TEMPORAL COMPLEXITY ALTERATIONS OF RESTING STATE FMRI IN PRETERM VERSUS TERM BORN INFANTS

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Abstract

Interrupted brain maturation from preterm birth increases the consequences of altered functional development (< 37 weeks gestational age (GA)). Mono-fractal analysis is an advanced functional magnetic resonance imaging (fMRI) analysis method that calculates the temporal auto-correlation characteristics from the blood oxygenation level dependent (BOLD) signal. This can be measured using the Hurst exponent (H). Our study goal was to measure H of the resting state-fMRI (rs-fMRI) BOLD signal to investigate alterations in brain signaling complexity at preterm age, term equivalent age and term healthy controls scanned at term age. Participant rs-fMRI and diffusion tensor imaging (DTI) data from 716 neonates born 23 to 43 weeks GA were obtained from the Developing Human Connectome Project. From the rsfMRI scans, independent component analysis was used to identify 13 resting state networks (RSNs). Temporal complexity was determined using H calculated from the power spectral density of the BOLD signal using Welch’s method. DTI scans from the preterm cohort were used to indirectly measure myelination with fractional anisotropy (FA) and radial diffusivity (RD) measurements. H in brain tissues and RSNs were assessed across gestational age and scan age, and Pearson's correlation was conducted between H and DTI measures. H significantly increased from preterm to TEA assessment, and earlier birth age contributed to lower H values. H begins below 0.5 at preterm age and crosses 0.5 at around term age in most regions. Motor and sensory networks were found to have the greatest increase in H. Correlations between DTI measures and H were moderate but significant, demonstrating somewhat parallel development of structural and functional systems. We found that H was an indicator for BOLD signal processing maturation in the infant brain. Accordingly, preterm infant signaling transforms from anticorrelated to correlated but is reduced by preterm birth compared to term born infants.
Lay summary

When birth occurs before 37 weeks, the brain’s growth development can be disrupted which increases the risk of impairments later in life. Investigations have explored how the brain’s functional activity differs from infants born at term through analyzing the signals produced from the brain’s blood flow. These signals contain patterns that repeat over time and can have varying levels of complexity. The Hurst exponent (H) measures the degree of complexity and can indicate whether a signal is chaotic or ordered. We used H measurements from functional brain scans to analyze the signal complexity in preterm infants and compared to term infants. We found that certain brain networks increase in H greater than others. Furthermore, the earlier an infant is born, the lower the H value. This demonstrates that preterm infants at term age have more chaotic signals compared to term born infants, which may be due to interrupted brain development.
Preface

This thesis presents the unpublished and independent work by the author, A, Mella under the supervision of Dr. Alexander Weber and supported by committee members Dr. Tamara Vanderwal and Dr. Steven Miller.

The magnetic resonance imaging data was collected by the Developing Human Connectome Project led by King’s College London, Imperial College London and Oxford University funded by the European Research Council under the European Union Seventh Framework Programme (FP/2007-2013) / ERC Grant Agreement no. [319456]. This included participant recruitment, MRI scanning, and image pre-processing.

A. Mella and A. Weber were both involved in further functional MRI scan processing and A. Weber performed diffusion MRI processing. Dr. Jeffrey Bone provided statistical analysis guidance and results interpretation.

This thesis is based on the concept formation and previous work done by J. Drayne and A. Weber titled “Long-range Temporal Correlation Development in Preterm Infants: Scanned Shortly After Birth and at Term-Equivalent Age” which was submitted for publication. All contents of this thesis including the manuscript writing, statistical analysis, results interpretation, figures and tables were done by the author. Manuscript edits and suggestions were provided by Dr. Alexander Rauscher, Dr. Tammy Vanderwal, Dr. Steven Miller and Dr. Deborah Giashi. The supervisor on this project, A. Weber provided guidance and support throughout the project and manuscript edits.
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List of Abbreviations

BOLD = Blood oxygen level dependent
CI = Confidence interval
CSF = Cerebrospinal fluid
dHCP = Developing Human Connectome Project
DTI = Diffusion tensor imaging
DWI = Diffusion weighted imaging
EEG = Electroencephalogram
FA = Fractional anisotropy
fBm = fractional Brownian motion
fc = Functional connectivity
fGn = fractional Gaussian noise
fMRI = Functional magnetic resonance imaging
GA = Gestational age
GABA = Gamma-aminobutyric acid
GM = Grey matter
H = Hurst exponent
ICA = Independent component analysis
IUGR = Intrauterine growth restriction
LRTC = Long range temporal correlations
MPT = Moderately preterm
MRI = Magnetic resonance imaging
NICU = Neo-intensive care units
PMA = Postmenstrual age
PSD = Power spectral density
RD = Radial diffusivity

rs-fMRI = Resting state functional magnetic resonance imaging

RSN = Resting state networks

TEA = Term age equivalent

TE = Echo time

THC = Term healthy control

TR = Repetition Time

VPT = Very preterm

WM = White matter
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Chapter 1: Introduction

1.1 Neurodevelopmental Processes during Pregnancy

The development of the nervous system is a complex, methodical and finely tuned process. A brief summary of major events is as follows. The sequences of events include neurogenesis, which is the formation of neural stem cell progenitors and neurons from neuroepithelial cells, that takes place from conception (0 weeks GA) until the third trimester of pregnancy (approximately 28 weeks GA) (Doi et al., 2022). GABAergic interneurons, however, continue to increase and are at the greatest numbers by term age (approx. 37 to 44 weeks GA) (Cheong et al., 2020). Neuronal migration is initiated from the end of the first trimester (13 weeks GA) and is completed roughly by the end of the second trimester (27 weeks GA) (Doi et al., 2022). Synaptogenesis and gliogenesis begin during the second trimester (14 to 27 weeks GA) and continue to progress after birth into postnatal development (Doi et al., 2022). Myelination begins in the third trimester (28 weeks GA) and persists into adolescence (Doi et al., 2022; Khodosevich & Sellgren, 2023). While these key trajectories are ongoing, thalamocortical projections have been identified at 20 to 23 weeks GA (Kostović & Jovanov-Milošević, 2006). By 24 to 32 weeks GA, there is an ingrowth of the thalamocortical axons within the cortical plate (Kostović & Jovanov-Milošević, 2006). Moreover, frontal, somatosensory, visual and auditory systems circuitry becomes established and by 36 weeks GA, sensory driven activity is evident (Kostović & Jovanov-Milošević, 2006). The elaboration of intracortical pathways occurs until birth and is further adjusted through auditory and visual stimulation (Kostović & Jovanov-Milošević, 2006). In the fetal cortex there is reformation of intracortical fibers, retraction of extraneous axons, and drastic increase of synapses which ultimately cause the brain to double in volume by the end of the third trimester (Kostović & Jovanov-Milošević, 2006). By term age, the KCCII transporter has matured to adjust GABAergic hyperpolarization (Kostović & Jovanov-Milošević, 2006). In the fetal brain, between weeks 30 and 40 GA, the structural and functional connectome are formed, as is evidenced by increased white matter (WM) structure, interhemispheric
functional connectivity, and short communication paths (van den Heuvel et al., 2015). The brain undergoes expansion of cytoarchitectural complexity in the final weeks of gestation (Dimitrova et al., 2021). As can be seen, development of the brain and its circuitry is a complicated process, and any disturbances have the potential to lead to vulnerabilities in the system.

### 1.2 Preterm Birth Neurologic Outcomes

According to the World Health Organization, 4% to 16% of babies in 2020 were born preterm globally (born less than 37 weeks GA) (WHO, 2023). In addition, in higher income countries, preterm birth rates are actually increasing (Vogel et al., 2018). The exact etiology of preterm birth is unknown but is suspected to be a combination of socio-demographic, nutritional, medical, obstetric and environmental factors (Vogel et al., 2018). Preterm birth is defined as babies born prior to 37 weeks GA and can be further categorized based on the gestational age of extremely preterm (born < 28 weeks), very preterm (29 to 32 weeks) and moderately preterm (33 to 37 weeks) (WHO, 2023). Gestational age (GA) is defined as the length of time in weeks between conception and birth, quantifying the period of time in the mother’s uterus. Postmenstrual age (PMA) is the sum of the gestational age and time elapsed since birth in weeks. The crucial developmental trajectories that are expected to occur in utero are interrupted with preterm birth and must continue in the less-than-ideal ex utero environment (El-Metwallly & Medina, 2020).

Preterm infants must then stay in neonatal intensive care units (NICU) for days to months, where they are vulnerable to harsh lights, painful procedures and disruptive noises (Cheong et al., 2020; El-Metwally & Medina, 2020). Preterm birth is associated with various consequences including dysfunction in the visual, auditory, somatic, pain, motor, cognition, emotion and language systems (Ream & Lehwald, 2018). It has been found that in preterm infants at term equivalent compared to term-born infants, there is a decreased total brain size and regional decreases in the corpus callosum, deep grey structures and cerebellum (Ream & Lehwald, 2018). These reductions in brain volumes persist into adolescence and adulthood, and volume deviations are positively associated with total intelligence quotient scores (Bjuland et al., 2014).

Furthermore, 35 to 50% of preterm born children and adolescents have neurodevelopmental disabilities
that require special education services and are more susceptible to motor deficits, chronic cognitive dysfunctions and have emotional difficulties (Gao et al., 2017; Luu et al., 2017). According to a child mortality study conducted from 2000 to 2015, preterm birth complications were the leading cause of death in children under 5 years (Liu et al., 2016). The interruption of brain development and early exposure of the extrauterine environment consequently leads to a more immature brain and merits further investigation. A way to safely investigate the possible sources of these neurologic outcomes is by using magnetic resonance imaging (MRI), which is non-invasive and facilitates multi-modal imaging techniques (anatomical, metabolic and functional).

