From the Institute of Systems Neuroscience
at Heinrich Heine University Düsseldorf

Computational Analysis of Multiscale Cortical Organization and Development

Dissertation

to obtain the academic title of Doctor rerum medicarum (Dr. rer. med.)

from the Faculty of Medicine at Heinrich Heine University Düsseldorf

submitted by

Mohammadamin "Amin" Saberi

(2025)

To Moniba, with all my love

Parts of this work have been published:

Saberi, A., Paquola, C., Wagstyl, K., Hettwer, M., Bernhardt, B.C., Eickhoff, S.B., Valk, S.L.* (2023) "The regional variation of laminar thickness in the human isocortex is related to cortical hierarchy and interregional connectivity." *PLOS Biology*, 21(11): e3002365. doi: 10.1371/journal.pbio.3002365

Saberi, A., Wischnewski, K.J., Jung, K., Lotter, L.D., Schaare, H.L., Banaschewski, T., Barker, G.J., Bokde, A.L.W., Desrivières, S., Flor, H., Grigis, A., Garavan, H., Gowland, P., Heinz, A., Brühl, R., Martinot, J.-L., Martinot, M.-L.P., Artiges, E., Nees, F., Orfanos, D.P., Lamaitre, H., Poustka, L., Hohmann, S., Holz, N., Baeuchl, C., Smolka, M.N., Vaidya, N., Walter, H., Whelan, R., Schumann, G., Consortium, I., Paus, T., Dukart, J., Bernhardt, B.C., Popovych, O.V., Eickhoff, S.B., Valk, S.L. * (2025) "Adolescent maturation of cortical excitation-inhibition ratio based on individualized biophysical network modeling." *Science Advances*, Accepted for publication.

Lotter, L.D., **Saberi, A.**, Hansen, J.Y., Misic, B., Paquola, C., Barker, G.J., Bokde, A.L.W., Desrivières, S., Flor, H., Grigis, A., Garavan, H., Gowland, P., Heinz, A., Brühl, R., Martinot, J.-L., Paillère, M.-L., Artiges, E., Papadopoulos Orfanos, D., Paus, T., Poustka, L., Hohmann, S., Fröhner, J.H., Smolka, M.N., Vaidya, N., Walter, H., Whelan, R., Schumann, G., Nees, F., Banaschewski, T., Eickhoff, S.B., Dukart, J.* (2024) "Regional patterns of human cortex development correlate with underlying neurobiology." *Nature Communications*, 15(1), 7987. doi: 10.1038/s41467-024-52366-7

Zusammenfassung

Die Großhirnrinde ist auf mehreren Skalen organisiert – von Ionenkanälen über neuronale Schaltkreise, die sich in verschiedenen kortikalen Schichten anordnen, bis hin zu einem weitreichenden Netzwerk kortikaler Areale. Die strukturellen und funktionellen Eigenschaften dieser Skalen variieren erheblich zwischen verschiedenen kortikalen Regionen. Diese heterogene Organisation über verschiedene Maßstäbe hinweg ist das Ergebnis einer kontinuierlichen Verfeinerung über die gesamte Lebensspanne. Ein umfassendes Verständnis der multiskaligen Organisation der Großhirnrinde und ihrer Entwicklung erfordert integrative und computergestützte Analysemethoden. Das Ziel dieser Arbeit war es, fortgeschrittene computergestützte Verfahren einzusetzen, um zu untersuchen, wie kortikale Phänomene auf der Mikro- und Mesoskala während der Entwicklung mit großräumiger kortikaler Organisation zusammenhängen. Insbesondere haben wir die kortikale **Zytoarchitektur** untersucht, die mit **kortiko-kortikaler Konnektivität** zusammenhängt (Studie 1), sowie kortikale **Mikroschaltkreise**, abgeleitet aus **funktioneller Dynamik und Konnektivität** (Studie 2), und **zelluläre und molekulare Muster**, die der kortikalen **Morphologie** zugrunde liegen (Studie 3).

Unsere Analysen in Studie 1 zeigten, dass die Struktur kortikaler Schichten auf der Mesoskala entlang einer Hauptachse variierte, die sich von kaudalen zu rostralen Arealen erstreckte und entlang der die relative Dicke der tieferen Schichten zunahm. Diese Achse spiegelte auch die hierarchische Organisation kortikaler Konnektivität wieder. Darüber hinaus war die Ähnlichkeit kortikaler Schichten mit der Wahrscheinlichkeit und Stärke der kortiko-kortikalen Konnektivität assoziiert, vermutlich ein entwicklungsbasiertes Phänomen.

In der zweiten Studie verwendeten wir als Nächstes einen individualisierten computergestützten Modellierungsansatz, um das Gleichgewicht zwischen neuronaler Exzitation und Inhibition in kortikalen Mikroschaltkreisen von Jugendlichen auf der Grundlage ihrer kortikalen Konnektivität und Dynamik, die in der funktionellen Bildgebung im Ruhezustand beobachtet wurden, zu erfassen. Um die für diesen Ansatz erforderlichen und aufwändigen Simulationen zu ermöglichen, haben wir ein neues und effizientes Simulationsverfahren implementiert, die als Python-Paket veröffentlicht wurde: *cuBNM*. Mithilfe dieses Ansatzes fanden wir in zwei unabhängigen Querschnitt- und Längsschnittdatensätzen eine weit verbreitete, entwicklungsbedingte Abnahme der Exzitation im Verhältnis zur Inhibition in Assoziationsarealen, die mit einer Zunahme oder Stabilität in den sensomotorischen Arealen einherging. Dieses Entwicklungsmuster stimmte mit bereits beschriebenen räumlich-zeitlichen Mustern der Hirnentwicklung in sensomotorischen und Assoziationsarealen überein.

Schließlich untersuchten wir in Studie 3 die räumliche Ko-Lokalisation zwischen kortikalen Mustern mikro- und mesoskaliger neurobiologischer Prozesse mit räumlich-zeitlichen Querschnitts- und Längsschnittmustern kortikaler Dickenveränderungen über die Lebensspanne. Ziel war es zu verstehen, welche zellulären und molekularen Prozesse der Reifung und den Veränderungen der kortikalen Morphologie auf der Makroebene über die Lebensspanne zugrunde liegen könnten. Unsere Ergebnisse deuten darauf hin, dass Prozesse wie dopaminerge, glutamaterge und cholinerge Neurotransmittersysteme sowie Gliazellen, inhibitorische Neuronen und der Hirnstoffwechsel zur Reifung der kortikalen Morphologie beitragen können.

Insgesamt fördert diese Arbeit unser Verständnis der kortikalen Organisation und ihrer Entwicklung auf mehreren Skalen und trägt gleichzeitig zur Weiterentwicklung computergestützter Verfahren für die zukünftige Forschung bei. Durch die Integration von mikro-, meso- und makroskaligen Perspektiven bieten unsere Erkenntnisse über die normative kortikale Organisation und Reifung eine Grundlage für die Untersuchung der gestörten kortikalen Entwicklung bei psychischen Störungen.

Summary

The cerebral cortex is organized at multiple scales, ranging from ion channels, to neuronal circuits organized across cortical layers, to the interconnected network of cortical areas. The structural and functional properties at these scales vary widely across cortical areas. This heterogeneous organization across different scales is the result of continuous refinement throughout the lifespan. Understanding the multiscale organization of the cerebral cortex and its maturation requires integrative computational approaches that bridge across scales. The goal of this work was to use advanced computational techniques to better understand how **micro- and mesoscale** cortical phenomena relate to **macroscale** cortical organization throughout development. Specifically, we examined cortical **cytoarchitecture** associated with **corticocortical connectivity** (Study 1), cortical **microcircuitry** inferred from **functional dynamics and connectivity** (Study 2), and **cellular and molecular processes** underlying cortical **morphology** (Study 3).

In Study 1, we found that cortical laminar structure at the mesoscale varied along a principal axis extending from caudal to rostral areas, along which the relative thickness of deeper layers increased. This axis was co-aligned with the hierarchical organization of macroscale cortical connectivity. Furthermore, similarity of laminar structure was associated with the likelihood and strength of corticocortical connectivity, a phenomenon thought to have developmental roots.

Next, in Study 2, we used an individualized computational modeling approach to infer the regional levels of excitation-inhibition balance in cortical microcircuits of developing adolescents based on their macroscale cortical connectivity and dynamics observed in resting-state functional imaging. To enable the large-scale simulations required for this approach, we developed a novel and efficient implementation of the simulations, released as a Python package, *cuBNM*. Using this approach, across two independent cross-sectional and longitudinal datasets, we found a widespread age-related decrease of excitation relative to inhibition within the association areas, paralleled by its increase or lack of change in sensorimotor areas. This developmental pattern was consistent with the previously proposed sensorimotor-association spatiotemporal pattern of neurodevelopment.

Finally, in study 3, we examined the spatial co-localization between cortical maps of micro- and mesoscale neurobiological processes with cross-sectional and longitudinal spatiotemporal patterns of cortical thickness changes across the lifespan to understand which cellular and molecular processes may underlie maturation and lifespan changes in cortical morphology at the macroscale. Our results suggest that processes such as dopaminergic, glutamatergic, and cholinergic neurotransmitter systems, as well as glial cells, inhibitory neurons, and brain metabolism, may contribute to the maturation of cortical morphology.

Overall, this work advances our understanding of multiscale cortical organization and its maturation while contributing to the development of computational tools for future research. By integrating micro-, meso-, and macroscale perspectives, our findings on normative cortical organization and maturation provide a foundation for investigating impaired cortical development in mental health disorders.

List of Abbreviations

ABCD Adolescent Brain Cognitive Development

BNM Biophysical Network Model; Biophysical Network Modeling

CPU Central Processing Unit

CT Cortical Thickness

DWI Diffusion Weighted Imaging

E-I Excitation-Inhibition; Excitation and Inhibition

FC Functional Connectivity

fMRI Functional Magnetic Resonance Imaging

GABA Gamma-Aminobutyric Acid

GPU Graphics Processing Unit

MRI Magnetic Resonance Imaging

PCA Principal Component Analysis

PET Positron Emission Tomography

PNC Philadelphia Neurodevelopmental Cohort

rs-fMRI Resting-State Functional Magnetic Resonance Imaging

Contents

Chapter 1

Introduction

The cerebral cortex is a thin, layered sheet of gray matter that forms the outer surface of the brain (Abeles, 1991). Throughout mammalian evolution, the cerebral cortex has expanded considerably. The cortical surface area in humans is nearly a thousand times larger than that of mice, and is therefore extensively folded to fit within the skull (Rakic, 2009). The expanded and folded cerebral cortex in humans has enabled a wide range of complex functions and intelligent behaviors that have been fundamental to the human civilization (Galakhova et al., 2022). This has placed the cerebral cortex at the center of neuroscience research aimed at understanding the neural underpinnings of complex human behavior and cognition, their changes across lifespan and the dysfunctions associated with psychiatric and neurological disorders.

1.1 Regional Variability of the Cerebral Cortex

The cerebral cortex consists of regions that exhibit a pronounced and systematic variability in their structural and functional properties, such as cytoarchitecture (Amunts & Zilles, 2015; García-Cabezas et al., 2019; Paquola, Vos De Wael, et al., 2019), neuronal and receptor diversity (Goulas et al., 2021; Hansen et al., 2022; Lake et al., 2016; Palomero-Gallagher et al., 2015), functional specifications (Mesulam, 1998), and connectivity profiles (Margulies et al., 2016; Yeo et al., 2011). These variations are predominantly found along a sensory-fugal axis, with unimodal sensorimotor areas, involved in sensation and action, at one end, and transmodal association areas, critical for complex and integrative functions, at the other end (Mesulam, 1998; Sydnor et al., 2021).

As the cortex transitions from sensory to association areas, the laminar structure becomes less differentiated (García-Cabezas et al., 2019) and neuronal density decreases (Finlay & Uchiyama, 2015), while the neurons become larger, with more complex dendritic arbors and increased dendritic spine density (Charvet & Finlay, 2014; Jacobs et al., 2001). This cytoarchitectonic variability is mirrored by gradients of excitation and inhibition, with varying distributions of neuronal subtypes organized across cortical layers (Burt et al., 2018; Dombrowski et al., 2001; Lake et al., 2016; X.-J. Wang, 2020). For instance, the ratio of input-controlling calbindin-positive interneurons to output-controlling parvalbumin-positive interneurons gradually increases from sensory to association areas (X.-J. Wang, 2020). Concurrently, along the same axis, the distribution of neurotransmitter receptors varies such that towards the association areas the diversity of receptor densities, the ratio of excitatory to inhibitory and the density of metabotropic receptors increase, while the density of ionotropic receptors decreases (Goulas et al., 2021). These microstructural, cellular and molecular distinctions ultimately adapt cortical areas for their specific

functional demands, from externally oriented sensation to internally focused cognition (Mesulam, 1998; Sydnor et al., 2021). The functional specialization of cortical areas mirrors formation of canonical cortical networks, such as the visual and somatomotor networks at one end, and the frontoparietal and default mode networks at the other end (Yeo et al., 2011).

Understanding the regional variability of the cerebral cortex has historically been an important focus of neuroscience, and in particular, the field of brain mapping. In this context, beyond characterizing the nature of cortical heterogeneity by investigating its different features, fundamental questions remain on the origin and the principles underlying the regional heterogeneity of the cortex: How are these diverse structural and functional properties interconnected across regions? What underlying principles govern the coordination of regional differentiation in cytoarchitecture, neurotransmitter distribution, and connectivity? Moreover, how these inter-regional differences vary over time, and what neurobiological processes shape these changes?

