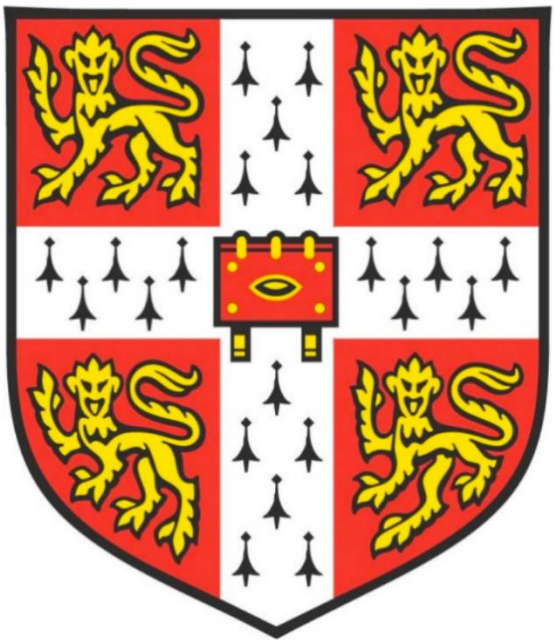
Reality Resists Classification: A Transdiagnostic, Network-Based Approach to Behavioural and Neural Variation in Childhood



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Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the preface and specified in the text. It is not substantially the same as any work that I have submitted, or is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the preface and specified in the text. It does not exceed the prescribed word limit for the Clinical Medicine Degree Committee.

Abstract

Reality Resists Classification: A Transdiagnostic, Network-Based Approach to Behavioural and Neural Variation in Childhood

By Natalia Zdorovtsova

Childhood development is shaped, and characterised, by a variety of interacting processes that encompass biological and environmental phenomena. Key developmental outcomes, such as cognitive ability and behaviour, are closely associated with the structure and function of the brain. These features of neurobiology are shaped concurrently by genetic factors, individuals' interactions with the environment, and stochastic effects that instantiate divergent trajectories of development over time. Some behavioural and cognitive profiles are recognised as being particularly divergent from the population-norm, such that they are included in clinical taxonomies of neurodevelopmental conditions. Research in developmental cognitive neuroscience, until relatively recently, has assumed that different neurodevelopmental conditions—such as ADHD, autism, and dyslexia—constitute fundamentally separate developmental trajectories, each with their own genetic, neurological, cognitive, and behavioural distinctions. However, there is considerable heterogeneity within, and overlap between, neurodevelopmental conditions, suggesting that diagnostic categories are not robust predictors of behavioural and cognitive differences between individuals. A growing number of researchers are therefore choosing to study neurodevelopmental heterogeneity in a manner that is agnostic to the presence, or absence, of formal diagnoses. This thesis builds on the current literature in developmental cognitive neuroscience by taking a *transdiagnostic* approach to studying the associations between neurology, cognition, and behaviour. We endeavoured to address these three questions:

1. Do the topological features of structural brain network connectivity differentiate children with elevated inattention and hyperactivity?
2. Do patterns of functional brain network connectivity differentiate the brains of children with elevated inattention and hyperactivity?
3. How are resting-state neural dynamics related to individual differences in behaviour and cognition?

We addressed the first two questions by analysing the relationships between structural MRI, functional MRI, cognitive, and behavioural data from the Centre for Attention, Learning, and Memory, which included participants aged 6-17 (CALM; n=383). To address our third question, we analysed the spontaneous, transient dynamics of resting-state MEG data from a sample of children aged 8-13 (n = 46). Additionally, we worked with a multidisciplinary team of academic researchers, charity leaders, educators, policymakers, and neurodivergent community partners to develop a set of freely-available online resources that help schools create inclusive educational frameworks.

Exploratory factor analysis indicated that inattention and hyperactivity are best represented as one latent factor in the CALM sample. No single component of structural brain organisation predicted linear differences in inattention and hyperactivity in our sample. However, a further analysis that combined multidimensional scaling with k-means clustering revealed two structural neural subtypes in children with elevated levels of inattention and hyperactivity (n = 232), differentiated primarily by communicability—a measure which demarcates the extent to which neural signals propagate through specific brain regions. These different clusters had similar behavioural profiles, which included high levels of inattention and hyperactivity. However, one of the clusters scored higher on multiple cognitive assessment measures of executive function. Further analyses that compared measures of localised functional connectivity between these clusters revealed no significant differences; however, between-cluster differences were found on measures of intra- and inter-network connectivity between global brain networks. In our third empirical study, we inferred a Hidden Markov Model using resting-state MEG data to investigate the relationships between neurodevelopmental features of interest and transient states of neural activity. The complexity of participants' MEG time-courses was positively related to their cognitive ability. Higher probabilities of transitioning into certain states, particularly those involving the default-mode network, fronto-parietal networks, and sensory processing regions, also predicted individual differences in cognitive ability. Finally, we completed a large public engagement project centred around neurodiversity and inclusive practices in schools. After running a multi-stakeholder workshop about barriers to learning and wellbeing in the UK, we collected

evidence-based recommendations for educational and social care policy change, which informed our comprehensive set of inclusion resources for schools.

This thesis represents an important advance towards the transdiagnostic understanding of neurodevelopmental differences. This work builds on previous research in cognitive neuroscience while placing brain network complexity and neural dynamics in a developmental context. We believe that the research and practical endeavours described here will help guide future efforts in the scientific study of neurodiversity, in addition to the creation of more equitable, evidence-based educational frameworks.

Acknowledgements

I would first like to thank my supervisor, Professor Duncan Astle, for his incredible support and guidance throughout my PhD. Before I began my research at the MRC Cognition and Brain Sciences Unit, I could not have imagined a more enriching collaborative experience. I am so grateful for your kindness, motivation, and humour throughout this entire process.

My PhD would not have been possible without the endless support of my parents, Alena Trofimova and Volodymyr Zdorovtsov, who have always encouraged me to prioritise my education. I am also thankful to my brother, Daniel Zdorovtsov, for making my life joyful. I hope that I can encourage you to pursue an educational path that inspires and invigorates you.

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List of Abbreviations and Acronyms

ADHD: Attention Deficit Hyperactivity Disorder

CEN: Central Executive Network

DMN: Default-Mode Network

EFA: Exploratory Factor Analysis

fMRI: Functional Magnetic Resonance Imaging

HMM: Hidden Markov Model

ICN: Intrinsic Connectivity Network

MEG: Magnetoencephalography

MRI: Magnetic Resonance Imaging

PLS: Partial Least Squares Regression

SEND: Special Educational Needs and Disabilities

SN: Salience Network

'Reality is infinitely diverse, compared with even the subtlest conclusions of abstract thought, and does not allow for clear-cut, sweeping distinctions. Reality resists classification.'

—Fyodor Dostoyevsky, 'The House of the Dead'

1 General Introduction

1.1 Child development and cognitive neuroscience

1.1.1 Overview of the field

Developmental cognitive neuroscience investigates the relationship between brain development and the emergence of cognitive and behavioural complexity, primarily in humans. This field draws upon many others, representing an amalgamation of epistemic activities and theoretical frameworks developed within psychology, neuroscience, informatics and computational modelling, biology, chemistry, and clinical medicine. Insights from cognitive developmental neuroscience have also been influenced by, and have contributed to, philosophical conceptions of science and mind. This tradition of multidisciplinary inclusion stems from the goal of evaluating developmental processes at various different levels of inquiry. These perspectives are complementary—rather than being limited to any particular domain of observability, developmental processes encompass a broad and varied range of interrelated phenomena. This highlights something salient about the very nature of development: while characteristics of change can be seen at all levels of observation—such as genetics, neurology, cognition, and so forth—the *interaction* between these levels is key to understanding how ontogenetic complexity comes to be. Development is not localised to the brain, or indeed to the body; it results from a unique and lifelong collaboration between an individual and their environmental context. If development can be thought of as a dance between causes and effects, then scientists can ask questions about the rhythms and forms of movement that bring this dance to life.

Much of developmental cognitive neuroscience is built on a foundation laid through the efforts of developmental psychologists. Theories of how cognitive capacities emerge across childhood development have, until about the Millennium, typically fallen into two camps: stage models, which highlight specific age-points at which certain domain-general features of cognition arise, and phase models, which describe changes within particular cognitive domains, such as language or spatial reasoning (Karmiloff-Smith, 1997). In *Beyond Modularity: A Developmental Perspective on*

Cognitive Science, the late Professor Annette Karmiloff-Smith, a former student of Piaget, writes:

> "For Piagetians, development involves the construction of domain-general changes in representational structures operating over all aspects of the cognitive system in a similar way." (p. 7)

Proponents of stage models, who often favour a domain-general view of cognitive development, take the stance that there is no particularly important distinction between identifiable cognitive modalities. In other words, they posit that 'cognition' is best represented as a single, measurable factor, and that changes in the expression of this factor can be tracked reliably across childhood. Phase models, on the other hand, carve this 'cognition factor' into several subdomains that can be assessed relatively independently. These cognitive subdomains include capacities like memory, language, and abstract or spatial reasoning. It is worthwhile to note that considering development to be domain-specific does not imply a strict functional modularity. Rather, domains can be said to effectively *constrain* cognitive development by limiting the mind's pragmatic hypothesis-space. Cognitive modules interact, enabling us to identify and manipulate different features of an informationally-rich environment. Karmiloff-Smith proposes a phase model that she terms 'Representational Redescription', in which domain-specific cognitive representations gradually become more internally-driven, adaptive, and refined as a child learns. While these representations exist within particular cognitive domains, there is also a multiple-encoding of semantic and procedural content across domains that steadily increases across developmental time. This process of 'modularisation', though which cognitive domains are both strengthened and strategically interconnected, coincides with the emergence of cognitive flexibility and abstraction, goal-oriented behavioural optimisation, and creative insight. Thus, developmental changes can be conceptualised as being both domain-specific *and* domain-general. The challenge, of course, is to understand precisely how 'the parts' interact to form 'the whole'. In 1997, when her seminal book was published, Karmiloff-Smith noted that

> "...if it turns out that across-the-board, domain-general changes do occur, we may be able to use them as a diagnostic for fundamental neural changes in the brain... The

> flourishing new field of developmental cognitive neuroscience may soon provide some of the relevant answers… Development will not turn out to be either domain-specific or domain-general. It is clearly the intricate interaction of both—more domain-general than is presupposed by most nativist/modularity views of development, but more domain-specific than Piagetian theory envisages." (p. 168)

In recent decades, neuroscience has made great strides in illuminating the mechanisms that underpin cognitive and behavioural development. Previously, psychological conceptual frameworks and methodological paradigms were the primary instruments used for mapping the features of developmental change. These 'maps', framed in terms of domain-general stages and domain-specific phases, informed descriptive theories of what can typically be expected to happen across childhood development. Neuroscience, meanwhile, builds upon these theories to provide an explanatory account of cognitive and behavioural development. In neuroscience, an 'explanatory' framework is one that can be used to reliably predict co-occurring features of behaviour, cognition, and neurology. Put very simply, what neuroscience offers is an understanding of neural mechanisms (the 'how') that may account for results reported by psychologists (the 'what'). Unified under the banner of developmental cognitive neuroscience, these co-occurring changes can be studied in the context of brain-cognition-behaviour relationships, with valuable implications for our understanding of developmental diversity, learning and educational outcomes, psychopathology, and comparative cognition. These epistemic domains, which branch from developmental cognitive neuroscience like the distributaries of a river, also feed back into our conceptualisations of *development itself*, both in terms of its observable characteristics and fundamental generative 'rules'. Practical considerations and hermeneutic breakthroughs in these areas of interest have also shaped the underlying assumptions and methodological practices that form the bread-and-butter of empirical research in the field. The study of change, itself, changes.

1.1.2 Establishing a 'baseline': ideas of typical childhood development and neural diversity

A long-existing assumption that lies at the core of developmental cognitive neuroscience is that there are 'typical' features of brain development—that is, those which occur across the vast majority of individuals in a temporally-predictable

manner. This is a fair assumption. Brain development across humans tends to exhibit a particular sequence of morphological changes. For instance, one change that constrains cortical white matter growth according to a trade-off between metabolic costs and adaptive benefits (Rubinov et al., 2015; Ma et al., 2020; Akarca et al., 2021; Liang et al., 2022). This trade-off tends to result in the emergence of certain consistencies in brain network topology across individuals and developmental timescales. Additionally, changes in domain-specific cognitive abilities and behavioural tendencies can be tracked according to the achievement of age-expected milestones (Denham, 1986; Dyck et al., 2007).

It is easy to assume that a trend robustly observed across individuals could constitute a 'typical developmental trajectory'. However, this assumption—while intuitive, and perhaps alluring in its parsimony—can sometimes be problematic. Unhesitatingly defining a general neurodevelopmental trend as a feature of 'typical' childhood development leads to a difficult question: what is it that makes children who deviate from this 'baseline' pattern *atypical*? The primary issue with this conflation of 'average' and 'typical' is that it neglects the reality of neurodevelopmental diversity—no individual develops precisely in accordance with a template of 'typicality', and differences between individuals should not automatically be interpreted as signs of deviation from a norm. While typical value ranges can be defined within specific cognitive, behavioural, and neurological domains, developmental heterogeneity is a feature of human populations (Linder et al., 2008; Li et al., 2009; Reardon et al., 2018; Eze et al., 2021). And, although mean values may usefully summarise the average features of a sample, they nonetheless fail to capture the possibility of neural, cognitive, and behavioural diversity. It is therefore key to consider *significant* deviations from the mean, as well as inter-individual variance in scores for a given measure, when attempting to define what it means to be 'atypically-developing'. Ultimately, creating a clear cut-off between developmental 'typicality' and 'atypicality' could result in crude and impractical distinctions being made, since individuals are capable of varying across a broad range of different measures. To what degree must someone differ within a particular domain of cognition or behaviour before they are labelled fundamentally 'atypical' with respect to the rest of the population? Or, if an individual shows a very small (but significant) degree of difference across multiple

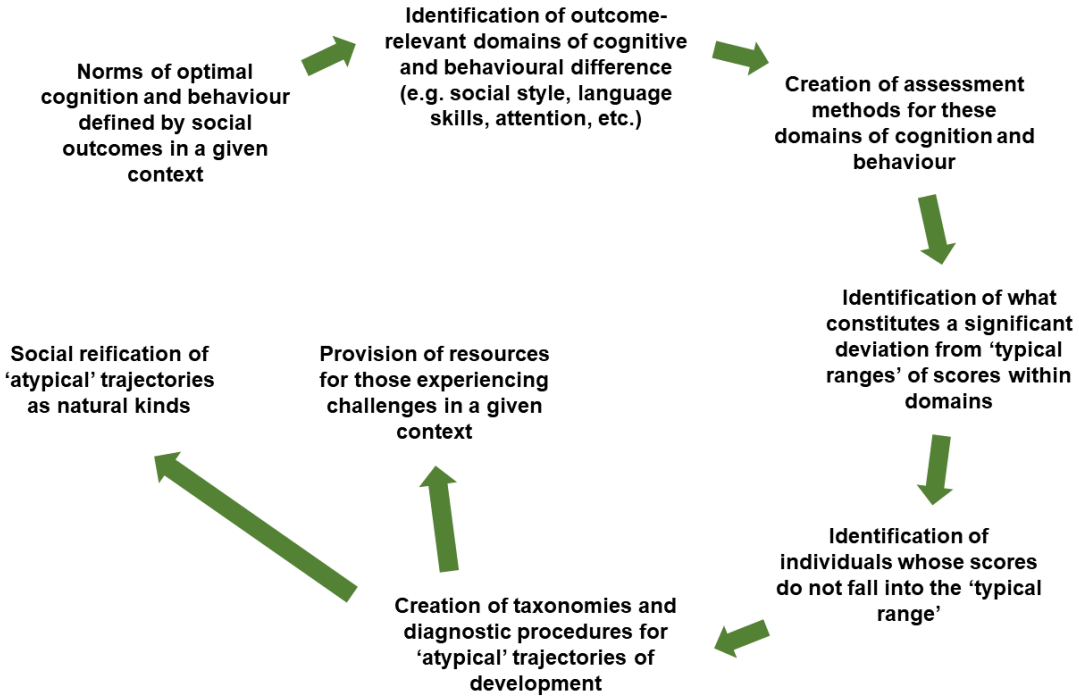
domains, at what point can they be said to exhibit an 'atypical developmental profile'? And, most importantly, when do these differences start to *matter*?

The challenge of classifying 'typicality' versus 'atypicality' has always been a pragmatic one; indeed, the identification of domains in which deviations from the norm begin to *matter* is usually based on context-dependent outcomes, which are given their value through the delineation of particular aims. Norms concerning socially-acceptable types of cognition and behaviour are defined by what our environmental contexts demand of us: that is, the forms of thinking and subsequent behaviours that allow us to navigate a rich and complex social environment, meet our needs, and potentially adapt to change (Neely-Prado et al., 2019; Constantino et al., 2021). In modern, industrialised societies, the ability to remain physically still in a classroom setting, sustain attention, read, write, and engage in abstract reasoning are commonly regarded as outcome-relevant domains of cognition and behaviour (Conrad & Potter, 2000; Ferriman Robertson et al., 2010). Because these abilities are important to an individual's flourishing within a societal context, assessment methods have been created to measure and monitor performance within these domains. As such, it has been possible to identify typical ranges of performance, as well as age-relevant milestones, within and across particular areas of cognition and behaviour (Slater et al., 1989; Thornton & Lukas, 2012; Hartshorne & Germine, 2015). Examining the extremes of these distributions further enables the identification of individuals who exhibit 'atypical' scores within certain domains.

Since assessments of cognition and behaviour are created on the basis that they measure something *functionally important* about an individual, it is often the case that those who deviate from the 'typical range' of scores also experience challenges in educational, occupational, and social settings. As a result, researchers, educators, and clinicians have produced taxonomies of neurodevelopmental difference, which mainly exist in the form of diagnostic labels and criteria. This type of labelling can facilitate the provision of resources for those encountering difficulties in a certain context. These may come, for instance, in the form of additional help in the classroom for a child struggling to read, or workplace adjustments for an adult experiencing sensory hypersensitivity (Southall, 2013; Jacobs et al., 2018). However, categorising forms of developmental difference can also result in the amplification of perceived distinctions

between 'typically-developing' versus 'atypically-developing' individuals. Through this process, diagnostic categories for neurodevelopmental conditions—which represent patterns of deviation from behavioural and cognitive 'normalcy', based on societally-preferred outcomes—can gain a sense of deeply-rooted ontological weight. As a consequence, 'typically-developing' versus 'atypically-developing', or 'Diagnosis A' versus 'Diagnosis B', can incorrectly come to be viewed, or treated, as natural kinds, which exist irrespective of the interests and actions of human beings (see Figure 1.1; for a further discussion of natural kinds, and the philosophical ambiguities surrounding their classification, see Kendig & Grey, 2021). Throughout this thesis, I argue that it is in the interest of developmentalists to reach beyond strict definitions of what it means to develop 'typically' in favour of a dimensional perspective. Theories which take a dimensional view, as opposed to one that applies top-down assumptions about individuals' placements within strict categories, examine how people differ across many domains of cognition, behaviour, and neurology. In section 1.2, I will discuss how characterising development in terms of cognitive and behavioural dimensions, rather than discrete categories, is one practice that characterises transdiagnostic research methodologies.

Figure 1.1: A simplified sequence through which outcome-relevant norms of cognition and behaviour, and deviations from those norms, might be defined and later reified in the form of diagnostic categories. Of course, many outcome-relevant domains of cognition are implicit, and it is sometimes the observation of individuals' deviations from cognitive norms that inspires the creation of cognitive assessment methods and forms of diagnostic categorisation.



1.1.3 Neurodevelopmental dimensions of interest

1.1.3.1 Cognition

Cognition is a broad term that describes various mental processes, including memory, attention, learning, decision-making, cognitive control, social cognition, and language. Additionally, the term 'cognition' has been used to refer to domain-general abilities, particularly in the context of general intelligence (Mishra et al., 1983; Duncan et al., 2000; Colom et al., 2010; Assem et al., 2020). Traditional perspectives in psychology and cognitive science have had the tendency to treat cognitive processes as categorically distinct from embodied (sensory-motor) and behavioural phenomena. According to this view, cognitive processes are computational in nature: amodal, propositional, and compositional (Smith & Sheya, 2010). On the surface, this view

reduces the varied dimensions of mental life to sensing, thinking, and acting, with cognition accounting for the computational processes governing thought (Pylyshyn, 1980). When considering the metaphysical intelligibility of a perspective such as this, it is important to remember that 'cognition', 'behaviour', and similar psychological terms merely describe constructs that can be used to represent useful features of the world. The degree of their tangibility, in a physical sense, is less important than their ability to facilitate sense-making in the context of scientific theorising and practice. Cognition—as a collection of mental processes, like memory, attention, or language—*is* a useful term, in a very pragmatic sense, because it allows us to explore finer-grained relationships between perception, thought, and action. This does not imply that cognition is *causally-separate* from embodied or behavioural phenomena; indeed, it is only meaningful to define 'cognition' as a level of intermediate processing that takes input from, and interacts dynamically with, both perception and behaviour (Bickhard, 2015). Throughout this thesis, I will argue that cognition, defined as an individual's *ability* to successfully engage with tasks that require them to recruit certain mental processes, can capture valuable features of childhood development. Defining and measuring cognitive sub-processes provides a window into inter-individual variance, potentially shedding light onto the dimensional characteristics of different profiles of neurodevelopmental change.

One of the things we might associate with 'atypical' childhood development is a difference in cognitive ability—both in terms of domain-general intelligence and cognitive flexibility, but also in the case of specific cognitive domains. Indeed, the way that we frame our definitions of what constitutes various neurodevelopmental conditions is highly dependent on the cognitive differences that we can observe between individuals. Peculiarities in behaviour are often framed as issues that stem from cognitive roots, and researchers have worked to understand how differences in cognition may 'produce' downstream behavioural effects and learning outcomes (Toates, 2006; Constantino et al., 2021). As discussed previously, cognition and behaviour represent theoretically separate, though causally intertwined, constructs within the mental sciences. The feedback loop between perception, computation, and action is ultimately what facilitates adaptation and learning within a given environmental context (Friston et al., 2010; Barela et al., 2011; Wang et al., 2015; Zhang et al., 2015; Jaswal, 2016; Kahl & Kopp, 2018). Cognitive differences are

therefore capable of impacting many aspects of an individual's psychological profile—and, indeed, the very means by which an individual interacts with the world. Below, I will give an account of cognitive differences in two neurodevelopmental conditions: Williams Syndrome and Autism Spectrum Disorder (hereafter 'autism'). I do this not for the sake of drawing stark boundaries between these neurodevelopmental conditions, but rather, to provide a holistic picture of how the perception, cognition, and behaviour can interact to produce particular developmental phenotypes that we observe 'out in the world'.

Williams Syndrome (WS) is a rare genetic microdeletion condition that occurs in approximately one out of every 7,500 individuals. WS has a range of physiological and cognitive markers, including intellectual disability and hypersociability (Kozel et al., 2021). Those with WS have been observed to have domain-specific difficulties in visuospatial reasoning and working memory, despite having no profound global difficulties in social or linguistic cognition (Palomares et al., 2008; Farran & Karmiloff-Smith, 2012; Foti et al., 2020; Serrano-Juárez et al., 2020). In other words, those with WS have what is sometimes called an 'uneven' cognitive profile, with atypical performance appearing only in certain domains. As Van Herwegen (2015) notes, however, this cognitive profile could result from a number of developmental differences that unfold across the lifespan. Namely, it has been suggested that domain-general cognitive tendencies, like sticky fixation and saccade planning difficulties, influence how domain-specific cognitive difficulties emerge over time (Brown et al., 2003). This is an important point that I will return to later in this section—the idea that broad difficulties that exist across cognitive domains can emerge from more primary, domain-specific differences that, over time, put selective constraints on an individual's interactions with the environment.

Autism is another neurodevelopmental condition with domain-specific cognitive features. The prevalence of autism has been estimated to be approximately 2%, although changing diagnostic standards and potential bias in the clinical diagnostic process make this metric somewhat ambiguous (Begeer et al., 2008; Kim et al., 2011). The main features of autism include differences in social cognition, communication, and sensory processing (Marco et al., 2011; Park et al., 2016). Though autism can co-occur alongside any other condition, it is not defined by intellectual disability (Crowley

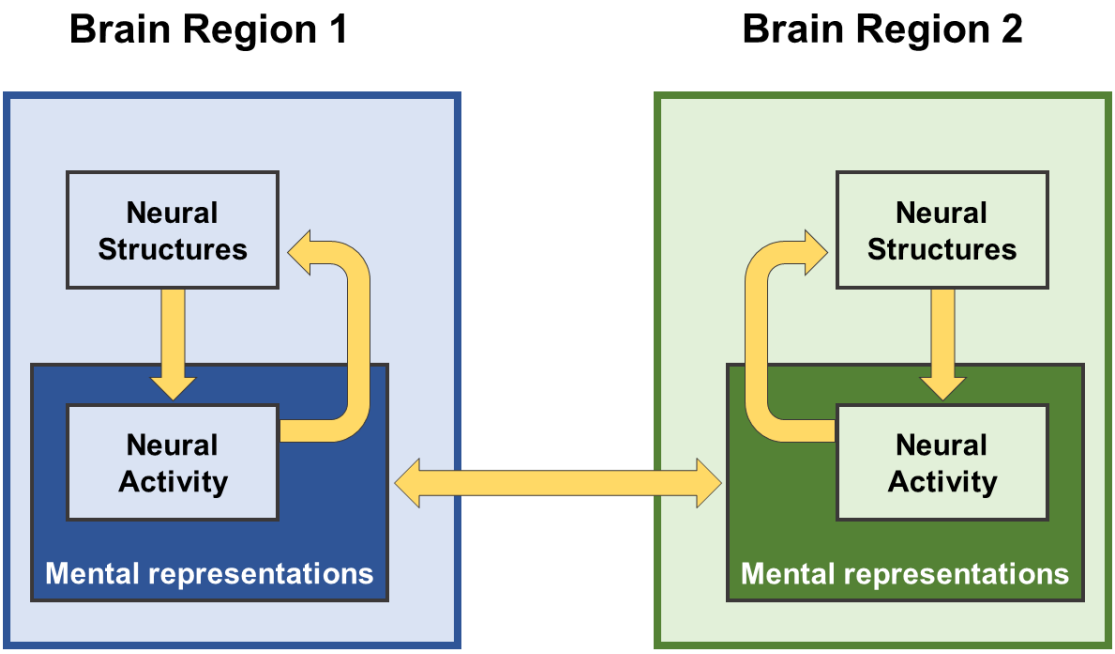
et al., 2018). However, multiple studies have suggested that initial social communication difficulties can have downstream effects on other areas of cognition. This can result in growing cognitive dissociations between, for instance, verbal versus nonverbal autistic individuals with age (Joseph et al., 2002; Vivanti et al., 2013). Additionally, the high incidence of psychiatric disorders among autistic people (up to 77%; Eaves & Ho, 2008) may be attributable to both innate cognitive differences *and* the lived experience of being autistic in a profoundly non-autistic world. On the one hand, sensory processing differences may result in an inability to maintain a subtle awareness of one's physical and mental states. This phenomenon is known as alexithymia, and it has been found to limit autistic individuals' ability to engage in emotional regulation (Morie et al., 2019). Additionally, differences in social and emotional cognition in autism can be partially explained by how an individual interacts with the world—and, crucially, with other people. Bullying due to social differences, the stigma of the 'autism' label, and feelings of social exclusion have all been found to contribute to autistic mental health difficulties (Cage et al., 2018). In this sense, it is clear that the cognitive phenotype of autism—one that includes social, sensory, and emotional processing differences—develops in a manner that depends on an individual's environmental context. As an individual interacts with their unique environment, more noticeable and domain-specific cognitive effects begin to emerge.

A great deal of research in developmental cognitive neuroscience has been dedicated to investigating exactly *how* individual cognitive differences arise, and what *about* these differences comes to shape development in such a major way. In other words, there has been a push to understand how the general architecture of cognition can facilitate complex, dynamic, and flexible forms of information processing. What kinds of computations could we say that the mind is performing when we engage in tasks with cognitively-demanding features? What is the central nervous system actually *doing* in order to support these computations? To explore how these questions might be answered, a useful terminology concerning the existence of *mental representations* has been developed. Mental representations are abstract 'information-bearing' structures that can[1] be tied to a range of embodied processes, including those that take place in the brain (Pitt, 2020). The idea of a mental representation has been highly

[1] Though do not need to be.

applicable to computational research in cognitive neuroscience, since it allows for the development of highly abstract, information-theoretic conceptions of cognitive processes (Piccinini, 2018). Representationalism has also shaped an emerging theoretical framework called neuroconstructivism, which strives to explain how mental representations are gradually constructed and refined in the developing brain. Neuroconstructivists give an account of cognitive development that is intimately tied to the formation of *experience-dependent* neural structures: ones which result from the dynamic feedback loop between perception, cognition, and action (Westermann et al., 2007). This framework posits that developmental trajectories originate from interactions between different constraints—both internally-generated and externally-imposed—that act upon neural physiology and gradually shape the structure of mental representations (Johnson, 2005a; Gottlieb, 2007). Importantly, neuroconstructivists take the view that mental representations are tied to the *activity* of certain neural structures, which develop interactively and exhibit a pattern of increasing modularity according to function (see Figure 1.2). This point is a particularly profound one, and it has influenced many of the ideas and interpretations of empirical findings that I present in later sections of this thesis.

Figure 1.2: Schematic of the process of 'embrainment' (Johnson, 2005a), adapted from Westermann et al. (2007), which describes how functional brain areas develop through an interchange of information, conveyed through mental representations that are generated by the anatomical structure and activity of brain regions.



The neuroconstructivist framing of development can be readily incorporated within explanations of how domain-general and domain-specific cognitive processes differ between individuals and change over time, particularly in the case of neurodevelopmental conditions. Consider, again, the case of Williams Syndrome. Based on my previous account of the condition, cognitive differences in those with WS are domain-specific—while visuospatial ability is affected, social cognition and language remain comparatively unaffected. One basic explanation we might provide for this observation is that neurodevelopmental conditions are characterised by differences within specific 'modules' of cognition. Within this framing, higher-order functions are the most relevant points of difference throughout development; that is, visuospatial ability is the *core* feature being 'acted upon' by various internally- and externally-driven developmental processes. This gives us a set of ideas about the nature of neurodevelopment in WS, and guides scientific inquiry in a certain direction. For instance, we may try to measure differences in visuospatial ability between

individuals, and then proceed in a top-down manner to uncover some of its correlates in the brain and genome. We might then predict that individuals who possess a particular genetic variant will exhibit difficulties with visuospatial reasoning, and conclude that this must be the 'gene for' visuospatial ability (Mitchell, 2007).

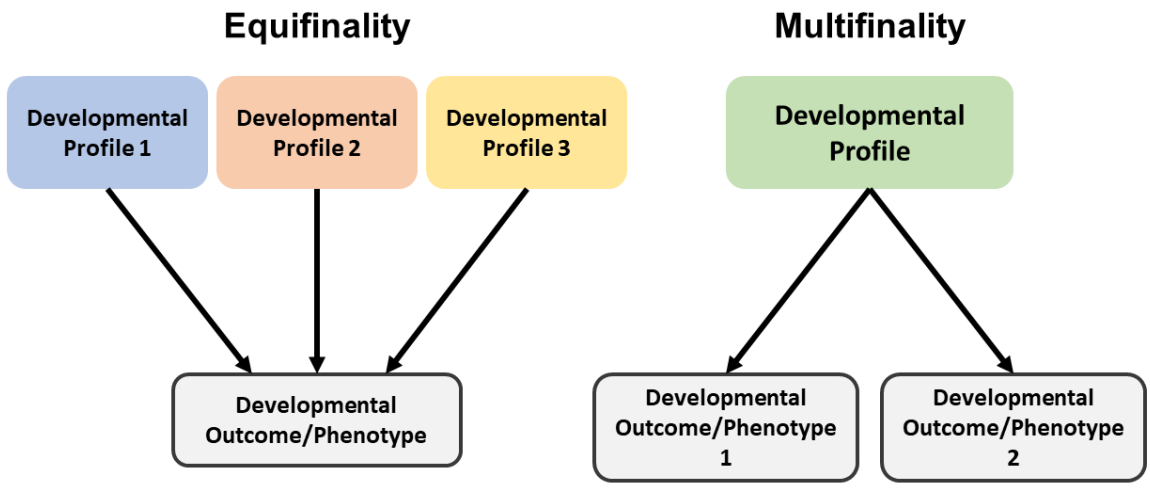
What I want to emphasise here is that this traditional perspective takes a *static* view of neurodevelopment. Rather than considering the dynamics of developmental change *over time*, it assumes that there is a clear, isomorphic mapping between genes, the brain, and cognition that exists independently of experience and interaction with the world. Additionally, the traditional perspective assumes that so-called cognitive deficits are intrinsically latent *within* cognitive domains themselves. As a result, differences in a particular cognitive domain are treated somewhat as 'core deficits', which happen to manifest themselves in different ways depending on an individual's developmental stage. Unfortunately, this assumption could potentially lead us to some oversimplistic conclusions about the complex and diverse nature of neurodevelopmental change.

Neuroconstructivism puts forward a different, and potentially more useful, perspective. In this framework, *small* and *primary-level* differences, which do not have an intrinsic, causal bearing on higher-order cognitive domains, can have cascading effects on various features of cognition across development (D'Souza & Karmiloff-Smith, 2017). Crucially, these cascading effects emerge from an individual's *interaction* with the environment over time. This interactive process may certainly result in significant differences within specific cognitive domains while performance in other domains remains in the typical range. However, it would be imprecise to assume that a major 'core deficit' within any given cognitive domain, specified from the start of development, is what really drives the emergence of a particular cognitive phenotype. Rather, very subtle and basic differences in the initial conditions of life, combined with a highly contextualised, embodied, and interactive process of development, produces the profound cognitive variability that we see between individuals.

The neuroconstructivist perspective gives us a different set of scientific motivations and predictions, too. Instead of attempting to find consistent one-to-one mappings

between specific genetic, neurological, and cognitive factors, we can accept that small individual differences—often undetectable, and situated within the context of subjective experience—can have considerable downstream effects on development. This also opens the doors to considerations of the *equifinality* and *multifinality* of developmental outcomes (see Figure 1.3). Equifinality refers to the idea that a diverse range of pathways, or initial conditions, could result in the same outcome—for instance, there are many combinations of genetic, neurological, and experiential conditions that could lead to a certain cognitive phenotype (Jordan-Arthur, 2015). Multifinality suggests the opposite kind of relationship, in which similar initial conditions could nonetheless result in a diverse range of outcomes (Cicchetti & Rogosch, 1996). Equifinality and multifinality in neurodevelopmental outcomes can be studied through the integration of findings at multiple levels of observation, particularly through the use of large developmental consortia (Astle & Fletcher-Watson, 2020).

Figure 1.3: Basic schematic representing how equifinality and multifinality could both describe processes by which different developmental trajectories emerge. The 'developmental profiles' depicted here can be defined by any relevant feature of investigation, including genetics, neurology, cognition, behaviour, and environmental context.



The challenge of understanding development in the context of equifinality and multifinality lies in bridging the explanatory gaps between genetics, the brain,

cognition, behaviour, and the environment. After all, it is the *close interaction* between these levels that characterises each individual's developmental trajectory. If there is no 'one path' towards any particular cognitive phenotype, then researchers should work towards an understanding of how subtle, time-dependent relationships between different factors bring about developmental diversity.