1.3 MRI in Preterm Infants

MRI is a non-invasive technique to explore the brain using a variety of biophysical properties and biomarkers. Advanced techniques in MRI can reveal brain injuries and alterations that would be undetectable with conventional techniques such as cranial ultrasound (Duerden et al., 2013). Furthermore, MRI methods are critical for early detection of brain dysfunctions and injuries in order to reduce adverse progression and thus allow the ability to provide immediate interventions (Locke & Kanekar, 2022). A study which used structural MRI and diffusion weighted imaging (DWI) found that preterm infants at term-equivalent age (TEA) compared to term infants deviated from normal cortical maturation (Dimitrova et al., 2021). The preterm infants had higher cortical tissue water content as shown with increased mean diffusivity and decreased neurite density index compared to the term born infants (Dimitrova et al., 2021). In assessing regional brain volumes, the preterm group had decreased volumes in the parieto-occipital, sensorimotor, orbitofrontal, thalamus, basal ganglia, cerebellar and premotor regions along with enlarged cerebral spinal fluid (CSF) volume compared to the term group (Ment et al., 2009; Thompson et al., 2007). Additionally, altered gyrification in an extremely preterm group at TEA has been found compared to term born infants evident through less intricate cortical folding (Ajayi-Obe et al., 2000; Duerden et al., 2013). DWI and its tensor-based analysis - diffusion tensor imaging (DTI) - is an MRI technique that can
indirectly assess the brain’s microstructure. Fractional anisotropy (FA) measures the degree or directional preference of diffusion and radial diffusivity (RD) measures the diffusion rate in the transverse direction of the main diffusion eigenvector (Soares et al., 2013). DTI can be used to indirectly measure myelination, where FA would be high and RD low with greater myelination (Feldman et al., 2010). Studies have shown that preterm infants at TEA have altered WM properties of increased RD and decreased FA compared to term born infants (Tusor et al., 2014). This trend of lower FA and higher RD in the preterm group has been replicated in other studies as well (Qiu et al., 2015; Vaher et al., 2022). Reductions in FA and increases in RD have been associated with preterm birth related non-neurological comorbidities of lung disease, punctate lesions and sepsis (Tusor et al., 2014). These alterations demonstrated with MRI techniques are found in childhood and adolescence as well (Ment et al., 2009). Taken together, this extensive literature illustrates how preterm infants have more structural deficits than term born infants which continue to persist with age.

1.4 rs-fMRI in Preterm Infants

While structural alterations in the preterm brain are evident, functional MRI (fMRI) methods have also found dysfunctions in brain activity. fMRI is based on the blood oxygen level dependent (BOLD) signal, which is sensitive to changes in magnetic susceptibility because of changes in oxygen concentration and red blood cells switching hemoglobin states (Glover, 2011). Interpretations of BOLD fMRI are discerned from factors of signal specificity and spatial and temporal resolution (Logothetis, 2008). Furthermore, signal specificity and spatial and temporal resolution are characteristics evident from neural activity changes, dimensions of activated networks and neural event time series respectively (Logothetis, 2008). Spontaneous low frequency fluctuations in the BOLD signal can be detected, and are primarily studied by using resting state-fMRI (rs-fMRI) to measure brain activity in the absence of a stimulus (Dong et al., 2018; Cao et al., 2017; Lee et al., 2013). These variations in the BOLD signal occur due to brain metabolism oscillations and neurophysiological signaling activity (Dong et al., 2018). Conventionally, rs-fMRI has been used to measure functional connectivity between brain regions to
determine spatially distinct or connected neural systems (Doria et al., 2010; Lee et al., 2013). Brain regions with synchronous neuronal activity are assumed to be functionally connected and form so-called resting state networks (RSNs).

RSNs have been defined in adults, and neonatal studies have found other distinct sets of networks. Doria et al. identified the presence of complete networks consisting of visual, auditory, somatosensory, motor, default mode, frontoparietal and executive regions in infants aged 29 to 43 weeks postmenstrual age (PMA) (2010). Networks in preterm born infants at TEA have been discovered encompassing visual, sensorimotor, auditory, parietal, and cerebellar regions (Fransson et al., 2007). A preterm longitudinal study done by Smyser et al. identified RSNs of the sensorimotor, cingulate, prefrontal, temporal, thalamus and cerebellum (2010). In term born infants scanned between 43 to 45 weeks PMA, networks including motor, somatosensory, visual, auditory, parietal and frontal were identified (Eyre et al., 2021). A study that sought to determine the maturation sequence of RSNs in the first year of infancy determined that primary sensorimotor and auditory networks developed first, then visual, attention and default mode and executive control networks developed last (Gao et al., 2015). These results are in agreement with other rs-fMRI and behavioral studies but most importantly, they offer new insights on the asymmetric development of RSNs in infancy (Gao et al., 2015). Altogether, there are a variety of rs-fMRI studies which have explored RSN development in infant populations. In examining functional connectivity, differences have been found in preterm infants revealing lower correlations, less connectivity and limited distribution in networks compared to term-born controls (Gao et al., 2017; Smyser et al., 2010). However, the BOLD signal in rs-fMRI is not restricted to connectivity measurements and can be analyzed in multiple other ways, including assessing the complexity level of the signal (Dong et al., 2018).
1.5 Brain Criticality and Complexity in Neurodevelopment

Criticality is defined as systems undergoing phase transitions between different states and is apparent throughout nature (O’Bryne & Jerbi, 2022). A simple example of a phase transition is the transition of water from gas to liquid (or vice versa); or the phase transition from paramagnetic to ferromagnetic in iron at the Curie temperature, where the magnetization changes from zero to nonzero continuously. When a system is at the critical state between order and chaos, any level of disturbances can cause subsequent events called avalanches (Bak, 1996; O’Bryne & Jerbi, 2022). Self-organized criticality describes a system where in a critical state of unbalance, balance will be regained through avalanches in a homeostatic-like function (Bak, 1996; O’Byrne & Jerbi, 2022). Complexity is produced from self-organized criticality (Bak, 1996). For example, this can be seen in building a pile of sand, where the more you sprinkle sand on top, the higher it gets. However, as the sand pile gets higher, individual grains will start to fall off. This will reach a point where larger amounts of sand will begin to slide off creating ‘sand slides’ (Bak, 1996). Thus, the sandpile has reached a critical point (tall enough) and the various sand slides (avalanches) bring the system back to stability (Bak, 1996 & Zimmern, 2020). Moreover, the sandpile can be understood as a complex system, where the avalanches are dynamic properties of the pile (Bak, 1996). These avalanche sand slides and number of individual sand grains follow a power law distribution, meaning that they are scale free and the shape will persist under a change of scale (O’Bryne & Jerbi, 2022; Zimmern, 2020). This self-similarity pattern suggests that avalanche activity behaves as a fractal (Zimmern, 2020). Furthermore, criticality applies beyond natural systems, and exists in living systems in which it has been suggested to be adaptive for information processing (O’Bryne & Jerbi, 2022). Organisms with innate criticality are thought to be advantageous for being highly sensitive to disturbances and have the aptitude to store and transfer information (O’Bryne & Jerbi, 2022).

In adults, the brain and its neural systems are thought to exist in a critical state, transitioning between order and disorder to optimize neural efficiency, storage capacity and flexibility (Zimmern,
In the nervous system, this chain of actions could be described as neuronal avalanches which is the propagation of neural activity from one point that then spreads throughout the system (O’Byrne & Jerbi, 2022). The critical brain hypothesis can describe how the brain dynamically processes information through phase transitions, as there must be equilibrium between order and disorder (O’Byrne & Jerbi, 2022). Criticality transition states have been measured in vitro by the formation of neural activity and connectivity during morphological development of cortical cell cultures (Tetzlaff et al., 2010). Therefore, the developing infant brain may also be conceptualized as operating with phase transitions. Long range temporal correlations (LRTCs), or long-memory time series, are features of the critical state. LRTCs found in the brain have been suggested to be the related of the ability to optimally process information, and thus help reveal the balance between stability and flexibility in the system (Cruz et al., 2021; Meisel et al., 2017; Moran et al., 2019; Zimmern, 2020). The dynamic characteristics of criticality and LRTC are dependent on excitation-inhibition/GABAergic-glutamatergic balance in neuronal groups (Cruz et al., 2021; Moran et al., 2019). Perturbations or imbalance in the critical system can describe neurological disorders or impairments (Cruz et al., 2021; Moran et al., 2019).

Criticality is thought to be a characteristic of the brain that produces complexity (Bak, 1996; O’Byrne & Jerbi, 2022). Neural complexity is a property which can quantify the correlation strength of signalling in a network across all scales (Timme et al., 2016). For example this can be evident in measuring the interaction of spiking activity within a neural system where no correlation is represented in random data (Timme et al., 2016). A variety of measures can describe different aspects of complexity which include fractal dimension, multifractality, entropy, integration-segregation and power laws (O’Byrne & Jerbi, 2022). Brain signalling oscillations in preterm born infants have been explored previously with respect to brain criticality, using various types of functional imaging such as electroencephalogram (EEG) or fMRI, and various types of analysis such as the hurst exponent, power-law, spectral density and/or phase locking (Zimmern, 2020). In brief, preterm infant studies have shown that LRTC (Hartley et al., 2012) and EEG bursts are predictive of neurodevelopmental outcomes.
(Iyer et al., 2015). By using EEG, term born infants at 6 and 12 months were found to have LRTCs, to demonstrate that these spatiotemporal dynamics are found in the first year of life (Jannesari et al., 2020). An fMRI-EEG study looking at term born infants assessed scale free frequency power distribution through a rs-fMRI power-law exponent (Fransson et al., 2013). In this study, we chose to use the Hurst exponent to investigate temporal complexity of the rs-fMRI in preterm and term infants.

### 1.6 Temporal Complexity Measured by the Hurst Exponent with fMRI

As discussed above, fMRI can be used to determine temporal complexity in the BOLD signal which goes beyond analyzing spatial patterns (Fransson et al., 2013). The BOLD signal has fractal or scale free properties, apparent through the naturally repeating patterns that exist in the time series over different scales of time (Campbell & Weber, 2022). Typical fMRI analysis methods assess BOLD signal amplitude to determine the functional properties of the brain with statistical methods or use linear models to conduct functional connectivity analyses (Campbell & Weber, 2022; He, 2011). Fractal analysis can provide novel information of the complex patterns in physiological processes and evaluate the chaotic and non-linear processes of neural activity (Campbell & Weber, 2022; Eke et al., 2002). The Hurst exponent globally measures these fractal properties to quantify the long memory processes that occur (Campbell & Weber, 2022; Dona et al., 2017; Zimmerm, 2020). There are a few mathematical techniques to yield H from the BOLD time series complexity, such as detrended fluctuation analysis, discrete wavelet transform and power spectrum estimators of fast fourier transform and Welch’s periodogram (Campbell & Weber, 2022; Rubin et al., 2013). Results from these computation methods will differ based on the signal processing, time series length, and scanner, all of which influence the accuracy and sensitivity of BOLD complexity (Rubin et al., 2013).

