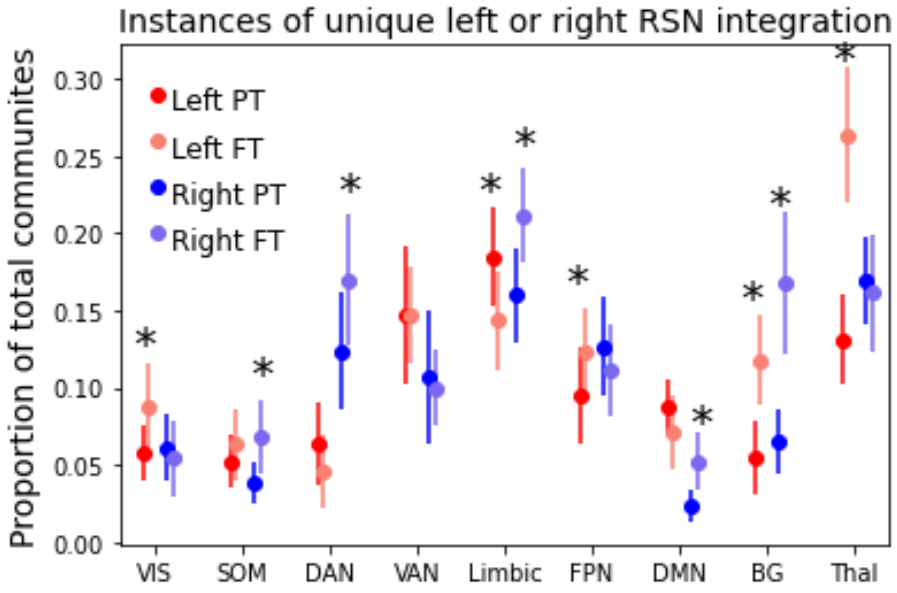

Figure 5. Lateralized integration. Frequency of unilateral integration for each RSN in the extremely preterm and term group. PT = Extremely preterm, FT = Full term, Red/pink = left, Blue/Purple =Right. * = statistically significant differences between groups after correction for multiple comparisons.

6 DISCUSSION

6.1 STUDY I

In this study, a novel method for time resolved analysis was developed based on flexible reconfiguration of networks that respects the temporal ordering. A strength of the method is that network integration and segregation can be tracked from time point to time point. This means that the relational properties in terms of phase relationships between simultaneously integrated networks is known. It also means that the gradual disintegration of networks and transient network constellations can be captured. Albeit imperfect, it also provides a birds' eye perspective on the recurrence of similar types of whole brain states of network configuration in the global state analysis. Clearly, the results of the study corroborate the large collection of previous studies that has shown that the definition of a network has a temporal constraint (Keilholz et al., 2017; Lurie et al., 2020; Preti et al., 2017). When considering the whole acquisition, we get the RSNs. During shorter time spans, the RSNs partially disintegrate and form transient constellations with each other to varied extent. An important result in the present study is that networks sometimes and in part remain integrated through cycles of activation and deactivation. This is already know from the early days of rs–fMRI where most notably the DMN regions showed synchronized deactivation during task performance (Fox et al., 2005; Fransson, 2005). However, the cyclic aspect of time resolved network integration and its meaning is not fully explored. Finally, in this study we also provide a novel way to estimate the relative flexibility and modularity of individual brain areas.

Importantly, the perspective taken in the study is that of network activity in a whole brain perspective. The importance of this perspective in neuroimaging research is increasingly recognized (Kringelbach et al., 2015). It is related to two unanswered questions regarding functional connectivity in the spatial and temporal domains. First, is the *effect* of the activation of a specific network dependent on the entire state of the brain? In other words, does it matter what state of partial or full disintegration other networks are and which networks that are in anti–phase with the network of focus? The second question has to do with the temporal trajectory. Beyond the purely auto–correlative aspects of the time series and the relative sluggishness of the BOLD–signal, does it matter for the function of network x at time point t_1 how the brain state Y was configured at time point t_0, t_{-1}, …, t_{-N} ? Important to remember for this last question is that the brain does not operate on one single time–scale, but rather works on multiple nested time scales simultaneously. Even the BOLD–signal contains multiple frequencies that are not straight forward to disentangle. However, studies that have investigated

functional connectivity in different frequency ranges has found important differences which still remain to be fully elucidated (Gohel and Biswal, 2015; Niazy et al., 2011). In preliminary unpublished work, we saw that subnetworks similar to those presented in this study could be obtained from all the IMFs. There were no significant differences in q_{int} between IMFs. However, the duration of integration was a function of the frequency spectrum of the IMF. This meant that faster frequencies led to a shorter duration of integration, while the subnetworks derived from IMFs with were characterized by slower frequencies had much fewer but substantially longer durations of integration. With or without considering the hemodynamic response function, these results beg the question which temporal scales should be considered when we talk about timing in (rs–) fMRI research. It also remains to be understood how these different frequency ranges modulate each other, if at all.

6.2 STUDY II

Mild WMI is prevalent in EPT born neonates. Few studies have investigated the long-term development of WMA/WMI. This study contributed novel information in the sense that discrete forms of WMA are prevalent in childhood in born EPT. Importantly, it does not relate to neuromotor outcome. The more important finding was that WMA/WMI at TEA was a predictor both of outcome in terms of processing speed as well as quantitative measures, such as white matter volume and global diffusivity than WMA/WMI at 8–11 years. Both scoring systems are based on visual inspection. The scoring used at TEA is based on compound scores from five parameters that each was scored from no (1 point) to severe (3 points). In contrast, the scoring at 8–11 years was much less fine grained and based on the presence or absence of 4 parameters. Therefore, it was much less robust to interrater variability that likely explains some of the results. Another possible reason for lower sensitivity of visual scoring at 8–11 years compared to TEA is the remodeling and development of the white matter that takes place during early childhood that might mask previous injury. One of the main aims of the study was to find a measure sensitive to very discrete signs of persisting WMA into childhood. It remains possible that the discrete WMA as defined in this study is such a sign. However, to confirm or discard such a hypothesis, further studies need to be conducted on larger samples preferably with independent neuroradiologists from different centers.