This thesis uses principles from neuroconstructivist theory to explore the correspondence between brain structure, brain function, cognition, and behaviour. The first empirical chapter of this thesis, specifically, outlines how equifinality may be used to describe the associations between behaviour and brain structure in a sample of highly inattentive and hyperactive individuals. In the next section, I turn to an explanation of the ways in which inattention and hyperactivity—two features of behaviour that occur along a continuous spectrum across the human population—are relevant to the broader study of childhood development.

1.1.3.2 Behavioural inattention and hyperactivity

In this thesis, I have chosen to focus on two neurodevelopmentally-relevant features of behaviour in children: inattention and hyperactivity. In this section, I will discuss how researchers and clinicians tend to conceptualise these elements of behaviour, and why they are valuable the study of neurodevelopmental differences. In particular, I will focus on the fact that elevated levels of inattention and hyperactivity occur across multiple neurodevelopmental conditions, even though they are treated as the cardinal symptoms of Attention Deficit Hyperactivity Disorder (ADHD).

1.1.3.2.1 Core characteristics, measurement in ADHD, and relevance for clinical subtyping

Inattention and hyperactivity have been implicated in a range of negative social and academic outcomes, including difficulties at school, risky behaviours during childhood and adolescence, and a heightened risk for developing psychiatric health issues (Spira & Fischel, 2005; Sciberras et al., 2009; Uh et al., 2021; Tan et al., 2022). These challenges to the wellbeing of those with heightened inattention and hyperactivity have led to the creation of diagnostic categories that classify certain behaviours within a clinical framework. Attention Deficit/Hyperactivity Disorder (ADHD) is one such diagnostic category, which includes three subcategories representing clinically-

observed cognitive and behavioural subtypes: inattentive ADHD (ADHD-I), hyperactive/impulsive ADHD (ADHD-H), and combined-type ADHD (ADHD-C) (August & Garfinkel, 1989; Mattingly et al., 2021). ADHD is a complex and heterogeneous disorder that affects approximately 5-10% of children (Liu et al., 2018). Typically, it is diagnosed in childhood on the basis of elevated inattention, hyperactivity, and impulsivity (World Health Organization, 2015). Although the multidimensionality of ADHD is widely recognised, questions remain about the extent of overlap between the behavioural attributes of the condition. Before we address this more complex topic, however, we must define our terms. What *are* inattention and hyperactivity, and how are they expressed through behaviour?

Inattention is common across many clinical conditions, and is thought to be related to limitations in working memory and behavioural self-regulation (Arabaci & Parris, 2020). In the clinic, 'inattention' does not refer to isolated instances of failing to orient one's attention to a contextually-relevant stimulus. This characteristic would relate to a more cognitive definition of attentional control (Oberauer, 2019). Rather, what clinicians mean by 'inattention' is the chronic inability to stay on-task or sustain focus in goal-oriented contexts, that has an impact across more than one setting (NIMH, 2021; DSM-V, 2013). In neurodevelopmental conditions, it is known that certain characteristics of behaviour can manifest themselves in various different ways, depending on the setting (McConaughy et al., 2010). This is true of behavioural inattention, which is often first recognised in the classroom and evaluated by teachers (Staff et al., 2020). As a result, up to 85% of clinicians involved in the process of diagnosing ADHD use teacher rating scales, teacher interviews, and/or direct classroom observations (Handler & DuPaul, 2005). Additionally, clinicians may use parent rating scales and interviews in assessing a child's level of behavioural inattention. Common inventories include the Strengths and Difficulties Questionnaire (SDQ, Inattention/Hyperactivity subscale; Goodman, 1997), Behaviour Rating Inventory of Executive Function (BRIEF, Monitor subscale; Gioia et al., 2000), and Conners Questionnaire (Inattention subscale; Conners, 2008). Subjective assessments from parents and teachers may, in some cases, be combined with neuropsychological testing, which enable the objective assessment of core symptoms of ADHD (Sims & Lonigan, 2012; Emser et al., 2018). If a child shows a significant amount of inattentive behavioural traits, and comparatively fewer signs of elevated

hyperactivity, then they may receive a diagnosis of inattentive-type ADHD, or ADHD-I. This is the second most common ADHD subtype diagnosis, which accounts for 20-30% of cases (NICE, 2021).

Hyperactivity constitutes another primary feature of ADHD, and about 15% of individuals diagnosed with ADHD are classified into the hyperactive subtype (NICE, 2021). Behavioural hyperactivity describes, broadly-speaking, a state of restlessness and 'excessive motor activity', particularly in the context of movement that is not directed towards a normatively-defined goal (Ross & Ross, 1976). Hyperactivity is generally regarded as being closely related to impulsivity and difficulties in cognitive inhibition (e.g. Burley et al., 2021), but may also be tied to processes of stimulation-seeking as a means of sensory self-regulation (Antrop et al., 2000). Like inattention, hyperactivity and impulsivity are commonly assessed using the SDQ (Inattention/Hyperactivity subscale), BRIEF (Inhibit subscale), and Conners Questionnaire (Hyperactivity/Impulsivity subscale), which may be completed by parents and/or teachers. Due to the close association between hyperactivity, impulsivity, and behavioural disinhibition studies have explored how hyperactivity may impact various social outcomes. Hyperactivity and impulsivity are associated with a range of closely-related negative outcomes for those with ADHD, including peer problems at school, lower educational attainment, employment difficulties, non-medicinal drug use, addiction, and antisocial behaviour (Shaw et al., 2012; Andrade & Tannock, 2014; Vingilis et al., 2015). The identification of elevated hyperactivity and impulsivity in those with ADHD is therefore highly important, since intervention on the part of families, schools, and communities can serve as a protective factor against these outcomes (Duh-Leong et al., 2020).

The third and most common form of ADHD is described as the combined subtype, or ADHD-C. This subtype accounts for approximately 50-75% of cases of ADHD (NICE, 2021), suggesting that inattention and hyperactivity are often observed as co-occurring, rather than separate, features of behaviour. Due to the very high proportional prevalence of ADHD-C, especially compared to that of ADHD-H, the validity and reliability of ADHD subtypes have been called into question (Woo & Rey, 2005; Nigg et al., 2010). While inattention and hyperactivity may often represent two highly-correlated characteristics, children with ADHD vary considerably in their

behavioural features, developmental trajectories, and clinical outcomes in a way that is not tracked by currently-existing diagnostic subtypes (Karalunas & Nigg, 2020). For instance, Tucha et al. (2006) found that children with ADHD-H and ADHD-C have significant, and similar, levels of attentional impairment compared to non-ADHD controls. This suggests a strong overlap between the behavioural profiles of these two ADHD subtypes, at least with regard to inattention-related symptom presentation and performance on a sustained attention task. Gibbins et al. (2010) found a similar trend in their adult ADHD sample, where those who had initially been diagnosed with ADHD-H and ADHD-C as children eventually came to exhibit comparable levels of both inattention and hyperactivity. One explanation for these findings may be the fact that ADHD subtypes tend to show poor temporal stability, as significant behavioural changes occur across development (e.g. Lahley et al., 2005; Todd et al., 2008). In the earlier stages of development, an individual may exhibit a tendency towards elevated inattention *or* hyperactivity, but it is not difficult to see how a co-presentation of these features could eventually be reached. If a child starts out primarily hyperactive, then their restless behaviour may pose issues within the classroom, where sustained, focused attention is best kept by remaining still—that is, orienting one's body towards the teacher, sitting in a chair, and continuously performing one type of motor action (like writing). Meanwhile, if a child begins with a higher tendency towards inattention, they could begin to exhibit hyperactivity-related behaviours as a result of boredom and disengagement from tasks set in the classroom. As a result, the behavioural phenotype of ADHD can be said to 'gravitate towards' the combined type, both in terms of its observed incidence within the population and its increasing proportional prevalence with age. Behavioural differences do not exist in isolation—they shape how an individual interacts with the world, which in turn affects how behavioural tendencies change over time. Even if an individual does not 'start out' with a particular set of traits, they may emerge as a result of context-dependent interactions, gradually shifting that individual's unique profile of differences and needs. It is worth noting, however, that both inattention and hyperactivity appear to broadly become less severe across childhood development, despite the possible interaction between these traits (Kofler et al., 2016; Wootton et al., 2022).

It has also been pointed out that the detection of hyperactivity symptoms is highly related to the context in which behavioural reports are being completed. Discrepancies

in parent versus teacher ratings of ADHD symptoms are common, and it has been suggested that these two observer types might even be capturing altogether different dimensions of children's behaviour, with parents reporting higher levels of hyperactivity (Hartman et al., 2007; Murray et al., 2018). Murray et al. (2019) argue that this stems from the somewhat mundane fact that children tend to exhibit different types of behaviours at school versus at home, depending on what is deemed contextually-appropriate and socially permissible. Hyperactivity, in particular, may be the more contextually-variable of ADHD-related behaviours. Counter to clinical accounts of ADHD in the DSM-5, a meta-analysis performed by Kofler et al. (2016) showed that hyperactivity is neither contextually-ubiquitous, nor a sufficiently-powerful differentiator of ADHD subtypes. It is therefore possible that children diagnosed with ADHD-I or ADHD-H could still be experiencing elevated inattention *and* hyperactivity, and that the co-presentation of these traits is often missed due to (1) the observed dominance of one feature over the other, (2) context/observer-dependent ratings, or (3) age-dependent ratings. It is thus unclear if the ADHD subtypes represent fundamentally distinct behavioural profiles, or if they stand as artefacts of a heavily subjective diagnostic process. Though a number of studies have found reliable relationships between ADHD subtypes and profiles of behaviour (e.g. Volk et al., 2005; Riersen & Todorov, 2013), the sheer diversity of findings across studies highlights ambiguities in the behaviour-based subtyping of ADHD. Most importantly, if ADHD subtypes do not lend much additional power to capturing unique developmental trajectories, their clinical utility ought to be called into question. At best, they may lend partial utility within individual cases of ADHD. At worst, they could mislead clinicians and educators into fixating on specific behaviours, rather than taking a holistic view of an individual's developmental circumstances.

The heterogeneous nature of ADHD symptomology is therefore threefold. Inattention and hyperactivity behaviours present themselves variably between individuals, within different contexts, and across developmental timescales. As we shall see in the following section, profiles of elevated inattention and hyperactivity can also be seen across a wide variety of other neurodevelopmental conditions. To make matters even more complicated, approximately two-thirds of individuals diagnosed with ADHD carry at least one additional developmental or psychiatric diagnosis (Larson et al.,

2011). Diversity is the rule, rather the exception, when it comes to the population-level expression of these traits.

1.1.3.2.2 Inattention and hyperactivity as general features of neurodevelopmental conditions

Although they are regarded as cardinal features of ADHD, inattention and hyperactivity do not *differentiate* ADHD from other neurodevelopmental conditions. In reality, elevated inattention and hyperactivity characterise a number of neurodevelopmental phenotypes, suggesting that these elements of behaviour reflect something more *general* about the emergence of 'divergent' developmental trajectories. Elevated levels of inattention and hyperactivity are closely associated with autism (Lyall et al., 2017), dyslexia and other conditions affecting linguistic ability (Boada, 2012), Tourette's Syndrome (Pauc, 2005), and Williams Syndrome (Rhodes et al., 2011; Lima et al., 2012). Multiple studies have also linked inattention and hyperactivity to the behavioural presentations of psychiatric conditions, such Major Depressive Disorder (Meinzer et al., 2012; Park & Chang, 2021), Obsessive-Compulsive Disorder (Blanco-Vieira et al., 2019), and Bipolar Disorder (Marangoni et al., 2015). Additionally, research has been devoted to looking at inattention and hyperactivity as behavioural dimensions that can become expressed across many different paths of development. Studies of large birth cohorts, like the Quebec Longitudinal Study of Child Development (n = 2,057) and Pelotas birth cohort (n = 4,676), have revealed that inattention and hyperactivity, despite being known as features of ADHD, characterise a wide range of developmental trajectories (Galera et al., 2011; Breda et al., 2020).

There are several perspectives that we could take when attempting to describe such a high level of behavioural overlap between diagnostic categories. One view, which gives more credence to the value of discrete diagnostic categories, treats overlap as clinical comorbidity. Through this lens, behavioural heterogeneity can be explained as the co-occurrence of different conditions. In practice, this would translate to giving an individual multiple diagnoses that can be interpreted in tandem, such that the individual's psychological profile is summarised sufficiently well.

However, this calls into question what exactly is meant by a 'discrete' clinical category. If there is so much overlap between conditions, and multiple-co-occurrence is the norm, many diagnostic labels must only be 'discrete' in the sense that their descriptions happen to be formatted on different pages of a diagnostic manual. The addition of new diagnostic labels and subtypes to these manuals constitutes a somewhat clumsy attempt to capture important subtleties of behaviour. Parsimony is not the enemy of complexity, and the sheer number of available diagnostic labels only showcases the limits of the strict categorical approach to understanding neurodevelopment. Perhaps, then, describing shared behavioural features in terms of comorbid conditions does not lend much power to explaining *why* they are so common in the first place. If we want to grasp the mechanisms behind inattention and hyperactivity, it may be more useful to reach beyond perspectives that reduce complex, heterogeneous phenotypes to collections of co-existing diagnostic labels.

One solution involves making some changes to our assumptions about the nature of inattention and hyperactivity. As discussed previously, there is already a 'top-down' account of neurodevelopmentally-relevant traits that relies upon the pre-definition of diagnostic categories. But why should we depend so heavily on partially-descriptive categories when we can return to something more basic—like behaviour itself? Rethinking our theoretical framings of neurodevelopmental conditions could mean studying behavioural *dimensions*, like inattention and hyperactivity, rather than diagnostic labels that happen to capture them partially, like ADHD and its potentially unreliable subtypes. The dimensional perspective affords numerous benefits, including superior reliability and greater statistical power (Hengartner & Lehmann, 2017). As we shall see in Section 1.2, transdiagnostic approaches to studying neurodevelopment tend to employ assumptions about the underlying dimensionality of cognitive and behavioural phenomena. This set of approaches, I argue, facilitates a more nuanced and theoretically-rewarding method of studying neurodevelopmental heterogeneity, especially in the context of traits like inattention and hyperactivity.

1.2 Transdiagnostic approaches in developmental cognitive neuroscience

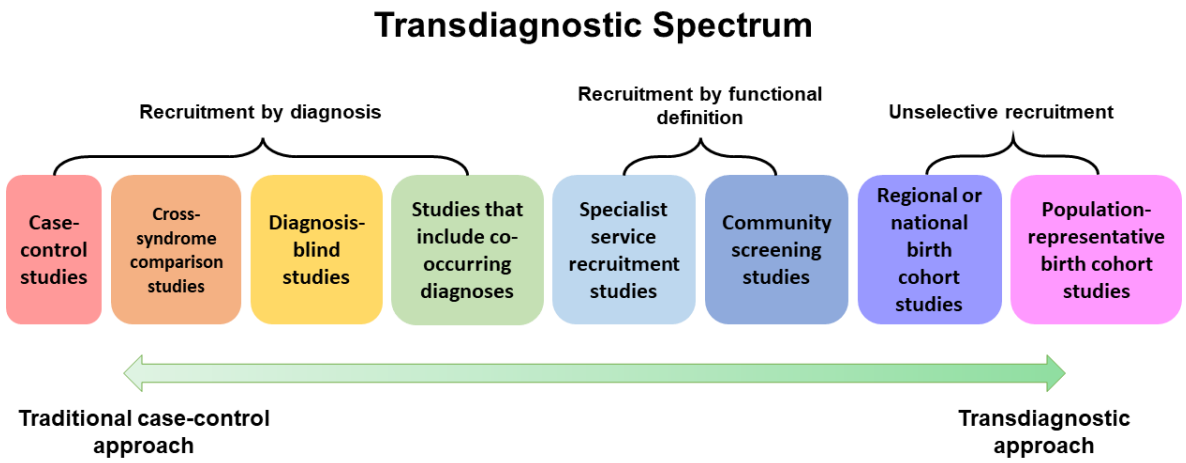
A classic paradigm for investigating neurodevelopmental differences between groups of individuals is the case-control method. This approach involves drawing comparisons between those with a particular diagnostic label, such as ADHD, and a control group of individuals without the diagnosis, or who have been deemed 'typically-developing' following a screening process (American Psychological Association). The reader will already be familiar with some of the problematic aspects of attempting to define behavioural 'typicality' from section 1.1.2, but case-control studies are nonetheless very common in the neurodevelopmental literature.

Some research groups have come to favour a transdiagnostic approach as an alternative to the conventional case-control design (e.g. Vanden Bussche et al., 2017; Holmes et al., 2019; Shephard et al., 2019; Gui et al., 2020; Hayiou-Thomas et al., 2021). Transdiagnostic approaches place less priority on the diagnostic categorisation of conditions, instead focusing on variations in the *dimensionality* of traits, often with a broader representation of co-occurring conditions within participant samples (e.g. Cuthbert, 2014; Newby et al., 2015; Talkovsky et al., 2017; Bathelt et al., 2018; Dalgleish et al., 2020; Siugzdaite et al., 2020). Advocates for transdiagnostic approaches endeavour to build an analytic and conceptual framework that accommodates heterogeneity within, and overlap between, neurodevelopmental conditions. One aim is to reconceptualise neurodevelopmental conditions as intrinsically related, not only in terms of their behavioural attributes, but also potentially the neural and cognitive mechanisms which underpin them (Forest, 2014). Since they strive not to make *a priori* assumptions of homogeneity within diagnostic categories, transdiagnostic studies fundamentally differ in their participant recruitment methodologies, which in turn influences factors like experimental design and chosen data analysis techniques. A simple, informed change in our basic assumptions about diagnostic categories can therefore transform the way that we practice developmental cognitive neuroscience.

Astle et al. (2021) previously defined a 'transdiagnostic spectrum', which orders different participant recruitment methodologies according to their degree of

dependence on category-based recruitment (see Figure 1.4). Studies which recruit participants by diagnosis are considered the least transdiagnostic, whereas those which employ unselective recruitment methodologies—for instance, data from representative birth cohorts—are viewed as the most transdiagnostic.

Figure 1.4: Basic schematic adapted from Astle et al. (2021) representing different research study designs along a continuous spectrum, which signifies a design's degree of alignment with a 'pure' transdiagnostic approach.



There is no discrete difference between a transdiagnostic study and a 'non-transdiagnostic' study. Rather, different transdiagnostic methods can be incorporated into various different research methodologies in order to deliver a desired output. This methodological flexibility enables work within existing theoretical and practical paradigms (e.g. diagnostic frameworks) while still examining how dimensional elements of cognition and behaviour might characterise neurodevelopmental trajectories *regardless* of diagnostic categories. Birth cohort studies are optimally used in research that seeks to uncover relationships between the brain, cognition, and behaviour, because data are collected at a very large scale. In addition to offering larger samples sizes, and therefore greater statistical power, cohort studies also tend to feature multimodal data and population-level information about the prevalence of neurodevelopmental conditions (e.g. SCALES, Vamvakas et al., 2019; ALSPAC, Lawlor et al., 2019). Because of the size and representative diversity of cohort samples, it also becomes possible to use a variety of data-driven methods to explore relationships between multiple overlapping features of development (see Astle et al., 2021, for

review). While recruitment-by-diagnosis methods isolate participant groups according to pre-defined (and potentially heterogeneous) categories, data-driven approaches enable the detection of subgroups of individuals with shared cognitive, behavioural, and/or neurological features. In other words, transdiagnostic recruitment methodologies, paired with data-driven statistical approaches, facilitate the delineation of more homogeneous neurodevelopmental subgroups. As a result, multimodal data from these subgroups can be compared with much greater statistical power.

One overarching challenge within the field of developmental cognitive neuroscience is ecological validity; if we are defining neurodevelopmental categories, it is important that they represent something 'true-to-life'. While transdiagnostic methods certainly constitute a new way of studying neurodevelopmental change, they also challenge a traditional diagnosis-centric dogma that permeates much of past research in psychology and neuroscience. Developmental cognitive neuroscience has a significant role to play in shaping clinical theory and practice; the field is embedded within the processes by which individuals are assessed, diagnosed, and allocated resources. If there is a better way of characterising and studying neurodevelopment than the standard diagnostic paradigm can afford—particularly in the case of neurodevelopmental conditions—then there is an imperative to change our methods accordingly. To some, the increasing use of transdiagnostic recruitment methods represents a 'revolution' in cognitive developmental neuroscience (Astle et al., 2021), much akin to a paradigm shift. In the upcoming section, I will discuss another recent and highly impactful advancement in the field of cognitive neuroscience: the emergence of connectomics.

1.3 The complex, dynamic brain: network science and the emergence of connectomics

1.3.1 The brain as a connectome

Historically, neuroscience has focused on studying nervous systems in the context of localised anatomical and functional elements, such as cortical gyrification, or the blood oxygen level dependent (BOLD) activity of a particular brain region (Betzel, 2020). In recent decades, however, the focus of many studies has shifted away from

spatially-isolated effects in favour of distributed, dynamical networks that develop across time (Sporns et al., 2005; Betzel, 2022). Characterising the topological properties of complex networks allows us to summarise network architectures across multiple scales and levels of interaction, rather than being limited to narrow, specific regions of the brain assumed to operate independently (Costa et al., 2007). The human brain is a complex system comprised of manifold intricate connections between neurons, optimised to maximise efficient information transfer whilst minimising energy usage (Bullmore and Sporns, 2012). The connection matrix of the human brain (hereafter 'connectome') provides a useful model of its anatomical structure and function (Sporns et al., 2005). Indeed, there are now a variety of network models used within the field of connectomics, which strive to bridge the gaps between structure and function in the brain, computational theories and empirical data, and micro- and macroscale attributes of neurology (Bassett et al., 2018). Different models are capable of representing a variety of brain network features and abstract entities. When complementary, connectomic models can inform broader theoretical frameworks that clarify relationships between modalities.

Graph theory, a branch of mathematics, enables the quantitative modelling of network characteristics. This provides a formal framework for characterising structural and functional connectomes (Trudeau, 2013). A graph's information is typically contained within an adjacency matrix, which represents connections ('edges') between entities ('nodes'). Edges can be weighted (continuous) or binary (present vs. absent), and they can represent directed or undirected relationships of connectivity between nodes. Macroscopic-level connectomics characterises brain regions, which are defined using a range of possible brain atlases, as nodes. Edges represent patterns and degrees of structural, functional, and effective (causal) relationships between those nodes (Rubinov & Sporns, 2010). Graph-theoretic measures at the level of nodes, commonly named centrality indices, contain information that can provide insight into the role of a specific brain region in the overall organisation of the brain (Buckholtz & Meyer-Lindenberg, 2012; van Essen & Barch, 2015).

From this basic conceptual foundation of network nodes and edges, a variety of descriptive graph measures can be derived across multiple scales of interest. These measures have made it possible to identify consistent and functionally-relevant motifs

of many biological networks, including the brain (Achard et al., 2007; Zuo et al., 2012; Bertolero et al., 2015; Srivastava et al., 2022). For instance, brain networks tend to exhibit short characteristic path lengths (Jahanshad et al., 2012; Jin et al., 2017), a structure that is made up of functionally-distinct modules (Meunier et al., 2010; Puzeddu et al., 2020), a collection of highly information-bearing hub nodes, termed the 'rich-club' (Ball et al., 2014; Kim & Min, 2020), and a propensity towards a small-world organisation (Muldoon et al., 2016; Bassett & Bullmore, 2017). Graph measures become theoretically-informative when we interpret them in the context of what they *represent* about different types of connectomes. For instance, the topology of the structural connectome reflects the emergence of constraints on which brain areas are able to 'communicate' with one another, which in turn shapes recurrent patterns of neural activity (Honey et al., 2009; Akarca et al., 2021; Esfahlani et al., 2022). By quantifying features of structural and functional brain organisation, particularly across ontogenetic timescales, we can begin to understand how brain regions communicate over time, what constraints act upon their wiring and communication patterns, and what internal and external factors might affect these processes.

1.3.2 Capturing developmental differences in brain structure and function

The human brain undergoes rapid changes over the course of childhood development, which leads to a diverse range of trajectories and outcomes later in life. Many recent studies have applied connectomics-based methods to examine relationships between structural connectivity, functional connectivity, cognition, behaviour, learning outcomes, and socioeconomic circumstances in childhood development. Additionally, there has been a push to study the human connectome with respect to neurodevelopmental conditions, especially when it comes to differences in outcome-relevant dimensions of cognition and behaviour.

Brain structure, captured primarily through Diffusion Tensor Imaging (DTI) mappings of the white matter connectome, has been one of the primary research areas of focus within network neuroscience (Tymofieva et al., 2014; Cao et al., 2017; Meoded et al., 2017). This is because the structural connectome is seen as a scaffold, and a physical constraint, to later changes in the functional connectome (Contereras et al., 2015; Melozzi et al., 2019). Additionally, emerging results from the field of connectome

fingerprinting have revealed that the topological features of an individual's structural connectome remain relatively stable throughout early childhood, to the extent that the structural connectome can be used to distinguish between unique individuals (Ciarrusta et al., 2022). As a result, a number of studies have successfully investigated how brain network structure differs between individuals on the basis of differences in cognition and behaviour (e.g. Caeyenberghs et al., 2016; Kesler et al., 2016; Zimmermann et al., 2018; Mareva et al., 2019; Astle et al., 2019; Siugzdaite et al., 2020; Bu et al., 2021; Jones et al., 2021; Qian et al., 2021). Additionally, the brain's structural organisation has been linked to childhood academic outcomes. Within the Centre for Attention, Learning, and Memory (CALM) cohort, Bathelt et al. (2018) showed that properties of structural white matter organisation can more sensitively capture individual differences in academic performance than a traditional, voxel-wise mappings of the brain. This is because voxel-wise effects rely on significant levels of spatial overlap across children, whereas the connectome captures effects in local and global white matter topology that do not rely on spatial overlap. The fact that connectomic differences can explain further variance in noisy and higher-phenomenological-level measures, like academic attainment, is a testament to their ability to preserve relevant brain network features while reducing noise (see also Bathelt et al. 2018b, Bathelt et al., 2019; Simpson-Kent et al., 2021). This is also shown by studies that link differences in the structural connectome to experiences of early adversity (e.g. Carozza et al., 2022) and socioeconomic status (Smith et al., 2015; Kim et al., 2019; Johnson et al., 2019). Importantly, studies like this show that brain structure—represented topologically, and in terms of various graph measures—can be understood in the context of a variety of different modalities. While it is superficially obvious that an association exists between biology, behaviour, and the outside world, the challenge comes with identifying the subtleties of that association in a methodologically-rigorous and reliable way. Connectomics offers a strong starting-point to tackling difficult questions in developmental cognitive neuroscience, including those that concern the relationships between different, and potentially noisy, levels of investigation.

The development of functional brain network connectivity is another area in which Connectomics has been able to offer significant insight. Previous studies have shown that the functional connectome changes drastically with chronological age, both in its

local and global patterns of connectivity (Zuo et al., 2012; Tomasi & Volkow, 2012; Gao et al., 2014; Gracia-Tabuenca et al., 2018). While infant brains do possess some of the characteristic functional network properties of adult brains, some important features do emerge, reflecting a child's process of interacting with, and gaining functional knowledge about, the environment (see Turk et al., 2019, for review). As a child develops, the segregation of functional brain networks occurs alongside processes of cognitive specialisation and learning (Fair et al., 2009; Satterthwaite et al., 2013; Rosenberg et al., 2020). Additionally, some studies have shown that spatially-distributed functional brain networks gradually become more integrated (Marek et al., 2015; Mohr et al., 2016; Cai et al., 2020). While these two core findings may initially appear to be in conflict, both segregation *and* integration contribute to the establishment of a modular, yet highly adaptive, functional architecture. The segregation and integration of functional connectivity networks in the brain reflects a process of increasing task-relevant specialisation that is coupled with increasingly flexible communication between networks. Patterns of co-activation between different functional connectivity networks have been studied in the context of task performance, age-dependent developmental change, and neurodevelopmental differences in behaviour and cognition (van den Heuvel et al., 2010; Laird et al., 2011; Ernst et al., 2015; Dajani et al., 2019; Lopez-Vicente et al., 2021; Harikumar et al., 2021; Jones et al., 2021; Zhang et al., 2021). If we can describe general trends of functional connectome development across childhood and adolescence, then it may also be possible to explain differences in cognition and behaviour in terms of these changes, both within and between individuals.

An ongoing challenge within connectomics is to understand how the structure and function of the brain relate to different cognitive and behavioural dimensions of interest, especially in the case of neurodevelopmental conditions. In the coming years, researchers in this area hope to apply these methods to larger and more complex datasets, develop generative and effective (causal) connectivity models of the brain, study shifts in brain network dynamics at a high temporal resolution, and understand how connectome differences may be able to track the progression of neurological conditions. Connectomics has certainly found a home within developmental cognitive neuroscience, where researchers continue to study development using parsimonious, yet information-rich, representations of the brain.

1.4 This thesis

1.4.1 Scope of the research

In this General Introduction I have discussed a wide range of subjects relating to developmental cognitive neuroscience. I began by giving an overview of the field, which included a discussion of some issues surrounding categorical ('typical' versus 'atypical') thinking about neurodevelopmental diversity. I then described cognitive and behavioural neurodevelopmental dimensions of interest to this thesis, with a specific focus on inattention and hyperactivity. Following this, I described a 'transdiagnostic revolution' in the field, which has encouraged researchers and clinicians to look beyond pre-defined diagnostic categories in favour of a dimensional approach coupled with a diagnosis-agnostic recruitment methodology. Finally, I talked about how connectomics, the study of the brain in terms of its graph-theoretic network topology, has been changing the way that we think about neurodevelopment. This Introduction, I believe, gives a broad overview of the topics and issues that will be covered throughout this thesis. More specific points of theoretical interest will be covered in the introductory sections of empirical chapters 1-3 of this thesis, based on what additional information might better inform the reader about the research at hand. I chose not to include a sweeping methodological overview at the beginning of this thesis, as my aim was to preserve a sense of narrative clarity. I believe that the reader should not need to flip back and forth more than is absolutely necessary. Instead, each empirical section of this thesis will include an outline of the research methodologies and statistical techniques used in each study. I will now turn to a short summary of the empirical chapters that form this thesis.

The first and second empirical chapters of this thesis are an exploration of neural heterogeneity among children with elevated levels of behavioural inattention and hyperactivity from the Centre for Attention, Learning, and Memory (CALM). The first empirical chapter explores profiles of structural brain topology, which is denoted by three nodal measures of interest: degree, clustering coefficient, and communicability. Based on these measures, a k-means clustering technique detected two profiles of brain structure among those with elevated inattention and hyperactivity. In the second empirical chapter, a subset of functional connectomes belonging to children from

these two profiles were compared on the same three nodal measures. I discuss the implications that these findings have for our understanding of neurological diversity among those with ADHD, as well as the relevance of the differences that can be seen between patterns of structural and functional connectivity.

In the third empirical chapter, I discuss findings from a magnetoencephalography (MEG) study examining the relationship between at-rest neural dynamics and variations in inattention and hyperactivity. In this study, I combined behavioural and MEG data from the Resilience in Education and Development (RED) study with new data collected from CALM participants. I recruited participants from the CALM cohort in order to represent the full breadth of the inattention and hyperactivity spectrum. MEG data were analysed using Hidden Markov Modelling, a machine learning technique which allows for the estimation of temporally-distinct transitions between states of dynamical activity in the brain.

The fourth empirical chapter describes a further policymaking project completed during my PhD. I discuss how I, alongside a small team at the MRC Cognition and Brain Sciences Unit, coordinated a multi-disciplinary workshop that focused on removing barriers to learning and wellbeing in UK schools and society. I also detail how we integrated notable pieces of evidence from this workshop to create a set of freely-available, comprehensive resources that empower schools to foster inclusive, collaborative environments.

In the general discussion for this thesis, I summarise the previous empirical chapters and provide some final thoughts about the theoretical and practical relevance of this work within the field of developmental cognitive neuroscience, along with some suggestions for further research in this area.

1.4.2 Methodological and theoretical implications

The title of this thesis, 'Reality Resists Classification', suggests something important about its focus, which I hope has become apparent to the reader throughout this General Introduction. The reality of neurodevelopmental heterogeneity, coupled with a complex subject matter—the links between brain, behaviour, and cognition—makes it difficult to accurately classify individuals within traditional diagnostic frameworks.

As a result, I have chosen to employ a transdiagnostic methodology to studying neurological and cognitive differences in the context of inattention and hyperactivity. Rather than structuring my recruitment protocols or analyses according to a traditional case-control framework, I have used a breadth of cognitive, behavioural, and brain data from the Centre for Attention, Learning, and Memory in a way that remains agnostic about the diagnostic status of participants.

There are a variety of methods that can be employed when studying the human brain, each of which carries unique benefits and limitations. To look at macroscopic differences in brain topology in relation to behaviour, I have chosen to use conceptual frameworks and analytic methods from connectomics. This has enabled me to perform connectome comparisons on a large sample of children from both the CALM cohort and RED study, yielding a range of results with implications for future research into neurodevelopmental change.

At the start of my PhD, I wanted to understand more about the neural underpinnings of developmental diversity, specifically with regard to inattention and hyperactivity. In bringing together connectomics, dynamics, and a transdiagnostic research framework, my hope is to bridge some explanatory gaps between behaviour, cognition, and the brain while avoiding the limitations of traditional approaches to participant recruitment, study design, and data modelling. This thesis is intended to contribute to a rapidly-growing literature in neuroscience that studies development in terms of dimensionality, neurological diversity, and the topological complexity of biological networks.

2 Exploring Heterogeneity in Inattention and Hyperactivity—A Structural Connectomics Approach

2.1 Introduction

2.1.1 A transdiagnostic approach

Neurodevelopmental conditions like ADHD, autism, and dyslexia have traditionally been regarded as fundamentally distinct diagnostic categories in both research and clinical practice. As a result, past research in developmental psychology, child psychiatry, and neuroscience has prioritised the comparison of highly selective clinical samples with 'typically-developing' controls. Approaches to sampling, experimental design, and data analysis have been shaped by the assumption of underlying uniformity within, and distinctiveness between, diagnostic categories (Coghill & Sonuga-Barke, 2012; Dalgleish et al., 2020; Astle et al., 2022). This creates an organisational framework for studying cognitive, behavioural, and neural differences between groups. However, this case-control framework struggles to accommodate the reality of neurodevelopmental diversity, and current diagnostic labels do not actually reflect self-contained developmental phenotypes.

Readers will recall from the General Introduction that the degree and co-occurrence of clinical features across individuals experiencing neurodevelopmental difficulties is highly heterogeneous. There is significant cognitive and behavioural overlap between individuals who supposedly have different disorders (e.g. Jette & Geschwind, 2014; Jacob et al., 2019; Kofler et al., 2019). Certain cognitive and behavioural symptoms—like emotional dysregulation, inattention, and differences in sensory perception—are also commonly observed across multiple neurodevelopmental conditions, as well as those with no formal diagnosis (Lau-Zhu et al., 2019; Krakowski et al., 2020; Dellapiazza et al., 2020). Additionally, ADHD and autism have diagnostic co-occurrence rates of up to 70% (Reiersen & Todd, 2008; Joshi et al., 2017). Due to the heterogeneity of symptoms across neurodevelopmental conditions, the traditional dichotomisation of 'typically-developing' and 'atypically-developing' or 'Diagnosis A' versus 'Diagnosis B' has been increasingly challenged (see Fusar-Poli et al., 2019 and

Astle & Fletcher-Watson, 2020, for review). Put simply, a rigid categorisation of individuals according to conventional diagnostic labels fails to adequately capture the similarities and differences that exist between individuals.