1.2 Developmental Processes Shaping the Cerebral Cortex

The organization of the cerebral cortex emerges and refines over years of development, from prenatal stages through adolescence and adulthood (Cadwell et al., 2019; Kostović & Judaš, 2015; Stiles & Jernigan, 2010; Sydnor et al., 2021). During embryonic and fetal stages, corticogenesis begins with the proliferation of neurons in the ventricular zone, that migrate radially to their destination in the prospective cerebral cortex (Kostović & Judaš, 2015; Stiles & Jernigan, 2010). Molecular processes establish an initial "protomap" that determines the specification of cortical areas, which is later refined by activity-dependent processes (Cadwell et al., 2019; Kostović & Judaš, 2015). This is followed by the development of neuronal processes, including dendritic arborization, axonal growth, spinogenesis and formation of synapses, which construct neuronal circuits. These early circuits are later refined by elimination of exuberant connectivity elements, through developmental apoptosis and synaptic pruning (Kostović & Judaš, 2015; Stiles & Jernigan, 2010).

The maturation of the cerebral cortex continues postnatally, and involves continuous refinement of the cortical circuits, through synaptic pruning, as well as maturation of excitatory and inhibitory neurons, glial cells, and intracortical myelination, mirroring changes in macroscale cortical structure, function and connectivity (Sydnor et al., 2021). These maturation processes are very protracted in humans, continuing into young adulthood (Kostović & Judaš, 2015; Stiles & Jernigan, 2010; Sydnor et al., 2021). Postnatal development of the cerebral cortex is proposed to unfold across a spatiotemporal sensorimotor-to-association pattern, with maturation of association cortices being more protracted and occurring later than sensorimotor areas (Sydnor et al., 2021). This spatiotemporal developmental pattern has been suggested to support the maturation of sensory and motor functions early in life toward higher-order executive and social functions during adolescence (Larsen & Luna, 2018; Toyoizumi et al., 2013). Consequently, adolescence is considered a critical developmental period during which the brain is particularly vulnerable to maturational impairments due to abnormal neurobiology or adverse experiences, which are associated with psychiatric disorders that often affect higher cognitive functions (Larsen & Luna, 2018; Paus et al., 2008).

The developmental origins of cortical organization, highlights the importance of studying

various structural and functional features of the cerebral cortex from a developmental perspective, focusing on the spatiotemporal trajectories of their maturation, mechanisms involved in shaping these trajectories, and their functional, behavioral and clinical consequences.

1.3 Multiscale Organization of the Cerebral Cortex

The organization of the cerebral cortex is complex and modular, spanning multiple spatial and temporal scales. **Spatially**, at the microscale, molecular processes govern neuronal morphology, synaptic connectivity, and the characterization of cell types. Excitatory and inhibitory neurons assemble into microcircuits which are arranged vertically in cortical layers and horizontally in minicolumns. These minicolumns then aggregate into columns, subareas, and areas, ultimately forming a macroscale network of interconnected regions and lobes. This multiscale organization provides the structural scaffolding for the dynamic inter-areal connections and large-scale integrative functions that underlie cognition and behavior (Bassett & Gazzaniga, 2011; van den Heuvel et al., 2019). **Temporally**, while ion channels and synapses operate on the millisecond scale, neural states unfold in seconds to minutes, and cortical structure and function change through learning that occurs over days to weeks and maturational changes that span lifetime (Bassett & Gazzaniga, 2011).

1.3.1 Scales of Investigation in Neuroscience and the Need for Their Integration

Understanding the complexity of the cerebral cortex and its implications for cognition and behavior requires a variety of methods, each specialized to investigate different spatial and temporal scales of organization (Fig. 1.1). At the **microscale**, electron microscopy or patch-clamp recordings can be used to study details of synaptic structure or ion channel dynamics. At the **mesoscale**, histological techniques can visualize cortical cytoarchitecture and laminar structure, calcium imaging allow the study of neural circuits and population activity across cortical layers, and electrophysiological recordings can capture neural signaling within specific cortical regions. At the **macroscale**, neuroimaging techniques such as functional magnetic resonance imaging (fMRI), diffusion weighted imaging (DWI), and positron emission tomography (PET) provide *in vivo* insights into large-scale brain activity, connectivity, metabolism, and molecular organization (Sejnowski et al., 2014).

Historically, neuroscience studies have predominantly focused on studying single problems at single levels and using single techniques (Sejnowski et al., 2014). However, each technique, when used in isolation, provides only a partial view of cortical organization due to its inherent limitations. For instance, neuroimaging techniques provide extensive coverage of the entire brain but lack the spatial and temporal resolution necessary to capture neuronal details. In contrast, techniques such as single-neuron recordings, provide detailed and high-resolution data but are confined to small, localized areas of the cerebral cortex. This raises the question of how different levels of cortical organization are interrelated, which has led to a growing interest in approaches that integrate across different scales of investigation (Sejnowski et al., 2014; van den Heuvel et al., 2019).

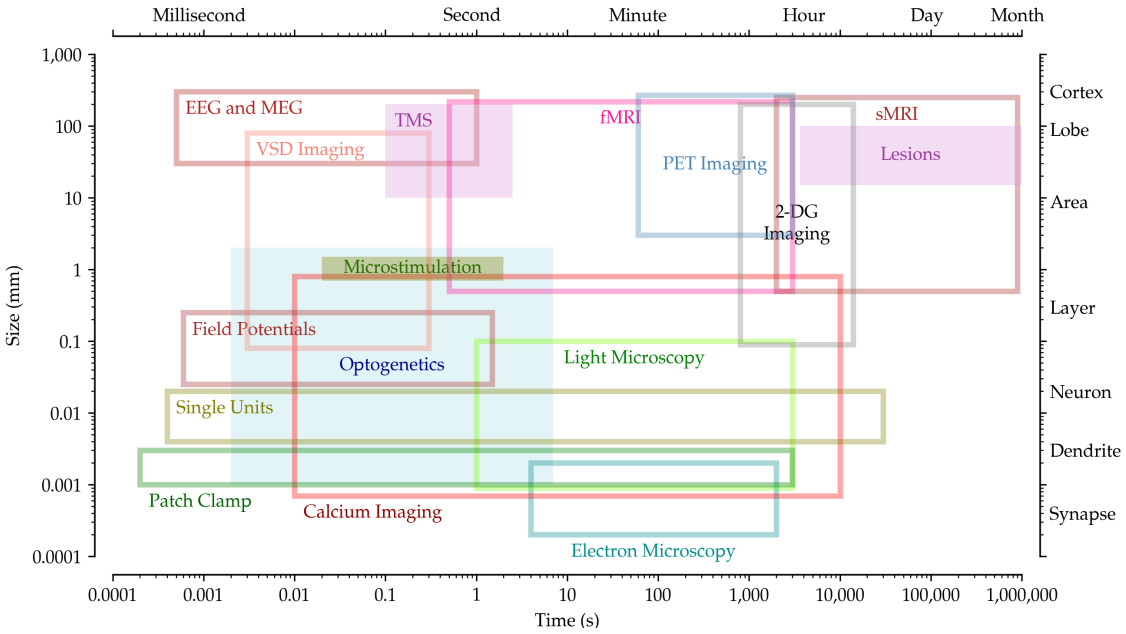

Fig. 1.1. Scales of investigation in neuroscience. The brain and cerebral cortex are organized into multiple spatial (Y axis) and temporal (X axis) scales. Each neuroscience method is specialized to study a specific range of the spatial and temporal scales. Filled boxes show perturbation-based methods whereas outlined boxes show observation-based methods. Adapted from Sejnowski et al., 2014.
EEG: electroencephalography; MEG: magnetoencephalography; VSD: voltage-sensitive dye; TMS: transcranial magnetic stimulation; fMRI: functional magnetic resonance imaging; sMRI: structural magnetic resonance imaging; PET: positron emission tomography, 2-DG: 2-deoxyglucose.

1.3.2 Integration of Scales Using Computational Approaches

Computational neuroscience plays an important role in bridging the scales of investigation. It relies on both theory-driven and data-driven frameworks to integrate findings and study interrelation of phenomena across different levels of cortical organization.

Theory-driven approaches use mathematical models based on physical rules and biological principles to address specific mechanistic hypotheses through computer simulations and mathematical analyses (Ferrante et al., 2018; Khaleghi et al., 2022). The Hodgkin-Huxley model of the action potential, developed over 70 years ago, is a seminal example of theory-driven models. This model demonstrated how action potentials at the neuronal level arise from ion channel dynamics at the subneuronal level (Catterall et al., 2012; Hodgkin & Huxley, 1952). Such theory-driven models have since been further developed and applied to various neural phenomena at different levels. For example, biophysical network modeling (BNM) of the brain describes mathematical models that characterize how the macroscale brain connectivity and dynamics emerge from the interactions of modeled neuronal populations at the mesoscale. This makes the BNM a valuable tool for deriving mechanistic insights into 'hidden' microscale phenomena, such as microcircuit dynamics, based on macroscale observations acquired using neuroimaging techniques (Deco & Kringelbach, 2014; Stephan et al., 2015).

Data-driven approaches apply mathematical techniques to complex and multidimensional data to either understand the latent structure of the data ('unsupervised learning' and 'dimensionality reduction') or assess relationships between variables to predict outcomes in unseen samples ('supervised learning') (Ferrante et al., 2018). These methods simplify complex, high-

dimensional data while preserving important features, allowing researchers to uncover patterns that link micro-, meso-, and macroscale processes. For example, principal component analysis (PCA), a dimensionality reduction technique, has been applied to single-neuron recording data from neuronal populations to reveal the latent state spaces underlying phenomena such as the integration of sensory inputs during decision making (Mante et al., 2013). In addition, similar methods are applied to high-resolution histological data at the mesoscale to describe the gradual variation of cytoarchitecture across the cortical mantle (Paquola, Vos De Wael, et al., 2019). Furthermore, at the macroscale, dimensionality reduction has been applied to resting-state fMRI (rs-fMRI) data to assess large-scale connectivity of the cerebral cortex, revealing distinct connectivity profiles of sensorimotor and association areas (Margulies et al., 2016; Yeo et al., 2011).

Notably, the theory-driven and data-driven approaches are not mutually exclusive: Theory-driven models are often informed by empirical data, whereas data-driven approaches can be guided by theoretical frameworks regarding the phenomena under study (Ferrante et al., 2018).

1.4 Understanding Organization and Development of the Cerebral Cortex Through Bridging of Scales

Our current understanding of cortical organization, its regional variability, and developmental factors shaping it is the result of decades of neuroscience research on the cerebral cortex. Most of neuroscience research, however, has been dominated by studies that investigate a single cortical feature at a specific scale and using a single methodology. However, as discussed in the previous section, the cerebral cortex (and more generally, the brain) is a multiscale and complex system, where the phenomena at micro-, meso- and macroscale interact with and inform each other. Given the focus of traditional studies on single scales of investigation, less is known about how cortical features at different scales interact. This calls for integrative computational approaches aimed at bridging the scales to better understand complexity of the cerebral cortex, including its regional variability and changes through development. These computational approaches can achieve two objectives: first, they can reveal the nature of whether and how different cortical features at micro-/mesoscale and macroscale interact and may influence each other; and second, they can use this knowledge to make inferences about cortical phenomena at micro-/mesoscale based on observations at the macroscale, or vice versa.

Following this paradigm, the research conducted in this thesis aims to extend our understanding of the complexity of the cerebral cortex through computational and developmental perspectives across multiple scales of organization. Specifically, I study **micro-/mesoscale** cortical phenomena in relation to **macroscale** cortical organization and development, including i) cortical **cytoarchitecture** associated with **corticocortical connectivity**, ii) cortical **microcircuitry** inferred based on **functional dynamics and connectivity**, and iii) **cellular and molecular processes** underlying cortical **morphology**. The following sections will further elaborate on these phenomena and highlight the gaps in our knowledge that were addressed in this thesis.

1.4.1 Cortical Cytoarchitecture: Links to Connectivity and Maturation

Cortical cytoarchitecture refers to the spatial arrangement and distribution of various subtypes of neurons across the depth of the cerebral cortex (Amunts & Zilles, 2015). The cerebral cortex is a layered structure, consisting of horizontally stacked layers with distinct histological features such as the morphology, density and size of neuronal cell bodies mirroring differences in their function and connectivity (Amunts & Zilles, 2015; Shipp, 2007; von Economo et al., 1925). Across the majority of the cortical extent, in the region referred to as the 'isocortex', six distinct cytoarchitectonic layers can be identified: Layer I ('molecular'), the outermost layer which has a low density of neuronal cell bodies and contains mostly dendrites and axons; Layer II ('external granular'), which consists of densely packed small pyramidal neurons; Layer III ('external pyramidal'), which contains larger pyramidal neurons; Layer IV ('internal granular'), which containing densely packed granular and pyramidal neurons; Layer V ('internal pyramidal') which consists of large and relatively sparse pyramidal neurons; Layer VI ('multiform') containing corticothalamic pyramidal cells and heterogeneously shaped neurons (Brodmann, 2007; Nieuwenhuys et al., 2008).