H values range from 0 to 1 and have been categorized in the literature to signify different levels of complexity. H values greater than 0.5 contain long-term memory and persistent time series; H values equal to 0.5 describe random noise with no correlation in the signal; H less than 0.5 contain short-term
memory series and are anti-persistent or anti-correlated time series (Diaz & Cordova, 2022; Dong et al., 2018; Eke et al., 2002; Maxim et al., 2005). Additionally, H values closer to 1 may demonstrate order appearing to be more smooth and synchronized, while values closer to 0 indicate chaotic signaling which appear more rough or ‘hairy’ (Diaz & Cordova, 2022; Eke et al., 2002). H describes the degree of complexity of the BOLD signal and provides some information about signal organization.

In the literature, the vast majority of which has been performed in adults, it has been found that H values are greater than 0.5 in the brain, with greater values in the grey matter (GM) (thought to be due to neuronal cell bodies producing neuronal activity) and decreased values in the WM and CSF (Campbell & Weber, 2022). In adults, Maxim et al. found that H in the GM is approximately 0.8, and in the CSF, H is less than 0.5 (2005). In general H values below 0.5 have not yet been thoroughly investigated. A review done by Campbell & Weber explored H values in various neurological disruptions and brain states (2022). To summarize, higher H is found in aging, Alzheimer's Disease, mild traumatic brain injury, emotional distress, introversion and resting state (Campbell & Weber, 2022). Lower H is found in schizophrenia, Huntington’s Disease, neuroticism, extraversion and with greater task difficulty/novelty (Campbell & Weber, 2022). There are few studies that have characterized H in preterm infants. Hartley et al. calculated H with EEG in 11 preterm babies born between 23 to 30 weeks GA (2012). They discovered that LRTC were similar in infants with and without intracranial bleeding, which suggests that even with injury, the temporal complexity in the brain is maintained (Hartley et al., 2012). Another study measured fractal dimensions of brain structure using MRI in cohorts of preterm infants with intrauterine growth restriction (IUGR), preterm infants without IUGR, and term born infants (Esteban et al., 2010). Esteban et al. found that the IUGR preterm infants had lower fractal dimension than both other groups in the GM and WM to signify decreased cortical folding complexity (2010). Another interesting finding from this study was that the preterm infants did not significantly differ from the term born infants with this structural measure (Esteban et al., 2010). All in all, there are no studies that explore the differences in BOLD temporal
complexity with H in preterm born infants compared to term born infants. Further investigation could provide new information about the disrupted and delayed development that occurs in preterm birth.

1.7 Study Objectives

Our study used mono-fractal analysis of the BOLD signal of high-speed and highly sampled (TR = 392 ms; 15 minutes) rs-fMRI to investigate alterations in brain signaling complexity in preterm infants (scanned shortly after birth and again at TEA) and term born controls. We set out to answer the following questions: 1) How does H develop over time? 2) Do different RSNs develop differently with regards to H values? 3) Do term born infants have greater H compared to preterm infants at scan age? 4) Is H associated with indirect measures of myelination (FA and RD)?
Chapter 2: Methods

2.1 dHCP Dataset

Data for this study was obtained from the open source Developing Human Connectome Project, KCL-Imperial-Oxford Consortium (dHCP), third release, which is publicly available on the dHCP website (http://www.developingconnectome.org/project/). The dHCP was funded by the European Research Council under the European Union Seventh Framework Programme (FP/2007-2013) / ERC Grant Agreement no. [319456]. Participants were recruited from St. Thomas Hospital and scanned at The Evelina Newborn Imaging Centre (Edwards et al., 2022). Preterm infants born < 32 weeks GA were defined as very preterm infants (VPT, n = 88) and those born ≤ 37 weeks GA were defined as moderately preterm infants (MPT, n = 110). Term healthy controls were defined as infants born > 37 weeks GA (THC, n=518).

2.2 MRI Acquisition

Images were acquired on a 3T Philips Achieva with a dedicated neonatal 32 channel phased array head coil (Hughes et al., 2017). Structural, resting state fMRI (rs-fMRI) and diffusion tensor imaging (DTI) scans of the participants were analyzed for this study. Participants, excluding 6 that were sedated with chloral hydrate, were scanned during natural sleep after bottle feeding and swaddling (Edwards et al., 2022). The total scanning time of anatomical, rs-fMRI, and diffusion images was 63 minutes (Edwards et al., 2022). Preterm infants were defined as infants born ≤ 37 weeks GA and term birth and term age equivalence is > 37 weeks GA. Majority of the infants were scanned once and a subset of preterm infants were scanned twice to provide longitudinal data (n = 69) at preterm and TEA (Edwards et al., 2022).
2.3  **Structural Parameters**

Anatomical images were acquired with the following parameters: T2-weighted (TR=12s; TE = 156 ms; SENSE factor 2.11 (axial) and 2.58 (sagittal)) and inversion recovery T1-weighted (TR = 4,795 ms; TI = 1,740 ms; TE = 8.7 ms; SENSE factor 2.27 (axial) and 2.66 (sagittal)) and 3D MPRAGE (TR = 11 ms; TI = 1,400 ms; TE = 4.6 ms; SENSE factor 1.2 (RL)) with 0.8 mm isotropic resolution. T2w and inversion recovery T1w multi-slice fast spin-echo images were acquired in sagittal and axial slice stacks with in-plane resolution 0.8 x 0.8 mm² and 1.6 mm slices overlapped by 0.8 mm (for T2w) and 0.74mm for (T1w sagittal). The structural images used for this study were preprocessed with the dHCP structural pipeline (Makropoulos et al., 2018).

2.4  **rs-fMRI Parameters**

Resting state fMRI (rsfMRI) was acquired with high temporal resolution echo planar imaging using the following parameters: TE = 38 ms; TR = 392 ms; MB factor = 9x; 2,300 volumes; isotropic resolution = 2.15 mm; scan time = 15 minutes. In-plane acceleration or partial Fourier was not used. rs-fMRI images analyzed for this study were preprocessed with the pipeline by Fitzgibbon et al., 2020. More details describing the fMRI acquisition parameters can be found (Fitzgibbon et al., 2020; Edwards et al., 2022). rsfMRI scans underwent further processing through manually applying FSLFix components to regress out noise components.

2.5  **DTI Parameters**

Diffusion MRI was acquired with echo planar imaging using the following parameters: TE = 90 ms; TR = 3,800 ms, MB factor = 4x, SENSE factor = 1.2, partial Fourier factor = 0.86, in-plane resolution = 1.5 x 1.5 mm, 3 mm slices with 1.5 overlap. For each subject 20 b0s were acquired and 3 different b-value shells (b = 400 s/mm²: 64, b = 1000 s/mm²: 88, b = 2600 s/mm²: 128) in 4 phase encoding directions (AP, PA, RL, and LR). The dMRI images analyzed for this study were preprocessed with the
pipeline by Bastiani et al., 2019. More details describing the diffusion MRI acquisition parameters can be found (Bastini et al., 2019; Edwards et al., 2022).

2.6 MRI Processing

2.6.1 Group-level Resting State Networks

A subgroup of 52 scans was selected by stratified random sampling for ICA analysis to manually identify group level resting state networks (RSN). rsfMRI scans were first registered to a 40-week template (Schuh, 2017; Schuh et al., 2018) and then were highpass filtered for 100s/0.01Hz to remove non-neuronal noise and spatially smoothed at 8mm. Group ICA was then performed using FSL’s MELODIC with 30 components. After visual inspection by AMW and AEM, and comparison to other published studies with preterm infants, 13 RSNs were identified. These included six lateralized networks that were combined to create three bilateral networks. The 13 networks identified were the motor medial, motor lateral, motor association, somatosensory, auditory, posterior parietal, posterior cingulate cortex, visual, dorsal visual stream, frontal pole, dorsolateral prefrontal, midbrain and cerebellum. These RSNs were then used to create RSN masks for averaging the Hurst exponent and DTI metrics (in combination with white matter segmentation masks). These steps are shown in Figure 1.
2.6.1 Hurst Exponent Calculation

fMRI BOLD complexity was determined with H measurements calculated from the power spectrum density (PSD) of the BOLD signal, replicating the approach used in our previous work (Drayne et al., 2022). The PSD describes the power of the fMRI signal and can be computed using various methods. Welch’s method to quantify the PSD has been shown to be advantageous over other methods in having higher sensitivity to activation and to the type of tissue (Rubin et al., 2013). The PSD was estimated by using the ‘welch’ command from Python’s ‘Scipy.Signal’ library (Virtanen et al., 2020). The data were divided into successive eight windows with 50% overlap, and averaged (Welch, 1967). β was calculated between the frequency range of 0.08 and 0.16 (Dona et al., 2017). These parameters were mirrored on Rubin et al. (2013). After determining the PSD, H was calculated from Equation 1 where β, is the negative of the slope from the log-power log-frequency plot of a power spectral density. This is shown in Figure 2.
\[ H = (1 + \beta)/2 \quad \text{Equation 1} \]

Here \( H \) is assumed to be a signal in the class of fractional Gaussian noise (fGn) (as opposed to fractional Brownian motion (fBm)). Bullmore et al. described that human fMRI signals can sometimes begin as fluctuating fBm signals with increasing variance that are then transformed to stationary fGn signals with constant variance when the fMRI data is motion corrected (2004). fBm signals cannot be completely removed, however, and as first conceptualized by Eke et al. (2000), are hereby assumed to be fGn between \( 0 < H < 1 \) and fBm between \( 1 < H < 2 \), also known as an ‘extended’ Hurst. Here we first calculated \( H \) in all voxels in the brain which were then averaged within individual RSNs using the previously created RSN masks. \( H \) of each of the RSNs masks were combined to provide the total RSN \( H \) value. \( H \) in the ventricles and grey and white matter were calculated from segmentations obtained using the DrawEm method (Makropoulous et al., 2014). These steps are shown in Figure 1.