Some research groups have come to favour a transdiagnostic approach as an alternative to the conventional case-control design (e.g. Vanden Bussche et al., 2017; Holmes et al., 2019; Shephard et al., 2019; Gui et al., 2020; Hayiou-Thomas et al., 2021). Transdiagnostic approaches place less priority on the diagnostic categorisation of conditions, instead focusing on variations in the dimensionality of traits, often with a broader representation of co-occurring conditions within participant samples (e.g. Cuthbert, 2014; Newby et al., 2015; Talkovsky et al., 2017; Bathelt et al., 2018; Dalgleish et al., 2020; Siugzdaite et al., 2020). Advocates for transdiagnostic approaches endeavour to build an analytic and conceptual framework that accommodates heterogeneity within, and overlap between, neurodevelopmental conditions. One aim is to reconceptualise neurodevelopmental conditions as intrinsically related, not only in terms of their behavioural attributes, but also potentially the neural and cognitive mechanisms which underpin them (Forest, 2014).

Inattention and hyperactivity are hallmark symptoms of ADHD, but they nonetheless occur across the entire population along a continuous spectrum (see Nigg, 2013, for review). Unusually high levels of inattention and hyperactivity are associated with multiple neurodevelopmental conditions, including ADHD, Autism, and Intellectual Disability (McClain et al., 2017; Krakowski et al., 2020). Inattention and hyperactivity, as features of behaviour, do not strongly delineate different neurodevelopmental conditions. The purpose of the current study was to explore inattention and hyperactivity as transdiagnostic symptom dimensions, and to understand how these dimensions relate to variability in brain organisation.

2.1.1.1 Statistical approaches in transdiagnostic research

A wide array of statistical approaches can be used to interrogate how cognitive and behavioural characteristics vary across development and between groups of interest. In discussing these approaches, we can make useful distinction between data-driven and theory-driven statistical analysis techniques. A key difference between these types of techniques is the degree to which certain assumptions are made about the structure

of the data prior to statistical testing. Theory-driven methods (sometimes called 'top-down' methods) rely on previously-identified or theorised statistical associations to establish a sound basis for hypothesis-testing. For instance, theory-driven approaches are often applied within case-control studies to ascertain whether two groups diverge on a given measure (see the General Introduction for a broader discussion of this experimental methodology within developmental cognitive neuroscience). Theory-driven methods necessitate a higher level of epistemic justification—they require us to place *confidence* in the robustness of our categories and models, which we delineate prior to engaging in statistical testing. On the other hand, data-driven methods (sometimes referred to as 'bottom-up' methods) can be used to extract the underlying structure of large dataset without the need for *a priori* classifications based on theoretical assumptions. In the context of transdiagnostic research, it is easy to see why data-driven methods constitute an alternative to approaches that rely on a pre-defined set of classifications.

Since transdiagnostic data are often complex and multi-dimensional, it can be useful to transform data into a simpler, more interpretable format that nonetheless retains a useful degree of explanatory power. Dimensionality-reduction analyses performed on cognitive and behavioural questionnaire data have previously been used to identify neurodevelopmentally- and clinically-meaningful dimensions that are unconstrained by diagnostic assumptions (Astle et al., 2021). To uncover the structure of these dimensions, transdiagnostic studies have used techniques like Exploratory Factor Analysis (EFA; e.g. Cowan & Mittal, 2021; Parkes et al., 2021), Principal Components Analysis (PCA; eg. Ramanan et al., 2023), and Partial Least-Squares Regression (PLS; e.g. Wise & Dolan, 2020), which are able to generate linear components that capture the covariance structure between variables in a dataset. Dimensionality-reduction techniques allow neurodevelopmental researchers to study where participants fall along behavioural and cognitive dimensions that are known to characterise the data, rather than assuming that the structure of a dataset closely aligns with theoretical predictions. In the current study, we used EFA to explore whether variations in inattention and hyperactivity were best represented by one, or multiple, underlying dimensions based on data from five behavioural questionnaires. We also used a PLS regression technique to ascertain whether localised variations in structural brain

organisation predicted linear variations in inattention and hyperactivity across our sample.

In addition to uncovering latent dimensions within a dataset, data-driven approaches have also been used to derive subgroupings (or 'clusters') of participants with similar relative profiles of behaviour, cognition, and neurology (Feczko et al., 2018). There is a multiplicity of clustering algorithms and approaches available to those who wish to undertake transdiagnostic research in the cognitive sciences. For instance, clustering techniques like community detection (e.g. Mareva et al., 2022), k-means clustering (e.g. Sumiyoshi et al., 2022), hierarchical clustering (e.g. Grisanzio et al., 2018), Gaussian finite mixture modeling (e.g. Stochl et al., 2023), and other unsupervised machine learning methods (e.g. Siugzdaite et al., 2020; Pelin et al., 2021) have been applied successfully within the context of transdiagnostic developmental research. These techniques are complementary to the dimensionality reduction approaches described in the previous paragraph, and can be used to find subgroupings of individuals along dimensions of behaviour, cognition, and neurology. In the current study, we used k-means clustering to identify neural subgroups of inattentive and hyperactive individuals in our sample.

The brief summary of statistical approaches offered above covers only a fraction of the methods available to researchers who are hoping to engage in transdiagnostic research. As computational resources expand and machine algorithms continue to become more refined, developmental scientists are able to investigate the links between genetics, neurology, cognition, and behaviour with increasing precision. Neurodevelopmental research will also be aided by advances in brain imaging and Connectomics, a growing field dedicated to modelling the brain as a complex network structure.

2.1.2 Connectomics

In recent decades, a variety of fields have embraced the study of complex networks (Sporns et al., 2005; Betzel, 2022). Characterising the topological properties of complex networks allows us to summarise network architecture across multiple scales and levels of interaction, rather than being limited to narrow, specific regions of the brain assumed to operate independently (Costa et al., 2007). The human brain is a

complex system comprised of manifold intricate connections between neurons, optimised to maximise efficient information transfer whilst minimising energy usage (Bullmore and Sporns, 2012). The connection matrix of the human brain provides a useful model of its anatomical structure and function (Sporns et al., 2005).

Graph theory, a branch of mathematics, enables the quantitative modelling of network characteristics. This provides a formal framework for characterising structural and functional connectomes (Trudeau, 2013). A graph's information is often summarised within an adjacency matrix, which represents connections ('edges') between entities ('nodes'). Edges can be weighted (continuous) or binary (present vs. absent), and they can represent directed or undirected relationships of connectivity between nodes. Macroscopic-level connectomics characterises brain regions, which are defined using a range of possible brain atlases, as nodes. Edges represent patterns and degrees of structural, functional, and effective (causal) relationships between those nodes (Rubinov & Sporns, 2010). Graph-theoretic measures at the level of nodes, commonly named centrality indices, contain information that can provide insight into the role of a specific brain region in the overall organisation of the brain (Buckholtz & Meyer-Lindenberg, 2012; van Essen & Barch, 2015).

The white matter connectome is thought to constrain the intertwined communication dynamics of the brain, facilitating function (Avena-Koenigsberger et al., 2017; Suárez et al., 2021). Variations in this communication network may coincide with differences in cognition and behaviour, in line with empirical observations in children (e.g. Mareva et al., 2019; Siugzdaite et al., 2020). In the current study, we explored how node-level measures in the structural brain network relate to variations in hyperactivity- and inattention-related behaviours. We tested how the number of connections (termed degree), triplets of connectivity (termed clustering coefficients) and their local patterning of communication (termed communicability) for different brain regions may vary according to a young person's levels of inattention and hyperactivity. We used these brain network measures as proxies for network architecture, reduced to the regional level, to enable appropriate statistical inferences. We chose these measures because they are capable of describing various attributes of neural organisation—such as the formation of structural modules around nodes with

high degree and clustering coefficient values, and the extent to which these nodes may facilitate information flow across the brain.

2.1.3 Structural brain differences in neurodevelopmental conditions

The study of structural brain differences in those with neurodevelopmental conditions has existed at the core of human developmental psychology and neuroscience since the emergence of modern neuroimaging techniques. Certain features of brain structure and function have been linked to individual differences in behaviour and cognition in childhood (e.g. Astle et al., 2019; see Gilmore et al., 2018 and Ziegler et al., 2020 for review). These findings come mostly from studies of neurodevelopmental conditions like ADHD, autism, and dyslexia, which have attempted to draw contrasts between these groups and so-called typically-developing children (Griffiths et al., 2016; Mizuno et al., 2019).

To provide some brief examples from this literature: several studies report brain structure differences in autistic individuals, including grey matter reductions and increased gyrification in sensorimotor and default-mode networks (Pereira et al., 2018), reduced interhemispheric connectivity (Bos et al., 2015), and differences in long-range white matter connectivity (Wilkinson et al., 2016). In the case of both ADHD and autism, studies have shown similar patterns of increased brain network modularity, coupled with a global decrease in long-range connections (Kern et al., 2015), as well as white matter differences in frontal and limbic brain networks (Connaughton et al., 2022). Structural connectivity has also been studied in relation to specific behavioural traits associated with ADHD. Most relevant here, Konrad et al. (2010) found that inattention and impulsivity are related to alterations in fronto-striatal circuitry, which persists into adulthood.

More recent approaches to studying neurodevelopmental differences in structural connectivity have probed the nature of diversity as a feature of human brain network configurations. For instance, Akarca et al. (2021) used generative modelling to simulate the wiring properties of children at heightened risk for divergent neurodevelopmental outcomes. This analysis, without putting particular priority on any specific neurodevelopmental condition, revealed that the structural diversity we see in the macroscopic brain networks of children can be explained by small,

constrained variations in generative parameter conditions. In other words, human brain development is not optimised to exhibit exactly the same wiring negotiations between regions, across individuals; rather, nature permits for structural differences across individuals, so long as some level of gross functionality is achieved. Diversity in the structure of human brains may be an adaptive or stochastic fundamental feature, not a flaw, of evolutionary and developmental processes. It is therefore valuable to investigate what, if anything, characterises structural brain differences in those experiencing impactful neurodevelopmental differences, such as heightened inattention and hyperactivity.

2.1.4 The current study

We used data taken from a transdiagnostic cohort called the Centre for Attention, Learning and Memory (CALM) to test how properties of structural connectomes relate to variations in inattention and hyperactivity behavioural traits. The members of this cohort are recruited via referral from children's specialist services on the basis of ongoing difficulties in cognition, learning or behaviour (Holmes et al., 2019). Cohort members can have single, multiple, or no formal diagnostic label(s).

We attempted to address one overarching question: how do properties of structural brain connectivity relate to variations along the transdiagnostic continua of inattention and hyperactivity within this intentionally heterogeneous sample? We take two approaches to addressing this question. First, we test whether variability in inattention and hyperactivity within the sample relates to continuous variations in node-wise properties of each individual's connectomes. Second, we test whether there are subgroups, with differently-organised connectomes, that experience inattention and hyperactivity.

Below, we report how we determined our sample size, all data exclusions, all data inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all the measures used in the study.

2.2 Methods

2.2.1 Participants

The CALM sample was recruited on the basis of ongoing difficulties with attention, learning and memory reported by professionals working in schools or specialist children's community services. Exclusion criteria for referrals were a known history of brain injury, significant or severe known problems in vision or hearing that were uncorrected, and not having an adequate level of English proficiency to complete the assessments. This study was approved by the local NHS research ethics committee (Reference: 13/EE/0157). Children attending the research clinic completed a cognitive test battery administered over approximately 4 hours, which covered a broad range of behavioural and cognitive attributes. Their parents also completed a set of standardised behavioural questionnaires assessing communication, inattention, hyperactivity, executive functioning and aspects of social functioning (details of the full protocol can be found in Holmes et al., 2019). Each child also underwent T1 structural MRI scanning at the MRC Cognition and Brain Sciences Unit. Several steps were taken to ensure good MRI data quality and minimize potential biases of participant movement, which has previously been found to affect statistical comparisons, particularly in hyperactive individuals (Yendiki et al., 2014). First, children were instructed to lie still and were trained to do so in a realistic mock scanner prior to the actual scan. Second, scans that showed a displacement of >3 mm within the diffusion-weighted sequence were excluded. We also used mean framewise displacement as a control regressor in our analyses across participants.

The main CALM cohort, from which we studied a subsample, includes n = 799 referred children and young people, alongside an additional n = 158 unreferred children and young people from the same schools. These additional unreferred participants were recruited as part of the cohort to ensure that the overall cohort captured the full range of cognitive and behavioural profiles in the wider population. There were no known incidences of genetic disorders in the CALM cohort, but our heterogeneous sample does include a large number of children with previously-diagnosed neurodevelopmental disorders. In the referred sample, 60.3% of participants were undiagnosed, 24.3% had an ADHD diagnosis, 7% had an autism diagnosis, and 5.9%

were diagnosed with dyslexia. In the unreferred sample, 98.1% were undiagnosed, 0.6% had an ADHD diagnosis, none had an autism diagnosis, and 1.3% were diagnosed with dyslexia (Mareva et al., 2019). At the time of our analysis, of the overall cohort (n = 957), 383 had complete and high-quality diffusion tensor imaging (DTI) data alongside cognitive and behavioural data (mean age = 10.33 years, SD = 2.27; 65.9% male, 33.1% female, 1% unspecified sex). In the current study, we analysed data from these 383 individuals.

2.2.2 Cognitive assessments and behavioural questionnaires

2.2.2.1 Behavioural questionnaires

The Conners 3 - Parent Rating Scale Short Form was used to assess symptoms related to ADHD (Conners Questionnaire; Conners, 2008). Scores on these items form six subscales consisting of Inattention, Hyperactivity/Impulsivity, Learning Problems, Executive Function, Aggression, and Peer Relations. The sum of raw scores on each subscale was converted to a T-score (M = 50, SD = 10).

The Behavior Rating Inventory of Executive Function questionnaire was completed by parents/carers (BRIEF, Gioia et al., 2000). T-scores (M = 50, SD = 10) were derived for eight subscales: Inhibit, Shift, Emotional control, Initiate, Working memory, Planning, Organisation and Monitor. Three composite scores were also derived: Metacognition, Behaviour Regulation and Global Executive Function.

The Strengths and Difficulties Questionnaire asked the parent/carer to rate 25 items measuring Emotional Symptoms, Conduct Problems, Hyperactivity/Inattention, Peer Relationship Problems and Prosocial Behaviour based on their child's behaviour in the six months prior to assessment (SDQ; Goodman, 1997). Because age-standardised scores are not available for the SDQ, z-scored raw scores were used in subsequent analyses.

2.2.2.2 Cognitive assessments

One subtest from the Phonological Assessment Battery was administered (PhAB; Frederickson et al., 1997). The Alliteration subtest measures the ability to isolate initial

sounds of simple words. Raw scores from the PhAB Alliteration subtest were converted to standard scores (M = 100, SD = 15).

Four subtests from the Automated Working Memory Assessment were administered: Digit Recall, Backward Digit Recall, Dot Matrix, and Mr X (AWMA; Alloway, 2007). All are simple or complex memory tasks, with 6 trials at each span length. Digit Recall (testing verbal short-term memory) involves immediate serial recall of sequences of spoken digits; Backward Digit Recall follows the same procedure, except children are asked to recall items in reverse sequence. The Dot Matrix subtest (testing visuo-spatial short-term memory) requires children to recall the locations of a series of dots presented one at a time in a four-by-four matrix. The Mr X subtest (testing visuospatial working memory) involves recalling the location of a ball held by a cartoon character ('Mr X') for several successive displays involving different rotations of Mr X and ball positions. For all AWMA subtests, tasks automatically progress up one span level if a child produces four or more correct answers in a block. Subtests end following three or more incorrect responses. Trials correct were converted to age-standardised scores for each task (M = 100, SD = 15).

The Matrix Reasoning subtest of the Wechsler Abbreviated Scales of Intelligence II is used as an index of general reasoning and executive function (WASI; Wechsler, 2011). In this test, children are presented with incomplete matrices of images and asked to select an image that would suitably complete each matrix from a choice of four options. Trial numbers vary by age; children up to the age of 8 complete up to 24 matrices. Children aged 9 years and older complete a possible total of 30 matrices. The matrix reasoning test is finished when the child produces three consecutive incorrect responses. Trials correct were converted to T-scores (M = 10, SD = 10).

The Peabody Picture Vocabulary Test measures receptive vocabulary (PPVT; Dunn & Dunn, 2007). In this test, children were asked to select one image from four options according to what best corresponds to a stimulus word. In this test, a basal set is established after a child has completed all 12 items in set with one or no errors. Previous sets are presented in reverse-order until a basal set is successfully established. Children are presented with subsequent sets of increasing difficulty until

a ‘ceiling’ set is established (defined by 8 or more errors out of twelve items). Raw scores were converted to standard scores (M = 100, SD = 15).

2.2.3 Neuroimaging data acquisition

Magnetic Resonance Imaging (MRI) data were acquired at the MRC Cognition and Brain Sciences Unit, University of Cambridge. All scans were obtained on a Siemens 3T Prisma-Fit system (Siemens Healthcare, Erlangen, Germany) using a 32-channel head coil. T1-weighted volume scans were acquired using a whole-brain coverage 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) sequence acquired using 1-mm isometric image resolution (TR = 2.25s, TE = 2.98ms, flip angle = 9 degrees, 1x1x1mm). Diffusion scans were acquired using echo-planar diffusion-weighted images with a set of 60 non-collinear directions, using a weighting factor of b = 1000 s*mm−2, interleaved with a T2-weighted (b = 0) volume. Whole brain coverage was obtained with 60 contiguous axial slices and isometric image resolution of 2 mm. Echo time was 90ms and repetition time was 8400ms.

2.2.4 Tractography and connectome construction

Pre-processing and reconstruction were performed using QSIPrep 0.14.2, which is based on Nipype 1.6.1 (nipype1; nipype2; Gorgolewski et al., 2011).

The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) using N4BiasFieldCorrection (n4; ANTs 2.3.1; Avants et al., 2014), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped using antsBrainExtraction.sh (ANTs 2.3.1), with OASIS as target template. Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c (MNI; Bowring et al., 2022) was performed through nonlinear registration with antsRegistration (ANTs 2.3.1), using brain-extracted versions of both T1w volume and template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and grey-matter (GM) was performed on the brain-extracted T1w using ‘FAST’ (FSL 6.0.3:b862cdd5; Jenkinson et al., 2011).

Any images with a b-value less than 100 s/mm^2 were treated as a b = 0 image. MP-PCA denoising as implemented in MRtrix3's dwidenoise (dwidenoise1; Tournier et al.,

2019) was applied with a 5-voxel window. After MP-PCA, B1 field inhomogeneity was corrected using dwibiascorrect from MRtrix3 with the N4 algorithm [n4]. After B1 bias correction, the mean intensity of the DWI series was adjusted so all the mean intensity of the b = 0 images matched across each separate DWI scanning sequence.

FSL (version 6.0.3:b862cdd5)'s Eddy was used for head motion correction and Eddy current correction. FSL's Eddy was configured with a q-space smoothing factor of 10, a total of 5 iterations, and 1000 voxels to estimate hyperparameters. A linear first-level model and a linear second-level model were used to characterize Eddy current-related spatial distortion. Q-space coordinates were forcefully assigned to shells. Field offset was attempted to be separated from subject movement. Shells were aligned post-Eddy. Eddy's outlier replacement was run [eddyrepol]. Data were grouped by slice, only including values from slices determined to contain at least 250 intracerebral voxels. Groups deviating by more than 4 standard deviations from the prediction had their data replaced with imputed values. In FSL eddy, 4 standard deviations is the recommended default setting in both FSL's eddy and qsiprep's implementation of it (Cieslak et al., 2021). As described by Andersson et al. (2016), in which this method was introduced, the reason for this recommendation is that 4 SDs represents a good compromise between excluding type 1 and 2 errors for 'standard' data sets (which includes ours) from their tests. They also state from their tests that any value between 3 and 5 does not have a major influence. Final interpolation was performed using the jac method.

Several confounding time-series were calculated based on the pre-processed DWI: framewise displacement (FD) using the implementation in Nipype (following the definitions by power_fd_dvars). The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. Slicewise cross-correlation was also calculated. The DWI time-series were resampled to ACPC, generating a pre-processed DWI run in ACPC space with 1mm isotropic voxels.

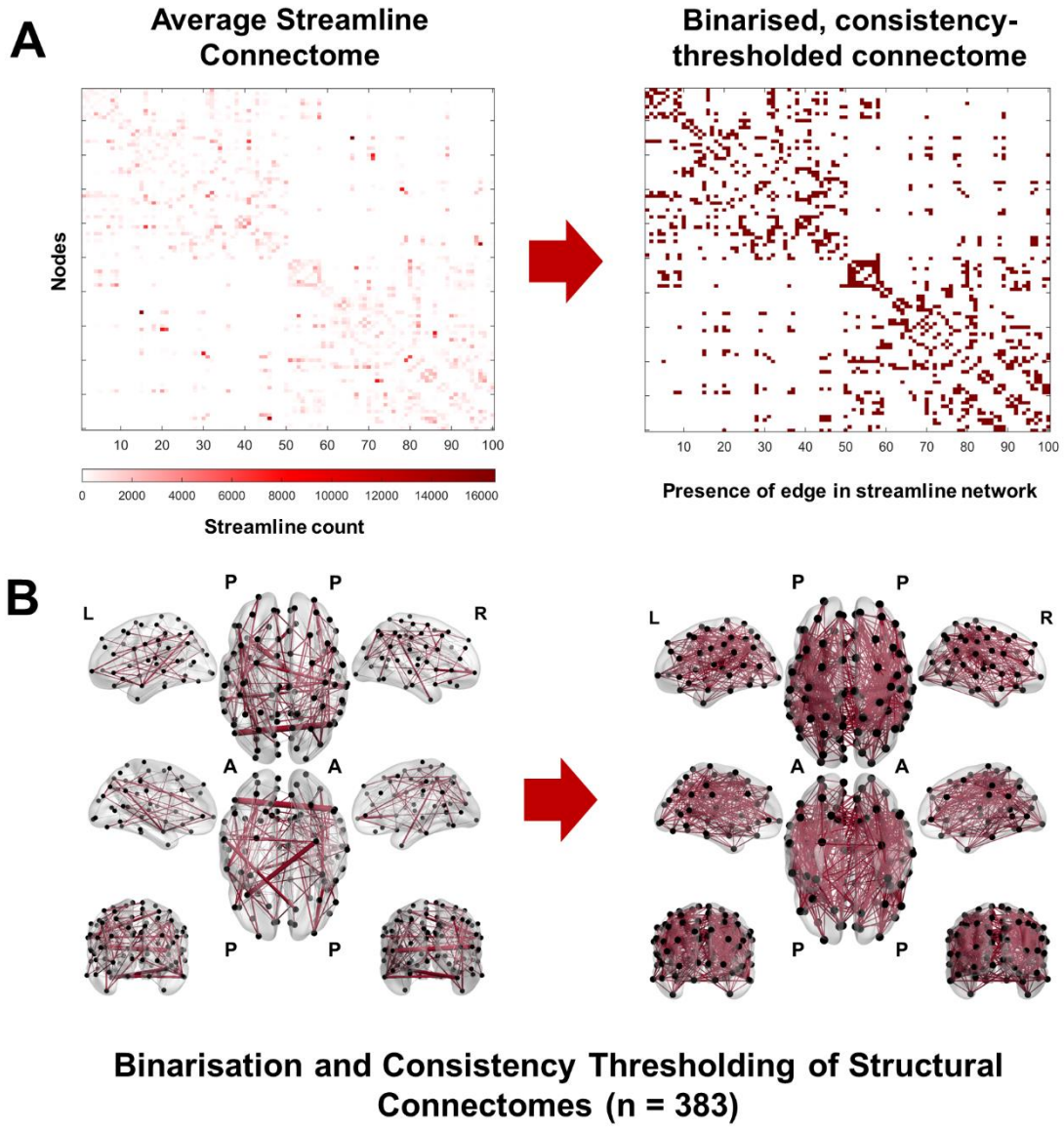
Diffusion orientation distribution functions were reconstructed using generalised q-sampling imaging (GQI; yeh2010gqi) with a ratio of mean diffusion distance of 1.250000.

Many internal operations of QSIPrep use Nilearn 0.8.0 (nilearn; Abraham et al., 2014) and Dipy. For more details of the pipeline, see QSIPrep's documentation at https://qsiprep.readthedocs.io.

2.2.5 Thresholding and binarisation of connectomes

Numerous different parcellation schemes can be used in the construction of connectomic models (e.g. DK-68, Desikan et al., 2016; AAL3, Rolls et al., 2020). In the current study, we used 100-node, Schaefer-parcellated streamline connectomes derived from DTI (Schaefer et al., 2018). We selected the Schaefer parcellation due to its functional correspondence to intrinsic connectivity networks in the brain. 100-node structural connectomes were binarised and then consensus-thresholded at 60%, in line with previous studies (e.g. de Reus & van den Heuvel, 2013). At a threshold of 39 streamlines (i.e. edges were required to have over 39 streamlines for us to assume an anatomical connection), a mean density of 9.18604% was calculated across connectomes. This approximate density value has previously been found to preserve the most informative, non-noisy edges in adjacency matrices, aiding the calculation of a range of graph-theoretic measures (van Wijk et al., 2010; Betzel et al., 2016; Akarca et al., 2021; Theis et al., 2021).

Figure 2.1: Here, we illustrate the binarisation and consensus-thresholding of connectomes across participants in our sample. This process is illustrated in two ways: through a heatmap of an averaged adjacency matrix from our sample (A) and a brain network plot (B), both of which demonstrate the process of binarisation and consensus-thresholding, from left to right.



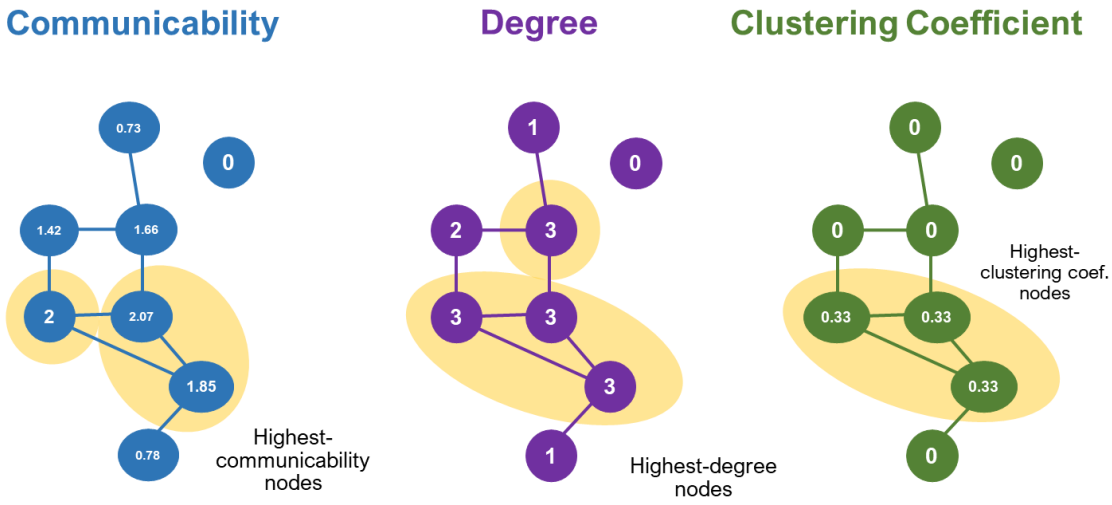
Binarisation and Consistency Thresholding of Structural Connectomes (n = 383)

2.2.6 Graph theoretic measures

Measures of brain networks can be represented in a number of ways, all of which capture different features of connectivity. In the current study, we used three graph theoretic measures at the nodal level in order to investigate the relationship between brain organisation and behaviour. These were nodal degree, clustering coefficient, and communicability (see Figure 2.2). To calculate these brain network properties across

our binarised, consensus-thresholded 100-node streamline connectomes, we used Brain Connectivity Toolbox package in MATLAB (Rubinov & Sporns, 2010).

Figure 2.2: Here, we illustrate the properties of our three nodal graph measures of interest using an example network, which contains eight nodes and eight unweighted, undirected edges. Nodes with the highest communicability, degree, and clustering coefficient values are highlighted.



2.2.6.1 Nodal degree

The degree of an individual node is equal to the number of links connected to that node. In many real-world networks, including the brain, the distribution of degree values across nodes is heterogeneous—many nodes have a small number of links, and a few key nodes act as hubs of high connectivity that facilitate integration across the network (Fornito et al., 2016). Thus, the degree of a node—or brain region—serves as a basic measure of its integration within the broader brain network.

2.2.6.2 Local clustering coefficient

The clustering coefficient of a node quantifies how well-connected its neighbours are. Put simply, the clustering coefficient of a node represents the fraction of the node's

neighbours that are also neighbours of each other (Watts and Strogatz, 1998). Clustering coefficient values give insight into the community structure, or modularity, of a network. Since the brain is organised into structural and functional clusters of interconnected nodes, which strengthen into modules across the developmental timespan, the clustering coefficient is a valuable measure for gauging the contributions of individual nodes to the formation of modules (Meunier et al., 2010; Chen & Deem, 2015; Betzel et al., 2016; Betzel et al., 2017; Bassett & Sporns, 2017; Gallen & D'Esposito, 2019).

2.2.6.3 Nodal Communicability

The communicability of a node represents its direct and indirect connectedness to other brain regions. However, unlike betweenness centrality—which is calculated using shortest path lengths between nodes in a network—communicability is calculated using simulated random walks. Like betweenness centrality, communicability can be interpreted as a measure of a node's ability to efficiently transmit information within a network (Funel, 2022). Communicability can also be thought of as the diffusion or propagation of a signal locally through a network. Since the brain develops in a way to minimise wiring costs and maximise information transfer, the efficiency with which brain regions are able to propagate a signal is a robust way of capturing this biological trade-off (Bullmore & Sporns, 2010; Power et al., 2010). Additionally, information transfer via short network paths and walks has been implicated in the development of psychiatric issues and cognitive difficulties, making it a useful measure for investigating the emergence of inattention and hyperactivity during childhood development (Seo et al., 2013; Makarov et al., 2018; Krukow et al., 2019; Silk et al., 2019).

2.3 Analyses

2.3.1 Exploratory Factor Analysis

We used Exploratory Factor Analysis (EFA) with a minimum-residual ('minres'; also known as Iterated Principal Axis) estimation method to establish whether inattention and hyperactivity represent separate, or the same, underlying construct(s) in questionnaire data derived from the CALM sample. This was done using the

factor_analyzer Python package (factor_analyzer version 0.4.1; Python version 3.9.7). No rotation was applied, as there was no specific aim to identify orthogonal underlying factors. Subscale scores from the Strengths and Difficulties Questionnaire (raw scores from the Hyperactivity subscale), Conners Questionnaire (T-scores from the Inattention and Hyperactivity/Impulsivity subscales), and BRIEF (T-scores from the Monitor and Working Memory subscales) were used. These questionnaires and their subscales have been found to have moderate-to-high internal consistency and reliability (Stone et al., 2015; Shaked et al., 2019; Zarrabi et al., 2015), and are regularly used in the clinical assessment of inattention and hyperactivity traits. The selection of the two BRIEF subscales, alongside the more traditional inattention and hyperactivity scales (e.g. from the SDQ and Conners Questionnaire), might initially seem like an unintuitive choice. In reality, however, the items in these two subscales are very similar and correlate highly with the other subscales included in the EFA (see Appendix C). While the BRIEF Monitor and Working Memory subscales were not constructed with the purpose of directly measuring hyperactivity and inattention, higher scores are significantly associated with elevated levels of both of these traits (Jacobson et al., 2020). All subscale scores were placed in a z-score format prior to the factor analysis, using the age normative sample mean and standard deviation where available.

2.3.2 Partial Least Squares (PLS) Analyses

PLS, a data reduction technique similar to Principal Components Analysis, can adequately summarise the complex relationships between high-dimensional datasets (such as structural connectomes) and continuous variables (such as those representing variations in behaviour). PLS extracts orthogonal latent variables that maximally explain the covariance between predictor and response variables (Wold, 1975, 2004; Johnson et al., 2021). In our analysis, it was important to establish a link between variations in the brain and those within behavioural data, such that significant variance in each could be explained by a common latent factor. PLS proved useful in achieving this, since it performs a dimensionality reduction that simultaneously considers patterns of variation in predictor variables and response variables, unlike PCA, which only uses principal components extracted from the predictor matrix as regressors on the response variable. The predictor variables for three separate PLS analyses were three node-level measures calculated using participants' structural connectomes: nodal degree, clustering coefficient, and communicability. Participants'

inattention/hyperactivity factor scores were defined as the response variable (see Appendix B for a schematic representation of our PLS procedure).

One potential issue with PLS is the risk of overfitting. In order to control for this risk, we used recommendations made by Helmer et al. (2020) regarding the use of PLS to explore brain-behaviour relationships. We began by running 1000 permutations on participants' nodal measures for each of our three PLS analyses. In our comparisons between empirical data and the probability distributions simulated using permutation, we calculated 95% confidence intervals using bootstrapped PLS outer weights (n = 1000, with replacement). This was done in order to test whether the bootstrapped confidence interval passed zero, and thus to establish which measures reliably load on the PLS components. For this bootstrapping we also applied a Procrustes rotation procedure to the outer weights. This was to account for sign flipping during the analysis (as previously recommended for PLS regressions; see Bastien, 2008).

2.3.3 K-means clustering analyses of brain data

Clustering is a data-driven approach that has previously been used to classify complex data, including both structural and functional whole-brain data (Rasero et al., 2019; Tokuda et al., 2021). We initially tested the strength of clustering solutions generated through hierarchical, k-means, and fuzzy clustering techniques. K-means clustering produced a solution with the highest silhouette value (the interpretation and implications of which we discuss further in this section). This technique carries additional benefits: k-means clustering scales to larger datasets and enables the identification of similarly-sized clusters, which allows for further statistical comparisons to be made between clusters (Jin et al., 2011). We performed k-means clustering on structural connectome data in order to establish whether our sample contains subgroups with differently-organised connectomes. This was done on the basis of three measures of brain network topology computed for nodes in binary, undirected connectomes: nodal degree, clustering coefficient, and communicability. These measures were z-score normalised across participants prior to the analysis.

We used metric multidimensional scaling, also known as principal coordinate analysis, to generate 2D representations of nodewise measures for each participant using the

MDS package on MATLAB version 2019a. In generating these 2D representations, we used the robustcov function in MATLAB version 2019a to identify multivariate outliers, who were excluded from the analysis. Following this, we concatenated three 232 x 100 participant-by-node matrices, representing the three nodewise measures, to make a 232 x 300 participant-by-node matrix. We then calculated the Euclidean distances in these measures between participants, creating a 232x232 matrix. This enabled us to conduct our k-means clustering analysis on pairwise distances across each of the measures, maintaining dimensionality but projecting the data into 2D space. To determine the optimal number of clusters to extract in our k-means clustering analysis, we applied a silhouetting method, which assessed the separation between clusters across different solutions. Dalmaijer et al. (2022) calculated the statistical power of different k-means clustering solutions according to the number of clusters detected, sample sizes, and silhouette scores. To assess the strength of each of our potential clustering solutions, we used their criteria for statistical power, ensuring that the solution we included in further analyses detected clusters with high accuracy. Dalmaijer et al. (2022) determined that a k-means clustering solution with $n \geq 160$ data points, and with a silhouette score $\Delta \geq 5$, has approximately 100% power to detect separation between clusters. A silhouette score threshold of $\Delta = 5$ was therefore deemed suitable for establishing high statistical power and clustering accuracy, though we selected the clustering solution with the highest silhouette value. After determining that a two-cluster solution would be optimal according to this threshold (with a silhouette score of $\Delta = 6.808$), we used two sets of General Linear Models (GLMs) to explore how these two neural profiles differ along measures of behaviour and cognition. Head motion (measured by mean framewise displacement), age of scan, age of test, and gender were included as regressors in the GLMs. To control for multiple comparisons, we applied a False Discovery Rate (FDR) correction with a 5% threshold to significant effects from these analyses.