The cortical cytoarchitecture and laminar structure show considerable variability across the cerebral cortex. Numerous histological studies over the past century have sought to characterize this variability through qualitative and quantitative assessment of cortical histological samples. These studies have demonstrated that: i) there are sharp or gradual boundaries of cytoarchitectonic variations that can define cortical *areas* (Amunts & Zilles, 2015; Brodmann, 2007); and ii) there are global patterns of cytoarchitectonic variation across the cerebral cortex, which can be characterized as a few discrete cortical *types* (García-Cabezas et al., 2019; von Economo et al., 1925) as well as continuous *gradients* of variability (Bailey, 1951; Bajada et al., 2020; Paquola, Vos De Wael, et al., 2019). While previous research has been instrumental to our understanding of laminar structure variability across the cortex and its functional significance, these studies have been constrained by using qualitative assessments which are prone to biases, and the limited density of histological samples that does not cover the entire cortex. This raises the question of how laminar structure varies across the entire cortex when a data-driven approach is used. Such investigations have been made possible using modern whole-brain and ultrahigh-resolution atlases such as the BigBrain (Amunts et al., 2013). In Study 1, our first aim was to leverage this atlas to ask, using a data-driven dimensionality reduction approach, how laminar structure varies across the isocortex.

The variability of cytoarchitecture and laminar structure at the mesoscale is suggested to relate to the macroscale corticocortical connections. This relationship has been formalized as the "structural model", which suggests that (dis)similarity of the cytoarchitecture between cortical areas can predict the laminar pattern and likelihood of their connectivity within a cortical hierarchy (Barbas, 2015; García-Cabezas et al., 2019; Goulas et al., 2018; Hilgetag et al., 2019). Notably, the cytoarchitectonic variability across the cerebral cortex and its relation to macroscale connectivity are thought to have developmental origins (Barbas, 2015; Dombrowski et al., 2001; Hilgetag et al., 2016). However, a comprehensive assessment of the association between hierarchically-organized corticocortical connectivity to cortical cytoarchitecture in the human isocortex is lacking. Therefore, in Study 1 we secondly aimed to study this association while exploring the role of cortical maturation in shaping laminar structure, within the context of the "structural model".

1.4.2 Cortical Microcircuitry: Maturation of the Excitation and Inhibition

The cortical cytoarchitecture provides the structural scaffolding wherein the excitatory and inhibitory neurons embedded across cortical layers and minicolumns form local microcircuits that exchange signals through both intracortical connections and long-range white matter pathways. The interactions of this complex and modular network of neurons and microcircuits emerge into dynamic cortical activity at the macroscale, which ultimately supports cognition and behavior (Bassett & Gazzaniga, 2011; Breakspear, 2017). The optimal functioning of these microcircuits crucially depends on maintaining a balanced state between excitation and inhibition (E-I) (Isaacson & Scanziani, 2011), which is essential for functional properties such as the dynamic stability of activity (Wu et al., 2022), the efficient coding of information (Denève & Machens, 2016), the tuning of sensory stimuli (Isaacson & Scanziani, 2011), and the generation of synchronous cortical oscillations (Atallah & Scanziani, 2009; Sohal et al., 2009).

The cortical microcircuits undergo substantial maturational changes during development (Caballero et al., 2021; Lewis et al., 2004). In particular, adolescence is considered a critical developmental period for the maturation of E-I ratio, which involves changes such as i) pruning of the excitatory synapses (Anderson et al., 1995; Huttenlocher, 1979), ii) modifications in the expression of genes associated with inhibitory neurons and gamma-aminobutyric acid (GABA) transmission (Caballero & Tseng, 2016), iii) changes in the concentration of excitatory and inhibitory neurotransmitters (Perica et al., 2022), and iv) maturation of inhibitory function leading to stronger and shorter inhibitory postsynaptic currents (Caballero & Tseng, 2016; Gonzalez-Burgos et al., 2015; Hashimoto et al., 2009). The maturation of excitatory and inhibitory processes during adolescence is critical for the healthy development of mental functions (Larsen & Luna, 2018). Impairments in this process may contribute to the emergence of disorders such as schizophrenia (Insel, 2010; Keshavan et al., 2014), in which a disturbed E-I ratio is considered a key pathophysiological mechanism (Dienel & Lewis, 2019; Hoftman et al., 2017; Rolls & Deco, 2011). This highlights the importance of characterizing E-I ratio maturation during adolescence.

However, given that excitation and inhibition are mesoscale phenomena, their direct *in vivo* measurement requires invasive neuronal recording methods which are impractical in human subjects. Functional imaging, on the other hand, can be performed more readily in adolescent human subjects. Consequently, *in vivo* proxies of E-I ratio have been suggested that focus on its proposed macroscale effects captured in functional imaging (Larsen et al., 2022; Trakoshis et al., 2020) and electrophysiology (Medel et al., 2023; Uhlhaas et al., 2010). Theory-driven computational modeling of cortical dynamics using BNMs is one such method, which can bridge macroscale *in vivo* functional imaging data to modeled activity of neuronal populations and the E-I ratio at the microscale (Deco et al., 2014). This approach involves simulating the dynamic spontaneous activity of modeled excitatory and inhibitory neurons across cortical areas based on biologically realistic models that are informed by, for instance, the observed functional connectivity and dynamics captured in resting-state fMRI (rs-fMRI) (Breakspear, 2017; Deco & Kringelbach, 2014; Stephan et al., 2015). In Study 2, leveraging this approach applied to imaging data of human adolescents, we asked how the regional E-I ratio matures during adolescence, to provide further human *in vivo* evidence for this important maturational processes. We aimed to achieve this by using individualized simulations of BNMs to non-invasively estimate regional E-I ratio at the mesoscale based on macroscale cortical connectivity and dynamics captured in

functional imaging data.

1.4.3 Cortical Cellular and Molecular Processes: Neurobiological Correlates of Cortical Morphological Maturation

The development of excitation and inhibition, glial cells, cortical cytoarchitecture and intracortical myelination at the microscale mirror substantial developmental changes of the macroscale cortical structure and morphology (Sydnor et al., 2021). Cortical thickness (CT), derived from structural MRI (Dale et al., 1999), is an important marker of cortical morphology which has been studied extensively through development and lifespan. Studies employing normative modeling approaches have revealed that, following an initial period of growth within the first two years of life, CT gradually decreases as development progresses (Bethlehem et al., 2022; Rutherford et al., 2022). However, the lifespan trajectories of CT changes through development and aging are heterogeneous across different cortical areas (Bethlehem et al., 2022; Rutherford et al., 2022). In this context, an intriguing question in developmental neuroscience is: What microscale neurobiological mechanisms may underlie the macroscale changes of cortical morphology, and in particular CT, throughout lifespan?

Various neurobiological mechanisms have been suggested to contribute to the lifespan changes of CT, most notably including: i) synaptic pruning and remodeling of dendritic arbor (Anderson et al., 1995; Huttenlocher, 1979; Petanjek et al., 2008), ii) restructuring of cortical neuronal and glial cells such as alterations in the number of glial cells due to changes in metabolic needs (Paus et al., 2008), and iii) intra- and pericortical myelination that can reduce the grey and white matter tissue contrast in structural MRI which may appear as cortical thinning (Paus et al., 2008). Indeed, these mechanisms are believed to interact and are additionally influenced by other biological factors such as neurotransmitter systems (Altamura et al., 2007). However, directly assessing the roles of these micro- and mesoscale biological processes in the patterns of CT maturation is challenging. This is due to the fact that evaluating markers of these neurobiological processes often require *postmortem* investigations, or nuclear imaging, which has inherent radioactive risks prohibiting its use in developing subjects. However, normative (adult) maps of these neurobiological markers are available and characterize their regional heterogeneity (Hansen et al., 2022; Hawrylycz et al., 2012; Markello et al., 2022). In turn, a promising computational approach known as 'virtual histology' relies on spatial colocalization of neurobiological markers (e.g., transcriptomic maps of neuronal and glial cell types) with *in vivo* MRI-derived markers of interest (e.g., CT or its maturational trajectories), aiming to bridge the gap between the two levels by estimating the contribution of various neurobiological markers in explaining regional variability of MRI-derived markers (Paus, 2018). In Study 3, using this approach we asked what cellular and molecular processes may underlie the maturation of cortical morphology, and particularly its thickness, by assessing spatial colocalization of CT change trajectories at the macroscale with maps of micro-/mesoscale neurobiological markers.

1.5 Ethics Protocols

The ethical approval for using publicly available datasets included in this research was granted by the Ethics Committee of Heinrich Heine University Düsseldorf (Study Number 2018-317).

The datasets used in this research have received specific ethical approvals for collection and sharing of the data from their respective local ethics committees, as detailed in the cited sources of each Study.

1.6 Aims of Thesis

The overall goal of this thesis was to advance our understanding of the complexity of cortical organization and its maturation by using computational methods to bridge micro-/meso- and macroscale. Together with my colleagues, I applied this computational and developmental perspective to study three specific aspects of cortical organization at mesoscale in relation to macroscale:

- In Study 1, we leveraged an ultra-high-resolution histological atlas and data-driven dimensionality reduction aiming to, first, characterize how laminar structure at mesoscale varies across cortical mantle, and second, examine its association with macroscale cortical connectivity and maturation in the context of the "structural model".
- In Study 2, we aimed to use computational simulations of BNMs to estimate individualized regional levels of mesoscale E-I ratio based on macroscale cortical connectivity and dynamics captured in functional imaging, and to examine its maturation through adolescence.
- In Study 3, we used a virtual histology approach aimed at assessing the spatial colocalization of macroscale CT change trajectories with the maps of micro- and mesoscale neurobiological markers to gain further insights into cellular and molecular processes that may underlie the lifespan changes of cortical morphology.

Chapter 2

Study 1: The regional variation of laminar thickness in the human isocortex is related to cortical hierarchy and interregional connectivity

Saberi, A., Paquola, C., Wagstyl, K., Hettwer, M., Bernhardt, B.C., Eickhoff, S.B., Valk, S.L.* (2023) "The regional variation of laminar thickness in the human isocortex is related to cortical hierarchy and interregional connectivity." *PLOS Biology*, 21(11): e3002365. doi: 10.1371/journal.pbio.3002365

Impact Factor (2023): 7.8

Own contribution according to CRediT

- Conceptualization
- Methodology
- Software
- Formal analysis
- Investigation
- Data Curation
- Writing - Original Draft
- Writing - Review & Editing
- Visualization

Chapter 3

Study 2: Adolescent maturation of cortical excitation-inhibition ratio based on individualized biophysical network modeling

Saberi, A., Wischnewski, K.J., Jung, K., Lotter, L.D., Schaare, H.L., Banaschewski, T., Barker, G.J., Bokde, A.L.W., Desrivières, S., Flor, H., Grigis, A., Garavan, H., Gowland, P., Heinz, A., Brühl, R., Martinot, J.-L., Martinot, M.-L.P., Artiges, E., Nees, F., Orfanos, D.P., Lamaitre, H., Poustka, L., Hohmann, S., Holz, N., Baeuchl, C., Smolka, M.N., Vaidya, N., Walter, H., Whelan, R., Schumann, G., Consortium, I., Paus, T., Dukart, J., Bernhardt, B.C., Popovych, O.V., Eickhoff, S.B., Valk, S.L. * (2025) "Adolescent maturation of cortical excitation-inhibition ratio based on individualized biophysical network modeling." *Science Advances*, Accepted for publication.

Impact Factor (2023): 11.7

Own contribution according to CRediT

- Conceptualization
- Methodology
- Software
- Formal analysis
- Investigation
- Resources
- Data Curation
- Writing - Original Draft
- Writing - Review & Editing
- Visualization

Chapter 4

Study 3: Regional patterns of human cortex development correlate with underlying neurobiology

Lotter, L.D., **Saberi, A.**, Hansen, J.Y., Misic, B., Paquola, C., Barker, G.J., Bokde, A.L.W., Desrivières, S., Flor, H., Grigis, A., Garavan, H., Gowland, P., Heinz, A., Brühl, R., Martinot, J.-L., Paillère, M.-L., Artiges, E., Papadopoulos Orfanos, D., Paus, T., Poustka, L., Hohmann, S., Fröhner, J.H., Smolka, M.N., Vaidya, N., Walter, H., Whelan, R., Schumann, G., Nees, F., Banaschewski, T., Eickhoff, S.B., Dukart, J.* (2024) "Regional patterns of human cortex development correlate with underlying neurobiology." *Nature Communications*, 15(1), 7987. doi: 10.1038/s41467-024-52366-7

Impact Factor (2023): 14.7

Own contribution according to CRediT

- Methodology
- Formal analysis
- Investigation
- Data Curation
- Writing - Review & Editing

Chapter 5

Discussion

5.1 Summary and Implications of Findings

The overall goal of this thesis was to study key mesoscale biological characteristics of the cortex in relation to its macroscale organization, structure, function and connectivity in the context of development. This goal was pursued by applying theory- and data-driven computational methods on multimodal brain imaging data at multiple scales (Fig. 5.1).

In Study 1 we used PCA dimensionality reduction on laminar thickness and density data at mesoscale which was obtained from the BigBrain atlas (Amunts et al., 2013; Wagstyl et al., 2020). This analysis identified a principal axis of laminar structure variation stretching from caudal to rostral areas (Saberi et al., 2023). Along this axis, the relative thickness of infragranular layers increased while the neuronal density across all layers decreased. Linking laminar structure variation to hierarchically-organized cortical connectivity at the macroscale, in accordance with the "structural model" (Barbas, 2015; García-Cabezas et al., 2019) we found that: i) the infragranular-dominant pattern of laminar thickness was associated with higher hierarchical positions of cortical areas, and ii) cortical areas with similar laminar structure were more likely and strongly connected to each other, following the homophilic principle of connectivity which is suggested to have developmental roots (Sebenius et al., 2024). Supporting this notion, we found areas with similar laminar structure to show higher structural covariance, potentially reflecting their shared genetic and maturational effects (Valk et al., 2020).