**Figure 2.** H Calculation from the BOLD signal. Schematic showing how \( H \) is calculated from the BOLD signal using Welch’s method in an example term born infant.
2.6.2 DTI Analysis

Diffusion measures of fractional anisotropy (FA) and radial diffusivity (RD) were calculated in the brain’s white matter for the preterm group using the preterm age (≤ 37 weeks GA) scan. The RSNs masks created from ICA analysis were used as regions of interest (ROIs) to determine diffusion measurements in the white matter. The cerebellum and midbrain RSN masks were excluded after the DrawEm segmentation failed to segment out white and grey matter in these regions (Makropoulos et al., 2014). This left 11 white matter regions for analysis: motor medial, motor lateral, motor association, somatosensory, auditory, posterior parietal, posterior cingulate cortex, visual, dorsal visual stream, frontal pole, and dorsolateral prefrontal. These WM region masks were also combined to provide a total white brain measure.

2.7 Statistics

Statistical analyses were completed using R and RStudio (v4.0) (R Core Team, 2022; RStudio Team). Birth age was used as a continuous variable to analyze the VPT, MPT and THC as groups were sorted by median birth age: VPT infants were analyzed at 29 weeks GA, MPT infants at 35 weeks GA and THC at 41 weeks GA. Mixed linear effects models (shown in Equations 2 and 3) were created using subjects as random effects to account for differences in within- and between-subject variance given that some preterm born infants were scanned twice (at preterm age and term, n = 85) and others were scanned only once (at preterm age, n = 69 or term, n = 44). Scan age, birth age and RSNs were set as fixed effects in the models.

\[ H \sim \text{scan}_\text{age} \times \text{birth}_\text{age} + (1|\text{Subject}) \]  
\[ H \sim \text{scan}_\text{age} \times \text{birth}_\text{age} \times \text{RSN} + (1|\text{Subject}) \]

Standardized parameters were obtained by fitting the model on a standardized version of the dataset. 95% Confidence Intervals (CIs) and p-values were computed using a Wald t-distribution approximation. Marginal means and trends were calculated and Holm’s method was used for p-value adjustment. Holm’s
The method is done for multiple testing by iteratively accepting or rejecting hypotheses (Holm, 1979). H values in the ventricles, GM, WM, combined RSN and individual RSNs were assessed by comparing the preterm group to term age equivalent (TEA) and preterm group at TEA to term healthy controls (THC). This was done by estimating H from median postmenstrual age scans. The preterm group (n = 198) was analyzed by assessing longitudinal H values in the brain tissues and RSN. The preterm scans at 35 weeks PMA were compared to the TEA scans at 41 weeks PMA using estimated marginal means (‘emmeans’) (Russel, 2022). Preterm groups of the VPT and MPT were compared with each other at the scan age of 35 weeks PMA. RSN slopes were calculated using estimated marginal trends (‘emtrends’) (Russel, 2022) to determine which has the greatest increase with age in the entire preterm group. The VPT and MPT groups at term age were each compared to the THC group at the scan age of 41 weeks PMA in the brain tissues and RSNs. Sex differences were assessed between biological males and females in the brain tissues, RSNs and sexes in the infant groups. Overall means in the sexes were calculated and compared. In the preterm group, FA and RD were assessed longitudinally in both the total WM and individual regions. White matter microstructural associations to H in the preterm group were assessed by computing Pearson correlations between FA and H and between RD and H.
Chapter 3: Results

3.1 Participant Demographics

Our study population included 716 neonates born between 23 and 43 weeks GA. The preterm group was composed of 198 infants including 69 infants with preterm only scans, 44 infants with term-equivalent only scans and 85 infants with both preterm and term-equivalent aged scans. Moreover, the preterm cohort was further subdivided according to the WHO thresholds into very preterm (VPT, infants born < 32 weeks GA) and moderately preterm (MPT, infants born ≤ 37 weeks GA but > 32 weeks GA). Within the VPT group there were 70 infants with preterm scans, of whom 18 also had TEA scans. The MPT groups had 74 infants with preterm scans and 36 infants with TEA scans. For the term healthy control group (THC) there were 518 infants included. All THC infants only had a single scan. These participant details are shown in Table 1 along with birth age and scan age information in Figure 3.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Sex (M/F)</th>
<th>Birth Age/GA in Weeks (Range)</th>
<th>Scan Age/PMA in Weeks (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPT</td>
<td>88</td>
<td>47/41</td>
<td>28.79 (23.00 to 31.86)</td>
<td>Preterm, n=70 32.57 (26.71 to 36.71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TEA, n=18 41.14 (38.14 to 44.29)</td>
</tr>
<tr>
<td>MPT</td>
<td>110</td>
<td>61/49</td>
<td>34.86 (32.14 to 37.00)</td>
<td>Preterm, n=74 35.57 (33.14 to 37.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TEA, n=36 40.29 (37.14 to 45.14)</td>
</tr>
<tr>
<td>THC</td>
<td>518</td>
<td>280/238</td>
<td>40.14 (37.14 to 42.71)</td>
<td>41.29 (37.43 to 44.86)</td>
</tr>
</tbody>
</table>

Table 1. Participant demographics. Sex (male/female) group numbers and median ages and ranges are shown. VPT = very preterm, MPT = moderately preterm, THC = term healthy control, GA = gestational age, PMA = postmenstrual age.
Figure 3. Birth age and scan age relationship in our data. a) Plot between the two variables, \( r = 0.15 \). Birth age and scan age are not collinear. b) Histogram of the infant group at term age. An even distribution to ensure we are not extrapolating our data for analysis at 41 weeks PMA.

3.2 H in All Subjects

H values in the whole brain are visually shown in Figure 4 in a single preterm born infant, the same infant at TEA, and a term born control. A corresponding sample Welch PSD is also displayed for a fitted frequency range of 0.08 to 0.16 Hz. When comparing the H values between males and females in the whole group, and in the VPT, MPT and THC groups separately there were no significant differences.
Figure 4. H values in the whole brain of a single term-born infant and a preterm infant both at 35 weeks PMA and at TEA, with corresponding Welch PSDs. Comparison of H values shown in a) a sample preterm infant scanned at 35 weeks PMA, b) the same infant at term of 41 weeks PMA and c) a single term control infant at 41 weeks PMA. Voxel location 32,33,25. Hurst maps were smoothed at 4mm for visualization purposes. Whole-brain averaged Welch’s power spectral densities shown (blue) with fitted frequency range of 0.08 to 0.16 (orange). d) to f) are from the same subjects/time-points as a) to c).

### 3.2.1 Grey Matter

The linear mixed effects model for H in the GM with scan age and birth age as fixed effects (Equation 2) was found to have a total substantial explanatory power with conditional $R^2 = 0.51$. The part related to the fixed effects alone (marginal $R^2$) was found to be 0.35. The model's intercept (corresponding to scan_age = 0 and birth_age = 0) was at -0.49 (95% CI [-0.90, -0.09], t(797) = -2.39, p = 0.017). Within this model: the effects of scan age were found to be statistically significant and positive, birth age was found to be statistically significant and positive and scan age * birth age was found to be statistically non-significant and negative. The values are provided in Table 2. In other words, for every extra week of
gestation, H measured at TEA increases by ~0.005 in the grey matter. H values increased with increasing scan age (PMA) when looking at the entire cohort in the GM (see Figure 5.a). Scan age and H were significantly and positively correlated in the GM with an r value of 0.554 (CI [0.504, 0.600], p<0.0001). Similarly, Birth age and H in the GM were significantly positively correlated with an r value of 0.486 (CI [0.431, 0.537], p<0.0001). When scan age was set at 41 weeks PMA, the slope of birth age and H in the GM was 0.00491 (see Figure 5.b).

<table>
<thead>
<tr>
<th>Parameters (fixed effects)</th>
<th>b</th>
<th>SE</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grey Matter, df = 797</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.492</td>
<td>0.206</td>
<td>-2.39</td>
<td>0.017</td>
</tr>
<tr>
<td>Scan age</td>
<td>0.021</td>
<td>0.005</td>
<td>4.08</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Birth age</td>
<td>0.017</td>
<td>0.006</td>
<td>2.59</td>
<td>0.010</td>
</tr>
<tr>
<td>Scan age x Birth age</td>
<td>-2.89x10^-4</td>
<td>1.59x10^-4</td>
<td>-1.82</td>
<td>0.069</td>
</tr>
<tr>
<td>White Matter, df = 797</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.211</td>
<td>0.144</td>
<td>-1.46</td>
<td>0.144</td>
</tr>
<tr>
<td>Scan age</td>
<td>0.014</td>
<td>0.004</td>
<td>3.81</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Birth age</td>
<td>0.015</td>
<td>0.004</td>
<td>3.33</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Scan age x Birth age</td>
<td>-2.87x10^-4</td>
<td>1.11x10^-4</td>
<td>-2.60</td>
<td>0.010</td>
</tr>
<tr>
<td>RSN (Motor Medial as Reference), df = 10385</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-1.44</td>
<td>0.153</td>
<td>-9.41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Scan age</td>
<td>0.047</td>
<td>0.004</td>
<td>12.69</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Birth age</td>
<td>0.040</td>
<td>0.005</td>
<td>8.21</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Table 2. Mixed linear effects model results.** Results from the whole group in the grey matter, white matter and RSN. Calculated b values, SE (standard error), t-value and p-values from the linear mixed effect models. All estimates are significant excluding the white matter intercept.
3.2.2 White Matter

The linear mixed effects model for H in the WM with scan age and birth age as fixed effects (Equation 2) was found to have a total substantial explanatory power (conditional $R^2 = 0.24$) and the part related to the fixed effects alone (marginal $R^2$) was 0.22. The model's intercept, corresponding to scan_age = 0 and birth_age = 0, was at -0.21 (95% CI [-0.49, 0.07], $t(797) = -1.46$, $p = 0.144$). Within this model the effects of scan age were statistically significant and positive, birth age was statistically significant and positive, scan age * birth age was statistically significant and negative. The values are presented in Table 2.