Though our primary k-means clustering analysis was performed for the purpose of exploring neural heterogeneity in particularly inattentive and hyperactive children, we also ran a clustering analysis to investigate whether there are neural subtypes within our entire sample (n = 383). Appendix E contains silhouette values for different *n*-cluster solutions across this broader sample.

2.4 Results

2.4.1 Exploratory Factor Analysis

First, we used an EFA to determine whether inattention and hyperactivity represent one, or multiple, underlying factors, each explaining variance across multiple behavioural questionnaires. Data from five subscales of three behavioural questionnaires measuring inattention and hyperactivity were used (see Methods section for further details). We found that a single Inattention/Hyperactivity factor explained 77.6% of the variance in questionnaire scores, indicating that these two features of behaviour tend to co-occur in the CALM sample (see Appendix A for scree plot representation of variance explained by *n* factors).

Table 2.1: Table representing factor loadings for the questionnaires used in the factor analysis, assuming the existence of a single factor.

Questionnaire	*Factor Loadings*	*Uniquenesses*
SDQ Hyperactivity	-0.9419	0.1129
Conners Inattention	-0.9266	0.1420
Conners Hyperactivity/Impulsivity	-0.8032	0.3549
BRIEF Working Memory	-0.8753	0.2339
BRIEF Monitor	-0.8517	0.2746
	Sum of Squares = 3.8824	

Note. Factor loadings represent weights and correlations between each variable and the factor. Uniqueness is the variance that is 'unique' to the variable and not shared with any of the other variables included in the factor analysis.

We also attempted additional EFAs in order to gauge whether specifying an extra variable, applying an oblique rotation, or excluding either the Monitor or Working Memory subscales of the BRIEF produces a better factor solution. As shown in Appendix D, dropping the BRIEF subscales from the EFA produces a variance explained that is very similar to the original result. Adding a second factor adds

relatively little additional variance, and rotating the loadings explains less variance than the original single-factor solution.

2.4.2 PLS analysis does not show continuous neural dimensions that explain inattention and hyperactivity

We performed three separate PLS analyses on three node-level brain network measures: nodal degree, clustering coefficient, and communicability. In each of the three PLS analyses, the predictor matrix was therefore a 383 x 100 matrix (participant by node) where each element was the statistical property (degree, clustering coefficient, or communicability) and the response vector consisted of 383 x 1 factor loadings. Following our permutation procedure, the PLS analyses did not reveal any significant neural components that could explain variation along the behavioural continuum of inattention/hyperactivity in our sample ($p_{permuted} > 0.2$ for degree, clustering coefficient, and communicability). This demonstrates that although there might be a relationship between elements of brain organisation and inattention/hyperactivity, this cannot be reduced to linear underlying statistical components, at least with a sample of this size and composition.

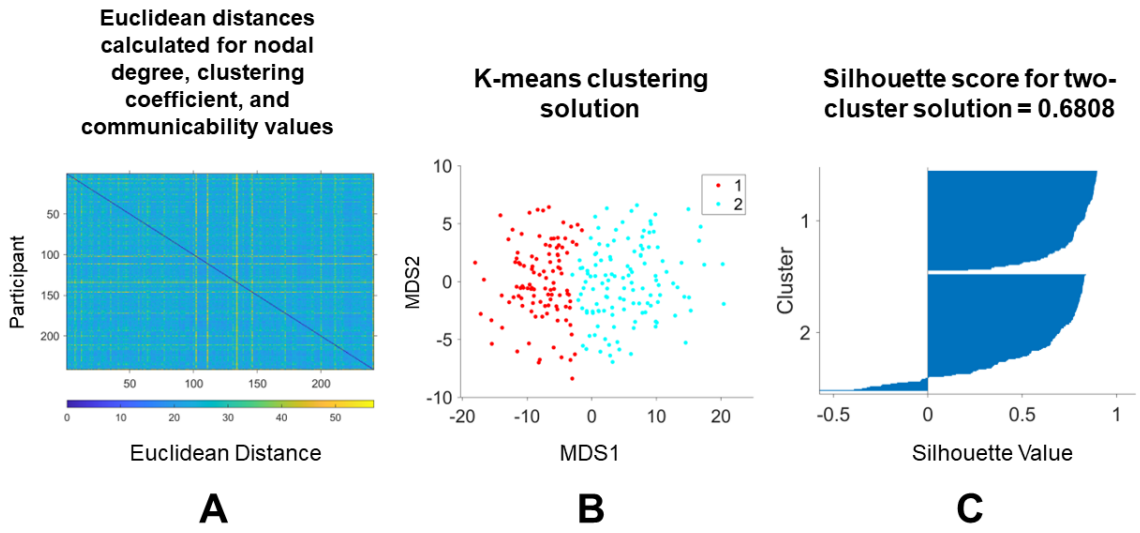
2.4.3 K-means clustering reveals two groups with high inattention and hyperactivity

We restricted our next analysis to participants with clinically-elevated levels of inattention and hyperactivity, and then explored this variability in a different way. This new sample, which was characterised by elevated levels of inattention and hyperactivity (defined as surpassing a clinically-relevant threshold of a T-score over 60 on the Inattention and Hyperactivity/Impulsivity subscales of the Conners Questionnaire) left us with data from n = 232 children, which were included in further analyses. In our sample, children with a high score on the Conners Questionnaire's subscales for Inattention and Hyperactivity/Impulsivity may have received a formal diagnosis ADHD, but it is also possible that they carry a different diagnosis, or indeed none at all. This clinically-relevant score provides a way of capturing impairing levels of inattention and hyperactivity in children, regardless of their diagnostic status. In Appendix G, we compare the mean behavioural questionnaire and cognitive test scores of this group to those from the discarded sample (who had Conners Questionnaire T-scores <60; n = 151) and total sample (n = 383). Our clustering analysis tested whether

individuals in this subsample, with high inattention and hyperactivity, are differentiated by three simple node-wise measures of their structural brain networks: degree, clustering coefficient, and communicability. We later explored which of these measures contributes the most to the clustering solution.

Following multidimensionality scaling across nodal measures, we calculated silhouette scores across a range of potential clustering solutions in order to find the optimal number of clusters to use in further analyses (see Appendix F for alternative *n*-cluster solutions and corresponding silhouette values). The maximum silhouette score across these solutions was 0.6808. This clustering solution was represented by two similarly-sized clusters (n = 109 and n = 123).

Figure 2.3: In this diagram, we demonstrate the steps we took in our k-means clustering analysis on graph theory measures derived from structural connectome data. First, we used multidimensionality scaling to generate a 2D Euclidean distance matrix between subjects (232 x 232), which was computed from nodal communicability, clustering coefficient, and degree values (A). Then, we applied a K-means clustering algorithm, which detected two groups based on these nodal graph measures (B). We then tested the strength of our clustering solution. This two-cluster solution was selected due to its silhouette coefficient of 0.6808, indicating a high degree of separation between clusters (C).

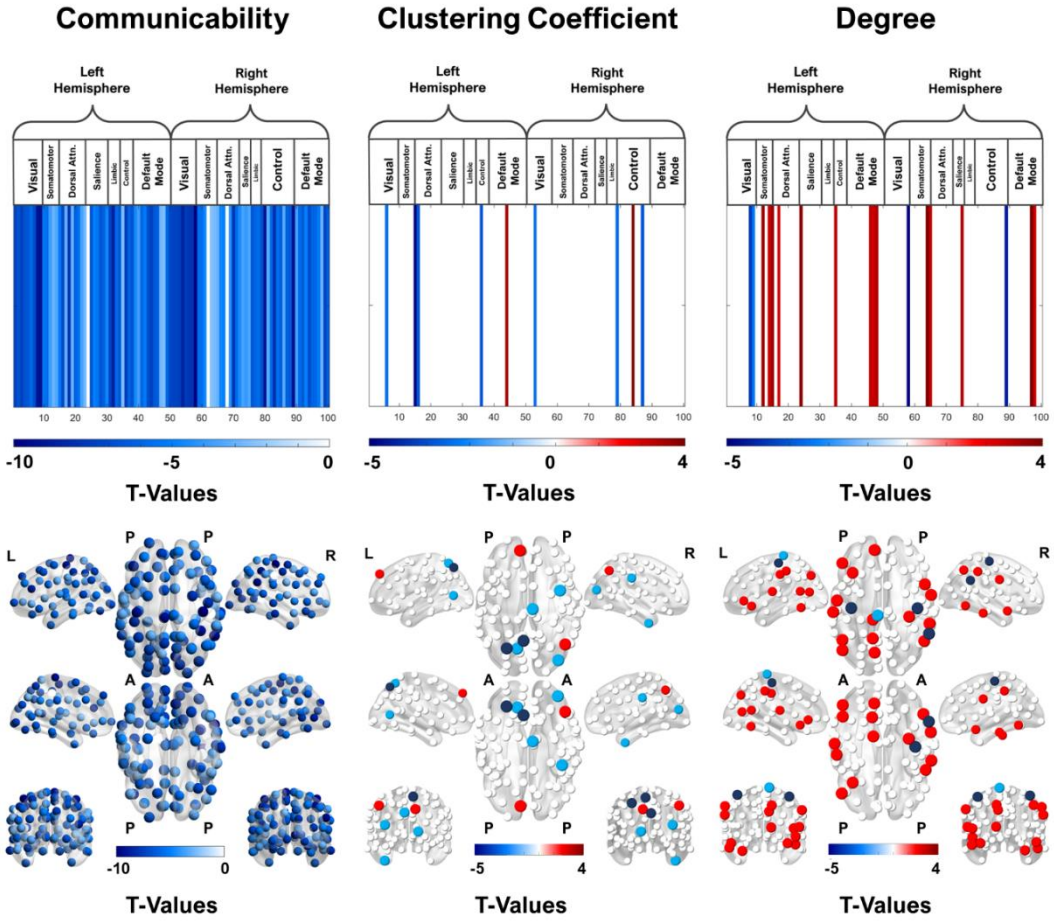


2.4.4 Differences in nodal degree, clustering coefficient, and communicability values between the clusters

After identifying two groups of highly inattentive and hyperactive children using k-means clustering, we tested the extent to which the degree, clustering coefficient, and communicability of each node differentiated the groups. Put simply, having used these measures to identify the clusters, we wanted to test which nodewise measures were driving cluster membership. We compared each of these nodewise measures between clusters using general linear models, where participant age, gender, and MRI head motion (quantified across participants using mean framewise displacement) were included as control regressors. FDR post-hoc corrections were applied to account for multiple comparisons across 100 nodes for each of the graph measures (see Appendix

H for a schematic of our GLM procedure, and Appendix K for frequency distributions of mean framewise displacement and age across participants).

Figure 2.4: Here, we illustrate contrasts in nodal degree, clustering coefficient, and communicability values between the two clusters. Negative t-values, shown in blue, highlight nodes where Cluster 2 has lower degree, clustering coefficient, and communicability values than Cluster 1. Positive t-values, shown in red, highlight the nodes on which Cluster 2 has higher values than Cluster 1. The strongest and most widespread neural differences between the groups were reflected in nodal communicability values, where Cluster 1 demonstrated consistently higher nodal communicability than Cluster 2.

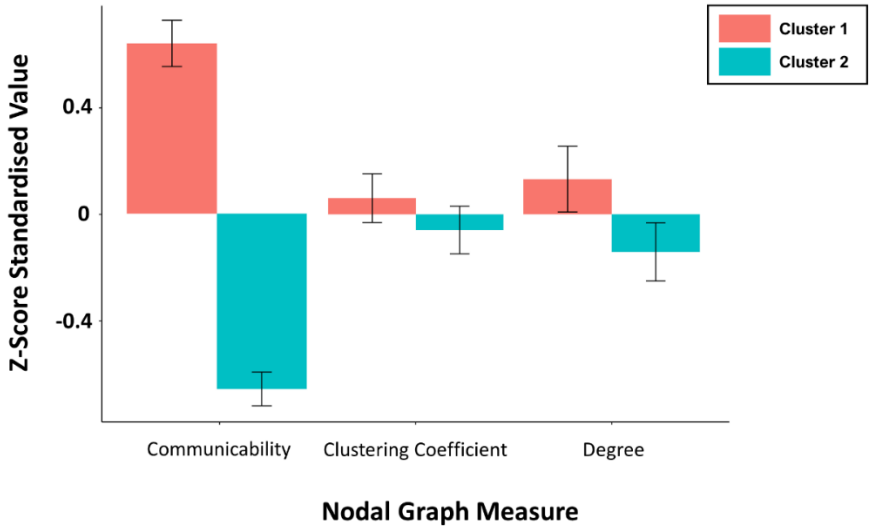


Structural Nodal Differences Between Groups of Children with High Inattention and Hyperactivity

2.4.5 Higher Widespread Communicability, Clustering Coefficient, and Degree Values in Cluster 1

Since widespread nodal communicability appears to differentiate the clusters most strongly, we decided to investigate which of the clusters had higher global communicability, clustering coefficient, and degree values. We conducted three paired-samples t-tests on averaged, z-score normalised communicability, clustering coefficient, and degree values. We found that Cluster 1 has higher global communicability (M = 0.6271, SD = 0.0851) than Cluster 2 (M = -0.6461, SD = 0.0623), $t_{(198)} = 120.6907$, $p = 2.3653 \times 10^{-187}$, 95% C.I. [1.2524, 1.2940]. Additionally, Cluster 1 was found to have higher global clustering coefficients (M = 0.0619, SD = 0.0930) than Cluster 2 (M = -0.0596, SD = 0.0903), $t_{(198)} = 9.3788$, $p = 1.5841 \times 10^{-17}$, 95% CI [0.0960, 0.1471]. The final t-test revealed that Cluster 1 exhibits higher global degree (M = 0.1317, SD = 0.1092) compared to Cluster 2 (M = -0.1412, SD = 0.1233), $t_{(198)} = 16.5693$, $p = 2.9489 \times 10^{-39}$, 95% C.I. [0.2404, 0.3053].

Figure 2.5: Paired-samples t-tests were used to compare global averages of nodewise measures between clusters of children with high inattention and hyperactivity. Children in Cluster 1 demonstrated higher global communicability, clustering coefficient, and degree values compared to Cluster 2. Error bars represent standard deviations of mean nodewise measure values.



Comparisons of average nodal graph measure values between clusters of children with high inattention and hyperactivity

2.4.6 Cognitive differences, but not behavioural differences, characterise the neurotypes

In order to test whether our clustering solution generalises to behavioural and cognitive characteristics, we performed additional analyses comparing the clusters on nineteen different behavioural questionnaires and cognitive tests.

First, we used a Pearson's Chi-Square Test to compare distributions of gender across groups. No significant differences in gender were found between the groups, X^2 (1, 232) = 0.521, p = 0.470. A paired-samples t-test was used to compare age (in months) between groups. Cluster 1 (M = 114.29, SD = 24.06) was found to be slightly younger than Cluster 2 (M = 123.29, SD = 27.96), $t_{(230)}$ = -2.6111, p = 0.0096, 95% CI [-15.7898, -2.2084].

We used twenty-seven separate general linear models to test how behavioural and cognitive measures vary between the communicability-driven subtypes of those with clinically elevated inattention/hyperactivity. A GLM was performed for each behavioural and cognitive measure, and False Discovery Rate corrections were used to control for multiple comparisons across GLMs that included the same data type (for instance, across GLMs that included cognitive test scores). In all GLMs, gender, age of scan, age of test, and mean framewise displacement (head motion) scores were included as control regressors (see Appendices I and J for schematic representations of our behavioural and cognitive GLM procedures).

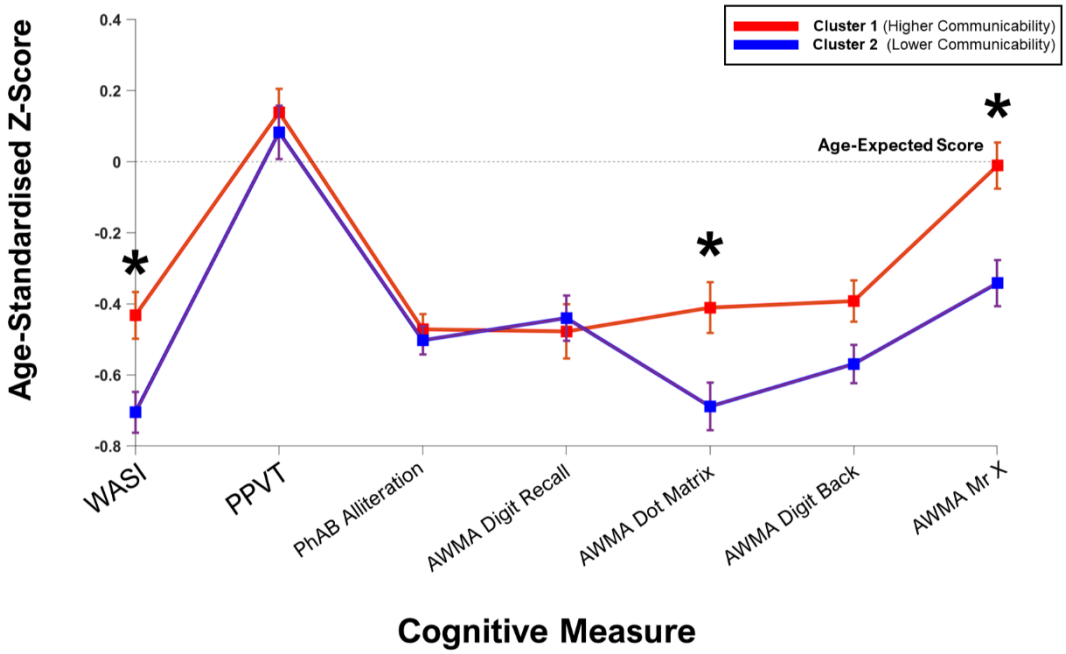
The first set of GLMs, each of which included cluster membership as an independent variable and scores on one of twenty behavioural questionnaires as a dependent variable, tested how participants' scores on behavioural questionnaires differed between the clusters. These questionnaires included the SDQ cumulative score, SDQ subscales (Emotion Regulation, Conduct, Hyperactivity, Peer Problems, and Prosocial), BRIEF subscales (Inhibit, Shift, Emotion Control, Initiate, Working Memory, Planning, Organisation, and Monitor), and Conners Questionnaire subscales (Inattention, Hyperactivity/Impulsivity, Peer Relations, Learning Problems, Executive Function, and Aggression). As the behavioural subscale scores do not use a common scale, the behavioural data from our entire sample were z-scored prior to analysis, using the age-standardised means and standard deviations, such that a score

of zero represents an age-expected score. Despite the fact that both clusters were already known to have clinically-elevated levels of inattention and hyperactivity, it was possible that there could be cluster-specific variations on inattention- and hyperactivity-related measures within the clinical range. However, no significant differences were found between the clusters on any of the questionnaire scales, $t(226) < |1.9771|$, $p_{corrected} > 0.05$.

The second set of GLMs, each of which included cluster membership as an independent variable and scores on one of seven cognitive tests as a dependent variable, tested cognitive test scores between the two clusters. Again, we corrected for multiple comparisons across tests using a False Discovery Rate correction. Cognitive data included T-scores from the WASI-II (Matrix Reasoning subtest), T-scores from the PPVT, scaled scores from the PhAB (Alliteration subtest), and standardised scores from the AWMA (Dot Matrix, Backward Digit Recall, and Mr X subtests). As cognitive subscale scores do not use a common scale, the cognitive data from our entire sample were z-score standardised for the purpose of this analysis, using the age-standardised means and standard deviations, such that a z-score of zero represents an age-expected score.

A significant difference was found in Wechsler Abbreviated Scale of Intelligence II (Matrix Reasoning subtest) scores between the clusters, $t_{(226)} = -2.3186$, $p_{corrected} = 0.0497$. WASI scores in Cluster 1 (M = -0.4321, SD = 0.0658) were higher than those in Cluster 2 (-0.7049, SD = 0.0576). The effect size for this comparison was small, with Cohen's $d = 0.2898$. A significant difference was also found between the clusters' scores on the Automated Working Memory Assessment (AWMA) Dot Matrix task, $t_{(226)} = -2.3665$, $p_{corrected} = 0.0497$, with a small effect size (Cohen's $d = 0.2637$). Further differences were found between the clusters on the AWMA Mr X task, $t_{(226)} = -2.4410$, $p_{corrected} = 0.0497$, with a small-to-moderate effect size (Cohen's $d = 0.3354$). AWMA Dot Matrix scores in Cluster 1 (M = -0.4106, SD = 0.0715) were higher than those in Cluster 2 (-0.6887, SD = 0.0669), and that AWMA Mr X scores in Cluster 1 (-0.0106, SD = 0.0649) were higher than those in Cluster 2 (-0.3415, SD = 0.0648; see Figure 2.6). No significant differences were found between the clusters on the other cognitive tests, $t_{(226)} < |1.7690|$, $p_{corrected} > 0.05$.

Figure 2.6: Age-standardised comparisons of cognitive differences between clusters based on cognitive test scores. Significant differences between clusters are labelled with an asterisk.



Note. Error bars represent standard errors of mean cognitive test scores. Differences between the groups' performance on cognitive tests were found on the Weschler Abbreviated Scale of Intelligence (WASI) and Automated Working Memory Assessment (AWMA; Dot Matrix and Mr X subtests).

2.5 Discussion

We investigated whether, and how, differences in structural brain organisation mirrored a common transdiagnostic characteristic of children and young people with neurodevelopmental difficulties. Within our sample, inattention and hyperactivity were well-captured by a common latent factor, but this could not be well explained by linear connectomic differences. Across individuals with clinically-elevated inattention and hyperactivity, there was substantial heterogeneity in connectome organisation. We found that a two-cluster k-means clustering solution best captured this heterogeneity. These clusters of inattentive and hyperactive children were differentiated primarily by nodewise communicability, but also by clustering coefficient and degree. The two clusters had statistically-indistinguishable behavioural profiles—they were equally inattentive and hyperactive, and were comparable across various other developmentally-relevant domains, such as gender. However, these two

groups did differ in their cognitive abilities, particularly on measures of executive function and visuospatial reasoning.

2.5.1 A single behavioural dimension

We first tested whether inattention and hyperactivity represent two separate behavioural constructs. We found that inattention and hyperactivity are highly related to one another within the CALM sample. One large inattention and hyperactivity factor can explain the majority of variance across subscales of the SDQ, Conners, and BRIEF questionnaires. This stands in contrast to accounts of inattention and hyperactivity that attribute these features of ADHD to separate behavioural 'subtypes' (August & Garfinkel, 1989). Indeed, there is increasing evidence of significant covariance between inattention and hyperactivity within ADHD, such that a general factor has better predictive power than two separate dimensions (Toplak et al., 2009; Sokolova et al., 2016). Additionally, Krakowski et al. (2020) found that variations in this latent inattention and hyperactivity factor do not differentiate the behavioural profiles of children with ADHD or autism, leading the authors of the study to suggest that this latent factor may also be more useful in the context of studying behaviour on a transdiagnostic basis.

It may be tempting to think that the demonstration of a common underlying factor for inattention and hyperactivity is somewhat at odds with the aims of transdiagnostic research. However, this does not logically follow. Determining the dimensional underpinnings of this characteristic is orthogonal to the question of the extent to which this factor extends across diagnostic boundaries, or co-occurs alongside other characteristics (Bathelt et al. 2018).

In interpreting this result, it is important to remember that although these specific scales are designed to capture the characteristics of inattention and hyperactivity, the single factor is also likely to represent a more general dimension of behavioural difficulty. This is in keeping with previous findings from this cohort (e.g. Holmes et al., 2021), who found that all the behavioural questionnaires in the CALM sample are characterised by a broad, general dimension (sometimes called a 'P' factor), in addition to a more specific neurodevelopmental dimension which represents symptoms of inattention, hyperactivity, and executive function. Thus, while we are explicitly

measuring inattention and hyperactivity, it is possible that our factor also captures something more general.

2.5.2 Structural connectome properties did not linearly explain inattention and hyperactivity

Since inattention and hyperactivity can be explained by the same underlying construct in CALM, we chose to analyse brain network properties with this in mind, using these factor scores. We used three partial least squares regressions to test whether there are underlying components that represent co-variation between three node-level graph measures and inattention/hyperactivity factor scores. We did not find any significant components. This suggests that within the CALM sample, it may be difficult to explain the broad spectrum of inattention and hyperactivity with linear components relating to structural brain organisation. There are multiple possible explanations for this finding, one of them being sample size. With larger sample sizes, associations between these characteristics of structural connectivity and inattention/hyperactivity may be detectable, but the absence of effects here would suggest they are weak and/or highly variable. Another possibility is that differences in brain *function*, rather than brain structure, may be more valuable in defining linear variations in inattention and hyperactivity across a broad sample. A range of studies have investigated how measures of functional connectivity (FC) may differ in inattentive and hyperactive individuals compared to those who are 'typically-developing' (for review, see Castellanos & Aoki, 2016). Graph-theoretic measures are often used to inspect how these differences are manifested in patterns of FC, both across the whole brain and within, or between, specific networks or brain regions of interest. In CALM, Jones et al. (2022) found that hyperactivity/impulsivity was linearly associated with reduced segregation between higher order resting-state networks. Additionally, decreased global efficiency—an inverse measure of the topological distance between nodes in a network—has been found both in adults (Lin et al., 2014) and in children (Wang et al., 2009; Wang et al., 2020) who are inattentive and hyperactive. While the current study investigated structural brain organisation along a spectrum of inattention and hyperactivity, it is possible that further studies of FC in the CALM cohort will reveal differences in global and region-specific network measures that coincide with linear variations in behaviour.

A second explanation for the null results in the PLS analysis is that there are multiple different configurations of structural brain organisation that generate equally inattentive and hyperactive behavioural phenotypes. The current study lends evidence to the idea that inattention and hyperactivity do not result from one specific 'type' of brain, but that these features of behaviour are shared by multiple structural neurotypes. This is reflected in the concept of equifinality, which describes the means by which open systems reach similar observable end-states through different means (e.g. Simmons et al., 2019). The brain is an example of an open system—one which takes input from the outside world and engages in various embodied computational processes, resulting in observable cognitive and behavioural phenomena (Yufik et al., 2017). While there may be some consistencies in structural brain organisation across those with elevated inattention and hyperactivity (Gehricke et al., 2017; Bayard et al., 2020; Zhang-James et al., 2021), this does not discount the existence of heterogeneity in the neural structures and processes that could generate this behavioural phenotype. In a recent study of neuroanatomic heterogeneity in ADHD, Li et al. (2021) found that a range of neural subtypes existed within a large sample of individuals with ADHD in comparison to non-ADHD controls. The severity of inattention, hyperactivity, and impulsivity symptoms did not differ between these neural subtypes, suggesting that there is no stable, one-to-one mapping between brain types and complex behavioural types. Additionally, a recent meta-analysis conducted by Cortese et al. (2021) found *no consistent differences* in functional connectivity across individuals with ADHD compared to controls, which may be accounted for by heterogeneity in study participants. The current study supports these findings in the context of a transdiagnostic framework, which enabled us to go beyond procedures that draw discrete distinctions between those with and without a diagnosis of ADHD.

2.5.3 Two clusters of brain organisation within inattention and hyperactivity

Because we did not find a linear component that explained variations in brain organisation along a broad spectrum of inattention and hyperactivity, we decided to explore possible nonlinearities between these behavioural traits and attributes of brain organisation. To investigate neurological diversity among children with particularly high levels of inattention and hyperactivity, we ran a k-means clustering analysis on the three nodal measures from the structural connectomes of children whose Conners

Questionnaire T-scores exceeded the clinical threshold of 60 on both of the relevant Conners Questionnaire subscales (Inattention and Hyperactivity/Impulsivity). The cleanest clustering solution produced two clusters of structural brain organisation (n = 109 and 123). Admittedly, one can see that the clustering algorithm is essentially carving a continuous distribution in half. Nonetheless, the silhouette score indicates that there is indeed a good separation between the two clusters. This suggests that these two groups can be distinguished on the basis of high or low MDS scores but that the boundary may not be well-defined.

The presence of neural heterogeneity, which can be characterised (albeit coarsely) as two clusters, is a demonstration that multiple different neural profiles coincide with the expression of clinically significant levels of inattention and hyperactivity. Our comparisons of nodal degree, clustering coefficient, and communicability across the two clusters revealed that all three of these measures pick up on nodewise differences between the groups. However, communicability shows the greatest nodewise differences, suggesting that they are best differentiated by this feature of structural brain network organisation.

Communicability is a representation of theoretical information flow through a network based on the number of short-path connections that link a single node to other nodes (Benzi et al., 2013). The differentiation of children using this measure has interesting implications within the context of brain development and neural-behavioural equifinality (Crofts & Higham, 2009; Andreotti et al., 2014). The first implication hinges on the widespread relevance of communicability across whole-brain networks in differentiating subgroups of inattentive and hyperactive children. The brain structure of one group of children is characterised by almost universally higher-communicability nodes than the other. However, both of these groups exhibit scores on the Conners Questionnaire that exceed the clinically-relevant threshold. Different neural subtypes can exist among children who express the same degree of behavioural inattention and hyperactivity, demonstrating the principle of neural-behavioural equifinality. Brain network topologies that facilitate more energetically-efficient information transfer support the development of more robust frontoparietal networks, which in turn are thought give rise to differences in executive function (Cui et al., 2020). Additionally, polysynaptic network communication models, captured by

communicability, have been shown to be predictive of human functional and behavioural characteristics, over and above models that do not capture this mode of connectivity (Seguin & Zalesky, 2020; Seguin et al., 2022). Our findings demonstrate that the structural architecture of whole-brain networks may play a role in directing cognitive and behavioural processes, and could provide new insights into the anatomical basis for developmental diversity. It is possible that communicability, alongside other measures of brain network topology, relates to a set of closely-associated cognitive capacities underpinned by a broader developmental process. Since communicability measures the ability of a node to propagate a signal through a network, increases in this neural measure may be expected to coincide with the development of more efficient forms of cognitive processing. Because differences in cognitive ability are widely seen across neurodevelopmental conditions, structural brain network communicability—and the biological mechanisms by which it changes over time—may provide a window into how these differences emerge.

In the current study, we show that group-based differences in structural brain organisation may have consequences for cognitive development. Although both clusters have similar behavioural profiles, they differ significantly on three cognitive assessments measuring visuospatial reasoning, spatial short-term memory, and spatial working memory. Children in Cluster 1 scored slightly higher than children in Cluster 2 on all three measures. Higher widespread nodal communicability, clustering coefficient, and degree values also characterises children from Cluster 1. This could suggest a link between global patterns of structural brain organisation, measured across nodes, and cognitive measures of executive function in children with elevated inattention and hyperactivity. ADHD has previously been associated with differences in inter- and intra-network connectivity across multiple brain networks, with additional evidence pointing towards global reductions in network-specific integration and segregation (Cao et al., 2016; Qian et al., 2019; Hilger & Fiebach, 2019; Griffiths et al., 2021; Jones et al., 2022). Across infancy and childhood, structural brain networks serve as an anatomical backbone to the development of functional modules (Giedd & Rapoport, 2010). These networks undergo a process of gradual refinement, characterised by changes in modular integration and segregation according to a rich-club topological structure that is well-established by the time of birth (Ball et al., 2014; Kim & Min, 2020). Over time, structural brain modules, or *hubs*, develop short-path

connections to other modules, enabling efficient long-range communication across brain networks (Park & Friston, 2016). As such, brain development is characterised by an optimisation in the balance between the global integration and local segregation of information transfer, which is revealed by features of structural brain network topologies. A number of studies have observed characteristic associations between intelligence and node-specific measures of within- and between-module connectivity, particularly in frontal and parietal brain regions (Gallen et al., 2016; Hilger et al., 2017; Chaddock & Heyman, 2020). Developmental differences in the emergence and interconnectivity of these structural modules may affect the type, rate, and degree of cognitive and behavioural change across childhood. In the case of children with elevated inattention and hyperactivity, widespread decreases in nodal degree and clustering, which has implications for connectivity within and between structural modules, may coincide with lower cognitive performance, as observed in Cluster 2. Additionally, multiple studies have identified nodal communicability as a relevant measure in the association between brain organisation and cognitive ability (Gilson et al., 2020; Lella & Vessio, 2021). This could reflect a trend of reduced communication across networks in the brain, indicated by the formation of fewer short paths between brain areas. However, the current study did not examine the directionality of the causal mechanisms underpinning differences in nodal communicability. Future longitudinal research might be able to reveal the temporal sequencing of the relationship between cognitive performance and communicability, shedding light on how these related measures change throughout development.

As discussed previously, the concurrent presentation of inattention and hyperactivity in our sample enabled us to explore these behavioural measures through one underlying dimension. The moderate cognitive differences between children in Cluster 1 and Cluster 2 indicate that these neurotypes might also reflect two phenotypic subtypes of high inattention and hyperactivity. Since we applied k-means clustering to participants' connectomes based on a clinical threshold, all of these children could arguably qualify for a clinical diagnosis of ADHD. However, they were not distinguished by inattention *or* hyperactivity—subtypes which exist in clinical definitions of ADHD—but by their cognitive ability, which also coincided with differences in their structural brain network topologies. This has potential implications for the treatment of ADHD, particularly in the provision of subtype-

specific accommodations in educational settings. Previously, Reiersen and Todorov (2013) found that current diagnostic criteria may fail to identify a subgroup of individuals with both inattention and hyperactivity who may have higher support needs than other individuals with an ADHD diagnosis. We argue that these heightened support needs may emerge from not only ADHD-specific symptoms, like inattention and hyperactivity, but the fact that a sizeable subgroup of children with ADHD also experience an additional degree of cognitive difficulty that may enhance barriers to learning in school.

2.5.4 Limitations

It is worth noting that the effect sizes for the cognitive comparisons between the clusters were small-to-moderate. Thus, although we identified cognitive differences between the two clusters, the magnitude of these differences is not profound according to commonly-used 'significance' benchmarks. Traditionally, one would interpret a Cohen's *d* value of 0.2 as small, one of 0.5 as medium, and one of 0.8 as large based on benchmarks suggested by Cohen (1988). These benchmarks are particularly applicable to cases where an observed effect is novel, and there is no strong basis for the cross-comparison of effects within the scientific literature. However, these pre-set values are ultimately arbitrary, and cannot be considered a perfect indicator of the downstream consequences of group-level differences or interventions. This is particularly true at the population level, where 'small' differences between groups can have profound consequences. The effects outlined in this study must be interpreted with consideration for what group-level developmental differences might mean in the context of certain outcomes, like academic attainment. Since much of neurodevelopmental research is geared towards enabling the improvement of these outcomes for the benefit of individuals and society, we believe that future research should strive to capture how moderate cognitive differences, given behavioural similarity, might explain variance on relevant outcome measures.