Study 2 focused on the E-I ratio, an important functional feature of the cerebral cortex at the mesoscale, and studied its adolescent maturation. The regional E-I ratio was estimated for each individual subject and imaging session through model inversion of BNMs, employing large-scale simulations which enabled the inference of E-I ratio at the mesoscale from macroscale cortical connectivity and dynamics observed in rs-fMRI. This approach was applied on two independent cross-sectional and longitudinal adolescent samples, revealing a developmental decrease of the E-I ratio (higher inhibition or lower excitation) in the association areas in contrast to its increase or lack of change in sensorimotor areas (Saberi et al., 2025). These findings support the current theories suggesting a sensorimotor-association neurodevelopmental hierarchy in the cerebral cortex (Sydnor et al., 2021).

Lastly, in Study 3, we employed a virtual histology approach to investigate the extent to which cellular and molecular processes at the micro- and mesoscale may underlie the maturation and lifespan changes of cortical morphology at the macroscale. By examining the spatial co-localization between modeled lifespan changes of CT and normative adult-derived maps of neurobiological markers we underscored the potential role of dopaminergic receptors, inhibitory

neurons, glial cell populations, and metabolic features during childhood and adolescence maturation of CT, and cholinergic and glutamatergic systems related to its changes during adulthood (Lotter et al., 2024).

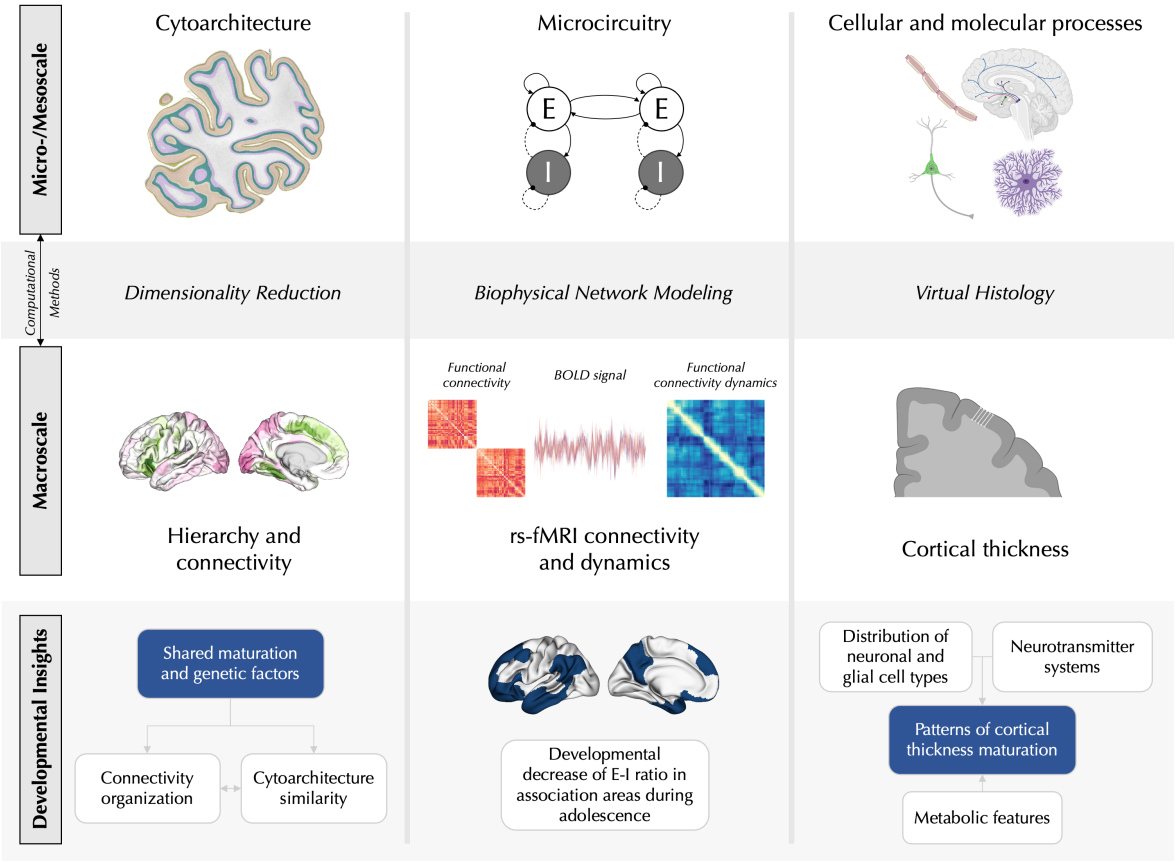

Fig. 5.1. Overview. Computational methods were used to integrate across micro-/mesoscale and macroscale cortical organization in the context of its development. Part of the figure was created with BioRender.com. BOLD: Blood-oxygen-level-dependent; rs-fMRI: resting-state functional magnetic resonance imaging.

Collectively, across the studies conducted in this thesis several key insights converge:

1. Macroscale cortical features such as its structure, function, connectivity and dynamics interact and emerge from micro- and mesoscale biological processes. In this context, computational neuroscience approaches are powerful tools to gain insights into how these different scales interact across both structural and functional domains.

2. The multiscale cortical features and their maturational trajectories vary across cortical areas organized along principal axes of variation, including the sensorimotor-association axis (Sydnor et al., 2021) and the rostrocaudal axis (Finlay & Uchiyama, 2015).

3. The regional heterogeneity of maturational trajectories and cortical features are spatially co-aligned. Although establishing causal links is difficult, this suggest that i) intrinsic and baseline differences across areas can influence the nature and timing of neurodevelopmental processes, and ii) the neurodevelopmental processes, on the other hand, can shape the adult patterns of how different features are distributed across the cerebral cortex. Notably, both of these processes are influenced by intrinsic genetic factors as well as extrinsic environmental factors and experience (Sydnor et al., 2021).

5.2 Laminar Structure and its Links to Connectivity

Our findings in Study 1 complemented previous qualitative and quantitative descriptions of laminar structure and cytoarchitecture (García-Cabezas et al., 2020; Paquola, Vos De Wael, et al., 2019) by providing more comprehensive and data-driven accounts of laminar structure based on an ultra-high-resolution *postmortem* atlas of a human brain (Amunts et al., 2013). We found that from rostral to caudal cortical areas, the relative thickness of infragranular layers decreased while neuronal density increased across all layers, but most prominently in layer IV. This finding was consistent with the reports of a previous study on non-human primates and rodents, which described rostrocaudal variability of supra- versus infragranular layers, though only using limited cortical samples rather than a complete mapping of the cortices (Charvet et al., 2015). However, the rostrocaudal axis of laminar structure variability identified in our study diverges from a sensory-fugal pattern of variability across the 'cortical types', which was identified by qualitative inspection of histological samples (García-Cabezas et al., 2019, 2020). This divergence can be attributed to the different quantitative versus qualitative approaches as well as the features considered in the models of the laminar structure variability (García-Cabezas et al., 2019, 2020). Indeed, different features of laminar structure (and more broadly cytoarchitecture) may be distributed differently across cortical areas, following distinct axes of variability. Relatedly, a previous data-driven and layer-agnostic characterization of microstructural variability across the BigBrain's cerebral cortex reported both the rostrocaudal and sensory-fugal axes as the principal axes of microstructural variability (Paquola et al., 2021). A similar rostrocaudal axis of variability was identified in another study that characterized the left-right asymmetry of cortical microstructure in the BigBrain (Wan et al., 2024).

Furthermore, supporting the "structural model" (Barbas, 2015; García-Cabezas et al., 2019; Goulas et al., 2018; Hilgetag et al., 2019), we showed that the laminar structure variability at the mesoscale is linked to the hierarchically-organized cortical connectome. This association has been previously shown in several other animal and human studies reporting higher likelihood and/or strength of connections related to the similarity of cytoarchitecture and laminar structure, based on the complexity of pyramidal neurons (Scholtens et al., 2014), neuronal density (Beul et al., 2017; Hilgetag et al., 2016), cortical types (Beul et al., 2015; Goulas et al., 2017, 2019; Hilgetag et al., 2016), and microstructural profiles (Wei et al., 2018). Furthermore, the cortical cytoarchitectonic variability has been associated with the laminar pattern of corticocortical connections (Aparicio-Rodríguez & García-Cabezas, 2023; Goulas et al., 2018; Hilgetag et al., 2019) which is thought to vary across cortical hierarchicy (Bastos et al., 2012; Goulas et al., 2018; Vezoli et al., 2021).

5.3 Adolescent Maturation of the Excitation-Inhibition Ratio

The findings from previous animal studies, as well as human *postmortem* and *in vivo* investigations suggest that adolescence is associated with key maturational changes in cortical E-I ratio (Caballero & Tseng, 2016; Caballero et al., 2021; Lewis et al., 2004). In Study 2, we used a computational model to infer individual-specific estimates of regional E-I ratio from *in vivo* observed data of functional connectivity and dynamics. Doing so enabled non-invasive and comprehensive investigation of spatiotemporal patterns of E-I ratio maturation in human adolescents, providing

further evidence for this important maturational process in the human cortex. Specifically, we observed a sensorimotor-association pattern of E-I ratio maturation during adolescence: The association areas showed a developmental decrease of the E-I ratio towards higher inhibition or lower excitation, while the sensorimotor areas showed an increase of the E-I ratio or its lack of change. This finding aligns with the findings of previous laboratory studies at molecular and cellular levels which have reported evidence suggesting a maturation of inhibition during adolescence, primarily within the association areas and particularly in the prefrontal cortex. *Postmortem* transcriptomics analyses in animals and humans have shown important changes in the expression of relevant genes, such as a shift in the composition of $GABA_A$ receptors from $\alpha 2$- to $\alpha 1$-containing receptors (Caballero & Tseng, 2016; Duncan et al., 2010; Hoftman & Lewis, 2011). This shift is believed to result in faster decay times of the receptors, and in turn, a maturational increase in the strength of inhibitory postsynaptic currents have been reported using *in vivo* neuronal recording of pyramidal neurons within this area (Gonzalez-Burgos et al., 2015; Hashimoto et al., 2009). In parallel, *postmortem* histological studies have shown a dramatic peri-adolescence pruning of the excitatory synapses in the prefrontal cortex, which is thought to result in a reduction of excitatory input to the neurons.

Human *in vivo* studies on adolescent maturation of the excitation and inhibition have used a variety of markers and functional proxies. Similar to our study, rs-fMRI data has been used to make inferences about E-I ratio in two other human studies aiming to map its maturation. Firstly, a study by Larsen et al., 2022 estimated the global E-I ratio across the cortex by assessing the similarity of functional connectivity (FC) patterns of adolescents to the FC patterns observed in adults who had received alprazolam, a GABAergic agonist, compared to placebo. Using this marker, an age-related reduction of the E-I ratio was found across the entire cortex. However, when this analysis was performed for association and sensorimotor areas separately, the decrease was found to occur selectively in the association and not the sensorimotor areas, which was consistent with the sensorimotor-association developmental pattern we observed. Secondly, Zhang et al., 2024 in a recent study used group-level BNMs to estimate E-I ratio and reported a widespread decrease of the E-I ratio which was most prominent in the sensorimotor areas. This study used BNMs constructed for 29 age groups of the Philadelphia Neurodevelopmental Cohort (PNC) dataset, which puts it in contrast to our study where we constructed individualized BNMs by using large-scale simulations powered by our Graphical Processing Unit (GPU)-based implementation (see section 5.5). The individualized models used in our study provided a subject-level precision, which is suggested to enhance reliability and fingerprinting accuracy of models (Domhof et al., 2022). Moreover, these models enabled longitudinal assessment of within-subject maturation of the E-I ratio. The observed discrepancy between our findings and those reported by Zhang et al., 2024 in the sensorimotor areas may be attributable to the utilization of individualized as opposed to group-level BNMs, the distinct simulation-based markers of the E-I ratio, and the differences in methodological details of image processing, modeling and optimization.

5.4 Neurobiological Processes Underlying Cortical Morphology Maturation

Our findings in Study 3 characterized the neurobiological processes that might underlie CT maturation across different stages of development and lifespan. During childhood development and adolescence we found contributions of neurobiological markers including dopaminergic receptors, microglia and oligodendrocyte progenitor cells, as well as somatostatin inhibitory neurons, in explaining the maturational CT changes. In line with the observed association of CT development with the distribution of dopaminergic receptors, regulatory effects of these receptors on cortical macrostructural development have been demonstrated, for example, linked to the adverse effects of *in utero* cocaine exposure (Bhide, 2009; Grewen et al., 2014). Furthermore, cortical glial cells have been shown to play an active role in developmental synaptic remodeling (Petanjek et al., 2008) as well as intracortical myelination (Kuhn et al., 2019; McNamara et al., 2023), while both of these processes are thought to contribute to the macroscale CT (Paus et al., 2008).