3.2.3 Resting State Networks

The linear mixed effects model for H with scan age, birth age, and RSN as fixed effects (Equation 3) was found to have a total substantial explanatory power (conditional $R^2 = 0.83$) and the part related to the fixed effects alone (marginal $R^2$) was 0.43. The model's intercept with the Motor Medial RSN as the reference corresponding to scan_age = 0, birth_age = 0 and RSN = H_MotorMedial, was at -1.44 (95% CI [-1.74, -1.14], $t(10385) = -9.41$, $p < .001$). Within this model, the effects of scan age and birth age were
each statistically significant and positive and birth age was statistically significant and positive. These values are presented in Table 2. All other beta values relative to the motor medial for the rest of the RSNs fixed effects are reported in the Appendix under Supplementary RSN Information.

### 3.3 H in the Preterm Group Only

#### 3.3.1 Tissues

H significantly increased (p<0.001) from preterm to TEA in the grey matter from 0.452 [0.444,0.459] to 0.520 [0.512,0.527], in the white matter from 0.432 [0.426,0.438] to 0.450 [0.438,0.456] and the combined RSN from 0.450 [0.442,0.457] to 0.513 [0.505,0.520]. H in the combined RSN and GM increased at similar rates and both at faster rates than the WM with slopes of 0.0101, 0.0109 and 0.00292 respectively (see Figure 6. a). The GM and combined RSNs slopes cross H = 0.5 at approximately 39 weeks PMA. When comparing the VPT and MPT groups at 35 weeks PMA the VPT had significantly lower (p<0.001) H values in the GM, WM and combined RSN than the MPT as shown in Figure 6. b). In the GM the VPT has a mean H value of 0.443 [0.433,0.452] while the MPT has a mean value of 0.468 [0.459,0.478], in the WM the VPT and MPT have 0.419 [0.412,0.427] and 0.450 [0.442,0.458] mean values respectively and values of 0.441 [0.431,0.450] and 0.466 [0.456,0.476] respectively in the combined RSN. These values are shown in Table 3.
Figure 6. **H analysis in the preterm infant group.** Predicted H values in the a) tissues and c) RSNs from 25 to 45 weeks PMA. Comparison between the VPT group at 29 weeks GA and MPT at 35 weeks GA in the b) tissues and d) RSN at 35 weeks PMA. The groups are illustrated with p-values (*) to show significant comparisons. The dashed line indicates $H = 0.5$. 
### Table 3. Preterm group H values.
Mean H values with confidence intervals and p-values from the VPT (n = 70) and MPT group (n = 74) comparison at 35 weeks PMA in the tissues and RSNs. NS = not significant.

<table>
<thead>
<tr>
<th>Region</th>
<th>VPT (29 weeks GA)</th>
<th>MPT (35 weeks GA)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray Matter</td>
<td>0.443 [0.433,0.452]</td>
<td>0.468 [0.459,0.478]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>White Matter</td>
<td>0.419 [0.412,0.427]</td>
<td>0.450 [0.442, 0.458]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Combined RSN</td>
<td>0.441 [0.431,0.450]</td>
<td>0.466 [0.456,0.476]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Motor Medial</td>
<td>0.492 [0.480, 0.504]</td>
<td>0.508 [0.493,0.523]</td>
<td>NS</td>
</tr>
<tr>
<td>Motor Lateral</td>
<td>0.461 [0.449,0.473]</td>
<td>0.490 [0.475, 0.504]</td>
<td>0.0077</td>
</tr>
<tr>
<td>Motor Association</td>
<td>0.452 [0.440,0.464]</td>
<td>0.477 [0.463,0.492]</td>
<td>0.0188</td>
</tr>
<tr>
<td>Somatosensory</td>
<td>0.449 [0.437,0.461]</td>
<td>0.471 [0.456,0.486]</td>
<td>0.0370</td>
</tr>
<tr>
<td>Auditory</td>
<td>0.449 [0.437,0.461]</td>
<td>0.474 [0.460,0.489]</td>
<td>0.0188</td>
</tr>
<tr>
<td>Visual</td>
<td>0.440 [0.428,0.452]</td>
<td>0.457 [0.442,0.471]</td>
<td>NS</td>
</tr>
<tr>
<td>Posterior Parietal</td>
<td>0.469 [0.457,0.481]</td>
<td>0.474 [0.460,0.489]</td>
<td>NS</td>
</tr>
<tr>
<td>Posterior Cingulate Cortex</td>
<td>0.436 [0.424,0.448]</td>
<td>0.460 [0.446,0.475]</td>
<td>0.0208</td>
</tr>
<tr>
<td>Dorsal Visual Stream</td>
<td>0.433 [0.421,0.445]</td>
<td>0.456 [0.441,0.471]</td>
<td>0.0370</td>
</tr>
<tr>
<td>Frontal Pole</td>
<td>0.444 [0.432,0.456]</td>
<td>0.479 [0.464,0.493]</td>
<td>0.0004</td>
</tr>
<tr>
<td>Dorsolateral Prefrontal</td>
<td>0.425 [0.413,0.437]</td>
<td>0.458 [0.444,0.473]</td>
<td>0.0009</td>
</tr>
<tr>
<td>Midbrain</td>
<td>0.445 [0.433,0.457]</td>
<td>0.471 [0.456,0.486]</td>
<td>0.0188</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.333 [0.321,0.345]</td>
<td>0.392 [0.377,0.406]</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

3.3.2 Resting State Networks

The 13 RSNs were analyzed to determine which network showed the greatest increase in H values from preterm to term equivalent age, using both single and longitudinal scans (Figure 7). All RSNs increased with scan age at different rates. The ventricles are also plotted with the RSNs to signify the noise floor, and the slope for each network surpassed the ventricle slope at different PMAs (see Figure 6 c.) and Table 4). The motor medial (0.0208), motor lateral (0.0157) and posterior parietal (0.0157) networks had the greatest increase in H with scan age (PMA). The dorsolateral prefrontal (0.00490), cerebellum (0.00282) and midbrain (0.00212) networks had the lowest increase in H with scan age (PMA). In Table 4, the midbrain (25.0 weeks PMA), frontal pole (29.1 weeks PMA) and motor association (31.8 weeks PMA) intercept the ventricular slope the earliest while the dorsal visual stream
(34.2 weeks PMA), visual (34.3 weeks PMA) and the dorsolateral prefrontal (34.4 weeks PMA) networks intercept it the latest. In analyzing the preterm groups separately, the VPT had lower H in all RSNs as shown in Figure 6. d). This was significant in 10 RSNs excluding the motor medial, posterior parietal and visual networks. The mean H values and p-values at 35 weeks PMA comparison for the VPT and MPT groups for the RSN are in Table 3.

**Figure 7. Resting state networks.** The 13 identified RSNs from 30 ICA components. The networks are composed of motor, sensory, frontal, midbrain and cerebellum regions.
### Table 4. Resting state network slopes and ventricle intersection age (PMA)

<table>
<thead>
<tr>
<th>RSN</th>
<th>Slope</th>
<th>Ventricle Crossing (Weeks PMA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor Medial</td>
<td>0.0208</td>
<td>31.9</td>
</tr>
<tr>
<td>Motor Lateral</td>
<td>0.0157</td>
<td>32.5</td>
</tr>
<tr>
<td>Posterior Parietal</td>
<td>0.0157</td>
<td>32.6</td>
</tr>
<tr>
<td>Visual</td>
<td>0.0153</td>
<td>34.3</td>
</tr>
<tr>
<td>Auditory</td>
<td>0.0127</td>
<td>33.0</td>
</tr>
<tr>
<td>Somatosensory</td>
<td>0.0114</td>
<td>32.9</td>
</tr>
<tr>
<td>Motor Association</td>
<td>0.00915</td>
<td>31.8</td>
</tr>
<tr>
<td>Dorsal Visual Stream</td>
<td>0.00832</td>
<td>34.2</td>
</tr>
<tr>
<td>Posterior Cingulate</td>
<td>0.00609</td>
<td>33.1</td>
</tr>
<tr>
<td>Frontal Pole</td>
<td>0.00499</td>
<td>29.1</td>
</tr>
<tr>
<td>Dorsolateral Prefrontal</td>
<td>0.00490</td>
<td>34.4</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.00282</td>
<td>NA</td>
</tr>
<tr>
<td>Midbrain</td>
<td>0.00212</td>
<td>25.0</td>
</tr>
</tbody>
</table>

*H* slopes in each of the RSN in descending order and calculated PMA intersection with the ventricle slope. The ventricle slope is 0.00131.

### 3.4 H: Preterm versus Term

*H* values in the preterm groups of VPT and MPT at TEA were compared to the THC in the brain tissues and RSNs at 41 weeks PMA (Figure 8. a) and b)) Both preterm groups were lower than the THC and the VPT group was significantly lower than the MPT group in all regions. These comparisons were significant in the GM, WM, and combined RSNs and all individual RSN excluding the posterior parietal, posterior cingulate and midbrain networks. The mean *H* values and p-values from the VPT versus MPT group comparison at 41 weeks PMA are provided in Table 5.
Figure 8. H analysis at term age comparison. H analysis in the preterm group at TEA compared to the term group in the a) tissues and b) RSNs. The mixed linear effects model in a) predicts H with scan age and birth age as fixed effects and in b) predicts H with scan age, birth age and the RSNs as fixed effects and both models account Subjects as random effects. The groups are illustrated with p-values (*) to show significant comparisons. The dashed line indicates H = 0.5.