Another potential limitation of the current study was its sample size. An initial dataset of n = 383 may have hindered the detection of linear components in brain organisation that could explain variance in inattention and hyperactivity. This was further reduced to n = 232 in analyses of participants with clinically elevated inattention and hyperactivity. Having more data available for our analyses may have allowed us to

identify more specific subgroups in our clustering analysis—perhaps with different, or more subtle, variations in cognition and behaviour. In the future, data from larger developmental cohorts should be incorporated into studies of brain network differences in the domain of heightened inattention and hyperactivity.

Additionally, our use of k-means clustering ensured that clusters were defined along a hard boundary, such that groups of a similar size were maintained in our clustering solution. Other methods, such as gaussian mixture modelling, have previously been used to identify the extent to which individual datapoints hold 'responsibility' within their respective clusters (McLachlan, 2004; Reynolds, 2009; Yang et al., 2012). This allows datapoints to be sorted along a gradient of contribution to a clustering solution, rather than strictly allocated to a particular cluster. In the future, we recommend that these methods be applied to ascertain the validity and reliability of clustering solutions—particularly those which are more ambiguous in their statistical power.

Following the identification of n = 232 children with elevated inattention and hyperactivity in our larger sample, we were left with an additional subset of n = 151 children whose Conners Questionnaire scores did not exceed 60. While considerations had been made about the possibility of using this subset as a 'control' group, and including these children into our comparisons between inattentive and hyperactive clusters, we made the decision to only retain participants who surpassed the clinical threshold. While the Conners Questionnaire defines a clinical threshold of >60 for the purpose of identifying children with ADHD-like characteristics, it does not define a range of scores for children who are 'typically-developing'. In the future, it may be possible to define hallmark features of 'typical' behavioural and cognitive development. However, this taxonomical project would also be challenging, since these features fall along their own severity spectrums, and significant heterogeneity exists between individuals (see Astle & Fletcher-Watson, 2020, for review). In Appendix G, we summarise the behavioural and cognitive characteristics of children across our whole sample, compared to those in the inattentive/hyperactive and Conners Questionnaire<60 subsamples.

The fact that the inattentive and hyperactive clusters were not found to differ on any behavioural measures could be attributable to the fact that functional connectivity is

typically better-associated with behaviour than structural connectivity (Jia et al., 2014; Fjell et al., 2017). In addition, structural brain connectivity has been linked robustly to cognitive ability (Ponsoda et al., 2017; Babaeeghazvini et al., 2021; Amunts et al., 2022). This coupling of structure-cognition and function-behaviour relationships could explain why cognitive differences, rather than behavioural differences, were found to exist between two different profiles of structural brain connectivity. Future studies should strive to investigate whether there are subgroups of inattentive and hyperactive children that are differentiable by their functional connectivity profiles, and whether additional contrasts on other behavioural measures can be observed between these groups.

2.6 Conclusion

In this first empirical chapter, we found that properties of structural brain networks differ among children with high levels of inattention and hyperactivity. Additionally, we were able to see how two neurotypes with the same behavioural presentation differ on measures of cognitive ability, which may represent a relevant dimension of assessment when characterising the needs of children with inattention and hyperactivity. In the next chapter, we investigated how the properties of functional connectivity might further differentiate subgroups of highly inattentive and hyperactive individuals. Additional studies that clarify these relationships will provide further insight into potential links between attributes of structural and functional brain organisation, as well as cognition and behaviour, in children with elevated inattention and hyperactivity. The current study represents a methodological and theoretical step towards the use of transdiagnostic approaches in the context of studying the development of the human connectome.

3 Functional Connectome Organisation in Children with Heightened Inattention and Hyperactivity

3.1 Introduction

3.1.1 Assessing intrinsic patterns of functional connectivity

The human brain is characterized by structural, functional, and effective connectivity within and between different neural elements (Sporns, 2013). In the context of functional magnetic resonance imaging (fMRI), functional connectivity refers to statistical dependencies between time series representations of blood oxygen-level dependent activity (BOLD) in distinct regions of the brain. The primary principle underlying resting-state functional connectivity is that the pattern of low-frequency fluctuations in the BOLD signal is more correlated between brain regions that form functional circuits (Hulvershorn et al., 2014). Since the BOLD signal—a measure of metabolic demand—provides indirect insight into neural activity itself, functional connectivity is represented through correlations of change in this measure. Importantly, functional connectivity does not imply the presence of temporally-constant, or causally-direct, relationships between different regions in the brain. Functional connections are continuously modulated by sensory information from the environment, alongside spontaneous patterns of brain activity, so causal directionality is challenging to establish (for review, see Smith et al., 2011). Nonetheless, fMRI-based representations of functional connectivity have proved useful in investigating a variety of neural properties, including structure-function relationships, intrinsic connectivity networks, and differences in brain activity across a wide range of developmental, cognitive, and neurological conditions (e.g. van Dijk et al., 2010; Xia et al., 2018; Jiang et al., 2018; Sripada et al., 2021).

Previous research has identified links between structural and functional connectivity in the brain, highlighting the overlap between the organisational features of anatomical brain networks and the emergence of both task-relevant and baseline activity (e.g. Suarez et al., 2021; Neudorf et al., 2022). A primary question in this field concerns the degree, and biological relevance, of this structural-functional overlap.

How do patterns of functional connectivity, which emerge from features of structural organisation, facilitate complex and adaptive cognition and behaviour? As we shall see, a range of spatially- and temporally-embedded networks of functional connectivity, identifiable through recurring patterns of brain activity across time, support these processes.

Intrinsic Connectivity Networks (ICNs) are widely regarded as fundamental organisational elements of the human brain. ICNs were first discovered in the form of functionally-correlated fMRI time series during resting-state scans (Biswal et al., 1995; Lowe et al., 1998; Xiong et al., 1999; Cordes et al., 2000). Later, researchers sought to identify and create taxonomies of ICNs using methods like independent components analysis (ICA), which have been applied to fMRI data in order to delineate prominent coactivation networks across the brain (Kiviniemi et al., 2003; van den Heuvel et al., 2009; Allen et al., 2011). Smith et al. (2009) highlight the correspondence between the brain's functional architecture during both task-relevant engagement and the resting-state; a broad range of findings from imaging studies conducted in the past twenty years points to a set of primary brain networks—ICNs—that tend to independently arise regardless of what the brain is 'doing'. They also conclude that assessing resting-state functional connectivity by measuring and quantifying certain features of ICNs allows for clinically- and empirically-relevant comparisons to be made between participants. This represented a conceptual breakthrough in cognitive neuroscience. The idea that there is a set of functional *networks* which facilitate dynamic information transfer and processing across the brain has been extremely valuable to the construction of theories surrounding large-scale and inter-regional brain activity. With the firm establishment of ICNs as a feature of the functional architecture of the brain, it became evident that these networks might enable distinct features of sensory processing, cognition, and behaviour—in other words, that they emerged across evolutionary timescales, and that they develop during infancy and childhood, in order to serve specific 'roles' in the brain (Yeo et al., 2011).

One key feature of the development of ICNs is the hierarchical nature of their emergence and refinement over time. The presence of ICNs has been observed in foetuses as young as 19 weeks (Thomason et al., 2015; Asis-Cruz et al., 2021), as well as in preterm infancy (He & Parikh, 2016). ICNs in early infancy typically encompass

a handful of primarily sensorimotor systems (e.g. visual, auditory, somatomotor), although these networks undergo substantial changes as they differentiate according to higher-order functional demands (Fransson et al., 2007; Mongerson et al., 2017). By the age of 7, children are known to demonstrate segregation across all of the major ICNs found in adults, including the visual, auditory, somatosensory, default-mode, and frontoparietal networks (Thornburgh et al., 2017). Higher-order association cortices, such as those known to mediate behavioural and attentional control processes, continue to form more spatially-refined and temporally-distinct networks throughout later childhood, adolescence, and into earlier adulthood (Thomason et al., 2011; Abrol et al., 2023). Importantly, these task-positive networks exhibit a trend of increasing functional segregation from the DMN across the entirety of childhood and adolescent development (Rosenberg et al., 2020; Fan et al., 2021). However, these characterisations of developmental processes describe broad, age-related effects, and there is still a considerable amount of individual variability in the functional segregation of certain networks, particularly those higher-order networks that are most shaped by cognitive and behavioural demands in childhood and adolescence (Peña-Gómez et al., 2018; Sun et al., 2022). The individually-variable spatiotemporal characteristics of ICNs suggest that path-dependent neurodevelopmental processes, which bring about the functional segregation of higher-order brain networks, could also explain differences in behaviour and cognition.

Laird et al. (2011) explored the behavioural relevance of these networks by employing the BrainMap database, a repository of published functional neuroimaging results, in a large-scale analysis (Fox & Lancaster, 2002). At the time, BrainMap included data from over 8,500 functional neuroimaging studies (31,724 participants), which enabled a broad representation of age groups (1 to 90 years) and a population-representative gender distribution. In line with previous research, Laird et al. (2011) identified 17 spatial components across the brain—a finding which would later inform the construction of network-based atlases like the Schaefer parcellation, which also defines brain regions in reference to their placement across 17 ICNs (Beckmann et al., 2005; Calhoun et al., 2008; Robinson et al., 2009; Zuo et al., 2010; Schaefer et al., 2018). Using a hierarchical clustering analysis, they investigated the extent to which these ICNs were associated with behavioural features of theoretical interest—constructs such as working memory, inhibition, emotional processing, and pain

perception. Collectively, the ICNs could be associated with and categorised along four dimensions: emotion/executive control, motor control/visuospatial reasoning, visual perception, and audition and speech. These findings were taken as evidence of unimodal neural systems that performed specific forms of processing, thus enabling domain-relevant forms of cognition and behaviour. Suffice to say, this represented significant step towards a theoretical conception of ICNs: not only could they be identified as functional elements of the brain, but also as systems that interact in order to facilitate complex cognitive and behavioural phenomena.

Recent studies also suggest that the modular organisation of functional connectivity across the brain is key to optimising cognitive and behavioural performance across a variety of domains. Suarez et al. (2022), in a study that simulated neural network parameters and their consequences for task performance, demonstrated that the modular organisation of intrinsic networks is computationally-relevant. These types of network topologies, whether simulated or organic, are argued to support biologically-realistic critical dynamics of network activity while minimising wiring costs. The functional ontogeny of underlying network architectures, reflected by the strengthening of ICNs, can be said to underpin a process of optimisation for a wide range of information-processing and problem-solving capacities, which allow for flexible and adaptive patterns of cognition and behaviour.

3.1.2 The developmental relevance of the resting-state functional connectome

The past decade of cognitive developmental neuroscience research has been characterised by ongoing methodological and conceptual refinements in the study of connectivity among distributed regions of the brain. A newly-emerging framework for studying these patterns of connectivity is developmental connectomics, which aims to chart the ontogeny of the topological organisation of the brain across infancy, childhood, and beyond (Stevens, 2009). Additionally, there has been a push to understand these trends in brain development in the context of the emergence and calibration of different perceptual, cognitive, and behavioural modalities. Cao et al. (2017b) highlight five major features of brain network change that have been identified through the study of connectomic development from birth to early adulthood. Here, I

summarise these features briefly and take note of more recent studies which have explored them in greater depth:

3.1.2.1 Global changes in segregation/integration balance

Throughout development, the human connectome undergoes a range of global and localised changes in its structural and functional configuration (Tymofiyeva et al., 2013; van den Heuvel et al., 2015; Cao et al., 2017a). One of these changes relates to the gradual segregation and identifiability of function-specific brain networks, which become optimised to process and transmit information as part of a larger, integrated set of networks across the brain (Betzel et al., 2013). This phenomenon has been shown in studies looking at age-dependent effects in the segregation of resting-state intrinsic connectivity networks (e.g. Solé-Padullés et al., 2016; Bruchhage et al., 2020). Across development, there are increases in both the regional specialisation and global integration of functional brain networks. A range of studies have concluded that functional connectivity between regions that are anatomically close to one another decreases across childhood development, whereas longer-range connections grow stronger (Fair et al., 2013; Tomasi & Volkow, 2014; de Lacy & Calhoun, 2018). Through increases in both functional integration and ICN segregation over time, ICNs gain their spatial coherence and functional specificity. As ICNs become refined, concurrent changes in functional connectivity between particular ICNs also take place. One well-replicated finding is the progressive segregation of the default-mode network from fronto-parietal networks, which is shown by their becoming more anti-correlated in their levels of activity (Sherman et al., 2014; Gu et al., 2015). This finding has been attributed to the fact that fronto-parietal networks, like the central executive network, are reliably task positive, whereas the default-mode network shows lower levels of task-synchronisation (Di & Biswal, 2014; Weber et al., 2022; Tripathi & Garg, 2022). This suggests that these patterns of developmental change are relevant within the context of environmental pressures—ICNs that show higher levels of segregation enable different types of cognition and behaviour to occur, thereby making an individual more capable of adapting flexibly to a broad range of possible situations. As will be discussed later, differences in how this feature of functional connectivity arises throughout childhood may be related to the emergence of neurodevelopmental conditions.

3.1.2.2 Hierarchical ordering from primary to higher-order regions

Several resting-state functional connectivity studies have highlighted the sequential consistency with which primary (e.g. visual and somatosensory) and then higher-order (e.g. default mode and executive) ICNs develop over time (Fransson et al., 2007; Kelly et al., 2009; Doria et al., 2010; Jones et al., 2022). Although functional brain development involves dramatic organisational changes from infancy to adulthood, these changes are nonetheless directed toward a certain type of functional topology. Primary functional brain networks, which emerge prenatally, scaffold and enrich the later and more prolonged development of higher-order networks.

3.1.2.3 Different maturation modes of structural and functional connectomes

While there is general overlap in the order of development and spatial organisation of structural and functional brain networks, there are differences in the rates at which they mature. More specifically, the structural network topology of the brain exhibits a rich-club organisation from birth, whereas this feature of functional brain networks develops over time, such that ICNs gradually become more specialised to higher-order functions (Gao et al., 2011). Although functional brain network organisation is shaped by the underlying structural architecture, it is also more flexible, allowing for a greater diversity of configurations and possible states (Wang et al., 2015, Yin et al., 2020). Structural networks can be said to 'scaffold' the emergence of functional networks, which adapt in real-time to the demands of the external environment. Thus, there is not a perfect one-to-one mapping between structural and functional brain networks, because the latter serve as more spatially- and temporally-refined responses to specific environmental contexts.

3.1.2.4 Substantial individual variability

There are significant individual differences in structural and functional brain connectivity, particularly in higher-order networks distributed across frontal and parietal areas of the brain (Mueller et al., 2013; Xu et al., 2019; Wang et al., 2021). The studies cited here note that functional connectomic variability could signal differences in brain network development between individuals. In a study of infant and toddler

functional connectomes, Kardan et al. (2022) found that the individual functional connectomes of infants and toddlers are distinct enough in order to be differentiated through functional connectome fingerprinting, meaning that each human brain has unique functional 'signatures' of connectivity. However, they also found that individual participants' ages could be predicted with high reliability based on the features of their functional connectomes. While individual differences abound, age-dependent effects make it possible to study general developmental trends surrounding patterns of functional connectivity.

3.1.2.5 High vulnerability to risk factors and developmental disorders

Rapid brain maturation necessitates, and ensures, a high degree of cortical plasticity. While this plasticity enables learning and adaptive cognitive change in response to a wide range of possible environments, it may also make the developing brain more vulnerable to certain forms of risk and adversity, such as preterm birth, exposure to harmful substances, socioeconomic deprivation, and traumatic events (Salzwedel et al., 2015; Thompson et al., 2016; Amso & Lynn, 2017; Moriguchi & Shinohara, 2019; Johnson et al., 2021).

Functional connectivity, measured using resting-state scans of the brain, offers a window into investigating the mechanisms which underpin general neurodevelopmental trends. The functional connectome is an informationally-rich tool for exploring questions about the development of the brain at multiple scales of interest—including individual regions, connections between regions, and topological features of connectivity at both local and global scales. As discussed in the first empirical chapter of this thesis, a variety of graph theoretic measures can be used to capture properties of interest in both structural and functional connectomes (for review, see Wang et al., 2010 and Farahani et al., 2021). Furthermore, Pourmotabbed et al. (2022) found that graph measures derived from resting-state functional connectomes have a high test-retest reliability, indicating that they capture intrinsic features of individuals' functional brain architectures. In the context of studying typical and general characteristics of brain development, functional connectivity is an incredibly valuable tool.

3.1.3 Functional brain differences in neurodevelopmental conditions

Functional connectivity has also been investigated in the context of neurodevelopmental conditions, such as ADHD, autism, and dyslexia. Since it has been possible to uncover general trends of typical development by studying how the functional connectome changes across time, research has recently begun to probe how patterns of functional connectivity might differ across individuals with different neurodevelopmental trajectories.

One notable finding among studies of functional connectivity differences in those with neurodevelopmental conditions is divergent ICN development. As mentioned previously, typical childhood development of the functional connectome includes a gradual segregation between the default-mode network and task-positive networks across the brain. Over-connectivity between these networks has been observed in children with cognitive difficulties, particularly ADHD (Cortese et al., 2012; Sripada et al., 2014; Francx et al., 2015; Jones et al., 2022). Additionally, Nomi and Uddin (2015) found that autistic individuals exhibit patterns of under-connectivity within the default-mode network, suggesting that differences in both default-mode integration *and* segregation coincide with behavioural and cognitive features of neurodevelopmental conditions. Increased connectivity between the default-mode network and task-positive networks has also been found to correlate with the degree to which children exhibit attentional difficulties, regardless of whether or not they have an ADHD diagnosis (Cai et al., 2018; de Lacy & Calhoun, 2018; Jones et al., 2022). To provide a theoretical basis for these findings, Menon (2011) outlined a *Triple Network Model* of general psychopathology, which also strives to explain characteristics of neurodevelopmental divergence in the context of ICN connectivity. According to the Triple Network Model, certain features of brain architecture—particularly across the salience (ventral attention), central executive, and default-mode networks—are common across a variety of psychiatric and neurodevelopmental conditions:

3.1.3.1 Node-level differences

Research has highlighted widespread alterations in network nodes across many psychopathologies. Node-level abnormalities are thought to impact inhibition-excitation balance at every level of brain circuitry, as well as processes of signalling and global information flow. Menon (2011) argues that these node-level differences can primarily be seen in fronto-parietal and fronto-temporal networks, particularly the ventromedial and dorsolateral areas of the prefrontal cortex, anterior cingulate cortex, and insula in autistic individuals, as well as those with schizophrenia and major depression (Santos et al., 2011; Penner et al., 2016; Helm et al., 2018).

3.1.3.2 Edge-level differences

Edges characterise patterns of connectivity between brain regions. Significant differences in processes of interregional wiring and signalling are reflected in both local and global patterns of connectivity. While the strength of individual edges may hold relevance in the context of understanding clinically-recognised conditions, Menon (2011) argues that these effects are best studied using characterisations of large-scale brain networks, which can summarise the architectural attributes of structural and functional connectivity.

3.1.3.3 Differences in small-world architecture

The small-worldedness of a network is defined as the ratio of its normalised global clustering coefficient to its characteristic path length. Small-world organisations have been observed across a variety of organic and digital networks, and are associated with scale-free network architectures (Barabási, 2016). This measure of small-worldness in functional connectivity networks has been shown to be reduced across a range of conditions, including schizophrenia, autism, and depression (Anderson & Cohen, 2013; Rudie et al., 2013; Guo et al., 2014).

3.1.3.4 Salience network (SN) connectivity differences

The SN is located across the dorsal anterior cingulate cortex, fronto-insular cortex, amygdala, and substantia nigra, and is thought to be involved in detecting, filtering, and integrating homeostatic information in order to coordinate appropriate behavioural responses (Seeley, 2019). In other words, the SN is comparable to a 'filter',

or detection system, which is attuned to relevant features of the environment. SN connectivity differences have been implicated in cognitive control and attentional difficulties across a variety of conditions (e.g. Palaniyappan et al., 2012; Chang et al., 2018; Lin et al., 2021), and the structural integrity of the SN in neurodegenerative disease has been shown to be negatively correlated with the degree of executive functional impairment (Galandra et al., 2018). Since the SN is involved in processing relevant environmental information, and facilitating attentional and executive-control processes, then one might expect individuals with ADHD to show divergent patterns of wiring within the SN, as well as between the SN and other regions. Indeed, a variety of studies suggest that reductions in SN segregation, and over-connectivity between the SN and DMN, have a role to play in the emergence of ADHD-related behavioural characteristics like elevated inattention and hyperactivity (Choi et al., 2013; Hilger et al., 2019; Wang et al., 2021).

3.1.3.5 Central executive network (CEN) connectivity differences

The CEN is a frontoparietal network which is spatially-anchored in the dorsolateral prefrontal cortex (Habas et al., 2009), and has been associated with cognitive processes like problem-solving, working memory, and goal-directed behaviour (Gerlach et al., 2011; Dixon et al., 2017; Wylie et al., 2019). Differences in structural and functional CEN connectivity has been implicated in a variety of conditions, including ADHD, schizophrenia, autism, and depression (Kofler et al, 2009; Manoliu et al., 2014; Zheng et al., 2015; Ge et al., 2019; Wang et al., 2021). Menon (2011) cites three major findings relating to CEN connectivity and function in the context of cognitive and behavioural differences: *'(i) weak intrinsic connectivity between its nodes, (ii) abnormal recruitment of other brain nodes into the network that are not typically part of the CEN or (iii) impaired access to salient task-relevant stimuli'.*

3.1.3.6 Default mode network (DMN) connectivity differences

The DMN was the first ICN network to be identified using resting-state fMRI (Greicius et al., 2003), and is found across medial areas of the prefrontal cortex and medial temporal gyrus (Korgaonkar et al., 2014; Alves et al., 2019). Though its role as a discretely 'task-negative' network has come into question (Spreng, 2012), the DMN has been associated with 'at rest' activities, introspection and selfhood, and emotional

regulation (Qin & Northoff, 2011; Callard & Margulies, 2014; Satpute & Lindquist, 2019). Abnormalities in DMN functional connectivity have been noted across a broad range of psychopathologies (for review, see Broyd et al., 2008, Mohan et al., 2016, and Nair et al., 2020; see also Farina et al., 2018). Though more research is needed in order to understand how DMN connectivity varies along transdiagnostic dimensions of divergent neurodevelopment, Jones et al. (2022) found that neurodevelopmentally 'at-risk' children—those with higher levels of traits indicative of potential cognitive, behavioural, and learning difficulties—exhibit less DMN segregation from central executive and salience (ventral attention) networks. This finding is in line with multiple other studies of specific neurodevelopmental conditions, such as ADHD and autism, as well as general learning difficulties (Sripada et al., 2014; Kessler et al., 2016; Abbott et al., 2016; Mills et al., 2018).

The diversity of aetiologies represented in studies underpinning the Triple Network Model suggests that these functional connectivity differences are not unique to any particular neurodevelopmental condition, and that atypical ICN connectivity might correspond to a variety of divergent behavioural and cognitive phenotypes.

Correspondence, rather than causality, is important to emphasise here. Differences in functional connectivity do not necessarily produce further changes in cognition and behaviour in a causally-unidirectional manner. There is no greater causal 'purity' to biologically-identifiable features of neurodevelopment as opposed to cognitive or behavioural phenomena; the process of development is a complex, embodied interaction between biological and environmental factors across time. From this process, certain features of 'order' emerge. That is, we are able to observe patterns of correspondence that can be traced to all levels of empirical observation: the biological, the intrapersonal, and the societal. Thus, divergent ICN development is but a feature of a more widely-interacting system of parts, though it is a valuable one if our aim is to uncover characteristics of brain development in children with cognitive, behavioural, and learning difficulties.

3.1.4 The current study

In the previous chapter, we used data from the CALM sample in order to test how three node-wise graph measures of structural connectomes—degree, local clustering coefficient, and communicability—relate to variations in inattention and hyperactivity in 392 children. Additionally, we explored how a subset of these children with clinically-elevated levels of inattention and hyperactivity (identified by Inattention and Hyperactivity/Impulsivity subscale scores of over 60 on the Conners Questionnaire) may differ along these graph measures. We found node-specific differences in degree, clustering coefficient, and communicability values between two subgroups identified using k-means clustering. Additionally, we found that one of the subgroups of inattentive and hyperactive children show lower performance on cognitive tests of visuospatial reasoning, despite the fact that no significant differences on a range of behavioural questionnaires, age, or gender were found between the groups.

In the next empirical chapter, we attempted to address one overarching question: are there functional connectivity differences between subgroups of inattentive and hyperactive children? We took two different approaches to investigating these group-level differences. First, we examined how nodal degree, local clustering coefficient, and communicability might differ between the resting-state functional connectomes of the two inattentive and hyperactive subgroups identified in the previous chapter. Additionally, we assessed whether there are differences in inter-network connectivity between the central-executive network, salience network, and default-mode network between the subgroups.

3.2 Methods

3.2.1 Participants

Participants included children and young people from CALM who were identified as having a Conners Questionnaire score over 60 on two subscales: Inattention and Hyperactivity/Impulsivity. After we completed k-means clustering on their structural connectome graph measures (see empirical chapter 1), two subgroups of inattentive and hyperactive children were identified (Cluster 1 and Cluster 2; n = 123 and 109,

respectively). In the analyses covered in the current study, subgroups of Cluster 1 and Cluster 2, for whom functional connectome data were available, were included (n = 54 and 69, respectively). Further exclusions, detailed in subsequent sections, brought sample sizes down to n = 50 and n = 60 for Clusters 1 and 2, respectively. Descriptive statistics for the clusters are presented in Table 3.1:

Table 3.1: Descriptive statistics for functional connectome subgroups of children in Cluster 1 and Cluster 2, following exclusions.

Measure	***Cluster 1***	***Cluster 2***
Sample Size	n = 50	n = 60
Age in Years	10.449 (SD = 2.2512)	11.457 (SD = 2.309)
Gender	86% male	71.7% male

An independent-samples t-test was performed in order to compare the reduced-sample-size clusters on their ages. A significant difference was found; children in Cluster 2 were older than those in Cluster 1, $t_{(108)} = -2.4214$, $p = 0.0171$. This finding is consistent with the age trends observed between clusters in the previous chapter.

We also used a Pearson's chi-square test to compare distributions of gender across groups. No significant differences in gender distributions between the clusters was found, X^2 (1, 108) =3.2847, p = 0.0699.

Next, our aim was to assess whether the reduced functional connectome subgroups differed on the cognitive and behavioural measures examined in the first empirical chapter. Additionally, we wanted to know if these effects were retained across children in our reduced functional connectome sample. In the original inattentive and hyperactive sample, which included 232 participants, no differences were found between Cluster 1 and Cluster 2 on twenty behavioural measures (subscales of the Conners Questionnaire, Strengths and Difficulties Questionnaire, and BRIEF). However, the clusters were found to differ on three cognitive tests, with Cluster 1 scoring higher on the Weschler Abbreviated Scale of Intelligence (Matrix Reasoning

subtest) and Automated Working Memory Assessment (Dot Matrix and Mr X subtests).

Here, we repeated the GLM procedure used in the previous chapter to test how behavioural and cognitive measures vary between children in Cluster 1 and Cluster 2. A GLM was performed for each behavioural and cognitive measure, and FDR corrections were used to control for multiple comparisons across GLMs that included the same data type (for instance, across GLMs that included cognitive test scores). In all GLMs, gender, age of scan, age of test, and mean framewise displacement (head motion) scores were included as control regressors (see Appendix M for distributions of these measures across our functional connectome subsample).

The first set of GLMs tested how participants' age-standardised scores on behavioural questionnaires differed between the clusters. These questionnaires included the SDQ cumulative score, SDQ subscales (Emotion Regulation, Conduct, Hyperactivity, Peer Problems, and Prosocial), BRIEF subscales (Inhibit, Shift, Emotion Control, Initiate, Working Memory, Planning, Organisation, and Monitor), and Conners Questionnaire subscales (Inattention, Hyperactivity/Impulsivity, Peer Relations, Learning Problems, Executive Function, and Aggression). No significant differences were found between the clusters on any of the questionnaires, $t_{(104)} < |2.0489|$, $p_{corrected} > 0.2454$. Thus, the lack of effects observed in the larger sample (n = 232) was retained in the subsample (n = 110).

The second set of GLMs, each of which included cluster membership as an independent variable and scores on one of seven cognitive tests as a dependent variable, tested age-standardised cognitive test scores between the two clusters. The cognitive tests included the WASI (Matrix Reasoning subtest), PPVT, PhAB (Alliteration subtest), and the AWMA (Dot Matrix, Backward Digit Recall, and Mr X subtests).

A significant difference was found in WASI Matrix Reasoning scores between the clusters, $t_{(104)} = -2.3890$, $p_{corrected} = 0.0436$. The effect size for this comparison was moderate, with Cohen's $d = 0.4136$. WASI scores in Cluster 1 (M = 47.0, SD = 10.568) were higher than those in Cluster 2 (M = 42.78, SD = 9.826). A significant difference

was also found between the clusters' scores on the Automated Working Memory Assessment (AWMA) Dot Matrix task, $t_{(104)} = -2.5607$, $p_{corrected} = 0.0415$. The effect size for this comparison was moderate-to-high, with Cohen's $d = 0.6613$. AWMA Dot Matrix scores in Cluster 1 (M = 102.09, SD = 16.403) were higher than those in Cluster 2 (M = 91.58, SD = 15.366). Lastly, a significant difference was found in clusters' scores on the AWMA Mr X task, $t_{(104)} = -3.3173$, $p_{corrected} = 0.0087$. The effect size for this comparison was moderate, with Cohen's $d = 0.4227$. AWMA Mr X scores in Cluster 1 (M = 97.41, SD = 15.634) were higher than those in Cluster 2 (M = 90.41, SD = 17.435). No significant differences were found between the clusters on the other cognitive tests, $t_{(104)} < |1.6152|$, $p_{corrected} > 0.1890$. The effects observed in the larger sample (n = 232) were thus retained in the subsample (n = 110) with the same directionality. In summary, despite a reduced sample size relative to the previous chapter, the same pattern of phenotypic differences between the groups was present.

3.2.2 Neuroimaging data acquisition

Magnetic Resonance Imaging (MRI) data were acquired at the MRC Cognition and Brain Sciences Unit, University of Cambridge. All scans were obtained on a Siemens 3T Prisma-Fit system (Siemens Healthcare, Erlangen, Germany) using a 32-channel head coil.

In the resting-state fMRI, 270 T2*-weighted whole-brain echo planar images (EPIs) were acquired over 9 min (time repetition [TR] = 2s; time echo [TE] = 30ms; flip angle = 78°, 3 × 3 × 3 mm). The first four volumes were discarded to ensure steady state magnetization. Participants were instructed to lie still with their eyes closed and to not fall asleep. For registration of functional images, T1-weighted volume scans were acquired using a whole-brain coverage 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MP RAGE) sequence acquired using 1-mm isometric image resolution (TR = 2.25s, TE = 2.99ms, flip angle = 9°, 1 × 1 × 1 mm).

3.2.3 Connectome construction

Available resting-state fMRI data from the CALM sample was minimally pre-processed in fMRIPrep version 1.5.0 (Esteban et al., 2019), which implements slice-timing correction, rigid-body realignment, boundary-based co-registration to the

structural T1, segmentation, and normalisation to the MNI template. The data were then smoothed by 6 mm full-width at half-maximum. Simultaneous confound regression across the wider CALM sample (n = 348) was performed in the Nipype (version 1.2.0) implementation of AFNI's 3dTproject (Cox, 1996). Children were first excluded for high average motion (mean framewise displacement >0.5 mm, n = 93) and then for a large number of motion spikes (>20% spikes, n = 18), where few temporal degrees of freedom would have remained. The final functional connectome sample in CALM included 237 children. Our initial sample, prior to the exclusion of outliers (n = 123), represented a further subset of these 237 children from CALM, since we were interested in the functional connectivity patterns of individuals who had elevated levels of inattention and hyperactivity.

The denoised fMRI data were parcellated into 100 cortical regions that were assigned to seven ICNs (Schaefer et al., 2018). Pearson correlations were computed for the regional time-series within each individual generating 100 × 100 connectivity matrices. Edge weights were transformed using Fisher's z-transformation.

3.2.4 Thresholding and binarisation of connectomes

Although a simple and potentially useful approach to pre-processing functional connectivity matrices, thresholding procedures that rely on the establishment of an absolute threshold (for example, a correlation coefficient exceeding |0.3|) can lead to different numbers of network edges, and therefore different levels of edge density, across participants. Edge density (also referred to as “graph density” or “network density”) has been shown to affect the computation of graph metrics (for further discussion of these issues, see van Wijk et al., 2010). Between-participant differences in edge density that result from absolute thresholding procedures can introduce statistical differences in network measures, thereby confounding additional comparisons between participants. Thresholding procedures must therefore ensure the preservation of consistent average connectome densities between groups.

In the current study, we applied a consensus threshold across connectomes in order to remove potentially spurious edges. In consensus thresholding, edges are retained if they exist across a prespecified fraction of participants—in this case, 60% of participants in this study. A 60% consensus threshold was also applied to structural

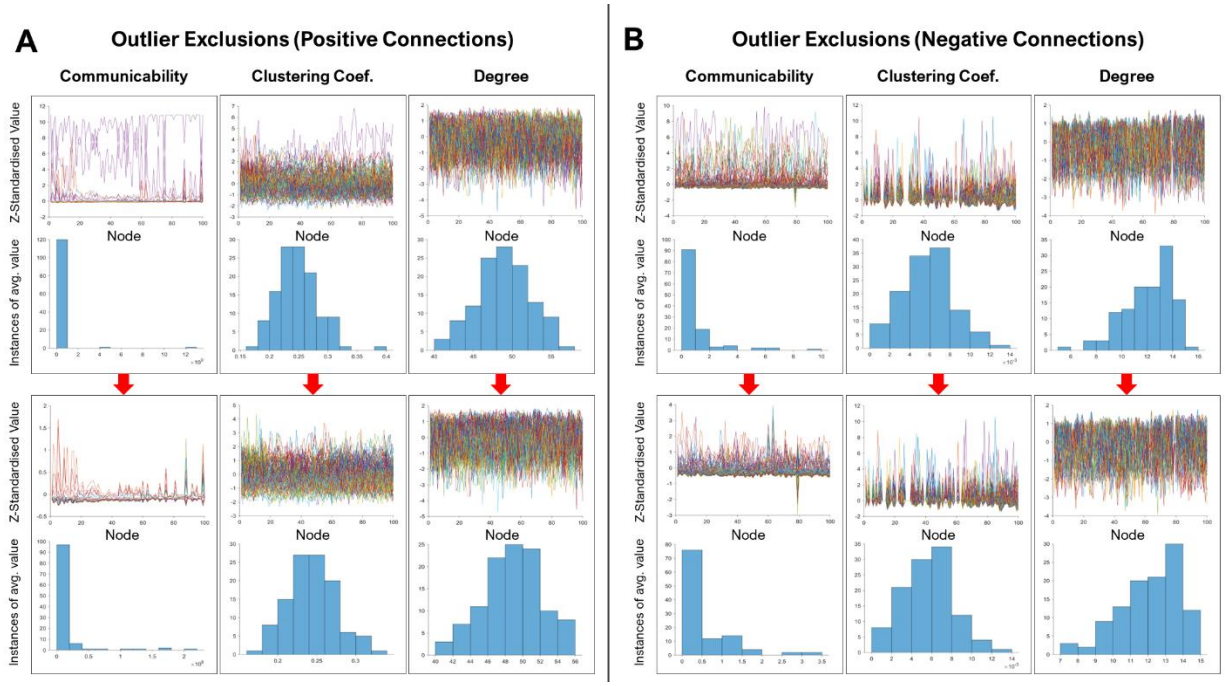
connectomes in the previous chapter, in line with recommendations from previous studies. Following the thresholding procedure, functional connectomes were binarised for the purpose of calculating graph metrics (nodal degrees, clustering coefficients, and communicabilities) for each participant.