In Study 3 we extended the findings of several previous studies on the neurobiological process underlying cortical macrostructural maturation (Ball et al., 2020; Parker et al., 2020; Paus, 2018, 2023; Shin et al., 2018; Vidal-Pineiro et al., 2020). For instance, Shin et al., 2018 investigated the association of gene expression maps of nine neuronal and glial cell types with the patterns of cortical thinning during adolescence and found it to relate to expression of genes marking subtypes of pyramidal neurons as well as astrocytes and microglia. Following, another study focused on cortical thinning pattern during childhood, and reported its spatial co-localization with gradients of gene expression involving genes that are expressed predominantly in excitatory and inhibitory neurons and are involved in synaptic remodeling (Ball et al., 2020). Subsequently, Parker et al., 2020 applied this approach to a wider age range and a larger sample, showing association of cortical thinning with gradients in the expression of genes associated with dendrites, dendritic spines, and myelin. Our study complemented these findings by applying more comprehensive analyses, including: i) estimation of CT changes using larger samples, including a cross-sectional normative model based on the data of 58,836 subjects (Bethlehem et al., 2022), as well as longitudinal maturational patterns estimated based on large-scale cohorts of Adolescent Brain Cognitive Development (ABCD) Study (N = 6789) and IMAGEN (N = 915–1142), ii) coverage of a wider age range enabled by the cross-sectional normative models of CT, and iii) inclusion of multiple imaging-based maps in addition to transcriptomic maps of cell types, reflecting a more diverse array of cellular and molecular biological processes.

5.5 Methodological Advances

In addition to extending our understanding of the cerebral cortex organization and development, our research in this thesis resulted in advances in methodology and development of tools that can be beneficial to the research community and future studies. These methodological advances were exemplified in Study 2, where a specialized toolbox named cuBNM (https://cubnm.readthedocs.io/en/latest/) was developed. This toolbox was designed to perform efficient simulation and optimization of high-dimensional BNMs by using GPUs. As detailed in Study 2, the process of fitting BNMs to the imaging data of an individual subject/session involves tuning model

parameters to produce simulated signals that closely match the target data. This process often necessitates several thousands of simulations - depending on the complexity and dimensionality of the model. Therefore, in typical BNM studies, the computational costs of simulations have been a significant bottleneck, limiting the scalability of this approach to larger samples and more complicated (higher dimensional) models. This is due to the fact that the traditional implementations of these simulations (e.g., The Virtual Brain (Ritter et al., 2013)) run on Central Processing Units (CPUs) and involve running a massive number of *serial* calculations across subjects, simulations, areas and time. GPUs, on the other hand, are designed for highly *parallelized* computations and can be used to accelerate BNM simulations. This motivated the development of the cuBNM toolbox, which utilizes GPUs to achieve a dramatic speed-up of calculations up to 1300 times faster than CPUs.[1] This innovation was integral for the feasibility of Study 2, which involved scaling of the BNM approach to approximately 1000 subjects/sessions, considerably higher than the typical samples used in the BNM studies, and using a rather higher-dimensional and biologically more realistic model that acknowledged regional heterogeneity of model parameters, compared to traditional models which assume homogeneity of parameters across areas. The cuBNM toolbox has been made freely available as an open source Python package, accompanied by documentation and tutorials for its usage (Fig. 5.2).

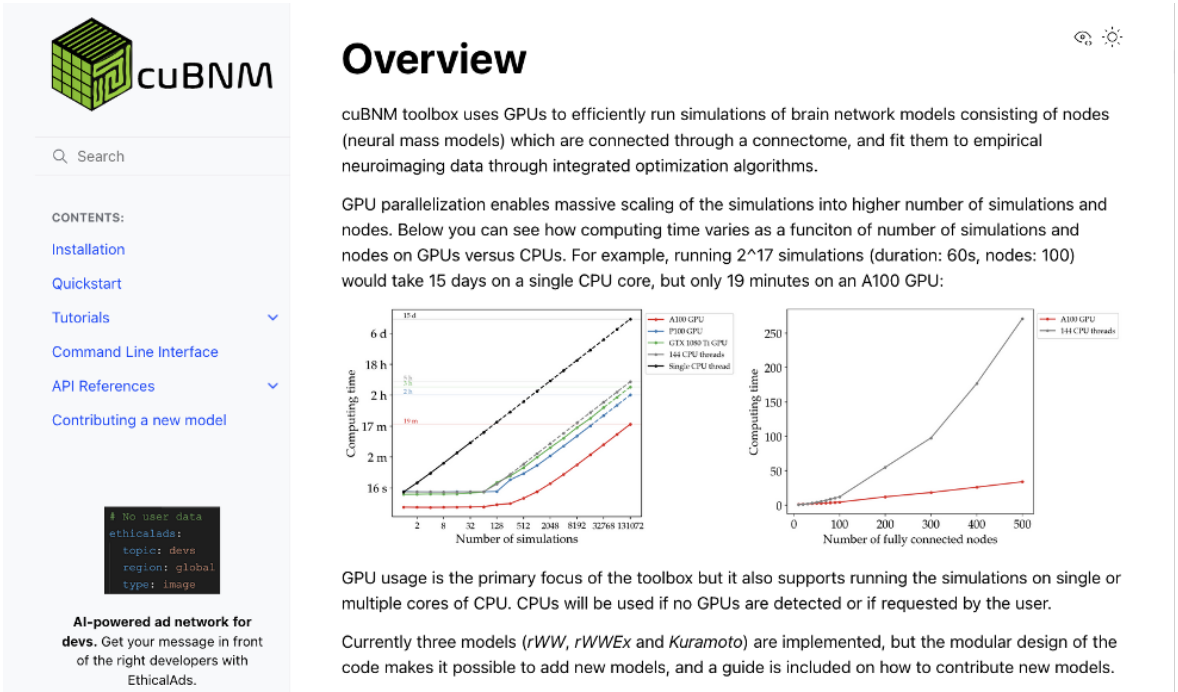

Fig. 5.2. The *cuBNM* toolbox documentation.

5.6 Future Directions

The research conducted in this thesis highlights outstanding questions and opens up new avenues of future research, focusing on i) advancing the experimental approaches towards improving the precision of the models and the data, ii) multimodal investigation of inter-related maturational processes during cortical development, and, ultimately, iii) the clinical translations of our findings and computational approaches.

[1]The speed-up is dependent on the GPU and CPU models as well as the number of simulations, nodes, simulation time, and type of the model.

5.6.1 Advancing the Experimental Approaches

Our laminar model in Study 1 was based on high-resolution histological data from a single adult brain (Amunts et al., 2013). Therefore, an intriguing question remains on how our observed pattern generalizes to additional subjects across a broader demographic range. This important step awaits the availability of similar *postmortem* atlases and the layer segmentation of their cortices. Until then, *in vivo* imaging of laminar structure using MRI is a promising area of research that can address this question (reviewed in Trampel et al., 2019). Additionally, depth-dependent analyses of cortical profiles provide an alternative, layer-agnostic framework for understanding microstructural gradients and functional differentiation across the cortex. Using such methods, future research can: i) assess the generalizability of the rostrocaudal pattern of increasing dominance of supragranular layers found in our study to other individuals, while understanding the impacts of its inter-individual differences, e.g., across genders (Küchenhoff et al., 2024), ii) investigate the links between laminar structure or microstructure with corticocortical connectivity (e.g. Valk et al., 2022) and its hierarchical organization *within the same individuals*, as opposed to our study in which the laminar structure and the connectomes were based on different individuals/groups, and iii) extend our initial findings on the relevance of maturational processes on laminar structure by assessing age-related changes of laminar structure or microstructure (e.g. Paquola, Bethlehem, et al., 2019).

Moreover, while our individualized biophysical network model in Study 2 captured key developmental shifts in the cortical E-I ratio, future work on computational modeling of the E-I ratio can benefit from incorporating biologically more realistic models. The model we used in Study 2 was described by neural mass models consisting of single excitatory and inhibitory neuronal ensembles in each area (Deco et al., 2014). This model, in turn, lacks certain biological details such as the layered structure of the cortex, the excitatory and inhibitory neurons distributed across the layers and their distinct functional properties (Lake et al., 2016; X.-J. Wang, 2020), as well as laminar pattern of feedforward and feedback connections between cortical areas (Bastos et al., 2012; Vezoli et al., 2021). More complex models that incorporate layers, subtypes of neurons and feedforward/-back connections have been developed (Froudist-Walsh et al., 2021; Mejias et al., 2016; P. Wang & Knösche, 2013) and can be used in future studies to investigate the E-I ratio at a finer level. Notably, application of such more complex models to the imaging data at a scale on par with Study 2, will require methodological advances in both the efficiency of simulation-optimization pipeline, as well as the spatial and temporal resolution of the data (e.g. layer-fMRI).

5.6.2 Multimodal Investigation of Cortical Maturation

Cortical maturation is a complex, multifaceted process that involves inter-related changes across different levels of cortical structure, function and connectivity (Larsen & Luna, 2018; Sydnor et al., 2021). The maturation of the E-I ratio, for instance, is suggested to mirror the onset of a critical period of plasticity associated with increased cortical myelination (Larsen & Luna, 2018). Notably, myelination of parvalbumin-positive interneurons, which account for 25-50% of the intracortical myelination, is essential for their function and generation of gamma oscillations (Stedehouder & Kushner, 2017). Conversely, GABAergic activity is shown to promote myelination (Vélez-Fort et al., 2012). These changes in cortical microstructure and microcircuitry

are mirrored by the development of neurotransmitter systems such as the dopaminergic system (Larsen & Luna, 2018). Animal studies have shown that dopamine D1 and D2 receptor densities in the prefrontal cortex peak during late childhood or early adolescence (Larsen & Luna, 2018; Lidow & Rakic, 1992), and functional changes lead to greater inhibition in response to dopamine release (Larsen & Luna, 2018; O'Donnell, 2010). On the other hand, in Study 3, our findings linked the maturation of cortical morphology to neurotransmitter systems, including the dopaminergic system, as well as specific glial and neuronal subtypes.

Taken together, evidence from animal studies, virtual histology, and overlapping maturational trajectories suggest that the development of cortical structure, myelination, microcircuitry and neurotransmitter systems are inter-related processes. However, direct, subject-level links between the maturation of these processes in the human brain remain limited and understudied. This highlights the need for future multimodal and integrative studies on the concurrent maturation of these neurobiological processes within the same developing individual or cohort, to better understand their dynamic interplay during development.

5.6.3 Clinical Translations

Several mental health disorders, such as psychosis, mood disorders, and substance abuse, are believed to emerge during development, particularly in adolescence. Their onset is thought to relate to alterations in typical maturation, influenced by genetic factors as well as biological and psychosocial environments (Paus et al., 2008). Understanding these neurodevelopmental alterations across multiple scales of cortical organization requires a clearer characterization of the typical maturation trajectories at the micro-, meso- and macroscale, alongside the development of computational methods to analyze them. These methods can then be applied to clinical or at-risk developing populations. In turn, comparing them with healthy individuals and the typical neurodevelomental trajectories, allows future research to understand how cortical organization is impaired in mental health disorders and whether these impairments reflect altered neurodevelopmental patterns.

Schizophrenia is a prominent example of a disorder with neurodevelopmental origins. It is suggested to emerge due to abnormal cortical maturation, in particular associated with imbalances in cortical excitation and inhibition, dopaminergic dysfunction, and structural changes such as cortical thinning and reduced myelination (Hoftman et al., 2017; Insel, 2010; Keshavan et al., 2014; Paus et al., 2008; Rolls & Deco, 2011). In this context, an important direction for future research is to apply computational approaches to multimodal imaging data from diagnosed and high-risk individuals for schizophrenia. This can help investigate maturational impairments in E-I ratio, the dopaminergic system and cortical (micro)structure, as well as their inter-relations, as potential underlying neurodevelopmental mechanisms of schizophrenia. Such insights into the neurodevelopmental model of schizophrenia may ultimately help in early detection of at-risk children and adolescents, aiming towards more effective management of the disease and potentially mitigating its progress.

5.7 Conclusion

In this thesis, my colleagues and I applied advanced computational methods to bridge different scales of investigation, exploring the links between micro- and mesoscale processes with the macroscale cortical organization and its development. First, we demonstrated that cortical laminar structure varies along a rostrocaudal axis and is linked to hierarchically-organized cortical connectome, which we hypothesized may have developmental origins. Second, we used computational biophysical models of the cerebral cortex to estimate regional E-I ratio in individual adolescents based on imaging data. Our findings revealed distinct maturational trajectories between association areas, showing a shift towards higher inhibition, and sensorimotor areas, showing a lack of change or shifts towards higher excitation. Notably, the large-scale simulations performed in this study were enabled by a novel GPU-based implementation of BNM simulations, which was released as an open-source Python toolbox, *cuBNM*. Third, we used a virtual histology approach to examine the relationship between spatiotemporal patterns of cortical morphology maturation and maps of neurobiological processes. Through this approach we provided evidence that specific cellular and molecular neurobiological processes, such as neurotransmitter systems, glial cells, and neuronal subtypes, may play a role in shaping cortical morphology throughout development and across the lifespan.

Together, this research advances our understanding of multiscale cortical organization and its maturation while also developing computational tools for future studies. Our findings and approach can serve as a foundation for further research into clinical translational applications, particularly in understanding how impaired cortical maturation and organization contribute to the emergence of mental health disorders.