<table>
<thead>
<tr>
<th>Region</th>
<th>VPT (29 weeks GA)</th>
<th>MPT (35 weeks GA)</th>
<th>THC (41 weeks GA)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray Matter</td>
<td>0.535 [0.529, 0.541]</td>
<td>0.542 [0.539, 0.545]</td>
<td>0.549 [0.547, 0.552]</td>
<td>0.0002</td>
</tr>
<tr>
<td>White Matter</td>
<td>0.429 [0.425, 0.432]</td>
<td>0.464 [0.462, 0.465]</td>
<td>0.499 [0.497, 0.500]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Combined RSN</td>
<td>0.503 [0.486, 0.520]</td>
<td>0.531 [0.523, 0.539]</td>
<td>0.559 [0.551, 0.567]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Motor Medial</td>
<td>0.618 [0.599, 0.637]</td>
<td>0.638 [0.629, 0.648]</td>
<td>0.659 [0.650, 0.668]</td>
<td>0.0078</td>
</tr>
<tr>
<td>Motor Lateral</td>
<td>0.550 [0.531, 0.569]</td>
<td>0.597 [0.588, 0.606]</td>
<td>0.644 [0.635, 0.653]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Motor Association</td>
<td>0.507 [0.488, 0.526]</td>
<td>0.539 [0.530, 0.548]</td>
<td>0.570 [0.561, 0.580]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Somatosensory</td>
<td>0.520 [0.501, 0.539]</td>
<td>0.549 [0.540, 0.559]</td>
<td>0.579 [0.570, 0.588]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Auditory</td>
<td>0.521 [0.502, 0.540]</td>
<td>0.560 [0.551, 0.569]</td>
<td>0.599 [0.590, 0.608]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Visual</td>
<td>0.529 [0.510, 0.548]</td>
<td>0.556 [0.547, 0.565]</td>
<td>0.583 [0.574, 0.592]</td>
<td>0.0002</td>
</tr>
<tr>
<td>Posterior Parietal</td>
<td>0.561 [0.542, 0.580]</td>
<td>0.575 [0.566, 0.584]</td>
<td>0.589 [0.579, 0.598]</td>
<td>NS</td>
</tr>
<tr>
<td>Posterior Cingulate Cortex</td>
<td>0.481 [0.462, 0.500]</td>
<td>0.497 [0.488, 0.507]</td>
<td>0.514 [0.504, 0.523]</td>
<td>NS</td>
</tr>
<tr>
<td>Dorsal Visual Stream</td>
<td>0.487 [0.468, 0.506]</td>
<td>0.512 [0.503, 0.521]</td>
<td>0.537 [0.527, 0.546]</td>
<td>0.0006</td>
</tr>
<tr>
<td>Frontal Pole</td>
<td>0.475 [0.456, 0.494]</td>
<td>0.505 [0.495, 0.514]</td>
<td>0.534 [0.525, 0.544]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Dorsolateral Prefrontal</td>
<td>0.460 [0.441, 0.479]</td>
<td>0.489 [0.480, 0.498]</td>
<td>0.518 [0.509, 0.527]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Midbrain</td>
<td>0.475 [0.456, 0.494]</td>
<td>0.478 [0.468, 0.487]</td>
<td>0.480 [0.471, 0.490]</td>
<td>NS</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.352 [0.333, 0.371]</td>
<td>0.411 [0.402, 0.421]</td>
<td>0.470 [0.461, 0.480]</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Table 5. Term age H values by group. Mean H values with confidence intervals and p-values in the VPT, MPT and THC groups compared at 41 weeks PMA in the tissues and RSNs. NS = not significant.
3.5 DTI correlations

The calculated FA at 41 weeks PMA in the 35 weeks GA preterm group was 0.189 [0.186, 0.192] compared to at 41 weeks GA group FA significantly increased (p = 0.01) to 0.194 [0.188, 0.200]. RD at 41 weeks PMA comparison was not significantly different with mean values at 35 weeks GA of 0.00108 and at 41 weeks GA of 0.00107. FA and RD trends along with the white matter regions are shown in Figure 9. DTI measures of FA and RD were correlated to H values in the preterm group (Figure 10). There was a significant positive correlation (p < 0.0001) between FA and H with an r value of 0.373 in the brain’s total white matter. RD and H had a significant negative correlation (p <0.0001) with an r value of -0.304. These associations were also present across the 11 white matter regions shown in Figure 11. The motor lateral, somatosensory, and motor medial regions had the strongest correlations of FA and H with r values of 0.552, 0.512 and 0.501 respectively. R values for RD and H were the highest in the motor medial, motor lateral and posterior cingulate areas with values of -0.523, -0.426 and -0.426 respectively.
Figure 9. DTI scalar plots and WM regions in the preterm group. a) FA plot with scan age (PMA) in the total white matter. b) RD plot with scan age. c) White matter regions analyzed using RSNs are regions of interests. FA = fractional anisotropy, RD = radial diffusivity, PMA = postmenstrual age, RSNs = resting state networks.

Figure 10. H and DTI correlations in the total white matter for all subjects and all scans. DTI measures of a) FA (fractional anisotropy) and b) RD (radial diffusivity) correlated to H values.
Figure 11. Individual WM region correlations. a) FA and H correlations in the individual white matter regions. The motor lateral, somatosensory, and motor medial regions had the strongest correlations. b) RD and H correlations in the individual white matter regions. The motor medial, motor lateral and posterior cingulate regions had the strongest correlations. c) R and p-values of FA and RD correlations with H.
Chapter 4: Discussion

4.1 Summary of Results

In this study, we used the Hurst exponent as a measure of temporal complexity of BOLD-signal from rs-fMRI to investigate the development and alterations of signal variability in preterm born infants compared to term born infants. In summary, we found that when the preterm group was assessed longitudinally, H increased with scan age in all brain tissues and resting state networks. Motor and sensory networks, such as the motor medial, motor lateral and posterior parietal networks, increased the most. Higher order and primary lower order networks such as the cerebellar and midbrain had the smallest increase in H from preterm to TEA scans. The mean H at preterm age (35 weeks PMA) was significantly lower than at TEA (41 weeks PMA). At preterm age the VPT group (29 weeks GA) was significantly lower than the MPT group (35 weeks GA) in all brain tissues and in each of the 10 RSNs. In comparing the VPT and MPT at TEA to THC, it was found that both preterm groups were significantly lower than the THC in the white matter, combined-RSN and 10 RSNs. At term, the VPT group had lower H values than the MPT group in 10 RSNs. Correlations to DTI measures revealed that H had a moderate but significant positive correlation to FA in the brain’s total white matter and the WM of all RSNs, while H had a moderate but significant negative correlation to RD in the brain’s total white matter and in the WM of 8 RSNs.

4.2 Comparison to Our Previous Infant Work

Our hypothesis for this study was that H in the tissues would be greater than 0.5, as is seen in all adult studies to date and in a previous study of ours in preterm infants. However, we found that H was less than 0.5 at preterm age in the GM, WM, and in all RSNs. In our previous work, we evaluated a very preterm group of 98 infants at preterm and TEA in the GM, WM, and 9 RSNs. In that study, H at around 32 weeks PMA was between 0.67-0.70 in various RSNs. In the current study, we have replicated our
previous findings (Drayne et al., 2022) that H increases longitudinally from preterm to term age and that certain RSNs show more rapid changes in H than others, specifically sensory networks. This previous work was the first study to assess BOLD temporal complexity with rs-fMRI in a preterm group. However, that study involved 98 subjects (64 scanned at preterm age), with a sampling rate of 3s and only 100 volumes/timepoints, compared to the present study which used 716 subjects (198 preterm), and a sampling rate of 0.39s and 2,300 volumes/timepoints. Due to the limited number of frequency values we could use to calculate H using Welch’s method, our previous study obtained the slope using the entire frequency range. In the current study, we limited the calculation of the slope over the range of 0.08 to 0.16, which previously used in adults is believed to better represent brain signaling in the BOLD signal (Dona et al., 2017). Thus, we were able to build and expand on these former findings through using a higher sampling rate and highly sampled rs-fMRI, a larger infant population and explore comparisons between preterm groups and to term born infants. For these reasons, we believe that this current study may better reflect the true H value in this population.

4.3  **Resting state network development**

In our RSNs, 11 networks have previously been identified in preterm or term infants (Doria et al., 2010; Eyre et al., 2021; Fransson et al., 2007; Smyser et al., 2010). Our specific networks of the frontal pole and midbrain have not yet been delineated in these age groups. However, brainstem networks (Doria et al., 2010) and frontal cortex networks (Eyre et al., 2021; Fransson et al., 2007; Fransson et al., 2009) are found which have regional similarities. The greater H values in the motor and sensory RSNs are consistent with previous rs-fMRI studies that looked at functional connectivity (rs-fcMRI; rather than BOLD Dynamics) (Cao et al., 2017; Doria et al., 2010; Eyre et al., 2021) and to our previous work (Drayne et al., 2022). A study which used an infant population of 29 to 43 weeks PMA concluded that their visual, auditory, somatosensory, motor, default mode, frontoparietal and executive control networks were all present at term age but developed asynchronously (Doria et al., 2010). It has been suggested that sensory-motor networks develop first for survival mechanisms and to trigger the formation of other RSNs
Furthermore, spontaneous neuronal activity and sensory system inputs such as visual stimuli are essential for the development of the nervous system, and thus the initiation of cortical networks (Doria et al., 2010). This can be indicated by the growth and expansion of thalamocortical axons to the cortical plate consisting of the frontal, somatosensory, visual and auditory cortex at 24 to 31 postconceptional weeks (Kostović & Jovanov-Milošević, 2006). From here, at 33 to 35 postconception weeks, the cortical pathways further progress with sensory processing alterations, maturation of auditory, visual and somatosensory evoked responses (as shown by EEG recording deflections) and development of motor cortex and motor periphery connections (Kostović & Jovanov-Milošević, 2006; Hrbek et al., 1973). Additionally these sensory input influences on network development is concurrent with the switch of GABA signalling from depolarizing to hyperpolarization -i.e from excitatory to inhibitory (Peerboom & Wierenga, 2021). Altogether, this may explain the higher H values and greater slopes in our motor and sensory networks compared to the prefrontal and frontal networks at both preterm and term ages. Fransson et al. found that power law exponents with fMRI in term born infants were larger in their primary motor, parietal operculum, auditory and visual networks compared to higher order association networks of attention, subcortical and saliency (2013). This trend was reversed in their adult cohort (Fransson et al., 2013). Thus, we see that the sensory complexity pattern is consistent not only throughout preterm assessment but also in at term born infants compared to adults.

In another study in adults, it was found that H at rest is greater in executive controls networks as opposed to visual and somatomotor networks (Campbell et al., 2022). This might demonstrate the switch from infancy to adulthood of transitioning from basic to more complex signalling that is apparent through more active higher order networks.