3.2.5 Removal of density and communicability outliers

After applying a 60% consensus threshold to our data, we discovered that some participants' connectome densities were unusually high or low. We defined density outliers as having a connectome density that is three standard deviations or more above the mean. To avoid the potentially confounding effects of this, density outliers were excluded from further analyses. On the basis of this procedure, one participant was excluded from Cluster 2, bringing this group's size down to n = 68.

After excluding one density outlier from Cluster 2, we calculated nodal graph measures across participants. We found that there were a number of participants who had unusually high average nodal communicability values, which we reasoned was likely due to the effects of artefacts from certain participants' fMRI scans. We applied an outlier exclusion approach that controlled for the most extreme cases of elevated communicability while still retaining some potentially meaningful variance between individuals. Participants with mean communicability values in the top 5% of the sample were excluded from further analyses (see Figure 3.3). Following this correction, Cluster 1 had a sample size of n = 50, and Cluster 2 had a sample size of n = 60.

Figure 3.1: Here, we illustrate the impact of removing one density outlier and twelve communicability outliers from our sample on the three graph metrics calculated for positive **(A)** and negative **(B)** functional connectomes. Line plots represent communicability, clustering coefficient, and degree values across 100 nodes. Histograms represent average communicability, clustering coefficient, and degree values across 123 and 110 participants in the upper and lower panels, respectively. Following the removal of outliers, z-scores were calculated for each graph measure across the reduced sample (n = 110).



3.2.6 Data acquisition and preprocessing for Triple Network Model analyses

For our Triple Network Model analyses, we used functional connectivity data from Jones et al. (2022) in order to see if we could replicate some of their findings in our inattentive and hyperactive subsample. As such, we retained their original data pre-processing and thresholding procedures, which were slightly different from those used in the rest of this chapter. Positive and negative connectomes were generated for each individual by thresholding the connectivity matrices to retain the top 25% of positive or negative edges at the group level, to ensure that the same edges across individuals are retained for comparison in subsequent analyses, as in Baum et al. (2017). Average functional connectivity was calculated within and between seven pre-defined ICNs: visual, somatomotor, dorsal attention, ventral attention, fronto-parietal, default

mode, and limbic (Yeo et al., 2011). A global intra- and inter-network functional connectivity measure ('global functional connectivity') was calculated for each participant by averaging these values within and between networks respectively. All measures were z-score standardised across participants.

3.3 Analyses

3.3.1 Node-wise comparisons between inattentive and hyperactive clusters

We used Generalized Linear Models (GLMs) to explore how the two clusters of inattentive and hyperactive children differ along three z-score normalised graph-theoretic nodewise measures: degree, clustering coefficient, and communicability. Separate GLMs for each node, across each graph measure, were performed across connectomes containing either positive or negative connections. Head motion (measured by mean framewise displacement), gender, age of scan, and age of test were included as regressors in the GLMs. FDR post-hoc corrections were applied to account for multiple comparisons across 100 nodes for each of the graph measures.

As in the previous chapter, we also conducted 6 paired-samples t-tests to assess average communicability, clustering coefficient, and degree values between the clusters across positive and negative connectomes.

3.3.2 Triple Network Model comparisons between inattentive and hyperactive clusters

After comparing positive and negative connectomes from the two clusters on three node-wise measures, we compared the groups on z-score normalised measures of integration between three ICNs: the central executive network (CEN), salience network (SN), and default-mode network (DMN). We also performed a comparison between the groups' global functional connectivity, which represented an average of within- and between-network connectivity for each participant. These comparisons were done using four separate paired-samples t-tests on measures of inter- and intra-network connectivity calculated across the CALM sample by Jonathan Jones (Jones et al., 2022).

3.4 Results

3.4.1 No differences detected in node-wise degree, clustering coefficient, and communicability between the clusters

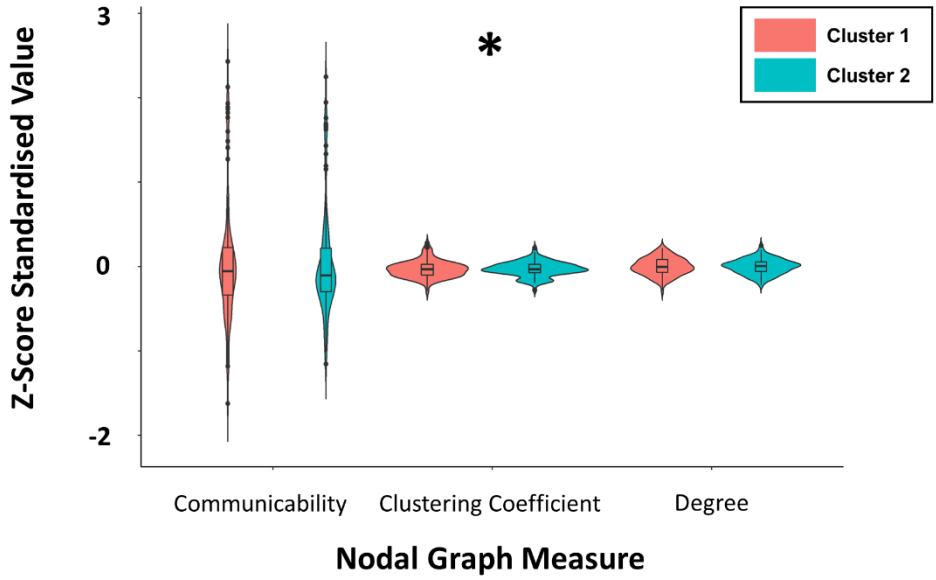
Through a series of GLMs, we tested the extent to which the z-scored degree, clustering coefficient, and communicability of each node differentiated the groups. Applying the same method used in the previous chapter, our aim was to test which node-level differences might correspond to cluster membership in our reduced functional connectome sample. These GLMs were performed separately across nodes in positive and negative connectomes.

Following FDR corrections for multiple comparisons, we did not find any node-level differences between Cluster 1 and Cluster 2 across all three graph measures of interest, $t_{(105)} < |3.8727|$, $p_{corrected} > 0.0562$ (whereas we determined statistical significance as $p < 0.05$). This was the case across positive and negative functional connectomes.

3.4.2 Higher global clustering coefficients in Cluster 1

We conducted six paired-samples t-tests on z-score standardised global clustering coefficient, degree, and communicability values across positive and negative connectomes. In positive connectomes only, we found that Cluster 1 has, on average, higher nodal clustering coefficients ($M = 1.1754 \times e^{-16}$, $SD = 0.0905$) than Cluster 2 ($M = -3.1919 \times e^{-17}$, $SD = 0.0798$), $t_{(108)} = 2.1588$, $p = 0.0331$ (see Figure 3.2). The effect size for this comparison was moderate, with Cohen's d = 0. 0.4156. No additional significant differences were found between the clusters in their average graph measure values, $t_{(108)} < |-0.5885|$, $p > 0.5574$. This was the case across both positive and negative connectomes.

Figure 3.2: Here, we use a violin plot to compare global communicability, clustering coefficient, and degree values between the clusters' positive connectomes. In the previous chapter, we illustrated global graph measure differences using a bar plot; this was not possible here, as the mean values for these measures were too small to be displayed as bars (see means and standard deviations reported above). Across all of our comparisons, only one significant difference was found—positive connectomes in Cluster 1 had a higher global clustering coefficient than those belonging to Cluster 2 (significant result marked with an asterisk).



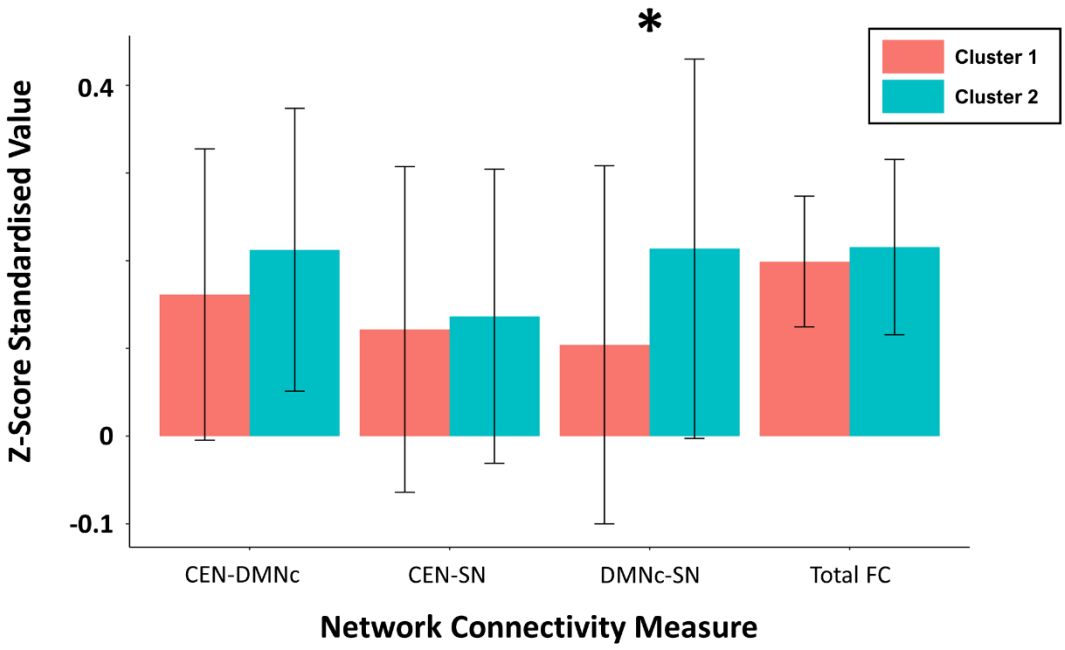
Comparisons of global graph measure values between clusters of children with high inattention and hyperactivity

3.4.3 Differences found in DMN-SN, but not CEN-SN interconnectivity, CEN-DMN interconnectivity, or global functional connectivity between clusters

We used four paired-samples t-tests to compare clusters of inattentive and hyperactive children on three measures of inter-network connectivity, as well as global functional connectivity. No significant differences were found between the clusters in comparisons of global functional connectivity, CEN-SN inter connectivity, or CEN-DMN interconnectivity, $t_{(108)} < |-1.6298|$, $p > 0.1061$. However, a significant difference was found between Cluster 1 and Cluster 2 on the measure of DMN-SN interconnectivity, $t_{(108)} = -2.7119$, $p = 0.0078$. Cluster 1 showed lower DMN-SN

interconnectivity (M = 0.1042, SD = 0.2043) than Cluster 2 (M = 0.2138, SD = 0.2164). The effect size for this comparison was moderate, with Cohen's d = 0.5208.

Figure 3.3: We used four paired-samples t-tests to compare measures of internetwork connectivity between clusters of children with high inattention and hyperactivity. Here, we illustrate between-cluster differences in CEN-DMN, CEN-SN, and DMN-SN interconnectivity, as well as total functional connectivity. One significant difference (marked with an asterisk) was found: Cluster 2 demonstrated higher DMN-SN interconnectivity than Cluster 1.



Comparisons of internetwork connectivity between clusters of children with high inattention and hyperactivity

3.5 Discussion

In this chapter, we investigated whether, and how, the two inattentive and hyperactive neural subgroups of children identified in preceding empirical chapter differed in the organisational properties of their functional connectomes. In contrast to the structural connectome analyses applied in the first empirical chapter, functional connectome analyses revealed no node-level graph measure differences between the clusters. However, Cluster 1 demonstrated a higher global clustering coefficient, as well as a greater degree of functional segregation between the default-mode and salience

networks. We discuss what these findings could mean for our understanding of the developmental segregation of functional brain networks, as well as the differences in interpreting findings concerning structural versus functional connectomes.

3.5.1 Structure versus function: nodal degrees, communicabilities, and clustering coefficients between clusters

In the previous chapter, where we looked at the structural connectomes of highly inattentive and hyperactive children, we found a range of nodewise differences between Cluster 1 and Cluster 2.

One possible explanation is that these differences emerged as a result of sampling error. From our structural connectome analyses in the first empirical chapter, to the analyses outlined here, our sample size was reduced from n = 232 to n = 110 due to data availability and the exclusion of connectome density and communicability outliers. When comparing two populations' distributions on a variety of measures, and then performing the same comparisons in subsamples of the original two populations, there may be differences in specific measure distributions between full- and subsamples.

A more likely explanation, however, is that structural and functional connectome topologies capture different developmental domains of interest. This is due to the fact that the correspondence between structural and functional brain network topologies is imperfect (Suarez et al., 2020). In the previous chapter, the two inattentive and hyperactive clusters were originally grouped according to differences in their brain structure; it need not follow, necessarily, that these groupings would align with differences in functional connectivity. Even though functional networks are constrained by their structural underpinnings, they necessarily diverge from structural networks when integrating context-specific information, making behavioural adaptation possible (Park & Friston, 2013). Put simply, the functional connectome optimally adapts to *context-specificity*, whereas the structural connectome serves as a *context-general* foundation from which functional networks can emerge. Past research indicates that general cognitive ability is not associated with any particular brain structure, but that it is characterised by global differences in structural brain network topology (Johnson, 2011; Siugzdaite et al., 2020).

Meanwhile, functional connectomes typically have weaker connections between modules, resulting in segregation between distinct intrinsic networks (Rubinov & Sporns, 2010). Typical development is also characterised by increased dynamic switching between fine-grained networks, particularly in regions that facilitate executive function and decision-making (Chai et al., 2017). This feature of the functional connectome facilitates behavioural flexibility, since patterns of brain network activity reflect a response to environmental stimuli in real-time. While differences in the structural connectome can certainly capture behavioural variation (e.g. Bathelt et al., 2018), it could be the case that behaviour is better reflected by differences in the functional connectome. Since our inattentive and hyperactive clusters were differentiated by their cognitive ability, and not by their behaviour, then it follows that between-groups differences might better be captured by structural, rather than functional, brain network characteristics. Future research should strive to evaluate the extent to which variations in cognition and behaviour are differentially captured by structural versus functional connectome properties.

3.5.2 Higher average clustering coefficient in Cluster 1

In the previous chapter, we investigated global differences in nodewise communicability, clustering coefficient, and degree values between the two inattentive/hyperactive clusters' structural connectomes. Cluster 1 demonstrated higher global values than Cluster 2 across all three graph metrics. In the current study, we repeated these comparisons and found that Cluster 1 demonstrates a higher global clustering coefficient than Cluster 2 across positive connectomes.

In the context of the functional connectome, nodal clustering coefficients represent specialised patterns of activation within interconnected groups of brain regions. A higher mean clustering coefficient reflects a higher degree of local information processing—in other words, a higher level of segregation between functional modules—across the brain. As mentioned previously, increases in brain network segregation are typically seen across childhood development, as function-specific brain networks emerge over time. The modularity of these networks enables more efficient information processing, as well as the integration of information across multiple function-specific brain regions (Betzel et al., 2013). In some ways, this description of functional brain network development aligns with the account put forth

by Karmiloff-Smith in *Beyond Modularity* (1997): as the brain develops, sensory information starts to assume multiple formats, and can be flexibly integrated across different modules to enable learning and behavioural change. In this chapter, as well as the previous chapter, Cluster 1 was found to have a higher global clustering coefficient than Cluster 2. Additionally, Cluster 1 was shown to have higher scores on cognitive tests measuring visuospatial reasoning, suggesting that the gradual modularisation of structural brain networks, as well as the spatiotemporal segregation of functional brain networks, may play a role in the refinement of certain cognitive capacities across development.

3.5.3 Applying the Triple Network Model of Neurodevelopmental Psychopathology: higher DMN-SN interconnectivity in Cluster 2

In our analyses, we compared internetwork connectivity measures between Cluster 1 and Cluster 2 for three networks: the central executive network (CEN), salience network (SN), and default-mode network (DMN). Additionally, we compared the clusters on a global measure of functional connectivity, which was an average of total within- and between-network connectivity for each participant. Between the clusters, we did not find differences in CEN-SN, CEN-DMN, or global connectivity. However, we found higher DMN-SN segregation in Cluster 1 compared to Cluster 2.

Previous research suggests that the activation profiles of the CEN and the DMN are temporally anti-correlated, and that the SN is responsible for facilitating functional switching between these two networks (Sridharan & Menon, 2008; Chand et al., 2017). While the CEN has been found to activate during externally-oriented, cognitively-demanding tasks, the DMN is typically deactivated during these tasks. Combined with other findings, this suggests that the DMN facilitates various 'internal' mental activities that are not directly influenced by the cognitive demands of external stimuli (Buckner & Krienen, 2013; Smallwood et al., 2021). The functioning of the DMN has been implicated in a number of psychopathologies, including neurodevelopmental conditions (see Nair et al., 2020, for review). As discussed in the Introduction to this chapter, Jones et al. (2022) established a link between behaviour and functional connectivity between the CEN, DMN, and SN. They found that hyperactivity/impulsivity is associated with greater functional connectivity between all three networks. Notably, the elevated connectivity between functional networks

seen in very hyperactive/impulsive individuals is similar to that of younger individuals without neurodevelopmental difficulties, since brain function increasingly segregates into localised networks across development. This finding suggests that a slower pace of brain network segregation in childhood can be tied to a number of behavioural differences that influence social, learning, and mental wellbeing outcomes across development. But what about cognition?

The connectivity profile of the SN in particular, which encapsulates multiple brain regions involved in cognitive control, has previously been associated with individual differences in cognitive ability. Increased regional homogeneity and grey matter volume in the SN (Yuan et al., 2012), as well as the functional efficiency of nodes belonging to the SN (Hilger et al., 2017), have both been found to be predictive of general cognitive ability. In a recent study, Cermakova et al. (2023) demonstrated that although other brain networks are related to cognitive ability, these associations are specific to the functioning of the SN, which mediates patterns of activation across multiple networks by 'filtering' salient information. It achieves this through a coordination between its constituent parts—the dorsal anterior cingulate cortex (dACC) and bilateral insulae, which generate and transmit error signals to brain networks involved in attention, decision-making, and learning (Ham et al., 2013). Previously, Li et al. (2019) showed that structural damage to the SN is associated with changes in SN-DMN functional connectivity, namely in the form of impaired DMN deactivation, which results in cognitive control difficulties. Cognitive control processes, such as response inhibition, involve SN activation and concurrent DMN deactivation; the disruption of this pattern is associated with lower performance on cognitive tasks (Bonnelle et al., 2012; Hampshire & Sharp, 2015). On the basis of these findings, we might therefore predict that SN-DMN segregation, particularly in the context of brain development, is associated with age-expected performance on cognitive tasks.

The current study, which found that children in Cluster 1 exhibit greater DMN-SN segregation compared to those in Cluster 2, aligns with this prediction. Since Cluster 1 exhibits higher performance on visuospatial reasoning tasks than Cluster 2, we may reason that children in Cluster 1 experience relatively fewer developmental difficulties, despite the fact that both clusters share a similar behavioural profile. The lack of a

strong behavioural distinction between the clusters means that the brain-behaviour association found in Jones et al. (2022) could not be replicated in the current study—across similarly inattentive and hyperactive individuals, cognitive ability, rather than behaviour, corresponded to differences in DMN-SN connectivity. It is worth noting that Jones et al. (2022) did not investigate the impact of other developmental features, including cognition, on functional connectivity between the DMN, SN, and CEN, remarking that future studies should address how other transdiagnostic developmental difficulties might be captured within the Triple Network Model framework. The current study presents some evidence that cognitive ability is related to differences in SN-DMN connectivity in a sample of highly inattentive and hyperactive individuals from CALM—namely, that there is a positive relationship between cognitive ability and SN-DMN segregation. Future studies should seek to gain a better understanding of these relationships by integrating behavioural, cognitive, and functional connectivity data across both typically-developing and neurodivergent individuals.

In addition to cognitive ability, individual differences in SN-DMN connectivity have also been linked to internalising psychiatric disorders, such as depression, anxiety, and PTSD (Broyd et al., 2009; Viard et al., 2019; McKinley et al., 2022). Some have suggested that this may be due to the over-connectivity between the DMN and specific regions within the SN, particularly the amygdala (Sylvester et al., 2020). To account for the possibility of mental health differences between Cluster 1 and Cluster 2, we compared the groups' rates of neurodevelopmental and psychiatric diagnoses (see Appendix N). Across both clusters, we found that none of our participants possessed a psychiatric diagnosis, and that the clusters were also comparable in their rates of neurodevelopmental diagnoses like ADHD, autism, and dyslexia. It may be the case, however, that our data do not capture fine-grained variations in transdiagnostic features of mental health, which could be related to differences in DMN-SN connectivity. Future research should further investigate the potential relationships between mental health and patterns of brain network segregation across development.

3.5.4 Limitations

One core limitation of this study is the use of a reduced sample size of children from the first empirical chapter, where the two inattentive and hyperactive clusters are first

identified and delineated. While certain between-groups effects were retained (for instance, gender distributions and between-cluster differences in cognition and behaviour), this substantial reduction in the amount of data available for analysis limits the certainty of our findings. Ideally, in future research that examines the properties of structural and functional connectivity between two groups of children, larger and comparably-sized datasets will be available.

Another potential limitation arises from difficulties which are innate to studying the brains of inattentive and hyperactive children. While inattention and hyperactivity characterise multiple neurodevelopmental conditions, and are therefore relevant to understanding these conditions, they also tend to lower the quality of neuroimaging data due to high levels of movement. Thompson et al. (2021) found that levels of head motion during MRI can be predicted by out-of-scanner performance on a sustained attention task in children aged 9-11. Additionally, Kong et al. (2014) found that individual differences in hyperactivity and impulsivity are highly correlated with in-scanner head motion. Head motion is generally considered a major confounder to be removed from MRI data (Power et al., 2012)—fortunately, by including mean framewise displacement as a confound regressor in our analyses, we were able to control for variations in head motion within our sample. However, an additional problem emerges from the fact that the most inattentive and hyperactive individuals—those of particular interest to our research—may exhibit such a high degree of head motion that their data are unusable, which necessitates exclusion at the preprocessing stage. Our strict inclusion cut-off on the basis of mean framewise displacement (<0.5mm) almost certainly resulted in the exclusion of participants who were particularly prone to high levels of hyperactivity. Tansey et al. (2022) also found this to be the case; the children they excluded from their MRI dataset due to head motion had higher levels of inattention and hyperactivity than those whose data were retained for analysis. This important factor reduces the generalisability of our findings to inattentive and hyperactive children who can nonetheless remain still enough to undergo an MRI scan.

3.6 Conclusion

In the current study, we investigated differences in functional connectivity between two clusters of inattentive and hyperactive children identified in the previous chapter. In our previous analyses, we found that the clusters are differentiated by their cognitive ability and three measures of structural network topology. Nodal communicability emerged as a strong differentiating feature between the clusters' structural connectomes. Here, we found that a subset of participants from the two clusters in the previous chapter are also differentiated by their cognitive ability. However, we did not detect any nodewise differences between the clusters' functional connectomes, despite finding that Cluster 2 has a higher average clustering coefficient at a global level. We also found that Cluster 2 exhibits a greater level of functional connectivity between the default-mode and salience networks, which are implicated in the Triple Network Model of developmental psychopathology.

We discuss how the differences between our findings across empirical chapters 1 and 2 may illustrate a more fundamental point about the divergence between structural and functional brain network characteristics. The first two empirical chapters of this thesis provide a transdiagnostic, connectomics-based view of neurodevelopment that integrates behavioural, cognitive, structural MRI, and functional MRI data from children with elevated inattention and hyperactivity.

4 The entropy of resting-state neural dynamics is a marker of general cognitive ability in childhood

4.1 Introduction

4.1.1 Resting-state networks, childhood development, and the emergence of individual differences

As discussed in the previous chapter, brain activity is characterised by intrinsic dynamics in the form of spatially-coherent and spontaneous fluctuations, which form intrinsic connectivity networks (ICNs). While typical childhood development of the functional connectome includes a gradual segregation between the default-mode network and task-positive networks across the brain, neurodevelopmental conditions have previously been associated with differences in the development of these ICNs. Given the fact that certain ICNs have been implicated in such a wide range of cognitive and behavioural phenotypes (for instance, those characterised by diagnostic labels), one primary challenge within developmental cognitive neuroscience lies in outlining the precise mechanisms by which differences in ICN function might correspond to population-level variations in cognitive ability and behavioural difficulty. In the previous chapter, we investigated how functional brain network characteristics vary between subgroups of children with elevated levels of inattention and hyperactivity. However, it remains unclear how other features of ICNs—such as their transient dynamical properties—relate to granular developmental differences in cognition and behaviour.

4.1.3 Using dynamical measures to characterise the spatiotemporal properties of spontaneous brain activity

As demonstrated in the previous chapter, it is possible to classify and describe spontaneous functional network activity using static, time-averaged representations of neural activation. However, computational models of neural activation, as well as empirical data themselves, suggest that the brain engages in rapid switching between distinct states of functional connectivity (Rabinovich et al., 2008; Nachstedt & Tetzlaff, 2017). One limitation of time-averaged representations, which are more

traditional within cognitive neuroscience research, is that they are unable to describe the transient temporal dynamics of brain activity. In other words, states of neural activity are not merely situated in space, but also in time, and transient, recurrent patterns of activity could represent a meaningful mode by which information is processed by the brain. Recent advances in neuroimaging technology and data analysis have generated novel insights into neural dynamics. These advances have motivated substantial interest in the concept of 'brain state', which is believed to reflect the facilitation of behavioural and cognitive processes through the recruitment of whole-brain networks across millisecond timescales. A recent review by Greene et al. (2023) defines brain states as widely distributed patterns of activity or coupling which necessarily affect the future physiology and/or behaviour of the organism. This definition aligns with, but is not limited to, a variety of conceptualisations of brain states that have been presented in the literature in recent years. For instance, brain states have been regarded as features of spontaneous, ongoing neural activity (e.g. Harris & Thiele, 2011; Flavell et al., 2022), internal cognitive or behavioural state with neuronal correlates (e.g. Beaman at al., 2017; McCormick et al., 2020), and even the degree of common fluctuation in population spiking activity (Poulet & Crochet, 2019). An emerging field of cognitive and computational neuroscience dedicated to measuring these rapid, spatiotemporally-defined dynamical states strives to overcome some of the interpretability constraints of time-averaged functional network identification techniques by proposing a new set of data-driven, temporally-embedded methods of representing neural activity.

One of these relatively novel methods is Hidden Markov Modelling (HMM), an unsupervised machine learning technique that reconstructs a sequence of patterns as a system of temporally-discrete states. Sequences of HMM states are Markovian in the sense that the state activated for each upcoming time-point depends only on the current state. Importantly, HMM states are not directly observable from the data themselves, and are therefore 'hidden'. An observation model, which constitutes the output of the HMM, serves as a link between observed data and hidden states. As a result, the HMM can be adapted to suit a wide variety of modalities, including neurophysiological data.

Previously, HMMs have been used to extract the underlying dynamical properties of neural data from MEG (Baker et al., 2014; Vidaurre et al., 2018b; Quinn et al., 2018), EEG (Obermaier et al., 2001; Williams et al., 2018; Dash & Kolekar, 2020; Marzetti, 2023), and fMRI (Duan et al., 2005; Dang et al., 2017; Goucher-Lambert & McComb, 2019; Hussain et al., 2023) at rest and in experimental task settings. In more limited cases, HMMs have been used to explore age- and cognition-related effects on neural dynamics. For instance, Tibon et al. (2021) found that older adults had more and longer occurrences of states involving 'higher order' areas, and that the duration of these states was also associated with poorer performance on a fluid intelligence task.

To our knowledge, there have not been any published studies of how resting-state neural dynamics vary in a developmental sample, or how these dynamics relate to the emergence of diverse profiles of behaviour and cognitive ability. Considering that the brain's patterns of functional connectivity are known to change dramatically across development, and also to vary considerably between individuals, it is reasonable to assume that spontaneous, transient neural dynamics also play a role in the developmental calibration of flexible, adaptive forms of behaviour and cognition.

4.1.4 The current study

In the two previous chapters, we investigated whether the topological network features of the structural and functional connectome differentiated groups of highly inattentive and hyperactive children. First, we found that two structural connectivity clusters characterised our sample. When we compared the groups' functional connectome properties, we did not find any significant effects. We did, however, find that children in Cluster 2, who scored lower on tests of cognitive ability than Cluster 1, exhibited higher levels of functional connectivity between the salience and default-mode networks. One limitation of the previous chapter was the fact that we relied on data from time-averaged representations of functional connectivity, rather than data that fully captured the dynamical properties of neural activity. This constrained our conceptualisation of functional connectivity, potentially obscuring any deviations in neural activity that can only be observed across transient time-scales.

In the current study, we used resting-state MEG data from children aged 8-13 to test how the temporal properties of spontaneous, transient neural dynamics—such as state

fractional occupancies and switching rates—vary with age, gender, measures of behavioural difficulty, and general cognitive ability in a sample of children aged 8-13 years. We also explored the extent to which the complexity of individual participants' resting-state time-courses, quantified using entropy rates, varied across these neurodevelopmental features of interest. By looking at these features across a more population-representative sample, as opposed to a sample of highly inattentive and hyperactive individuals, we hoped to gain an understanding of how granular variations in behaviour and cognition relate to differences in resting-state neural dynamics. Additionally, by investigating whether features of neural dynamics predict cognitive and behavioural differences, we hoped to formulate a more comprehensive framework that describes how patterns of functional connectivity vary across development.

4.2 Methods

4.2.1 Participants

Our MEG analysis sample, following exclusions (n = 46), included children aged 8-13 (M = 10.09, SD = 1.19). Children were all part of ongoing studies at the MRC Cognition and Brain Sciences Unit, and all underwent an identical MEG protocol. Specifically, all the children were originally part of two studies, either the Resilience in Education and Development (RED) study (n = 40, PRE.2017.102) or the Centre for Attention, Learning, and Memory (CALM) cohort (n = 6, 22/WM/0082), and agreed to take part in this MEG session. Combined, this sample reflects a range of common behavioural difficulties typically seen in mainstream education.

4.2.2 Cognitive Assessments and Behavioural Questionnaires

4.2.2.1 Wechsler Abbreviated Scales of Intelligence II – Matrix Reasoning Subtest (WASI-II MR)

The Matrix Reasoning subtest of the Wechsler Abbreviated Scales of Intelligence II is a general measure of cognitive ability and executive function. In this subtest, children are presented with incomplete matrices of images and asked to select an image that would suitably complete each matrix from a choice of four options. Children aged 9 years and older complete a possible total of 30 matrices, which become progressively

more difficult. The matrix reasoning test is finished when the child produces three incorrect answers in a row. Trials correct were converted to age-standardised T-scores.

4.2.2.2 Strengths and Difficulties Questionnaire

The Strengths and Difficulties Questionnaire (SDQ) asked parents/carers to answer 25 questions measuring a variety of behavioural challenges (with possible responses being 'Not True', 'Somewhat True', and 'Certainly True') based on their child's behaviour in the six months prior to assessment. A total SDQ score is calculated, in addition to scores for five behavioural subscales: Hyperactivity, Conduct Problems, Emotional Regulation Problems, Peer Relationship Problems, and Prosocial Behaviour (see Table 4.1). See Appendix M for plots representing how cognitive, behavioural, and demographic traits were distributed across our combined sample.

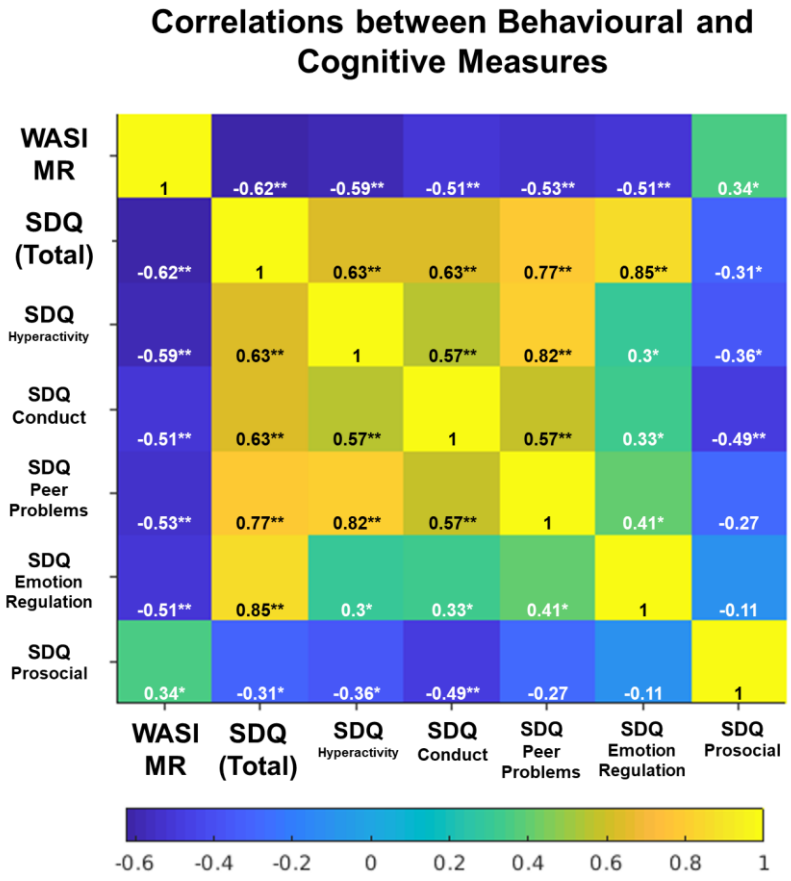
Table 4.1: Means, standard deviations, and range values were calculated for cognitive subtest and behavioural subscale scores across our sample, which combined data from the RED study and CALM cohorts. Here, we summarise these scores, in addition to some additional sample characteristics.

Measure	***Combined Sample***
N	46
Age in Years	10.09 (± 1.19; range = 8-13)
Gender	47.8% male
WASI-II Matrix Reasoning	55.91 (± 9.70; range = 37-80)
SDQ (Total)	7.78 (± 5.83; range = 0-10)
SDQ (Hyperactivity)	4.11 (± 2.74; range = 0-10)
SDQ (Conduct Problems)	1.67 (± 1.99; range = 0-8)
SDQ (Peer Problems)	2.76 (± 2.52; range = 0-9)
SDQ (Emotion Regulation Problems)	2.83 (± 2.9; range = 0-10)
SDQ (Prosocial)	7.83 (± 2.58; range = 0-10)

Correlations were performed between each of the cognitive and behavioural measures (see Figure 4.1). A significant negative relationship was found between WASI-II MR scores and all subscales within the SDQ ($rs < -0.51$, $ps < 0.0002$). Additionally, scores

on the WASI-II MR were positively correlated with the SDQ Prosocial Behaviour subscale ($r = 0.34$, $p = 0.0201$).

Figure 4.1: Here, we display a correlation matrix representing relationships between scores on the WASI-II MR subtest, total SDQ scores, and SDQ subscale scores. Significant relationships at $p < 0.05$ are marked by one asterisk, and significant relationships at $p < 0.001$ are marked by two asterisks.