6.3 STUDY III

In this study, a novel way to estimate RSN flexibility and modularity was introduced. After correcting for multiple comparisons, contrary to the initial hypothesis, no significant differences between the extremely preterm born and the control group was seen for any of the networks. This does not however preclude that differences do exist. The methodological approach treated every area in an RSN as interchangeable with any other. It is possible that if the individual areas had been accounted for in a more specific way, differences would have been seen. Particularly, this would be expected for the thalamic and basal ganglia networks that both show lower levels of flexibility when treated as individual areas in the extremely preterm group. They also show significantly decreased levels of lateralization. These results indicate that the subcortical regions in the two hemispheres in extremely preterm born children are linked by increased functional connectivity and have reduced flexibility. This is a novel finding with a new methodology and hence needs to be corroborated in a larger independent sample and with complimentary methodological approaches. Most rs–fMRI studies in preterm born subjects are conducted in the neonatal period (Doria et al., 2010; Eyre et al., 2021b; Fransson et al., 2011; Smyser et al., 2016; Toulmin et al., 2015). Only a few studies have investigated functional network organization in preterm born children and young adults (Myers et al., 2010; Wehrle et al., 2018; Wheelock et al., 2018; White et al., 2014). Importantly, these do not exclusively include extremely preterm born subjects, but also very preterm (< 32 weeks). In most cases, the focus has been on only a few RSNs and none has investigated time resolved connectivity and flexibility. In contrast to the studies of preterm neonates that have included subjects with macroscopic brain injury (Smyser et al., 2013), the studies in older children and young adults typically do not include subjects with brain injury. Common to these studies and the present study is that only that which can be classified as minor differences between the preterm and control groups has been identified. This could be because the methods are not sensitive enough to capture differences that do exist. The results are also likely related to the selection of preterm subjects that are include in the studies. Like the present study, most subjects are doing relatively well with no major brain injuries, normal IQ and are going to normal schools. Finally, it remains possible that the BOLD–level of investigation is in itself insensitive to the differences in brain function that exist between groups.

7 CONCLUSIONS

The first study aimed at better capture and understand the dynamic changes in intrinsic functional connectivity in the brain. A novel method was developed for this purpose. While far from perfect in all its detail, it still provides a novel framework to capture time resolved connectivity changes that can potentially be helpful in the context of resting–state and cognitive neuroscience. Potentially it might also find applicability in data with higher temporal resolution such as EEG and MEG.

In Study II, the prevalence and clinical relevance of discrete macroscopic white matter alterations in school aged children born extremely preterm was investigated. More than half of the subjects had signs of discrete white matter alterations but it was not related to more negative neuromotor and cognitive outcomes at 12 years than for the group as a whole. The study also found a positive association between neonatal white matter injury of any grade and smaller white matter volume and lower FA at school age. Importantly, a neonatal diagnosis of WMI was associated with lower processing speed at 12 years. From a pathophysiological perspective this finding makes sense. Damage to the myelin producing cells leads both to slower conduction rates for signal transmission, lower FA and lower volume since myelin makes up a substantial portion of the white matter.

The third study is the logical bridge between Study I and Study II and encompasses both of the themes explored separately in the first two studies; intrinsic time resolved connectivity changes in the brain and brain development in extremely preterm born children at school age. This study is not yet peer–review and published and is likely to change before it finds its final form. It explores the concept RSN flexibility and modularity in a novel way using the method developed in Study I. No significant differences were seen between groups in flexibility or modularity at the RSN level. However, at the level of individual areas, basal ganglia and thalamic areas showed significantly reduced flexibility. Also, several RSNs in the preterm grouped exhibited significantly fewer instances of lateralization. Lateralization can also be understood as an aspect of flexibility. Together these results indicate that flexibility in functional organization to some extent is reduced in the preterm subjects compared to the control group. It is likely linked to other aspects of subtle functional reorganization not captured by this study.

8 POINTS OF PERSPECTIVE

Perhaps the most salient question in neuroimaging research that needs to be addressed is: Will ever more detailed and sophisticated methods of time resolved analysis be enough to truly understand how the brain functions and creates our internal experience as well as helps us survive in the world? The answer will partly depend on what is meant by understanding. Cleary, tracking and timing brain events with cognitive and motor events is important not least since it has the potential to identify a brain that suffers from malfunctioning. However, in some sense it remains a form of cartography unless the questions *why* and *how* can also be answered. Causative models and direct interventions with brain stimulation methods does not solve these fundamental questions. As of date, the motor system and perception are much better understood in neuroscience than higher order cognition and the subjective experience where consciousness itself is at the center. The concept of computation which is widely accepted way to think about how the brain operates does not solve the essence of the problem. For that, a theory for how computation creates subjective experience is needed. Several theories have been proposed but none has convincingly bridged the explanatory gap (Baars, 2005; Tononi and Edelman, 1998). With this said, I do believe the field of neuroimaging has a lot to offer in terms of understanding the fundamental principles of the dynamics of neuronal events and its correspondence to cognition and bodily events. I also believe it has a diagnostic potential in the clinic beyond what is seen at the moment. An increased integration between the available windows into the brain are necessary, i.e. combining fMRI, EEG, ECoG, MEG, TMS and other techniques in order to untangle the multilayered spatiotemporal activity in the brain.

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