The cerebellum RSN had low H values in all the groups compared to the other networks. It also had the greatest increase from 24 to 40 weeks compared to the rest of the cortex. Perhaps this increased growth is disrupted during preterm birth and may explain why our H values are particularly low in the preterm group (Volpe, 2009; Spoto et al., 2021). Herzmann et al. (2019) assessed the functional
connectivity in the cerebellum in comparing term to very preterm infants. They found decreased positive and negative functional connectivity correlation in the VPT group which they attributed in part to suppressed BOLD signal fluctuations that are associated with preterm birth (Herzmann et al., 2019). Here we show that cerebellar H values in the THC group in the current study were also low (below <0.5). This may be due to the lack of robust temporal complexity signaling with H that can be detected specifically in the cerebellum. If an analysis of H were conducted beyond the term ages, we might observe greater BOLD complexity in the cerebellum. Overall we find that the cerebellum network in our analysis displayed the lowest H values, however, it is still unclear of the contributing mechanism that differentiates this region and poses future work.

In comparing how H develops in the RSNs to the ventricles, it is evident that all RSNs except the cerebellum eventually surpass the ventricles during preterm age (25-34 weeks PMA). This could signify the functional organization that occurs during the 3rd trimester of pregnancy. fMRI measures in the CSF have been largely attributed to cardiac and respiratory pulsations, however recently, this has been debated (Attarpour et al., 2021). Williams et al. (2023) found that there is increased CSF flow in the fourth ventricle with high-intensity visual stimulation in adults. They determined that global cortical BOLD alterations drives an influx of CSF (Williams et al., 2023). Furthermore, with more mature functional systems such as in adulthood, H signaling in the ventricles could have more significance beyond noise. In the current study, we compared our RSN values to the ventricles to indicate the baseline level of H signaling. Since all but one RSN surpassed the ventricles, we infer that the H measure of temporal complexity in the BOLD signal is not just capturing fMRI signal noise, but replication and further investigation is needed.

4.4 H and Myelination Relationship

To determine if H follows the trend of myelination in the brain, we explored the associations between DTI estimates for myelination – FA and RD – with H. We discovered modest but significant
correlations between FA with H and RD with H. These correlations were consistent in both the total white matter and individual white matter regions. Motor, somatosensory, and limbic structures had the greatest associations between temporal complexity and myelination. We used increased FA and decreased RD as indicators of myelination. However, this combination of measures can also suggest dense axonal packing which increases neural conduction efficiency similar to high myelination (Feldman et al., 2010). High anisotropy and restricted radial diffusivity are usually thought to represent a more healthy and maturing white matter structure and we observe this trend in the preterm group white matter analysis (Feldman et al., 2010). Myelination is thought to commence at 20 to 28 weeks gestation, and to continue into the first year of life (Smyser et al., 2011). Previous studies have explored the relationship between myelination and functional connectivity. There is a theory that structural connectivity precedes—and is essential to—the formation of functional connectivity networks. For example, Vo Van et al. showed that functional RSNs exist in more underdeveloped forms compared to more highly developed structural connectivity at the third trimester (Vo Van et al., 2022). Another study which utilised rs-fcMRI and DTI tractography in preterm infants at TEA showed that motor and visual functional connectivity was associated with WM maturation (Weinstein et al., 2016). However, it has also been theorized that activity dependent neuronal signals trigger myelination through sufficient blood and oxygen levels (Yuen et al., 2014). To date, it is clear that development of the brain’s structure and function are highly integrated, but they are not identical (Smyser et al., 2011). Furthermore, it is crucial to understand their relationship in the developing brain. Additional studies with alternative methods are required to understand the functional processing and patterns of development apart from spatial connectivity in newborns and infants. One study investigated the relationship between BOLD variability and WM maturation in children aged 2 to 8 years old (Wang et al., 2021). BOLD variability was found to increase with age and white matter development in frontal, temporal and parietal areas and decrease in the hippocampus and parahippocampus areas (Wang et al., 2021). We found that in our preterm cohort the diffusion metrics are consistent in all regions, however, the results revealed by Wang et al. (2021) signify that region specific asynchronous development can occur in childhood to modify the structural and functional relationship. Thus, it is
necessary to explore the relationship between BOLD complexity and myelination throughout the human lifespan. There is still much to learn about this crucial interrelationship, especially in preterm infants, and our results suggest that H may provide a novel signal-based tool in this line of work going forward.

4.5 H interpretations of temporal complexity in infants

Our results provide a novel rs-fMRI method to investigate criticality and complexity of the BOLD signal in infants, and these findings build on prior work in EEG. For example, Hartley et al. identified long range signaling with H in EEG in very preterm infants and concluded that the immature brain is capable of non-trivial electrical activity (2012). Results here confirm the presence of long-range temporal correlations that are higher –and we infer more developed– in all our infants by term-age. At older ages of 6 months, H measured with EEG was found to be greater than 0.5, suggesting the presence of long-range temporal correlations (LRTC) (Jannesari et al., 2020). As shown in these other studies, when an infant’s brain develops functionally, the findings of LRTCs are indicative of a more dynamic critical system. We found short memory series in our preterm group (H<0.5) and at term we found mostly long memory series (H>0.5). Similar to our methods, Fransson et al. used Welch’s method for PSD estimation in a term born cohort with fMRI and speculated that the observed increase of power law exponent in their multiple sensory networks demonstrated neuronal processes with longer internal memory (Fransson et al., 2013). Furthermore, an increase in power law exponents in a functional network is thought to signify more information flow and storage for longer time lengths (Fransson et al., 2013).

We can see this difference of internal memory storage in functional networks between our birth age cohorts. Based on this, we postulate that the earlier the infant is born, the less internal signaling memory is permitted to promote information flow and storage given lower H values. With EEG and according to the critical brain hypothesis, it is apparent that there is a transition between the preterm infant asymmetric discontinuous brain activity to term age symmetrically continuous activity (Meisel et al., 2017; Jannesari et al., 2020). This is perhaps shown by the bursting scale-free neuronal activity in preterm infants and scale-free avalanche activity beyond the newborn ages at 6 to 12 months (Jannesari et al., 2020).
Additionally as shown with EEG, the periods of bursting become shorter and by 30 weeks PMA low voltage activity is apparent to demonstrate the presence of continuous activity (Colonnese & Khazipov, 2012). Furthermore, with the initiation of synaptogenesis in the second trimester that proceeds into the first year of life there is a simultaneous increase in cortical activity and matured activity patterns (Colonnese & Khazipov, 2012). With the use of rsfMRI and H measurements, the preterm infants here may exemplify the critical state transition from asynchronous/anticorrelated to synchronous/correlated processing. This type of BOLD signal processing information cannot be revealed through functional connectivity measurements. Functional connectivity describes the spatial correlation in the BOLD signal within a network to convey the strength or weakness in connectivity. Temporal complexity (as measured by H) provides a different way to investigate and characterize the BOLD signal.

### 4.6 H as a biomarker for neurodevelopment

The very and moderately born preterm groups were found to be significantly different at both preterm and term age comparisons. Furthermore, the VPT had the lowest H values overall. Structural abnormalities have been identified in infants born less than 32 weeks, with reduced overall brain volume (Ream & Lehwald, 2018), and we now show temporal complexity alterations in the functional signal in the preterm group. Clinically, infants born less than 32 weeks GA have higher NICU admission rates, need more respiratory support, and are at higher risk of neurodevelopmental delays in measures of gross motor, fine motor and adaptability than preterm infants born 34 to 37 weeks GA (Smyrni et al., 2021; Chen et al., 2022). Infants born less than 37 weeks GA are also at a greater risk for neurodevelopmental delays, but more likely in the area of fine motor skills (Chen et al., 2022). Overall, as seen in our preterm PMA assessment, the VPT group has lower H values in all regions, and it is possible that this measure reflects or is associated with the increased susceptibility to developmental impairments in this population. When we assessed H in the GM, we discovered that the earlier the infant was born, H decreased by 0.005 per week by TEA. This is in line with the clinical literature where there are more negative adverse
outcomes for the infant with earlier gestational age (Smyrni et al., 2021). At this broad level of clinical acuity, our findings map onto the higher risk cohort.

At term age, the THC group had higher H values than preterm infants at TEA. We found that the term born infants had decreased complexity with higher H values which may suggest more organized and correlated BOLD signaling (Diaz & Cordova, 2022; Dong et al., 2018; Wink et al., 2008). The preterm groups had lower H values which could signify less organized, more chaotic, and anti-correlated signaling within their functional systems (Diaz & Cordova, 2022; Dong et al., 2018; Wink et al., 2008). The VPT and THC groups showed the greatest difference in H in the term-equivalent analysis. The significant differences between these different birth-age groups are potentially relevant to executive function as VPT children will likely show lower scores in planning, fluency, working memory, and response inhibition than term born children (Rogers et al., 2018). These intellectual challenges in children born preterm can persist into adolescence and adulthood (Ment et al., 2009). A brain dynamics study which compared extremely preterm born (<27 weeks GA) and term born children at 10 years of age used structural, diffusion and functional MRI to measure the functional organization and neural activity propagation (Padilla et al., 2020). They showed that there is an alternative information processing pattern and inferior synchronicity and criticality with the whole-brain Hopf model meaning that the EPT group may have impaired adaptability to external and internal stimuli (Padilla et al., 2020). Longitudinal studies with both preterm and term infants in measuring H would better assess if these differences remain throughout the lifetime, and if preterm birth permanently impacts temporal complexity.

With regards to H trends in aging, it was found that in a cohort of 116 healthy adults aged 19 to 85 years, H was significantly correlated with age in the GM with a correlation coefficient of 0.35 (Dong et al., 2018). This is the same general trend that we find when we correlate H with scan age and birth age for all subjects. H values in adult and senior populations are approximately 0.50 to 0.90 (Dong et al. 2018) and values ranged from 0.69 to 1.24 in another adult study (Campbell et al., 2022; using the
‘extended Hurst’ model). In the current infant study, H values ranged from 0.33 to 0.65. Previous studies with H measurements in the brain have all been greater than 0.5, creating the belief that the brain only produced long memory signals of $0.5 < H < 1$ (Wink et al., 2008; Ciuciu et al., 2014; He, 2011; Churchill et al., 2016; Dong et al., 2018; Lei et al., 2013). Our results in the preterm cohort contrast with these previous works. Cortical activity in infants differs from adults as the resting state activity is not similar to the infraslow activity in adults (Colonnese & Khazipov, 2012). Additionally, neurovascular coupling is still immature in the developing brain compared to adults (Colonnese & Khazipov, 2012). The uniquely low H values observed here could reflect a unique developmental stage in the brain that simply doesn’t exist at any other point in life, and could include contributions from neural, vascular and other complex processes.