4.2.3 Resting-state MEG data acquisition

MEG data were acquired using a high-density VectorView MEG system (Elekta-Neuromag) with 102 magnetometers and 102 orthogonal pairs of planar gradiometers (306 sensors in total). Five head position indicator (HPI) coils were attached to the child's head (one on each mastoid bone, two on the child's forehead, and one on the top of their head) in order to monitor changes in head position throughout the recording. The positions of the HPI coils was recorded using a 3D digitizer (FASTRACK, Polhemus) in addition to over 200 additional points distributed over the

scalp. Pulse was measured using an electrocardiogram electrode attached to each wrist and eye movements were recorded using horizontal and vertical electrooculograms. Data were sampled at 1Khz. Smaller children were seated on a booster seat to ensure that the tops of their heads were in contact with the scanner and that they could remain in a comfortable position for the duration of the scan.

Children were monitored by video camera throughout the scan. During the 10-minute resting-state scan, children were asked to sit as still as possible, close their eyes and let their minds wander, without falling asleep.

4.2.4 Structural MRI data acquisition

Out of the 52 participants in our original sample (prior to outlier exclusions), 40 participants took part in a structural MRI scan, which yielded T1-weighted images from a Siemens 3T Tim Trio system. For these images, a magnetization-prepared rapid acquisition gradient echo sequence with 1mm isometric image resolution and 2.98ms echo time was used.

4.2.5 MEG Preprocessing and Source Reconstruction

4.2.5.1 Maxwell filtering and artefact removal

Maxwell filtering was performed using a script and repository of functions developed by Alex Anwyl-Irvine called RED Tools, which implements MNE Python's Maxfiltering procedure (https://github.com/u01ai11/RED_Rest/tree/master/REDTools). Blinks, saccades, and pulse-related artefacts were removed by running an automated temporal independent components analysis (ICA), which applied MNE's fastICA function to the sensor-space time-courses. Following this, we performed an additional ICA for which components were manually inspected, and any remaining ECG and EOG components were removed. Additionally, components dominated by 50Hz noise were removed to reduce electrical interference.

4.2.5.2 Co-registration and bandpass filtering

40 participants' MEG data from our original sample (n = 52) were co-registered to their T1-weigthed structural MRI image acquired using a 3T Siemens Tim Trio and an MPRAGE sequence. A natural (asymmetric) NIHPD Objective 1 scan template

intended for children in pre- to mid-puberty (aged 7.5 to 13.5) was used for the remaining 12 participants in our original sample (6 from the RED subsample and 6 from the CALM subsample) who did not undergo a T1-weighted MRI scan (Fonov et al., 2011). Co-registration was performed using the digitized scalp locations and fiducial markers using an iterative closest point algorithm in SPM12 (Penny et al., 2011; Wellcome Trust Centre for Neuroimaging, 2014). A forward model was fitted using a single sphere homogeneous head shape model for each subject (Mosher et al., 1999). Then, data were bandpass filtered to be between 1-30Hz in SPM12, as it has been found that these slower frequencies are better for considering functional connectivity with MEG (Luckhoo et al., 2012).

4.2.5.3 Source-localisation and parcellation

The remaining preprocessing steps were implemented using the OHBA Software Library (OSL v2.0.3; OHBA Analysis Group, 2017; https://github.com/OHBA-analysis/osl-core) and OHBA's Hidden Markov Model Library (HMM-MAR; Vidaurre et al., 2016). First, a covariance matrix was computed across the whole time-course for each participant and was regularized to 50 dimensions using PCA rank reduction. Sensor normalisation was then performed across planar gradiometers and magnetometers. Following this, we used a linearly-constrained minimum variance beamformer to estimate whole-brain source-space activity for points in an 8mm grid (Van Veen et al., 1997). The signal-space separation algorithm reduced the dimensionality of the data, resulting in a set of estimated time-courses of brain activity for each child for 3,559 source locations across the brain (Woolrich et al., 2011). At this point in preprocessing pipeline, we excluded 5 participants from our original sample (n = 52) who had a very high predominance of bad segments across their time-series (>60%), which was assessed using the OSL function 'osl_detect_artefacts.m'. We excluded an additional participant on the basis of their having a poor co-registration solution. Upon visually inspecting the co-registration solution using SPM 12's GUI, it became clear to us that scalp locations had been digitised improperly (with points placed too far from the scalp). These exclusions reduced our MEG sample from n=52 to n=46.

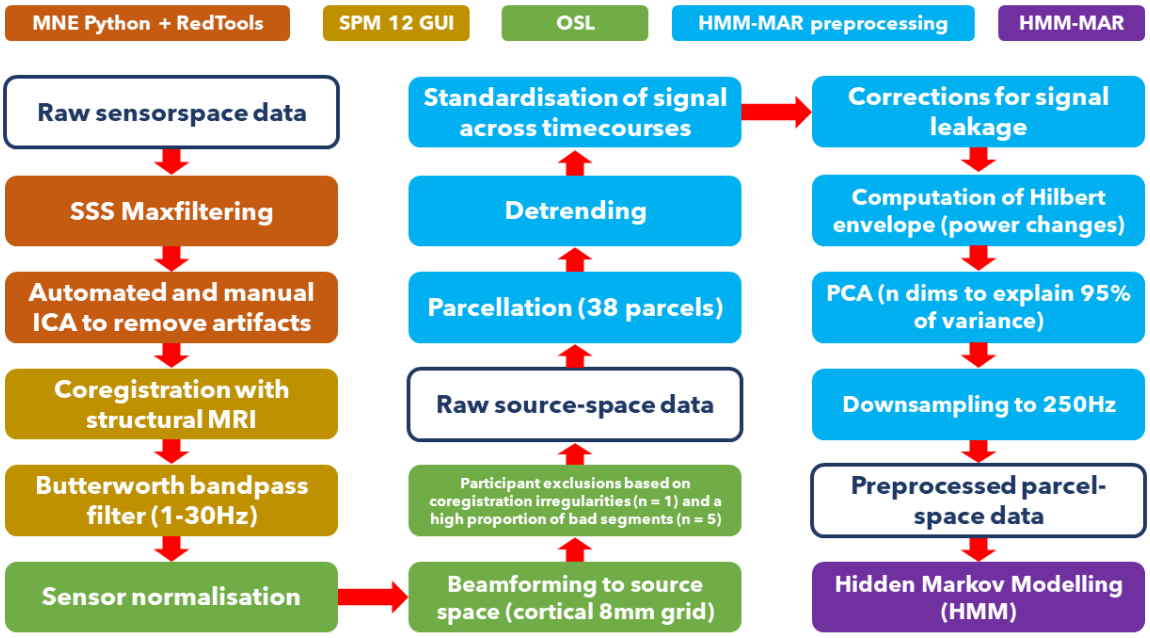
Following artefact-related exclusions, MEG data were further reduced down into a 38-node parcellation following the method outlined in Quinn et al. (2018). A binarised

parcellation with 38 cortical regions was applied and a single time-course was estimated per node from the first principal component across voxels. This further reduced each time-course down to 38 parcels, as opposed to 3,559 voxels, and made it possible to perform additional corrections for signal leakage.

4.2.5.4 Additional pre-processing steps

Following parcellation, further pre-processing was conducted according to OHBA's HMM-MAR library, which recommends an additional set of pre-processing steps prior to the initialisation of the Hidden Markov Model: detrending, signal standardisation, corrections for signal leakage, and downsampling. We first completed detrending, which removes linear trends in the data for each channel separately, which was followed by a standardisation of the signal across participants' concatenated time-courses. Next, symmetric multivariate orthogonalization was used to correct for signal leakage introduced by source reconstruction with zero temporal lag according to the methods specified in Colclough et al. (2015). Following this, the absolute signal amplitude for each source at each timepoint was estimated using the Hilbert transform. To reduce dimensionality in the data, we performed a PCA, which retained the number of dimensions necessary to explain 95% of variance in the data. Finally, MEG time-courses were downsampled to 250Hz. For a full schematic of our preprocessing procedure, see Figure 4.2.

Figure 4.2: Here, we outline each step of our MEG data preprocessing pipeline, in addition to the software packages and toolboxes used to complete each step of the pipeline.



4.2.6 Hidden Markov Modelling (HMM)

In the current study, we used the HMM-MAR toolbox, developed by the Oxford Centre for Human Brain Activity (OHBA) to infer a Hidden Markov Model from resting-state timeseries MEG data. The base code and set of functions that we adapted to suit our analyses is publicly-available on GitHub (https://github.com/OHBA-analysis/HMM-MAR). The analysis scripts for this study are also publicly-available on GitHub (https://github.com/nataliazdorovtsova/HMM_MEG).

4.2.6.1 Model description and specifications

Hidden Markov Models (HMMs) comprise a set of unsupervised machine learning techniques that extract the spatial and temporal structure of timeseries of data by inferring discrete number of mutually-exclusive states. The HMM assumes that timeseries data, which are comprised of a set of *observed* features, can be described using a sequence of a finite, *hidden* variables (HMM states). Within a single model, HMM states are inferred on the basis that they belong to the same family of distributions, but are each parameterised differently. HMM states correspond to distinct patterns of brain activity that occur at different points across a timeseries.

More formally, if we take x_t to represent the time-series data and s_t to represent a given state at time point t, we assume that

$$x_t|s_t = k \sim \text{Multivariate Gaussian}(\mu_k, \Sigma_k),$$

where μ_k is a vector with (number of channels) elements containing the mean activation and Σ_k is the (number of channels x number of channels) covariance matrix that represents the activation relationships between channels when state k is active. This is commonly referred to as the observational model. In this case, the observation model characterises a multivariate Gaussian distribution of each state k by parameters (μ_k, Σ_k). Although we use a multivariate Gaussian distribution to characterise states in the current study, there are a number of different methods that can be applied depending on the context-dependent theoretical goals of the researcher (e.g. Baker et al., 2014; Vidaurre et al., 2016; Vidaurre et al., 2018a; Quinn et al., 2018; Gohil et al., 2022). Here, we chose to use a multivariate Gaussian HMM with state-specific means and covariances, which can be treated as a Multivariate Autoregressive (MAR) model with an order equal to zero. This meant that the segmentation of states within our model was based on instantaneous patterns of activation and connectivity—two features of resting-state brain activity that we were interested in capturing for the purposes of this study. Previously, Vidaurre et al. (2018b) also demonstrated that multivariate Gaussian HMMs are suitable for exploring the temporal features of spontaneous transitions between large-scale resting-state brain networks.

The sequence of HMM states across a time-course is characterised by modelling the joint transition probabilities between state pairs. Put more simply, the probability *Pr* of a given state at time point t depends on which state was active at time point $t-1$:

$$Pr(s_t = k) = \sum_l \Theta_{l,k} \, Pr(s_{t-1} = l),$$

where $\Theta_{l,k}$ refers to the transition probabilities. Within matrix Θ, we can further distinguish between the diagonal elements, Θ_{kk}, which control the persistence of each state, and the off-diagonal elements, Θ_{kl}, which refer to transitions between mutually-exclusive states. The observed data at each time point are modelled as a mixture of Gaussian distributions, with weights given by $w_{tk} = Pr(s_t = k)$.

In the current study, we ran a Hidden Markov Model on concatenated time-series data from all of the participants included in our dataset, which allowed us to obtain a group-level estimate of the states. Whereas the states were calculated at the group level, information pertaining to when a state is most likely to be active (the state time-course) were calculated independently for each participant.

The HMM applies an inference algorithm to estimate the parameters of each state (characterised by parameters μ_k and Σ_k), the probability of each state being active at each time point (s_t), and the joint transition probabilities for each pair of states ($\Theta_{l,k}$).

4.2.6.2 Model outputs

The *hmmmar.m* function from the HMM-MAR toolbox produces a range of outputs that can be used to estimate different features of HMM states. Below, we provide a brief description of the state properties that we used within subsequent analyses.

Following HMM inference, the temporal characteristics of each state can be quantified in terms of state fractional occupancies (the fraction of the total time spent in a state), state lifetimes (the time spent in a given state before transitioning out of that state), and interval lengths (the time it takes to re-enter a given state). Additionally, a switching rate can be calculated for each participant. Switching rates provide a measure of stability for each subject, since they represent the frequency of state switching across an individual time-course.

Using the *hmmmar.m* output Ξ (which holds matrices containing joint posterior probabilities of transitions between pairs of states), it is also possible to compute state transition probability matrices for each individual participant, as well as for an entire concatenated time-course. The relationships between transition probabilities and other measures of interest can be investigated in their own right, as we shall explore in the next section.

In the current study, we also used these probability matrices to derive an entropy rate estimate for each participant's MEG timeseries data. The entropy rate measures the average uncertainty, or information, generated by a transition within a sequence. In

general, the entropy rate of a sequence of random variables (s_t) is defined as the limit of $H[s_0,s_1,\ldots,s_n]/n$ as n is taken to infinity. Although this is not feasible to evaluate the entropy rate for general sequences, a sequence taken from a homogenous Markov chain yields a compact and computationally-efficient formula for the entropy rate.

Given a transition matrix $Pr(s_t|s_{t-1})$ defining an irreducible Markov chain over a finite state space, there exists a unique invariant distribution for that chain, π, satisfying $\pi(s) = \sum_{s'} Pr(s|s')\pi(s')$. The entropy rate can then be computed as $-\sum_{s'} \pi(s') \Pr(s|s') \log Pr(s|s')$. We can understand this formula as follows: the entropy rate quantifies the average entropy of a transition within the sequence. Hence, another equivalent formula (in the case of a strongly stationary process, such as a Markov chain) is the limit of $H[s_{t+1}|s_t]$. At long timescales, the convergence theorem tells us that the distribution of s_t is given by invariant distribution. Hence, the entropy rate is the sum of the conditional entropies $H[s_{t+1}|s_t = s']$ weighted by the invariant distribution $\pi(s')$.

4.3 Analyses

4.3.1 HMM inference and calculation of state characteristics

HMM inference requires an a priori specification of the number of states used in the model, k. Free energy metrics lend some objectivity to state number selection—in theory, the 'optimal' number of states should be determined by the model that has the smallest free energy (measured in arbitrary units). However, it is questionable whether this practice lends itself to parsimony and theoretical coherence; the aim of the current study was to establish whether a limited collection of neural states can track differences in behaviour and cognition across our sample. Baker et al. (2014), for instance, found that free energy often increases monotonically up to $k = 15$ states, suggesting that an even higher number of states would be needed to yield a Bayes-optimal solution. A similar limitation exists for more traditional dimensionality reduction methods like Independent Components Analysis, which is driven by the goals and constraints of the research question at hand. A smaller number of prespecified components often yields canonical resting-state networks, whereas a larger number can be used to extract finer-grained distinctions between patterns of activity (Smith et al., 2011, Smitha et al., 2017).

In the current study, we trained 11 separate HMMs on our resting-state MEG dataset with prespecified states ranging from k = 4 to k = 14. Free energy metrics and information about cycles to model convergence can be found in Appendix N. After inspecting the topological features of states for each solution, we chose a HMM with k = 7 in order to achieve a good representation of spatially-segregated states while minimising redundancy. Varying the number of states between 4 and 14 did not appear to change the topographical features of the most prominent HMM states, which appear across solutions regardless of the addition of extra states (see Appendix O for plots of different model results).

4.3.2 Comparisons between measures of neural dynamics and measures of cognition and behaviour

We first used an array of General Linear Models (GLMs) to explore how participants' switching rates, entropy rates, state fractional occupancies, and maximum fractional occupancies vary with age in order to explore developmental effects among our participants (who were 8 to 13 years old). Gender was included as a regressor in these models. Additionally, we ran a series of between-subjects t-tests to isolate any unique relationships between gender and states' temporal properties.

We then investigated how the state measures listed above vary with measures of cognitive ability (WASI-II MR scores) and behaviour (SDQ Total and SDQ Hyperactivity, Conduct Problems, Peer Problems, Emotion Regulation Problems, and Prosocial Behaviour subscale scores). To control for potential confounds, we included gender and age as regressors in each of these models at the level of the cognitive and behavioural outcome measures.

To control for multiple comparisons, we applied a False Discovery Rate (FDR) correction with a 5% threshold in each of these analyses (see Appendices P and Q for schematic representations of the cognitive and behavioural GLMs).

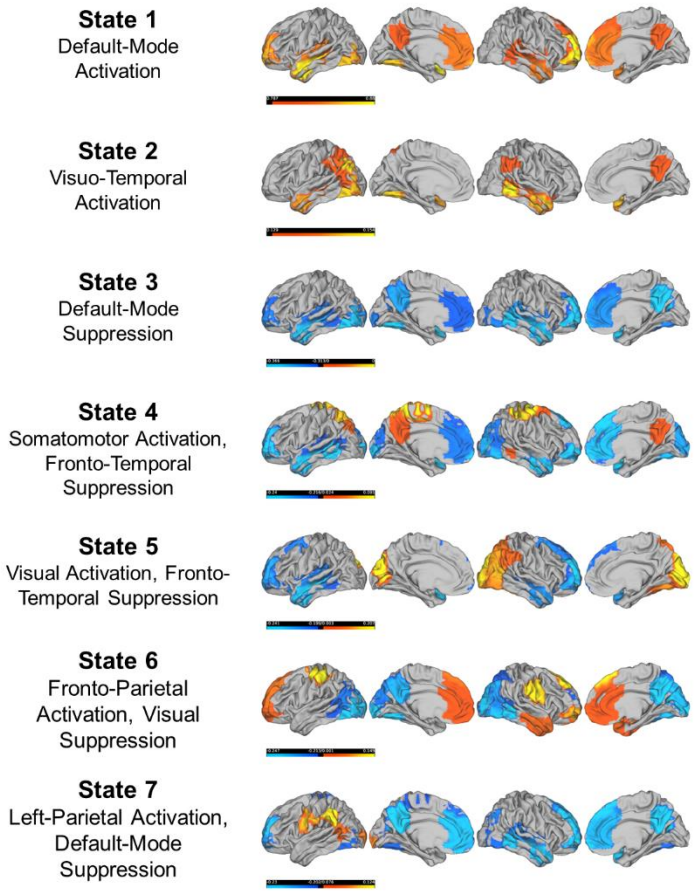
4.4 Results

4.4.1 State characteristics for the seven-state HMM

A seven-state HMM revealed distinct spatial patterns of activity and variations in oscillatory amplitude (see Figure 4.3). Each state-map represents the mean activation profile of each parcel for the concatenated MEG dataset. State-specific increases and decreases in oscillatory amplitude are plotted as yellow/orange and cyan/blue, and represent neural activation and suppression, respectively.

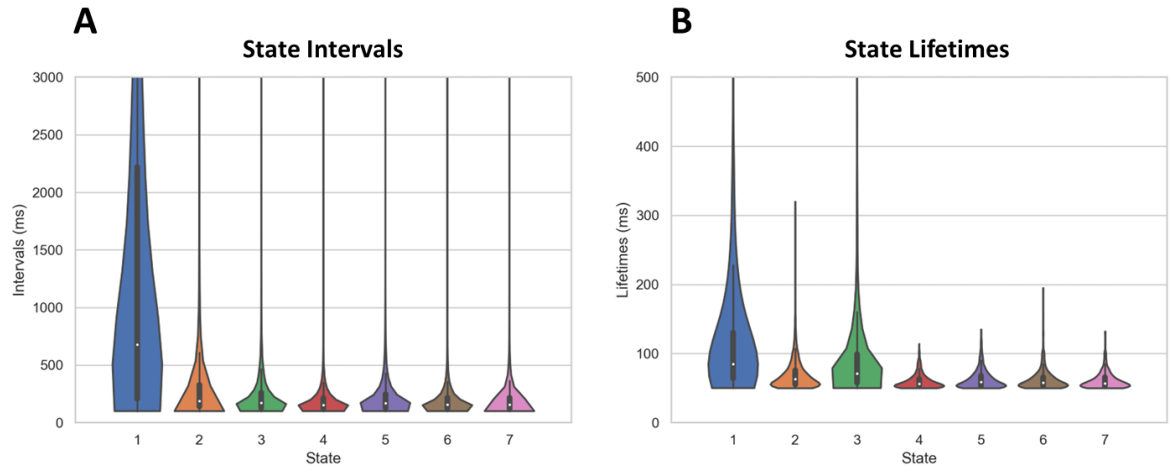
State 1 is primarily characterised by DMN activation, and state 2 shows prominent patterns of activation in visuo-temporal regions of the cortex. States 3 and 7 both demonstrate patterns of default-mode suppression, although state 7 is also characterised by concurrent left-parietal activation. Similarly, states 4 and 5 both show fronto-temporal suppression, along with patterns of somatomotor and visual activation, respectively. State 6, meanwhile, is characterised by fronto-parietal activation and visual suppression.

Figure 4.3: Here, we illustrate the results from our seven-state HMM. For each state, we plotted the top 20% of positive activations and bottom 20% of negative activations on a cortical surface using the HCP Workbench GUI. State labels correspond to our descriptions of the macroscopic features of cortical activation and suppression patterns.



Using the state time-courses, it was possible to calculate some temporal properties of each state. As illustrated in Figure 4.4, the temporal characteristics of the states vary considerably. Notably, state 1 has the most variable distribution in both lifetimes and intervals, which can be explained by the fact that it is the first state represented in participants' MEG time-courses—what seems to vary, in this case, is how long participants remain in this first state that is characterised by DMN activation.

Figure 4.4: Here, we plot the intervals **(A)** and lifetimes **(B)** of the states in our k = 7 HMM. Note that state intervals and lifetimes were thresholded at 50ms, such that state appearances that were sub-50ms were not included in the calculation of these temporal metrics.



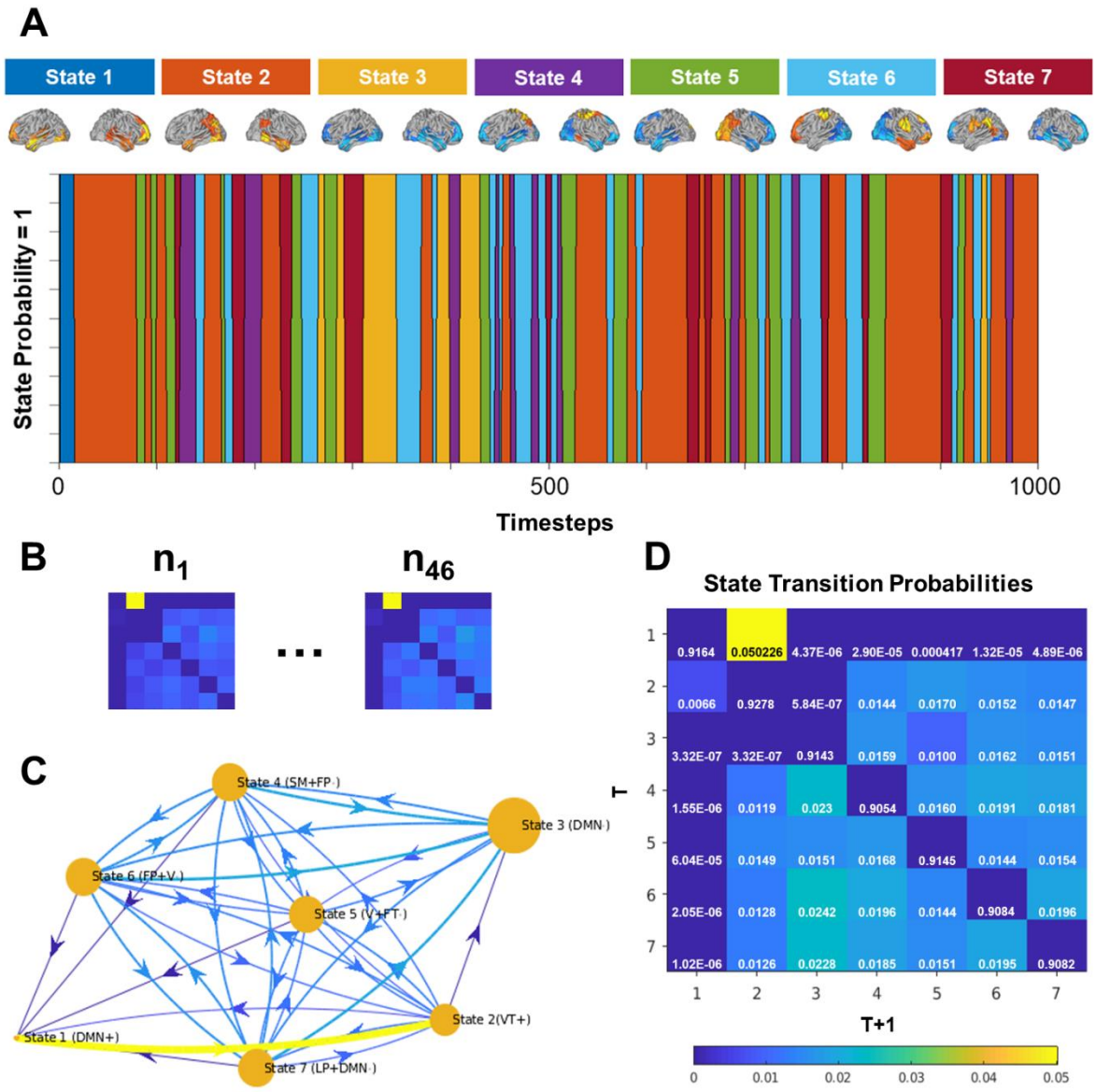
A one-way ANOVA revealed significant differences between the states' fractional occupancies, $F_{(6,315)} = 81.42$, $p = 4.16 \times e^{-61}$. Because intervals and lifetimes were calculated for each individual state, and not between participants, it was not possible to compare them in the same fashion as fractional occupancies. Nonetheless, their means and standard deviations, along with those of states' fractional occupancies, are summarised in Table 4.2.

Table 4.2: Means and standard deviations (in brackets) for state intervals, lifetimes, and fractional occupancies.

State	***Intervals (ms)***	***Lifetimes (ms)***	***Fractional occupancies (proportion)***
State 1 (DMN+)	1925.9 (± 3344)	129.49 (± 158.14)	0.0177 (± 0.0145)
State 2 (VT+)	293.9 (± 395.18)	69.09 (± 20.90)	0.1311 (± 0.0210)
State 3 (DMN-)	230.38 (± 192.23)	95.24 (± 94.50)	0.2330 (± 0.1085)
State 4 (SM+, FP-)	191.31 (± 143.90)	59.75 (± 10.24)	0.1578 (± 0.0314)
State 5 (V+, FT-)	223.52 (± 200.73)	63.05 (± 13.90)	0.1524 (± 0.0229)
State 6 (FP+, V-)	194.75 (± 149.74)	61.99 (± 14.08)	0.1542 (± 0.0320)
State 7 (LP+, DMN-)	196.42 (± 170.58)	61.20 (± 12.05)	0.1538 (± 0.0290)

In addition to calculating state lifetimes, intervals, and fractional occupancies, as well as generating state-maps, we also calculated state transition probabilities between and across participants. As anticipated, the most common timepoint-to-timepoint transition was the self-transition, forming the diagonal of the state transition probability matrix. State-to-state transition probabilities, which are less probable than self-transitions, are still readily-visualised when the diagonal of the matrix is zeroed-out (see Figure 4.5). State transition matrices with all values retained were used in later analyses.

Figure 4.5: In panel **(A)**, we present the first 1000 timesteps (4 seconds sampled at 250Hz) of the Viterbi path, which represents the maximum *a posteriori* probability estimate of the most likely sequence of states in a HMM. Notably, state-switching is rapid, and can be detected at very short timescales. Using the joint posterior probabilities of state transitions, we computed transition matrices for each of our participants, as shown in **(B)**. Panels **(C)** and **(D)**, in which self-transitions have been intentionally excluded for the purposes of plotting state-to-state transitions, display the average transition probabilities across our entire sample (n = 46). No thresholds were applied in the generation of these plots. The node sizes in panel **(C)** reflect the fractional occupancies of each of the states.



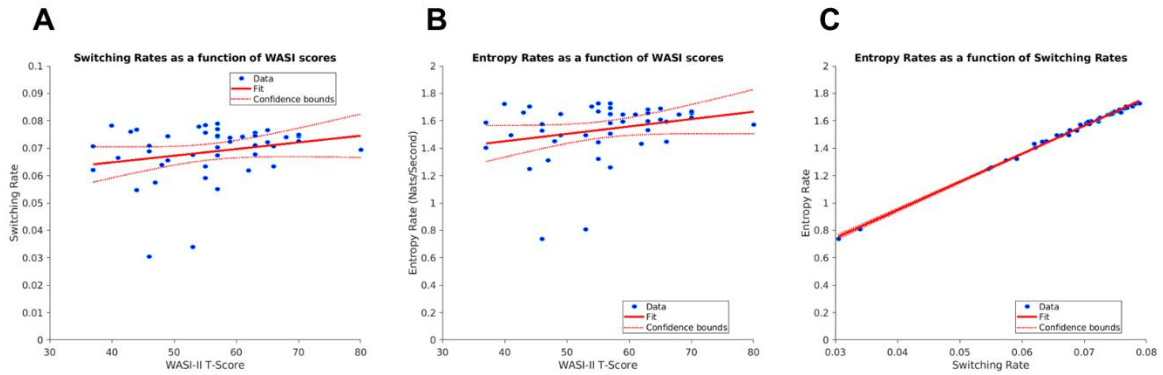
4.4.2 Entropy-related measures of neural dynamics are related to cognitive ability, but not age, gender, or behaviour

First, we used a series of general Linear Models (GLMs) to investigate the effect of age on states' temporal properties. Gender was included as a control regressor in these models. We did not find any significant effects of age on switching rates ($t_{(43)} = 0.7221$, $p_{adjusted} = 0.4741$), entropy rates ($t_{(43)} = 0.61$, $p_{adjusted} = 0.5451$), state fractional occupancies ($t_{(43)} < |-0.5611|$, $p_{adjusted} = 0.9333$), or maximum fractional occupancies ($t_{(43)} = 0.0763$, $p_{adjusted} = 0.9395$).

Similarly, t-tests comparing these state measures between genders did not find any significant effects for switching rates ($t_{(44)} = -0.3125$, $p = 0.7562$), entropy rates ($t(44) = -0.3078$, $p = 0.7597$), state fractional occupancies ($t_{(44)} < |-0.5020|$, $p_{adjusted} = 0.9851$), or maximum fractional occupancies ($t_{(44)} = -0.1576$, $p = 0.8755$).

Next, we investigated whether the temporal properties of states varied with six measures of behaviour (SDQ Total and SDQ Hyperactivity, Conduct Problems, Emotional Regulation Problems, Peer Problems, and Prosocial Behaviour subscales) and one measure of cognitive ability (WASI-II Matrix Reasoning). To do this, we used a series of GLMs in which age and gender were included as control regressors. No significant relationships were found between any measures of behaviour or state measures, $t_{(43)} < |-2.1504|$, $p_{adjusted} > 0.0932$ (see Appendix R for a full summary of these non-significant results). We did, however, find significant relationships between cognitive ability and entropy rates ($t_{(43)} = 2.2704$, $p_{adjusted} = 0.0284$), and cognitive ability and switching rates ($t_{(43)} = 2.1688$, $p_{adjusted} = 0.0358$). Additionally, entropy rates and switching rates were found to be highly correlated ($r = 0.9979$, $p < 0.00001$), indicating that individual variations in entropy are almost fully explained by state switching (see Figure 4.6).

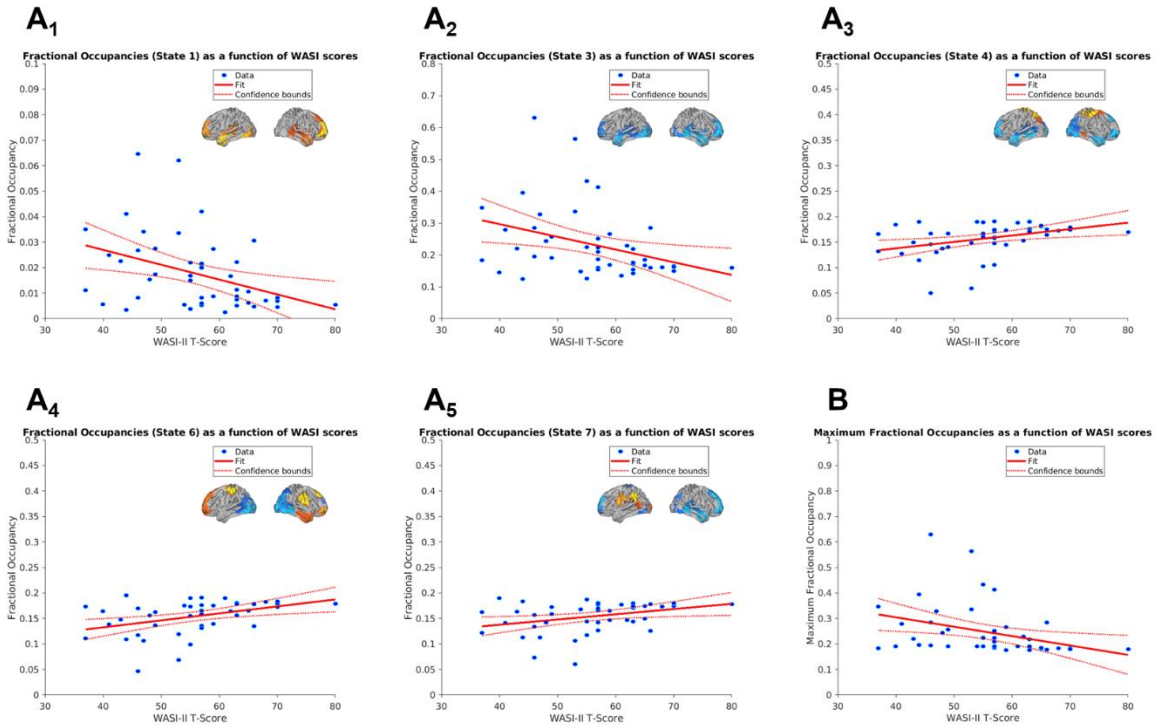
Figure 4.6: Panels **(A)** and **(B)** display the significant linear relationships between switching rates and entropy rates, respectively, and cognitive ability. Panel **(C)** shows the strong linear relationship between switching rates and entropy rates.



4.4.3 Switching is not random—state-specific fractional occupancies are related to cognitive ability

Although we found positive correlations between state switching, entropy, and cognitive ability, we wanted to investigate whether spending longer amounts of time in *specific* states could further explain the relationships between neural dynamics and cognition. Again, we used a series of GLMs in which age and gender were included as control regressors. We found significant relationships between cognitive ability and fractional occupancies in state 1 ($t_{(43)}$ = -2.7178, $p_{adjusted}$ = 0.0162), state 3 ($t_{(43)}$ = -2.7693, $p_{adjusted}$ = 0.0162), state 4 ($t_{(43)}$ = 2.9467, $p_{adjusted}$ = 0.0162), state 6 ($t_{(43)}$ = 3.2673, $p_{adjusted}$ = 0.0152), and state 7 ($t_{(43)}$ = 2.6402, $p_{adjusted}$ = 0.0162). An additional GLM revealed a significant relationship between cognitive ability and maximum fractional occupancies, $t_{(43)}$ = -2.6754, $p_{adjusted}$ = 0.0106 (see Figure 4.7).