Bibliography

Abeles, M. (1991). Anatomy of the cerebral cortex. In *Corticonics: Neural Circuits of the Cerebral Cortex* (pp. 1–64). Cambridge University Press. https://doi.org/10.1017/CBO9780511574566.002

Altamura, C., Dell'Acqua, M. L., Moessner, R., Murphy, D. L., Lesch, K. P., & Persico, A. M. (2007). Altered neocortical cell density and layer thickness in serotonin transporter knockout mice: A quantitation study. *Cerebral Cortex (New York, N.Y.: 1991)*, *17*(6), 1394–1401. https://doi.org/10.1093/cercor/bhl051

Amunts, K., Lepage, C., Borgeat, L., Mohlberg, H., Dickscheid, T., Rousseau, M.-É., Bludau, S., Bazin, P.-L., Lewis, L. B., Oros-Peusquens, A.-M., Shah, N. J., Lippert, T., Zilles, K., & Evans, A. C. (2013). BigBrain: An Ultrahigh-Resolution 3D Human Brain Model. *Science*, *340*(6139), 1472–1475. https://doi.org/10.1126/science.1235381

Amunts, K., & Zilles, K. (2015). Architectonic Mapping of the Human Brain beyond Brodmann. *Neuron*, *88*(6), 1086–1107. https://doi.org/10.1016/j.neuron.2015.12.001

Anderson, S. A., Classey, J. D., Condé, F., Lund, J. S., & Lewis, D. A. (1995). Synchronous development of pyramidal neuron dendritic spines and parvalbumin-immunoreactive chandelier neuron axon terminals in layer III of monkey prefrontal cortex. *Neuroscience*, *67*(1), 7–22. https://doi.org/10.1016/0306-4522(95)00051-j

Aparicio-Rodríguez, G., & García-Cabezas, M. Á. (2023). Comparison of the predictive power of two models of cortico-cortical connections in primates: The distance rule model and the structural model. *Cerebral Cortex (New York, N.Y.: 1991)*, *33*(13), 8131–8149. https://doi.org/10.1093/cercor/bhad104

Atallah, B. V., & Scanziani, M. (2009). Instantaneous modulation of gamma oscillation frequency by balancing excitation with inhibition. *Neuron*, *62*(4), 566–577. https://doi.org/10.1016/j.neuron.2009.04.027

Bailey, P. (1951). The isocortex of man. *Urbana*, *3*.

Bajada, C. J., Campos, L. Q. C., Caspers, S., Muscat, R., Parker, G. J. M., Ralph, M. A. L., Cloutman, L. L., & Trujillo-Barreto, N. J. (2020). A tutorial and tool for exploring feature similarity gradients with MRI data. *NeuroImage*, *221*, 117140. https://doi.org/https://doi.org/10.1016/j.neuroimage.2020.117140

Ball, G., Seidlitz, J., Beare, R., & Seal, M. L. (2020). Cortical remodelling in childhood is associated with genes enriched for neurodevelopmental disorders. *NeuroImage*, *215*, 116803. https://doi.org/10.1016/j.neuroimage.2020.116803

Barbas, H. (2015). General cortical and special prefrontal connections: Principles from structure to function. *Annual Review of Neuroscience*, *38*, 269–289. https://doi.org/10.1146/annurev-neuro-071714-033936

Bassett, D. S., & Gazzaniga, M. S. (2011). Understanding complexity in the human brain. *Trends in cognitive sciences*, *15*(5), 200–209. https://doi.org/10.1016/j.tics.2011.03.006

Bastos, A. M., Usrey, W. M., Adams, R. A., Mangun, G. R., Fries, P., & Friston, K. J. (2012). Canonical Microcircuits for Predictive Coding. *Neuron*, *76*(4), 695–711. https://doi.org/10.1016/j.neuron.2012.10.038

Bethlehem, R. a. I., Seidlitz, J., White, S. R., Vogel, J. W., Anderson, K. M., Adamson, C., Adler, S., Alexopoulos, G. S., Anagnostou, E., Areces-Gonzalez, A., Astle, D. E., Auyeung, B., Ayub, M., Bae, J., Ball, G., Baron-Cohen, S., Beare, R., Bedford, S. A., Benegal, V., ... Alexander-Bloch, A. F. (2022). Brain charts for the human lifespan. *Nature*, 1–11. https://doi.org/10.1038/s41586-022-04554-y

Beul, S. F., Barbas, H., & Hilgetag, C. C. (2017). A Predictive Structural Model of the Primate Connectome. *Scientific Reports*, *7*(1), 43176. https://doi.org/10.1038/srep43176

Beul, S. F., Grant, S., & Hilgetag, C. C. (2015). A predictive model of the cat cortical connectome based on cytoarchitecture and distance. *Brain Structure & Function*, *220*(6), 3167–3184. https://doi.org/10.1007/s00429-014-0849-y

Bhide, P. G. (2009). Dopamine, cocaine and the development of cerebral cortical cytoarchitecture: A review of current concepts. *Seminars in Cell & Developmental Biology*, *20*(4), 395–402. https://doi.org/10.1016/j.semcdb.2009.01.006

Breakspear, M. (2017). Dynamic models of large-scale brain activity. *Nature Neuroscience*, *20*(3), 340–352. https://doi.org/10.1038/nn.4497

Brodmann, K. (2007, February). *Brodmann's: Localisation in the Cerebral Cortex*. Springer Science & Business Media.

Burt, J. B., Demirtaş, M., Eckner, W. J., Navejar, N. M., Ji, J. L., Martin, W. J., Bernacchia, A., Anticevic, A., & Murray, J. D. (2018). Hierarchy of transcriptomic specialization across human cortex captured by structural neuroimaging topography. *Nature Neuroscience*, *21*(9), 1251–1259. https://doi.org/10.1038/s41593-018-0195-0

Caballero, A., Orozco, A., & Tseng, K. Y. (2021). Developmental regulation of excitatory-inhibitory synaptic balance in the prefrontal cortex during adolescence. *Seminars in Cell & Developmental Biology*, *118*, 60–63. https://doi.org/10.1016/j.semcdb.2021.02.008

Caballero, A., & Tseng, K. Y. (2016). GABAergic Function as a Limiting Factor for Prefrontal Maturation during Adolescence. *Trends in Neurosciences*, *39*(7), 441–448. https://doi.org/10.1016/j.tins.2016.04.010

Cadwell, C. R., Bhaduri, A., Mostajo-Radji, M. A., Keefe, M. G., & Nowakowski, T. J. (2019). Development and Arealization of the Cerebral Cortex. *Neuron*, *103*(6), 980–1004. https://doi.org/10.1016/j.neuron.2019.07.009

Catterall, W. A., Raman, I. M., Robinson, H. P. C., Sejnowski, T. J., & Paulsen, O. (2012). The Hodgkin-Huxley Heritage: From Channels to Circuits. *Journal of Neuroscience*, *32*(41), 14064–14073. https://doi.org/10.1523/JNEUROSCI.3403-12.2012

Charvet, C. J., Cahalane, D. J., & Finlay, B. L. (2015). Systematic, Cross-Cortex Variation in Neuron Numbers in Rodents and Primates. *Cerebral Cortex*, *25*(1), 147–160. https://doi.org/10.1093/cercor/bht214

Charvet, C. J., & Finlay, B. L. (2014). Evo-devo and the primate isocortex: The central organizing role of intrinsic gradients of neurogenesis. *Brain, Behavior and Evolution*, *84*(2), 81–92. https://doi.org/10.1159/000365181

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *NeuroImage*, *9*(2), 179–194. https://doi.org/10.1006/nimg.1998.0395

Deco, G., & Kringelbach, M. L. (2014). Great Expectations: Using Whole-Brain Computational Connectomics for Understanding Neuropsychiatric Disorders. *Neuron*, *84*(5), 892–905. https://doi.org/10.1016/j.neuron.2014.08.034

Deco, G., Ponce-Alvarez, A., Hagmann, P., Romani, G. L., Mantini, D., & Corbetta, M. (2014). How local excitation-inhibition ratio impacts the whole brain dynamics. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *34*(23), 7886–7898. https://doi.org/10.1523/JNEUROSCI.5068-13.2014

Denève, S., & Machens, C. K. (2016). Efficient codes and balanced networks. *Nature Neuroscience*, *19*(3), 375–382. https://doi.org/10.1038/nn.4243

Dienel, S. J., & Lewis, D. A. (2019). Alterations in cortical interneurons and cognitive function in schizophrenia. *Neurobiology of Disease*, *131*, 104208. https://doi.org/10.1016/j.nbd.2018.06.020

Dombrowski, S. M., Hilgetag, C. C., & Barbas, H. (2001). Quantitative architecture distinguishes prefrontal cortical systems in the rhesus monkey. *Cerebral Cortex (New York, N.Y.: 1991)*, *11*(10), 975–988. https://doi.org/10.1093/cercor/11.10.975

Domhof, J. W. M., Eickhoff, S. B., & Popovych, O. V. (2022). Reliability and subject specificity of personalized whole-brain dynamical models. *NeuroImage*, *257*, 119321. https://doi.org/10.1016/j.neuroimage.2022.119321

Duncan, C. E., Webster, M. J., Rothmond, D. A., Bahn, S., Elashoff, M., & Shannon Weickert, C. (2010). Prefrontal GABAA receptor -subunit expression in normal postnatal human development and schizophrenia. *Journal of Psychiatric Research*, *44*(10), 673–681. https://doi.org/10.1016/j.jpsychires.2009.12.007

Ferrante, M., Redish, A. D., Oquendo, M. A., Averbeck, B. B., Kinnane, M. E., & Gordon, J. A. (2018). Computational psychiatry: A report from the 2017 NIMH workshop on opportunities and challenges. *Molecular Psychiatry*, *24*(4), 479. https://doi.org/10.1038/s41380-018-0063-z

Finlay, B. L., & Uchiyama, R. (2015). Developmental mechanisms channeling cortical evolution. *Trends in Neurosciences*, *38*(2), 69–76. https://doi.org/10.1016/j.tins.2014.11.004

Froudist-Walsh, S., Bliss, D. P., Ding, X., Rapan, L., Niu, M., Knoblauch, K., Zilles, K., Kennedy, H., Palomero-Gallagher, N., & Wang, X.-J. (2021). A dopamine gradient controls access to distributed working memory in the large-scale monkey cortex. *Neuron*, *109*(21), 3500–3520.e13. https://doi.org/10.1016/j.neuron.2021.08.024

Galakhova, A. A., Hunt, S., Wilbers, R., Heyer, D. B., Kock, C. P. J. d., Mansvelder, H. D., & Goriounova, N. A. (2022). Evolution of cortical neurons supporting human cognition. *Trends in Cognitive Sciences*, *26*(11), 909–922. https://doi.org/10.1016/j.tics.2022.08.012

García-Cabezas, M. Á., Hacker, J. L., & Zikopoulos, B. (2020). A Protocol for Cortical Type Analysis of the Human Neocortex Applied on Histological Samples, the Atlas of Von Economo and Koskinas, and Magnetic Resonance Imaging. *Frontiers in Neuroanatomy*, *14*. https://doi.org/10.3389/fnana.2020.576015

García-Cabezas, M. Á., Zikopoulos, B., & Barbas, H. (2019). The Structural Model: A theory linking connections, plasticity, pathology, development and evolution of the cerebral cortex. *Brain Structure & Function*, *224*(3), 985–1008. https://doi.org/10.1007/s00429-019-01841-9

Gonzalez-Burgos, G., Miyamae, T., Pafundo, D. E., Yoshino, H., Rotaru, D. C., Hoftman, G., Datta, D., Zhang, Y., Hammond, M., Sampson, A. R., Fish, K. N., Bard Ermentrout, G., & Lewis, D. A. (2015). Functional Maturation of GABA Synapses During Postnatal

Development of the Monkey Dorsolateral Prefrontal Cortex. *Cerebral Cortex*, *25*(11), 4076–4093. https://doi.org/10.1093/cercor/bhu122

Goulas, A., Changeux, J.-P., Wagstyl, K., Amunts, K., Palomero-Gallagher, N., & Hilgetag, C. C. (2021). The natural axis of transmitter receptor distribution in the human cerebral cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *118*(3). https://doi.org/10.1073/pnas.2020574118

Goulas, A., Margulies, D. S., Bezgin, G., & Hilgetag, C. C. (2019). The architecture of mammalian cortical connectomes in light of the theory of the dual origin of the cerebral cortex. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *118*, 244–261. https://doi.org/10.1016/j.cortex.2019.03.002

Goulas, A., Uylings, H. B. M., & Hilgetag, C. C. (2017). Principles of ipsilateral and contralateral cortico-cortical connectivity in the mouse. *Brain Structure & Function*, *222*(3), 1281–1295. https://doi.org/10.1007/s00429-016-1277-y

Goulas, A., Zilles, K., & Hilgetag, C. C. (2018). Cortical Gradients and Laminar Projections in Mammals. *Trends in Neurosciences*, *41*(11), 775–788. https://doi.org/10.1016/j.tins.2018.06.003

Grewen, K., Burchinal, M., Vachet, C., Gouttard, S., Gilmore, J. H., Lin, W., Johns, J., Elam, M., & Gerig, G. (2014). Prenatal cocaine effects on brain structure in early infancy. *NeuroImage*, *101*, 114–123. https://doi.org/10.1016/j.neuroimage.2014.06.070

Hansen, J. Y., Shafiei, G., Markello, R. D., Smart, K., Cox, S. M. L., Nørgaard, M., Beliveau, V., Wu, Y., Gallezot, J.-D., Aumont, É., Servaes, S., Scala, S. G., DuBois, J. M., Wainstein, G., Bezgin, G., Funck, T., Schmitz, T. W., Spreng, R. N., Galovic, M., … Misic, B. (2022). Mapping neurotransmitter systems to the structural and functional organization of the human neocortex. *Nature Neuroscience*, *25*(11), 1569–1581. https://doi.org/10.1038/s41593-022-01186-3