### 4.7 Analysis Strengths

We categorized our infants based on birth age cohorts to better illustrate group comparisons and to try to produce interpretable results. However, all linear mixed effects models were performed with birth age as a continuous variable, and the cohorts were compared later using estimated marginal means or trends with fixed median birth ages for each cohort. This approach increased the statistical power of our main analysis. We ensured that birth age and scan age variables were not collinear (Figure 3) and that we were not extrapolating data during the scan age assessment. We assessed $H$ at birth age instead of birth weight as it is generally understood to be a better predictor of neonatal health (Leviton et al., 2005). The choice of mixed linear effects models was used to account for any between subject and within subject variation in the data given the mix of cross-sectional and longitudinal scans (Springer, 2006).

$H$ measurements in the brain are method and calculation dependent. Other fMRI studies measuring $H$ in the brain have used detrended fluctuation analysis (Churchill et al., 2016; Ciuciu et al., 2014; He et al., 2011), rescaled range analysis (Dong et al., 2019; Wei et al., 2013) or discrete wavelet
transform (Maxim et al., 2005; Wink et al., 2008) to name a few. We chose to calculate the PSD using Welch’s method as it has been demonstrated to be more advantageous over alternative methods (Rubin et al., 2013) and was used in our previous studies (Campbell et al., 2022; Drayne et al., 2022). Based on the criteria of sensitivity to spikes, activation, and tissue type Welch’s outperformed other more commonly used methods such as detrended fluctuation, rescaled range and wavelet analysis (Rubin et al., 2013). Churchill et al., suggested that this finding is dependent on the number of timepoints in the fMRI scans and deduced that detrended fluctuation analysis is more robust for shorter time windows (2016).

However, in order to conduct fractal analysis, a higher sampling rate or approximately 500 timepoints are proposed to improve accuracy of the fractal method analysis and to prevent incorrect estimates (Campbell & Weber, 2022; Eke et al., 2022; Maxim et al., 2005). This optimal higher sampling rate is noted to be a TR less than 1 second (Dilharreguy et al., 2003) and greater reliability and more detailed analysis are provided with scans of approximately 13 minutes (Soares et al., 2016). Our fMRI data included a long time window for a total of 2,300 timepoints or 15 minutes scan length with a TR of 392ms. This is a strength of the current study.

4.8 Limitations

As stated in the Introduction, preterm birth is a complex, multifactorial phenomenon with both medical and sociocultural factors which were not controlled for in this study. In addition, we note the various definitions of “complexity” used in the literature, the fact that we did not assess non-linear development, the presence of possible brain injuries, unequal sized study cohorts, lack of sex differences and MRI method limitations.

The aim of the study was to investigate a measure of brain complexity in the infant brain. There are a variety of metrics to measure brain complexity (O’Bryne & Jerbi, 2022), and the term is used to mean different things. With this diversity in measurements and methods it becomes more difficult to directly compare results. Smyser et al. measured dimensionality estimation based on functional
connectivity of rs-fMRI to signify complexity in brain intrinsic activity (2016). They concluded that preterm infants had reduced signal complexity (Smyser et al., 2016). Complexity in the EEG times series was used to explore brain maturation; Wel et al. determined that complexity was positively correlated with PMA (2021). Overall, the use of the term brain complexity and the significance of the results produced is heavily dependent on the methods of neuroimaging and computation of values utilized. We have tried to synthesize our findings with other work in the field, but these efforts are limited by the specificity and diversity of complexity related measures.

Another potential limitation of this study is that we used linear models, and neurodevelopmental trajectories are sometimes non-linear (Wang et al., 2021). This is apparent in a longitudinal assessment using DTI in a group of 5 to 30 years where measures in the white matter developed non-linearly (Lebel & Beaulieu, 2011). Faghiri et al. assessed the functional connectivity in a group of 3 to 21 years and found that there were both linear and non-linear patterns (2019). It may be the case that longitudinally from infancy to adolescent and adult ages, trajectories are non-linear and will plateau but within smaller age ranges, it is perhaps more defensible to assume that these trajectories are linear, as we have done here in this initial study.

Radiologic scores were given to each scan ranging from 1 (normal appearance) to 5 (incidental findings possible/likely significance for imaging analysis). There were 26 VPT, 14 MPT and 18 THC that had a radiologic score of 5, meaning that there is a possibility of brain injuries or lesions affecting analysis. We did not exclude these infants from analysis as the preterm group already was significantly smaller than the term born group. Moreover, our vast group number differences between preterm to term born infants is a disadvantage. Additionally, the preterm group only had a small number of longitudinal scans available in the preterm group. According to the WHO, infants born less than 28 weeks GA are categorically defined as extremely born preterm (EPT) (WHO, 2023). We had to combine the EPT and VPT infants at the median age of 29 week GA for analysis due to the EPT group only containing 9
infants. Therefore, we could not conduct any analysis nor make any interpretations specific to EPT infants. All the dHCP infants except 6 THC were scanned during natural sleep to minimize motion during scan acquisition. There are implications for the type of ‘resting’ activity that occurs during awake versus sleep states (Eyre et al., 2021). Although we did not find any sex differences in our analysis, a previous structural study including preterm and term born infants assessed at 12 months found male and female differences in intracranial volume, grey matter, and white matter (Benavides et al., 2018). Sex differences were found with rsfMRI in GA related changes in functional connectivity between and within networks 26 to 40 weeks in utero (Wheelock et al., 2019). It is not clear why we did not identify sex-based differences in this sample.

Some limitations also apply to the processing of the rs-fMRI data. In creating the group level RSNs, ICA was used to produce 30 components. However, the number of components is arbitrary and there is no standard value (Cole et al., 2010). We selected thirty components based on the literature and our previous methods. Although the DTI assessment was not the main focus of this study, some relevant limitations in that analysis warrant discussion. DTI provides only indirect measurements of the degree of anisotropy and structural orientation in the brain’s microstructure (Soares et al., 2013). RD indicates diffusion perpendicular to the axon and thus indirectly measures differences in myelination; however, it relies on the degree orientation order of fibers within a voxel and is susceptible to crossing fibers and GM/WM interfaces (Laule et al., 2007). A superior method could be used to measure myelination with higher specificity in the developing brain such as inhomogeneous magnetization transfer, multicomponent relaxation analysis or myelin water volume fraction (Deoni et al., 2011; Mackay & Laule, 2016; van der Weijden et al., 2023). For our study, there was a lack of white and grey matter segmentation in the cerebellum and midbrain from the DrawEm analysis. Due to this, we removed these regions from the DTI analysis and were left with 11 RSNs.
4.9 Future Directions

It would be advantageous in future work to have more equally sized groups when comparing the preterm born infants to term born controls. Longitudinal measurements of H would be crucial to better understanding how temporal complexity develops from infancy to older ages and across the lifespan. This has been done by Dong et al. in adults to seniors in a study cohort of 19 to 85 years (2018). Additionally it would be interesting to investigate whether white matter injuries or hemorrhages within the preterm groups would impact H values as the BOLD signal could be impacted due to brain injuries. It has previously shown in adults that H decreases with task (Churchill et al., 2016; He et al., 2011) and increases during movie-watching (Campbell et al., 2022) relative to resting state. Task based fMRI in infants has been done, for example, sensory stimuli presented to sleeping infants have been shown to evoke neural responses (Batalle et al., 2018). Blasi et al. used auditory stimuli of voice and environmental noises in infants ages 4 to 7 months while asleep (2015). Therefore, it would be possible to explore H with task-based fMRI in infants. A multimodal neuroimaging study with rs-fMRI and EEG and H measurements in this preterm group might also be beneficial. Concurrent rsfMRI and EEG could enable the correlation of neural electricity activity and hemodynamic function, and would combine the high spatial resolution of fMRI with the high temporal resolution of EEG (Mele et al., 2019). Adult studies have implemented simultaneous fMRI and EEG acquisition (Mele et al., 2019), however creating infant suitable devices poses a challenge.
Chapter 5: Conclusion

We investigated the Hurst exponent as a measure of temporal complexity of rs-fMRI signaling in comparing preterm born infants to term born infants. We found a clear positive relationship such that H increases with age. We also showed somewhat curiously that H begins below 0.5 at preterm age and crosses 0.5 at term age in most regions. This could mean that the brain signaling develops from anti-correlated to correlated processing. Our results indicate that H values below 0.5 are found in infants which has not yet been previously identified in the literature. Earlier birth age contributed to lower H values at both preterm and term age, which is particularly seen in the VPT group. Motor and sensory networks increased the greatest in H than other regions which could signify the importance of these systems for survival at birth and to initiate the development of other networks. This motor-sensory priority is apparent with other functional activity measures as well. H values and myelination follow similar patterns, perhaps demonstrating that structural and functional development occurs in parallel. In our interpretation, preterm birth interrupts development in the third trimester of gestation leading to disrupted functional signal organization at a foundational, BOLD-signal based level. This could be one of the delayed markers of development that ultimately leads to behavioural and cognitive disabilities in many patients. We suggest that H could be further investigated as a potential biomarker for brain development. This is the first study to use H measurements in fMRI to assess the development of preterm born infants to term equivalent age and to provide a comparison to term born infants. The results of this study suggest that in preterm birth as early as 23 weeks GA, the Hurst exponent values can be used to index developmentally relevant differences in BOLD-signal temporal complexity. Overall, there is much work to be done to more fully delineate the altered neurodevelopment that occurs in preterm born infants, and this study suggests that measuring signal complexity in the brain could play a role in that work going forward.
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Appendix: Supplementary RSN Information

Resting State Networks in the Whole Group

<table>
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<th>Fixed Effects</th>
<th>Estimate (b)</th>
<th>Std. Error</th>
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