Hashimoto, T., Nguyen, Q. L., Rotaru, D., Keenan, T., Arion, D., Beneyto, M., Gonzalez-Burgos, G., & Lewis, D. A. (2009). Protracted Developmental Trajectories of GABAA Receptor 1 and 2 Subunit Expression in Primate Prefrontal Cortex. *Biological psychiatry*, *65*(12), 1015–1023. https://doi.org/10.1016/j.biopsych.2009.01.004

Hawrylycz, M. J., Lein, E. S., Guillozet-Bongaarts, A. L., Shen, E. H., Ng, L., Miller, J. A., van de Lagemaat, L. N., Smith, K. A., Ebbert, A., Riley, Z. L., Abajian, C., Beckmann, C. F., Bernard, A., Bertagnolli, D., Boe, A. F., Cartagena, P. M., Chakravarty, M. M., Chapin, M., Chong, J., … Jones, A. R. (2012). An anatomically comprehensive atlas of the adult human brain transcriptome. *Nature*, *489*(7416), 391–399. https://doi.org/10.1038/nature11405

Hilgetag, C. C., Beul, S. F., van Albada, S. J., & Goulas, A. (2019). An architectonic type principle integrates macroscopic cortico-cortical connections with intrinsic cortical circuits of the primate brain. *Network Neuroscience*, *3*(4), 905–923. https://doi.org/10.1162/netn_a_00100

Hilgetag, C. C., Medalla, M., Beul, S. F., & Barbas, H. (2016). The primate connectome in context: Principles of connections of the cortical visual system. *NeuroImage*, *134*, 685–702. https://doi.org/10.1016/j.neuroimage.2016.04.017

Hodgkin, A. L., & Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *The Journal of Physiology*, *117*(4), 500–544. https://doi.org/10.1113/jphysiol.1952.sp004764

Hoftman, G. D., Datta, D., & Lewis, D. A. (2017). Layer 3 excitatory and inhibitory circuitry in the prefrontal cortex: Developmental trajectories and alterations in schizophrenia. *Biological psychiatry*, *81*(10), 862. https://doi.org/10.1016/j.biopsych.2016.05.022

Hoftman, G. D., & Lewis, D. A. (2011). Postnatal Developmental Trajectories of Neural Circuits in the Primate Prefrontal Cortex: Identifying Sensitive Periods for Vulnerability to Schizophrenia. *Schizophrenia Bulletin*, *37*(3), 493. https://doi.org/10.1093/schbul/sbr029

Huttenlocher, P. R. (1979). Synaptic density in human frontal cortex - developmental changes and effects of aging. *Brain Research*, *163*(2), 195–205. https://doi.org/10.1016/0006-8993(79)90349-4

Insel, T. R. (2010). Rethinking schizophrenia. *Nature*, *468*(7321), 187–193. https://doi.org/10.1038/nature09552

Isaacson, J. S., & Scanziani, M. (2011). How Inhibition Shapes Cortical Activity. *Neuron*, *72*(2), 231–243. https://doi.org/10.1016/j.neuron.2011.09.027

Jacobs, B., Schall, M., Prather, M., Kapler, E., Driscoll, L., Baca, S., Jacobs, J., Ford, K., Wainwright, M., & Treml, M. (2001). Regional Dendritic and Spine Variation in Human Cerebral Cortex: A Quantitative Golgi Study. *Cerebral Cortex*, *11*(6), 558–571. https://doi.org/10.1093/cercor/11.6.558

Keshavan, M. S., Giedd, J., Lau, J. Y. F., Lewis, D. A., & Paus, T. (2014). Changes in the adolescent brain and the pathophysiology of psychotic disorders. *The Lancet. Psychiatry*, *1*(7), 549–558. https://doi.org/10.1016/S2215-0366(14)00081-9

Khaleghi, A., Mohammadi, M. R., Shahi, K., & Nasrabadi, A. M. (2022). Computational Neuroscience Approach to Psychiatry: A Review on Theory-driven Approaches. *Clinical Psychopharmacology and Neuroscience*, *20*(1), 26–36. https://doi.org/10.9758/cpn.2022.20.1.26

Kostović, I., & Judaš, M. (2015, January). Embryonic and Fetal Development of the Human Cerebral Cortex. In *Brain Mapping* (pp. 167–175). Academic Press. https://doi.org/10.1016/B978-0-12-397025-1.00193-7

Küchenhoff, S., Bayrak, Ş., Zsido, R. G., Saberi, A., Bernhardt, B. C., Weis, S., Schaare, H. L., Sacher, J., Eickhoff, S., & Valk, S. L. (2024). Relating sex-bias in human cortical and hippocampal microstructure to sex hormones. *Nature Communications*, *15*(1), 1–19. https://doi.org/10.1038/s41467-024-51459-7

Kuhn, S., Gritti, L., Crooks, D., & Dombrowski, Y. (2019). Oligodendrocytes in Development, Myelin Generation and Beyond. *Cells*, *8*(11), 1424. https://doi.org/10.3390/cells8111424

Lake, B. B., Ai, R., Kaeser, G. E., Salathia, N. S., Yung, Y. C., Liu, R., Wildberg, A., Gao, D., Fung, H.-L., Chen, S., Vijayaraghavan, R., Wong, J., Chen, A., Sheng, X., Kaper, F., Shen, R., Ronaghi, M., Fan, J.-B., Wang, W., … Zhang, K. (2016). Neuronal subtypes and diversity revealed by single-nucleus RNA sequencing of the human brain. *Science*, *352*(6293), 1586–1590. https://doi.org/10.1126/science.aaf1204

Larsen, B., Cui, Z., Adebimpe, A., Pines, A., Alexander-Bloch, A., Bertolero, M., Calkins, M. E., Gur, R. E., Gur, R. C., Mahadevan, A. S., Moore, T. M., Roalf, D. R., Seidlitz, J., Sydnor, V. J., Wolf, D. H., & Satterthwaite, T. D. (2022). A developmental reduction of the excitation:inhibition ratio in association cortex during adolescence. *Science Advances*. https://doi.org/10.1126/sciadv.abj8750

Larsen, B., & Luna, B. (2018). Adolescence as a neurobiological critical period for the development of higher-order cognition. *Neuroscience & Biobehavioral Reviews*, *94*, 179–195. https://doi.org/10.1016/j.neubiorev.2018.09.005

Lewis, D. A., Cruz, D., Eggan, S., & Erickson, S. (2004). Postnatal development of prefrontal inhibitory circuits and the pathophysiology of cognitive dysfunction in schizophrenia. *Annals of the New York Academy of Sciences*, *1021*, 64–76. https://doi.org/10.1196/annals.1308.008

Lidow, M. S., & Rakic, P. (1992). Scheduling of Monoaminergic Neurotransmitter Receptor Expression in the Primate Neocortex during Postnatal Development. *Cerebral Cortex*, *2*(5), 401–416. https://doi.org/10.1093/cercor/2.5.401

Lotter, L. D., Saberi, A., Hansen, J. Y., Misic, B., Paquola, C., Barker, G. J., Bokde, A. L. W., Desrivières, S., Flor, H., Grigis, A., Garavan, H., Gowland, P., Heinz, A., Brühl, R., Martinot, J.-L., Paillère, M.-L., Artiges, E., Papadopoulos Orfanos, D., Paus, T., … Dukart, J. (2024). Regional patterns of human cortex development correlate with underlying neurobiology. *Nature Communications*, *15*(1), 7987. https://doi.org/10.1038/s41467-024-52366-7

Mante, V., Sussillo, D., Shenoy, K. V., & Newsome, W. T. (2013). Context-dependent computation by recurrent dynamics in prefrontal cortex. *Nature*, *503*(7474), 78–84. https://doi.org/10.1038/nature12742

Margulies, D. S., Ghosh, S. S., Goulas, A., Falkiewicz, M., Huntenburg, J. M., Langs, G., Bezgin, G., Eickhoff, S. B., Castellanos, F. X., Petrides, M., Jefferies, E., & Smallwood, J. (2016). Situating the default-mode network along a principal gradient of macroscale cortical organization. *Proceedings of the National Academy of Sciences*, *113*(44), 12574–12579. https://doi.org/10.1073/pnas.1608282113

Markello, R. D., Hansen, J. Y., Liu, Z.-Q., Bazinet, V., Shafiei, G., Suárez, L. E., Blostein, N., Seidlitz, J., Baillet, S., Satterthwaite, T. D., Chakravarty, M. M., Raznahan, A., & Misic, B. (2022). Neuromaps: Structural and functional interpretation of brain maps. *Nature Methods*, *19*(11), 1472–1479. https://doi.org/10.1038/s41592-022-01625-w

McNamara, N. B., Munro, D. A. D., Bestard-Cuche, N., Uyeda, A., Bogie, J. F. J., Hoffmann, A., Holloway, R. K., Molina-Gonzalez, I., Askew, K. E., Mitchell, S., Mungall, W., Dodds, M., Dittmayer, C., Moss, J., Rose, J., Szymkowiak, S., Amann, L., McColl, B. W., Prinz, M., … Miron, V. E. (2023). Microglia regulate central nervous system myelin growth and integrity. *Nature*, *613*(7942), 120–129. https://doi.org/10.1038/s41586-022-05534-y

Medel, V., Irani, M., Crossley, N., Ossandón, T., & Boncompte, G. (2023). Complexity and 1/f slope jointly reflect brain states. *Scientific Reports*, *13*(1), 21700. https://doi.org/10.1038/s41598-023-47316-0

Mejias, J. F., Murray, J. D., Kennedy, H., & Wang, X.-J. (2016). Feedforward and feedback frequency-dependent interactions in a large-scale laminar network of the primate cortex. *Science Advances*, *2*(11), e1601335. https://doi.org/10.1126/sciadv.1601335

Mesulam, M. M. (1998). From sensation to cognition. *Brain: A Journal of Neurology*, *121 (Pt 6)*, 1013–1052. https://doi.org/10.1093/brain/121.6.1013

Nieuwenhuys, R., Voogd, J., & van Huijzen, C. (2008). Telencephalon: Neocortex. In *The Human Central Nervous System* (pp. 491–679). Springer. https://doi.org/10.1007/978-3-540-34686-9_15

O'Donnell, P. (2010). Adolescent Maturation of Cortical Dopamine. *Neurotoxicity Research*, *18*(3), 306–312. https://doi.org/10.1007/s12640-010-9157-3

Palomero-Gallagher, N., Amunts, K., & Zilles, K. (2015, January). Transmitter Receptor Distribution in the Human Brain. In *Brain Mapping* (pp. 261–275). Academic Press. https://doi.org/10.1016/B978-0-12-397025-1.00221-9

Paquola, C., Bethlehem, R., Seidlitz, J., Wagstyl, K., Romero-Garcia, R., Whitaker, K., Vos De Wael, R., Williams, G., Vértes, P., Margulies, D., Bernhardt, B., & Bullmore, E. (2019). Shifts in myeloarchitecture characterise adolescent development of cortical gradients. *eLife*, *8*. https://doi.org/10.7554/eLife.50482

Paquola, C., Royer, J., Lewis, L. B., Lepage, C., Glatard, T., Wagstyl, K., DeKraker, J., Toussaint, P.-J., Valk, S. L., Collins, L., Khan, A. R., Amunts, K., Evans, A. C., Dickscheid, T., & Bernhardt, B. (2021). The BigBrainWarp toolbox for integration of BigBrain 3D histology with multimodal neuroimaging. *eLife*, *10*, e70119. https://doi.org/10.7554/eLife.70119

Paquola, C., Vos De Wael, R., Wagstyl, K., Bethlehem, R. A. I., Hong, S.-J., Seidlitz, J., Bullmore, E. T., Evans, A. C., Misic, B., Margulies, D. S., Smallwood, J., & Bernhardt, B. C. (2019). Microstructural and functional gradients are increasingly dissociated in transmodal cortices. *PLOS Biology*, *17*(5), e3000284. https://doi.org/10.1371/journal.pbio.3000284

Parker, N., Patel, Y., Jackowski, A. P., Pan, P. M., Salum, G. A., Pausova, Z., Paus, T., & Saguenay Youth Study and the IMAGEN Consortium. (2020). Assessment of Neurobiological Mechanisms of Cortical Thinning During Childhood and Adolescence and Their Implications for Psychiatric Disorders. *JAMA Psychiatry*, *77*(11), 1127–1136. https://doi.org/10.1001/jamapsychiatry.2020.1495

Paus, T. (2018). Imaging microstructure in the living human brain: A viewpoint. *NeuroImage*, *182*, 3–7. https://doi.org/10.1016/j.neuroimage.2017.10.013

Paus, T. (2023). Tracking Development of Connectivity in the Human Brain: Axons and Dendrites. *Biological Psychiatry*, *93*(5), 455–463. https://doi.org/10.1016/j.biopsych.2022.08.019

Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews Neuroscience*, *9*(12), 947–957. https://doi.org/10.1038/nrn2513

Perica, M. I., Calabro, F. J., Larsen, B., Foran, W., Yushmanov, V. E., Hetherington, H., Tervo-Clemmens, B., Moon, C.-H., & Luna, B. (2022). Development of frontal GABA and glutamate supports excitation/inhibition balance from adolescence into adulthood. *Progress in Neurobiology*, 102370. https://doi.org/10.1016/j.pneurobio.2022.102370

Petanjek, Z., Judas, M., Kostović, I., & Uylings, H. B. M. (2008). Lifespan alterations of basal dendritic trees of pyramidal neurons in the human prefrontal cortex: A layer-specific pattern. *Cerebral Cortex (New York, N.Y.: 1991)*, *18*(4), 915–929. https://doi.org/10.1093/cercor/bhm124

Rakic, P. (2009). Evolution of the neocortex: A perspective from developmental biology. *Nature Reviews Neuroscience*, *10*(10), 724–735. https://doi.org/10.1038/nrn2719

Ritter, P., Schirner, M., McIntosh, A. R., & Jirsa, V. K. (2013). The Virtual Brain Integrates Computational Modeling and Multimodal Neuroimaging. *Brain Connectivity*, *3*(2), 121–145. https://doi.org/10.1089/brain.2012.0120

Rolls, E. T., & Deco, G. (2011). A computational neuroscience approach to schizophrenia and its onset. *Neuroscience & Biobehavioral Reviews*, *35*(8), 1644–1653. https://doi.org/10.1016/j.neubiorev.2010.09.001

Rutherford, S., Fraza, C., Dinga, R., Kia, S. M., Wolfers, T., Zabihi, M., Berthet, P., Worker, A., Verdi, S., Andrews, D., Han, L. K., Bayer, J. M., Dazzan, P., McGuire, P., Mocking, R. T., Schene, A., Sripada, C., Tso, I. F., Duval, E. R., … Marquand, A. F. (2022).

Charting brain growth and aging at high spatial precision. *eLife*, *11*, e72904. https://doi.org/10.7554/eLife.72904

Saberi, A., Paquola, C., Wagstyl, K., Hettwer, M. D., Bernhardt, B. C., Eickhoff, S. B., & Valk, S. L. (2023). The regional variation of laminar thickness in the human isocortex is related to cortical hierarchy and interregional connectivity. *PLOS Biology*, *21*(11), e3002365. https://doi.org/10.1371/journal.pbio.3002365

Saberi, A., Wischnewski, K. J., Jung, K., Lotter, L. D., Schaare, H. L., Banaschewski, T., Barker, G. J., Bokde, A. L. W., Desrivières, S., Flor, H., Grigis, A., Garavan, H., Gowland, P., Heinz, A., Brühl, R., Martinot, J.-L., Martinot, M.-L. P., Artiges, E., Nees, F., ... Valk, S. L. (2025). Adolescent maturation of cortical excitation-inhibition ratio based on individualized biophysical network modeling. *Science Advances*, Accepted for publication.

Scholtens, L. H., Schmidt, R., Reus, M. A. d., & Heuvel, M. P. v. d. (2014). Linking Macroscale Graph Analytical Organization to Microscale Neuroarchitectonics in the Macaque Connectome. *Journal of Neuroscience*, *34*(36), 12192–12205. https://doi.org/10.1523/JNEUROSCI.0752-14.2014

Sebenius, I., Dorfschmidt, L., Seidlitz, J., Alexander-Bloch, A., Morgan, S. E., & Bullmore, E. (2024). Structural MRI of brain similarity networks. *Nature Reviews Neuroscience*, 1–18. https://doi.org/10.1038/s41583-024-00882-2

Sejnowski, T. J., Churchland, P. S., & Movshon, J. A. (2014). Putting big data to good use in neuroscience. *Nature Neuroscience*, *17*(11), 1440–1441. https://doi.org/10.1038/nn.3839

Shin, J., French, L., Xu, T., Leonard, G., Perron, M., Pike, G. B., Richer, L., Veillette, S., Pausova, Z., & Paus, T. (2018). Cell-Specific Gene-Expression Profiles and Cortical Thickness in the Human Brain. *Cerebral Cortex*, *28*(9), 3267–3277. https://doi.org/10.1093/cercor/bhx197

Shipp, S. (2007). Structure and function of the cerebral cortex. *Current Biology*, *17*(12), R443–R449. https://doi.org/10.1016/j.cub.2007.03.044

Sohal, V. S., Zhang, F., Yizhar, O., & Deisseroth, K. (2009). Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature*, *459*(7247), 698–702. https://doi.org/10.1038/nature07991

Stedehouder, J., & Kushner, S. A. (2017). Myelination of parvalbumin interneurons: A parsimonious locus of pathophysiological convergence in schizophrenia. *Molecular Psychiatry*, *22*(1), 4–12. https://doi.org/10.1038/mp.2016.147

Stephan, K. E., Iglesias, S., Heinzle, J., & Diaconescu, A. O. (2015). Translational Perspectives for Computational Neuroimaging. *Neuron*, *87*(4), 716–732. https://doi.org/10.1016/j.neuron.2015.07.008

Stiles, J., & Jernigan, T. L. (2010). The Basics of Brain Development. *Neuropsychology Review*, *20*(4), 327–348. https://doi.org/10.1007/s11065-010-9148-4

Sydnor, V. J., Larsen, B., Bassett, D. S., Alexander-Bloch, A., Fair, D. A., Liston, C., Mackey, A. P., Milham, M. P., Pines, A., Roalf, D. R., Seidlitz, J., Xu, T., Raznahan, A., & Satterthwaite, T. D. (2021). Neurodevelopment of the association cortices: Patterns, mechanisms, and implications for psychopathology. *Neuron*. https://doi.org/10.1016/j.neuron.2021.06.016

Toyoizumi, T., Miyamoto, H., Yazaki-Sugiyama, Y., Atapour, N., Hensch, T. K., & Miller, K. D. (2013). A Theory of the Transition to Critical Period Plasticity: Inhibition Selectively Suppresses Spontaneous Activity. *Neuron*, *80*(1), 51–63. https://doi.org/10.1016/j.neuron.2013.07.022

Trakoshis, S., Martínez-Cañada, P., Rocchi, F., Canella, C., You, W., Chakrabarti, B., Ruigrok, A. N., Bullmore, E. T., Suckling, J., Markicevic, M., Zerbi, V., MRC AIMS Consortium, Baron-Cohen, S., Gozzi, A., Lai, M.-C., Panzeri, S., & Lombardo, M. V. (2020). Intrinsic excitation-inhibition imbalance affects medial prefrontal cortex differently in autistic men versus women. *eLife*, *9*, e55684. https://doi.org/10.7554/eLife.55684

Trampel, R., Bazin, P.-L., Pine, K., & Weiskopf, N. (2019). In-vivo magnetic resonance imaging (MRI) of laminae in the human cortex. *NeuroImage*, *197*, 707–715. https://doi.org/10.1016/j.neuroimage.2017.09.037

Uhlhaas, P. J., Roux, F., Rodriguez, E., Rotarska-Jagiela, A., & Singer, W. (2010). Neural synchrony and the development of cortical networks. *Trends in Cognitive Sciences*, *14*(2), 72–80. https://doi.org/10.1016/j.tics.2009.12.002

Valk, S. L., Xu, T., Margulies, D. S., Masouleh, S. K., Paquola, C., Goulas, A., Kochunov, P., Smallwood, J., Yeo, B. T. T., Bernhardt, B. C., & Eickhoff, S. B. (2020). Shaping brain structure: Genetic and phylogenetic axes of macroscale organization of cortical thickness. *Science Advances*, *6*(39), eabb3417. https://doi.org/10.1126/sciadv.abb3417

Valk, S. L., Xu, T., Paquola, C., Park, B.-y., Bethlehem, R. A. I., Vos de Wael, R., Royer, J., Masouleh, S. K., Bayrak, Ş., Kochunov, P., Yeo, B. T. T., Margulies, D., Smallwood, J., Eickhoff, S. B., & Bernhardt, B. C. (2022). Genetic and phylogenetic uncoupling of structure and function in human transmodal cortex. *Nature Communications*, *13*(1), 2341. https://doi.org/10.1038/s41467-022-29886-1

van den Heuvel, M. P., Scholtens, L. H., & Kahn, R. S. (2019). Multiscale Neuroscience of Psychiatric Disorders. *Biological Psychiatry*, *86*(7), 512–522. https://doi.org/10.1016/j.biopsych.2019.05.015

Vélez-Fort, M., Audinat, E., & Angulo, M. C. (2012). Central role of GABA in neuron-glia interactions. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *18*(3), 237–250. https://doi.org/10.1177/1073858411403317

Vezoli, J., Magrou, L., Goebel, R., Wang, X.-J., Knoblauch, K., Vinck, M., & Kennedy, H. (2021). Cortical hierarchy, dual counterstream architecture and the importance of top-down generative networks. *NeuroImage*, *225*, 117479. https://doi.org/10.1016/j.neuroimage.2020.117479

Vidal-Pineiro, D., Parker, N., Shin, J., French, L., Grydeland, H., Jackowski, A. P., Mowinckel, A. M., Patel, Y., Pausova, Z., Salum, G., Sørensen, Ø., Walhovd, K. B., Paus, T., Fjell, A. M., & Alzheimer's Disease Neuroimaging Initiative and the Australian Imaging Biomarkers and Lifestyle flagship study of ageing. (2020). Cellular correlates of cortical thinning throughout the lifespan. *Scientific Reports*, *10*(1), 21803. https://doi.org/10.1038/s41598-020-78471-3

von Economo, C. F., Koskinas, G. N., & Triarhou, L. C. (1925). *Atlas of cytoarchitectonics of the adult human cerebral cortex* (Vol. 10). Karger Basel.

Wagstyl, K., Larocque, S., Cucurull, G., Lepage, C., Cohen, J. P., Bludau, S., Palomero-Gallagher, N., Lewis, L. B., Funck, T., Spitzer, H., Dickscheid, T., Fletcher, P. C., Romero, A., Zilles, K., Amunts, K., Bengio, Y., & Evans, A. C. (2020). BigBrain 3D atlas of cortical layers: Cortical and laminar thickness gradients diverge in sensory and motor cortices. *PLOS Biology*, *18*(4), e3000678. https://doi.org/10.1371/journal.pbio.3000678

Wan, B., Saberi, A., Paquola, C., Schaare, H. L., Hettwer, M. D., Royer, J., John, A., Dorfschmidt, L., Bayrak, Ş., Bethlehem, R. A. I., Eickhoff, S. B., Bernhardt, B. C., & Valk, S. L. (2024, April). Microstructural asymmetry in the human cortex. https://doi.org/10.1101/2024.04.08.587194

Wang, P., & Knösche, T. R. (2013). A Realistic Neural Mass Model of the Cortex with Laminar-Specific Connections and Synaptic Plasticity – Evaluation with Auditory Habituation. *PLOS ONE*, *8*(10), e77876. https://doi.org/10.1371/journal.pone.0077876

Wang, X.-J. (2020). Macroscopic gradients of synaptic excitation and inhibition in the neocortex. *Nature Reviews. Neuroscience*, *21*(3), 169–178. https://doi.org/10.1038/s41583-020-0262-x

Wei, Y., Scholtens, L. H., Turk, E., & van den Heuvel, M. P. (2018). Multiscale examination of cytoarchitectonic similarity and human brain connectivity. *Network Neuroscience*, *3*(1), 124–137. https://doi.org/10.1162/netn_a_00057

Wu, Y. K., Miehl, C., & Gjorgjieva, J. (2022). Regulation of circuit organization and function through inhibitory synaptic plasticity. *Trends in Neurosciences*, *0*(0). https://doi.org/10.1016/j.tins.2022.10.006

Yeo, B. T. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–1165. https://doi.org/10.1152/jn.00338.2011

Zhang, S., Larsen, B., Sydnor, V. J., Zeng, T., An, L., Yan, X., Kong, R., Kong, X., Gur, R. C., Gur, R. E., Moore, T. M., Wolf, D. H., Holmes, A. J., Xie, Y., Zhou, J. H., Fortier, M. V., Tan, A. P., Gluckman, P., Chong, Y. S., … Yeo, B. T. T. (2024). In vivo whole-cortex marker of excitation-inhibition ratio indexes cortical maturation and cognitive ability in youth. *Proceedings of the National Academy of Sciences*, *121*(23), e2318641121. https://doi.org/10.1073/pnas.2318641121

Acknowledgments

I want to thank all who have helped and supported me during my PhD.

I am especially grateful to my mentors, Dr. Sofie Valk and Prof. Dr. Simon Eickhoff, who provided great support in designing and conducting this research, gave me the freedom and confidence to explore new ideas, and created a collaborative and inspiring research environment within both our group and institute, which I greatly enjoyed. I would also like to thank Prof. Dr. Leonhard Schilbach, my PhD co-supervisor, for his helpful guidance during my PhD.

Thank you to my former mentor Dr. Masoud Tahmasian, who introduced me to the field of neuroimaging, and offered both professional guidance and personal support to help me get adjusted to life in Germany at the start of this journey.

This research would not have been possible without the contributions of my co-authors, to whom I am very grateful. My thanks also go to the Data and Platforms group at INM-7, whose support in managing the IT infrastructure was fundamental to this research. Additionally, I appreciate the support of Jülich Supercomputing Center and the Max Planck Computing and Data Facility. I am also thankful to those who contributed to collecting the data used in this research, as well as the study participants.

A huge thank you to my colleagues and friends from the Neurobiosocial / Cognitive Neurogenetics group, INM-7, and MPI-CBS, Meike, Alex, Neville, Bin, Bianca, Katerina, Svenja, Lina, Kyesam, Thanos, Kevin, Leon, Mostafa, and many others, who made my time at the institutes both productive and enjoyable.

Lastly, I want to thank my friends and family. I am forever grateful to my parents and siblings for their unconditional support throughout my life. I also appreciate my in-laws for their kindness and support. Above all, my deepest gratitude goes to my wife, Moniba. She stood by me without hesitation when I chose to transition from clinical work to research, faced challenges in moving to Germany and completing her exams, and has been my rock throughout this entire journey.