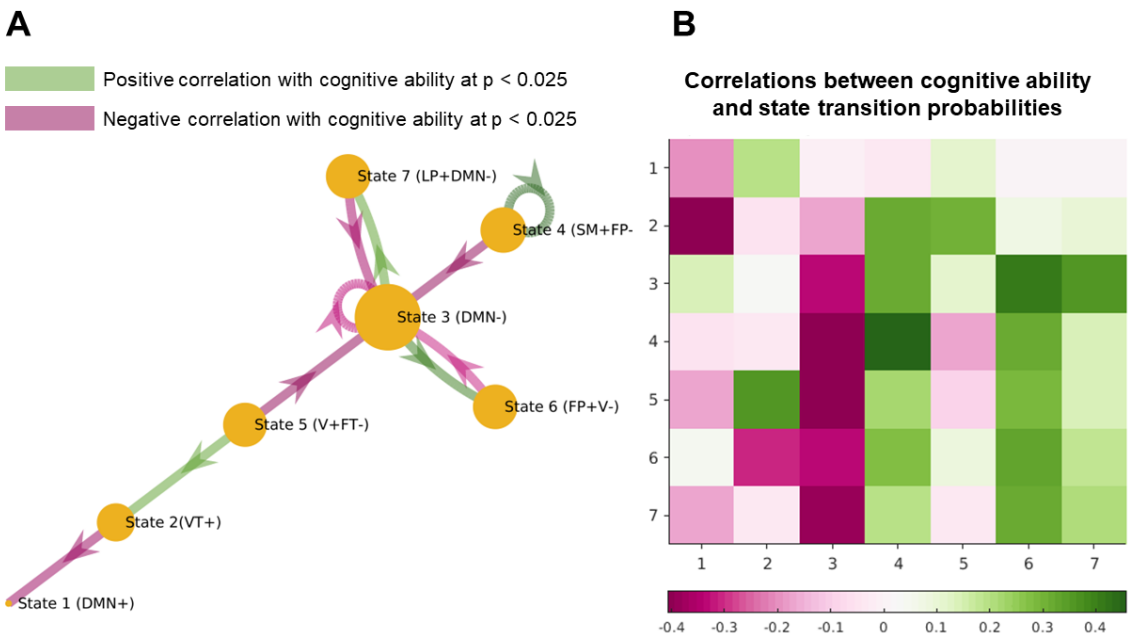
Figure 4.7: Panels **(A_1)** to **(A_5)** display the significant linear relationships between state fractional occupancies and cognitive ability. Panel **(B)** displays the significant negative linear relationship that was found between maximum fractional occupancies and cognitive ability.



4.4.4 Specific state transition probabilities are related to cognitive ability

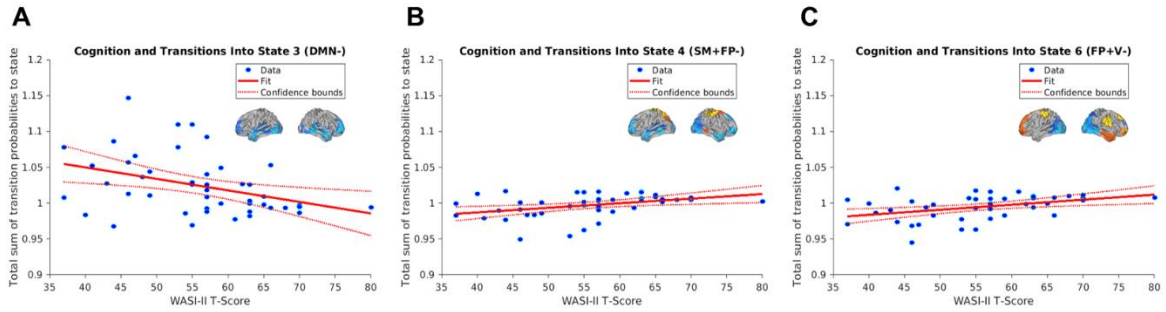
Our next aim was to test whether specific state transitions were related to cognitive ability. Using the transition matrices we previously extracted for each participant, we ran a series of correlations between each cell of the 7-by-7 transition matrices and WASI-II MR scores. Although a number of significant effects at $p < 0.025$ were initially found (see Figure 4.8), indicating the presence of strong positive and negative correlations between cognitive ability and state transitions, these effects did not survive corrections for multiple comparisons at the 95% confidence interval.

Figure 4.8: On the left, we illustrate significant relationships found between cognitive ability and transitions into specific states at $p < 0.025$. Node sizes represent states' fractional occupancies, and green versus pink transition arrows represent positive and negative correlations with cognitive ability, respectively. On the right, we have plotted a heatmap representing correlations between cognitive ability and state transitions in a 7-by-7 matrix. Notably, the columns for states 3, 4 and 6 show the highest correlation coefficients, suggesting that transitions *into* these states are most strongly associated with cognitive ability.



Instead of performing correlations across 49 separate cells of the state transition matrix, we decided to investigate how transitions *into* states 1-7, represented by the columns of the matrix (which, unlike the rows, do not sum to 1), might relate to individual differences in cognitive ability. We performed 7 correlations to this effect, and found that three states were significantly correlated with cognitive ability following corrections for multiple comparisons: state 3 ($r = -0.3794$, $p_{adjusted} = 0.0217$), state 4 ($r = 0.3889$, $p_{adjusted} = 0.0217$), and state 6 ($r = 0.4095$, $p_{adjusted} = 0.0217$). We did not find any significant relationships between transitions into states 1, 2, 5, or 7 ($r < |0.3154|$, $p_{adjusted} > 0.0573$). While state 3 was negatively correlated with cognitive ability, states 4 and 6 were positively correlated with cognitive ability (see Figure 4.9).

Figure 4.9: Here, we provide a finer-grained illustration of the linear relationships between transitions into specific HMM states and cognitive ability. Transitions into state 3 **(A)**, state 4 **(B)**, and state 6 **(C)** were found to be significantly correlated with cognitive ability following corrections for multiple comparisons.



4.5 Discussion

In the current study, we inferred a Hidden Markov Model using resting-state MEG data to investigate whether properties resting-state neural dynamics were related to aspects of cognition and behaviour in a developmental sample. We found that an HMM with seven states appropriately captured spatially-distinct activity networks while minimising redundancy in the model. The spatial topographies of multiple prominent resting-state networks were represented across the HMM, including the DMN, fronto-parietal and fronto-temporal networks, and multiple sensory and somatomotor networks. These networks were found to differ in their temporal characteristics, including their fractional occupancies across participants. We found that cognitive ability—but not behaviour, gender, or age—was positively associated with participants' state-switching and entropy rates. Additionally, there were significant relationships between cognitive ability and states' fractional occupancies. The directionality of these relationships was preserved in analyses exploring whether transitions *into* each of the states is predictive of cognitive ability. Transitions into and time spent within DMN-heavy states was associated with lower cognitive ability, whereas the opposite was true of states with more fronto-parietal and sensory network activation profiles.

4.5.1 Resting-state HMM inference is possible within a developmental sample

By inferring an HMM using group-concatenated MEG data from our developmental sample, we identified spatiotemporally-defined states that corresponded to well-known ICNs, including the default mode, fronto-temporal, visual, and sensorimotor networks. The spatial topographies of states in our HMM mirrored that of numerous other studies that utilised this method to extract the underlying features of resting-state MEG data, including Baker et al. (2014) and Becker et al (2020). Additionally, we found that state time-courses were characterised by a predominance of self-transitions, and that states exhibited transient (<100ms) average lifetimes. Across participants, there were individual differences in how long participants spent in each state. In further analyses, we explored whether various neurodevelopmental features of interest could shed light on what drives these differences.

The broad alignment between our findings and those outlined in previous research suggests that an HMM approach can be applied successfully in the study of transient neural dynamics in the developing brain. Although data quality issues are known to typically affect the reliability of MEG scans in children (e.g. Wehner et al., 2008; Pang, 2011), and particularly those with high levels of behavioural difficulties (Kaiser et al., 2021), we believe our findings demonstrate that HMM inference is robust to these potential issues, provided that data are pre-processed with enough attention to noise removal and the exclusion of scans with high proportions of outliers.

4.5.2 Time-course entropy and state-switching are positively associated with cognitive ability

After inferring an HMM with seven states, we first tested whether various neurodevelopmental features—age, gender, behavioural difficulties, and cognitive ability—predicted further differences in measures that characterised participants' time-courses. The switching and entropy rates of participants' time-courses, which we found to be highly intercorrelated in our sample, were positively associated with cognitive ability. However, we did not find any significant effects of age, gender, or behaviour on switching and entropy rates.

Although state-switching and entropy were highly correlated in the current study, they have different formal definitions, and therefore have different possible interpretations. While the switching rate quantifies the extent to which a participant engages in state-to-state transitions, as opposed to self-transitions, the entropy rate can be regarded as a measure of the complexity of a participant's time-course. Since switching rates explained the majority of the variance in participants' entropy rates, it is reasonable to conclude that the information of MEG timeseries data increased in proportion to the number of rapid and largely stochastic transitions between neural states. Had non-random and recurrent patterns of state transition sequences dominated the time-series, entropy rates would have been lower and more weakly associated with state-switching. Since the information of a time-course in our sample relies so heavily upon the flexibility and speed with which state-switching takes place, it may be useful to regard the neural entropy rate as a more complex measure that is nonetheless heavily driven by a latent switching factor.

Cortical feedback and feedforward pathways are known to rapidly control local brain network states, and this process is optimised to flexibly change the gain, precision, and synchronisation of neural activity (Zagha & McCormick, 2014). Furthermore, dynamic transitions between hidden neural states are believed to enable the flexible reconfiguration of functional circuits across the brain, thereby enabling adaptive cognitive and behavioural processes. A number of previous studies have highlighted the positive associations between state switching and cognitive ability. For instance, Taghia et al. (2018) found that cognitive task performance is strongly predicted by state-switching at rest, and that considering task-related neural dynamics only minimally improves the ability to predict task performance. Additionally, Cabral et al. (2017) found that more flexible patterns of state-switching predict better cognitive performance in older adults, and that this relationship is mediated by the tendency to transition between particular states in the neural attractor landscape. In the context of neurodevelopment, rapid switching between states is known to increase during adolescence (Medaglia et al., 2018) and accompany motor-skill acquisition (Reddy et al., 2018). Entropy, like state-switching, has also been found to increase throughout childhood development, reflecting a gradual expansion in the diversity of neural processes available to the child (Amalric & Cantlon, 2023). More broadly, brain entropy has been positively associated with general intelligence in samples with large

age ranges, suggesting this brain-cognition relationship persists across the lifetime (Saxe et al., 2018; Wang, 2021; Thiele et al., 2023). Although there are many different operationalisations of brain signal complexity (e.g. Shannon entropy, multiscale entropy, Fuzzy entropy, and microstate characteristics; see Keshmiri, 2020, for review), the entropy rate of the neurophysiological HMM timeseries may also provide a useful means of exploring individual differences in neural activity.

4.5.3 Tendency to stay within, and transition into, certain HMM states predicts differences in cognitive ability

Although the relationship between cognitive ability and neural entropy rates was largely defined by rapid, stochastic patterns of brain switching, we wanted to investigate whether there were state-specific relationships between different neurodevelopmental characteristics and neural dynamics. While we did not find any relationships between the seven states' fractional occupancies and age, gender, or behaviour, cognition was positively associated with time spent in states 4, 6, and 7, and negatively associated with time spent in states 1 and 3. Upon examining whether transitions into certain states also characterised these relationships, we found a similar profile of results. Transitions into states 4 and 6 had positive associations with cognition, whereas the opposite was true for state 3.

The spatial topographies of these states may provide some insight into why this was the case. One benefit of using MEG data to study these relationships is its high temporal resolution, which allows one to record patterns of neural activation and suppression (inhibition) that occur in very short time-windows. States 4 and 6, for instance, were primarily characterised by fronto-parietal activation *and* suppression, whereas state 3 was dominated by suppression across the default-mode network. As mentioned in the Introduction, previous research indicates that the emergence and spatiotemporal segregation of fronto-parietal networks supports executive function across development (Keller et al., 2023), whereas the overactivation and hyper-integrated spatiotemporal patterning of the DMN is associated with cognitive and behavioural difficulties (Cortese et al., 2012). The fact that both fronto-parietal activation and suppression predicts increases in cognitive ability may relate to large-scale coordination of brain activity performed by fronto-parietal networks (Marek & Dosenbach, 2018; Chen et al., 2022). Indeed, Gu et al. (2020) found that transitions

to, and between, different task-positive states was positively related to performance on a cognitive task.

While DMN suppression has previously been viewed as a process that optimises for goal-directed cognition (Anticevik et al., 2012; Leonards et al., 2023), it is possible that an increased *need* to suppress DMN activity could also be viewed as a hindrance to cognitive functioning. In the current study, we found that the time spent within states corresponding to DMN activation and suppression was negatively associated with cognitive ability. The same was true of transitions from other states into the DMN-suppression state, which suggests that broad differences in DMN control may contribute to cognitive differences in childhood. Of course, there are many developmental paths that could lead to the emergence of isomorphic differences in cognitive ability and DMN function, among them being mood difficulties (Whitfield-Gabrieli & Ford, 2012; Rai et al., 2021). Although we did not collect data about our participants' experiences of emotional challenges or psychiatric disorders, other than through the SDQ Emotion Regulation subscale, it is possible that the relationships between DMN state activity and cognition are mediated by effects in these domains. For instance, emotional difficulties in childhood may lead to subsequent cognitive difficulties, resulting in a tendency to engage in DMN overactivation and suppression (Rokita et al., 2018). Similarly, childhood cognitive difficulties are associated with the emergence of persistent emotional struggles later on (Nachshon & Horowitz-Kraus, 2019). To build a coherent theoretical model of the directionality of these effects, future studies of HMM states in childhood should aim to collect a wider breadth of data, and to assess how the activity of these states changes throughout development.

4.5.4 Limitations

The primary limitations of the current study are its small sample size and relatively constrained age range, which could account for why we did not find any effects of age or gender on HMM state properties. Our sample size was reduced from n=52 to n=46 due to exclusions based on data quality, which is a common difficulty within research in developmental cognitive neuroscience. While the size of our dataset was sufficient for inferring robust HMM states, it is possible that we would have been able to explore more granular neurodevelopmental effects had we had access to a larger sample. In the same vein, a sample that included a wider age range would have enabled us to

investigate how neural dynamics change over time, rather than how they exist at one phase of development. We encourage future research in this area to build upon our findings with these core limitations in mind.

In this study, we also used a 38-node parcellation developed by Colclough et al. (2015) and subsequently used in other studies that applied HMM to MEG data (e.g. Colclough et al., 2017; Quinn et al., 2018). We chose this parcellation because the effective dimensionality of MEG data in source-space is approximately 60-70 (Quinn et al., 2018; Farahibozorg et al., 2018), and the number of parcels should be less than the rank of the data in order for corrections for signal leakage to work. Although using this parcellation allowed us to infer an HMM, it also reduced the spatial resolution at which we were able to observe neural effects. Additionally, it meant that we had to rely on a parcellation that was different from the one applied in the first and second empirical chapters of this thesis, making interpretability somewhat more challenging. Although it was necessary to use a coarse parcellation in the current study, we believe that researchers should continue to look for solutions to this limitation, such that a better balance is achieved between spatial granularity and MEG data dimensionality constraints.

4.6 Conclusion

The current chapter, like the previous chapter, provides a transdiagnostic view of the associations between behaviour, cognition, and features of neural activity. Using a multivariate Gaussian Hidden Markov Model, we inferred a seven-state model of resting-state neural dynamics in a developmental sample. We found spatial and temporal differences between each of the states identified in our model. Entropy-related metrics of dynamic neural activity were positively associated with cognitive ability. Additionally, particular states provided more clarity about the nature of these relationships; DMN states were negatively associated, and fronto-parietal states were positively associated, with cognitive ability in our sample. A future avenue for research in this area might involve the collection of larger datasets that represent a wider distribution of ages. This will provide insight into how neural dynamics change across childhood and adolescence, and how they might correspond to different trajectories of behavioural and cognitive development.

5 Diverse Trajectories to Good Developmental Outcomes—a practical approach to inclusion in schools

5.1 Introduction

The previous chapters of this thesis have outlined findings from empirical studies that explored the neural underpinnings of individual and developmental differences in behaviour and cognition. The goal of this research has been to elucidate how the structural, functional, and dynamical features of brain networks are associated with neurodevelopmental diversity and divergence from 'typical' profiles of behaviour and cognition.

The study of neurodevelopmental diversity has gained prominence within cognitive neuroscience for a number of reasons. Firstly, neurodevelopmental conditions offer a window into how genetic, neurological, and environmental differences coincide with—and potentially cause—variations in cognition and behaviour. Tracking the complex associations between these factors enables researchers to work towards a set of fundamental principles that describe development itself, and perhaps even predict important outcomes on the basis of genetic, neurological, cognitive, and behavioural data. Aside from seeking biological mechanisms that contribute to neurodevelopmental diversity, many researchers in this area are also interested in identifying what can be done to ensure positive outcomes for those who encounter cognitive or behavioural barriers to learning and wellbeing in childhood and adolescence. Basic research certainly contributes to this goal, as it creates an evidence-base that can inform policymaking efforts. Unfortunately, information from scientific studies often fails to reach key decision-makers in government and the education sector, meaning that progress towards better policy and practice can be slow. There is an extensive literature describing this 'evidence-policy gap' (e.g. Cairney & Oliver, 2017; Oliver & Boaz, 2019), and numerous proposals for how it can be narrowed. Strategies for overcoming the evidence-policy gap, perhaps rightly so, tend to focus on what scientists can do to make their research more convincing to policymakers (Oliver et al., 2014). However, scientists are trained to appraise their assumptions, methods,

and results with scepticism. Ironically, this results in a state of affairs where the most informed members of society tend to act with far less confidence than those who are less informed.

As researchers, we often have a first-hand perspective on the needs and struggles of the populations we study. Those who took part in data collection for the Centre for Attention, Learning, and Memory cohort, for instance, did far more than simply perform MRI scans and assess participants' cognitive and behavioural characteristics. The CALM cohort was a gateway to thousands of discussions between researchers, parents, educators, and practitioners, all of whom learned something new about the barriers that neurodivergent individuals face in accessing much-needed support. Simple conversations that I had with parents in the waiting room of the MRC CBU's MRI scanning facility revealed their eagerness to share details about the struggles their children faced. These conversations converged on a handful of themes—the inadequate provision of resources in schools, the difficulty of obtaining a diagnosis, bullying, and the mental health problems that emerge when a child's needs are not being met. As I progressed through my PhD, I became more interested in the life circumstances and needs of the community I was studying—a community that, I came to understand, was facing marginalisation due to the fact that the UK's education and social care systems are so under-resourced. I wondered whether there was something more I could do, outside of my scientific work, in order to help young people and their families overcome some of these challenges.

In October 2022, I began a new type of project. This new venture would allow me to explore how neurodiversity and neurodivergence interact with children's experiences at school, and the extent to which current research can positively influence educational practices. This is a project that I completed alongside my PhD supervisor, Duncan Astle, and many others who helped us along the way. It had two phases: the organisation of a multidisciplinary workshop, during which key barriers to learning and wellbeing in schools would be identified, and the subsequent creation of a set of resources that would help schools create inclusive school policies. Sections 5.1.1-2 serve as a brief description of the primary issues currently affecting inclusive practices in mainstream English school settings. The text from these sections has been adapted from a policy briefing developed in collaboration with science writer Dr Sian Lewis,

who helped our team identify the major themes and statistical trends discussed at our multidisciplinary workshop. We then summarise our process for planning and facilitating this workshop, as well as producing an inclusion guide for schools. Finally, this chapter gives an account of our findings, key outputs, and medium-term plans for the future of these initiatives.

5.1.1 Systemic shortcomings and barriers to inclusion

Inclusion for children with SEND (Special Educational Needs and Disabilities) is mandated practice in England. The Needs and Disability Code of Practice (Department for Education & Department of Health and Social Care, 2014) dictates that every school must have a dedicated budget and system to provide accommodations and inclusion resources to pupils with SEND. Similar policies exist across the rest of the UK—Scotland, for instance, mandates that provisions are held for children with additional support needs (ASN), although this category is broader than SEND and includes characteristics like care experience.

The system for achieving inclusive practices is partially informed by the use of diagnostic labelling, which can help pupils, parents, and educators secure additional resources and support. The Special Educational Disability Code of Practice dictates that every school must have a system to identify children in need of support and to assess, monitor, and secure appropriate resources for any SEND condition they may have. The UK government provides schools with a delegated budget to achieve this, but the system suffers from several major failings that make it challenging for schools to implement effective inclusion strategies.

5.1.1.1 Unsustainable funding models

Fuelled by a growing awareness of learning differences and a focus on early identification, the number of students with SEND is rising. In 2022, there were an estimated 1.4 million state students with SEND; in England, 1 in 25 schoolchildren had an Education, Health, and Care Plan (EHCP). However, even though an estimated 13% of children have SEND, only 4% of children receive an EHCP. Those with SEND, but no EHCP, face a difficult situation: with no legal protection or plan for provisioning care and reasonable accommodations, there is no guarantee that their needs will be met (Ofsted, 2021; Ahad et al., 2021).

Local authorities across the country have faced huge shortfalls in SEND funding as they struggled to keep up with demand. By 2021, the national deficit in dedicated schools' budgets was more than £1 billion (Department for Education, 2022). Given the scale of the issue, even significant increases in SEND funding are unlikely to reach all those in need.

5.1.1.2 Impractical, non-scalable approaches

SEND encompasses a large range of conditions, from specific and modest difficulties to substantial cognitive and behavioural barriers to learning. Deciding which interventions are appropriate is made more difficult by the fact that those with SEND rarely meet the criteria for only one condition (Dewey, 2018). Although co-occurring needs can be addressed by 'stacking' individual interventions, this approach often fails to address the interactions between different needs, and the manifestation of these interactions across development.

5.1.1.3 A misguided focus on diagnostic labels

Diagnostic labels, which often gate access to support, provide only a limited and static snapshot of a child's needs. This means that they are ill-suited to capturing the developmental context in which difficulties occur. As a result, these rigid categories do not adequately accommodate the real-world needs of most children, such as those who do not align with the stereotypical characteristics of their diagnostic label(s), or those whose difficulties fall below the threshold for formal diagnosis but still hinder learning. Nonetheless, the presence of a formal diagnosis is still seen as crucial for accessing 'the right support at the right time', despite the limitations that this tacit requirement imposes on access to support (Office for National Statistics, 2021).

Configuring support around diagnostic labels can also skew perceptions of cognitive and academic ability, potentially leading children to feel discouraged in achieving their academic potential. Although diagnostic labels can be useful in configuring avenues for support and providing valuable information to individuals and their families, the experience of being labelled is not always a positive one. For instance, the use of diagnostic labelling is known to sometimes diminish individuals' feelings of agency

over their behavioural tendencies and future outcomes (Mooney, 2016). This is especially true in cases where a diagnosis provides an inaccurate or insufficient description of an individual's needs. The goal of a supportive educational framework should be to empower pupils, parents, and educators to make beneficial judgements and decisions, rather than to create inappropriately low expectations for academic engagement and flourishing.

5.1.1.4 Differences in access to assessment

In theory, any child with suspected learning differences in the UK is entitled to an assessment of needs. In practice, these assessments are unequally-accessed due to very long waiting times for NHS-based services, and minimal access to publicly funded educational psychologists. Higher-income families thus have preferential access to resources and assessment, and are often in a strong position to push for accommodations to be made at school. Inequalities in access to support combine with other learning barriers (such as poverty, unstable home environments, and other forms of early life adversity) to compound this problem, with working-class boys and ethnic minorities most likely to be punitively excluded from school (Ball et al., 2023).

5.1.1.5 Stigmatisation of neurodevelopmental differences

Because children with SEND labels are more likely to be bullied than their peers, they may choose not to access the adjustments to which they are entitled (Mukolo et al., 2010; Fink et al., 2015). For teachers, the focus on formal SEND diagnoses reinforces the idea that staff need specific neuropsychological expertise to be able to support their students, which can leave teachers feeling unskilled and apprehensive. They may be inclined to distance themselves from their pupils with SEND or look for costly 'expert' support outside of school rather than drawing on their own knowledge to help meet children's needs (Able et al., 2015; Jaffal, 2022).

5.1.2 Is inclusion on the agenda?

Legal provisions designed to facilitate inclusive practices in UK schools are ill-suited to managing the complexities of neurodevelopmental conditions. The systemic failings that contribute to this are widely acknowledged. The UK government's long-awaited 2022 SEND review confirmed that decisions about resource provision and inclusion

are often made on the basis of where a child lives or attends school, rather than on their profile of needs. The review found that many children face significant delays in accessing support, or fail to ever receive appropriate support. The government recognises the need to change some elements of inclusive educational practices in the UK, and has set out proposals for reforms. These reforms focus on improving the early identification of needs and ensuring prompt access to targeted support (without necessarily requiring a diagnostic label). Broader reforms of the education system are also planned. The goal remains better educational attainment, measured as the national GCSE average in English and Maths, and more socialisation, measured through behaviour and attendance. While these changes may be useful in the context of the broader educational system, they do not provide a coherent strategy for inclusion in schools, and may further disadvantage those with SEND. Attendance and attainment are not in and of themselves inclusion goals.

5.2 Methods

5.2.1 Diverse Trajectories to Good Developmental Outcomes Workshop

5.2.1.1 Aims

In October 2022, we received a grant from the Templeton World Charity Foundation (TWCF) to run a multi-disciplinary workshop as part of TWCF's Global Scientific Conference on Global Flourishing. Our *Diverse Trajectories to Good Developmental Outcomes Workshop* aimed to integrate our growing scientific understanding of the diversity that exists in neurodevelopment with pragmatic policy recommendations for achieving good developmental outcomes. 'Achieving good developmental outcomes', in this case, also meant avoiding negative developmental outcomes—for instance, suspension or expulsion from school, bullying, mental health difficulties, and the imposition of limitations on what students can achieve at school.

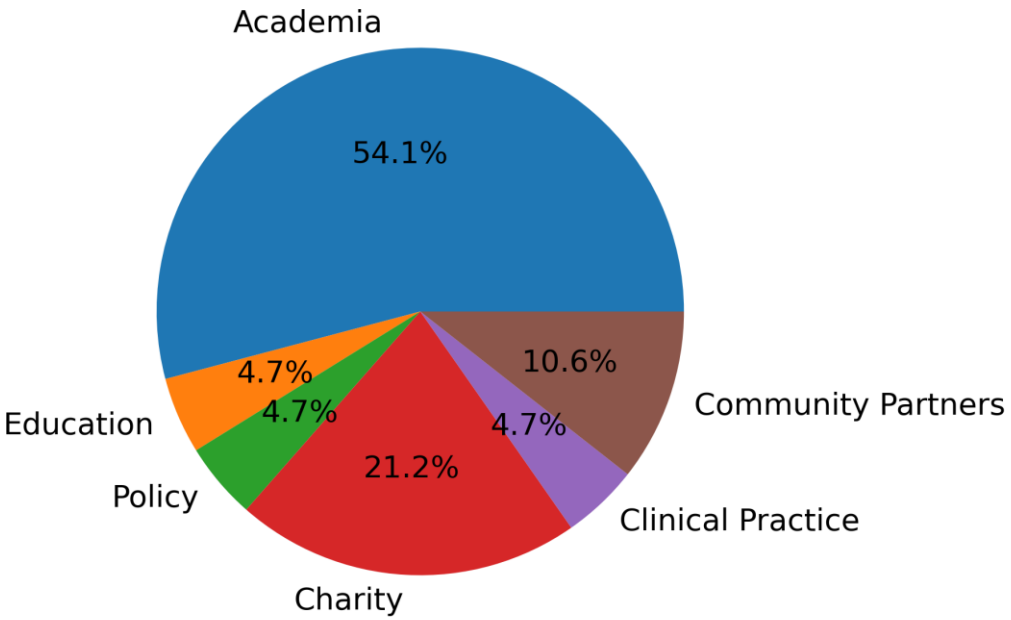
Another primary goal of the workshop was to identify the nature and extent of unmet need in educational and social care systems across the UK. While it was clear to us that limitations at both the local and national levels create disparities in learning and wellbeing, we wanted to understand these problems with greater specificity, such that we could begin constructing practical solutions.

This event brought together dozens of leaders in academic research, the charity sector, policy, education, and clinical practice, alongside those with lived experience of neurodivergence, to engage in collaborative processes aimed at improving school-level and national policies in the UK. The structure of the event consisted of four main sessions that featured evidence-focused talks, guided discussions, and targeted focus groups. Across the four workshop sessions, we hoped to identify how certain characteristics of education policy in the UK can act as barriers to learning and wellbeing. We also wanted to outline the factors that characterise effective school-level inclusion policies and discuss ways in which national-level policies could be innovated. One key planned output of the workshop was a policy briefing about barriers and solutions to inclusion in UK schools. The Diverse Trajectories to Good Developmental Outcomes Workshop took place at Robinson College, Cambridge, on the 29th and 30th of November 2022.

5.2.1.2 Recruitment of workshop attendees

From October 2022, our small team began recruiting attendees for the Diverse Trajectories to Good Developmental Outcomes Workshop. Attendees were carefully considered and selected to represent leaders in academia, policymaking, education, the charity sector, and clinical practice. We advertised some additional workshop places for 'community partners'—those with lived experiences of neurodivergence and an interest in sharing their views on how the education and social care systems could be transformed to better serve those with cognitive and behavioural differences. Many of the workshop attendees occupied multiple of these categories—for instance, many academics who took part also held positions as clinical practitioners. Additionally, there is no doubt that all of these career trajectories included neurodivergent individuals, even though they were not explicitly recruited as community partners. In total, we successfully recruited 85 attendees to participate in the workshop. The sector demographics for these workshop attendees are displayed in Figure 5.1.

Figure 5.1: Here, we illustrate the sector demographics for those who attended the Diverse Trajectories to Good Developmental Outcomes Workshop.



5.2.1.3 Structure of the event

5.2.1.3.1 Sessions

As mentioned previously, the Diverse Trajectories to Good Developmental Outcomes Workshop consisted of 4 main 'sessions' spread across two days. These topics of these sessions were as follows:

1. What are the primary barriers to learning in childhood?
2. What are the primary barriers to wellbeing in childhood?
3. What factors go into a good school-level inclusion policy?
4. What factors go into a good national-level inclusion policy?

Each of these sessions began with four 15-minute talks from workshop attendees who had expertise in the given topics. Following the talks, the entire delegation engaged in an open discussion, during which attendees could ask members of the session panel questions about the content of their talks. During these discussions, members of our team took detailed notes that would later inform a policy document focused on

neurodiversity and inclusion in schools. Although poverty and early life adversity were continually discussed as primary barriers to learning and wellbeing, it was not possible to address these challenges within a single policy document. We decided to focus on inclusion in *schools*, specifically, because it became apparent that we could best promote sustainable recommendations at the local level.

5.2.1.3.2 Focus groups

After the talks and discussion portions of each session, a subset of workshop attendees were asked to convene in a separate room for an hour-long, targeted discussion about the topic at hand. Each focus group (consisting of approximately 10 workshop attendees) included a mix of community partners, academics, clinicians, and leaders in the charity, policy, and education sectors. The purpose of these groups was to identify possibilities for policy recommendations—that is, create a long-list of about 10 recommendations that corresponded to the theme of each session. These long-lists were then presented to the rest of the delegation, who ranked policymaking priorities using a digital platform. These priority rankings then informed the later policy document.

5.2.1.4 Facilitating productive conversations between workshop attendees

In order to ensure that the Diverse Trajectories to Good Developmental Outcomes Workshop fostered useful discussions between attendees, our team created a list of ground rules and guidelines to be followed throughout the event. We adapted our guidelines from the one implemented by *Shaping Our Lives*, a think tank for service - users and disabled people.

Because our workshop was multi-disciplinary by design, it was important to account for potential knowledge-gaps, differences in terminology, and cultural differences among its attendees. Among these rules, we included the following message: “Please respect what others might need in order to contribute to the meeting as best as they can. Everyone is coming from a different background, and will think and talk differently about things. In describing your point of view, please use language that you think will be interpretable by people outside of your area of expertise.” We believe that this helped workshop attendees (particularly academics) shift their frame of reference

away from theoretical models and technical jargon, and towards a more pragmatic approach to discussing their work.

A full list of these guidelines, as well as the full programme for the Diverse Trajectories to Good Developmental Outcomes Workshop, can be found here: https://github.com/nataliazdorovtsova/Diverse-Trajectories-Workshop/blob/main/DTW%20Official%20Programme%20PDF.pdf

5.2.2. Belonging in School: a practical guide to creating inclusive policies in primary schools

Following the Diverse Trajectories to Good Developmental Outcomes Workshop, our goal was to create a set of resources that would help schools implement inclusive policies. Initially, we worked with Dr Sian Lewis, a professional science writer, to create a broad policy document that provided an overview of issues in this area and compiled recommendations made by workshop attendees (available here: https://github.com/nataliazdorovtsova/Diverse-Trajectories-Workshop/blob/main/InclusionBrief.pdf). This was our initial output from the workshop. Once this deadline was met, we had a longer period to engage in a subsequent stage of considering how to best disseminate this information to the relevant stakeholders. It became clear to us that a more comprehensive set of resources would help schools implement inclusive practices at the local level. In the spring of 2023, we decided to begin working on a resource pack called *Belonging in School: a practical guide to creating inclusive policies in primary schools*, which would enable school staff to consider how to best implement inclusive practices. To this end, we recruited the help of Dr Alyssa Alcorn, who joined our team as a Public Engagement Lead. Throughout the summer, we worked alongside her to create a set of freely-accessible online materials to be released in September 2023.

5.3 Results & Outputs

5.3.1. Diverse Trajectories to Good Developmental Outcomes Workshop

5.3.1.1 Addressing barriers to learning

A variety of priorities were identified as relevant to tackling barriers to learning in UK schools and society. Our focus group participants helped outline a list of these priorities, which were ranked in order of importance by the rest of the delegation:

1. Better universal access to basic necessities, i.e. policies that reduce poverty and socioeconomic hardship,
2. Teaching approaches, integrated at the level of the whole school, that can meet a broad spectrum of developmental needs (for instance, the Universal Design for Learning framework),
3. More funding for resources in health and social care, and more recognition within government agencies that education is tied to these factors,
4. More initiatives that promote integration between schools, families, and local communities,
5. Community initiatives and interventions at the pre-school level that promote school readiness,
6. Reduction of stigma around profile assessment and education about diversity in schools.
7. Better implementations of efficient, high quality screening methods for cognitive difficulties in schools,
8. More varied curricula—for instance, ones that give students opportunities to engage in spatial and verbal reasoning across multiple domains, and
9. Clearer guidance for teachers and parents on what to do with cognitive screening results.

5.3.1.2 Addressing barriers to wellbeing

Workshop attendees also recognised a range of barriers to wellbeing that affect children and families in the UK. Again, we asked attendees to rank a long-list of policy priorities outlined by a focus group, which are listed below:

1. Reformation of government agencies (like Ofsted), such that wellbeing has parity with educational attainment,
2. Legislation for public wellbeing as a priority for policymaking across all government departments,
3. The creation of pragmatic toolkits and pipelines for addressing wellbeing needs in educational settings,
4. Universal free school meals across the UK and further funding for school amenities (like uniforms),
5. Higher pay for teachers and smaller class sizes,
6. Removal of high-stakes, deterministic testing systems at the very end of school in favour of more gradual assessments of attainment throughout school,
7. Thorough assessment of teacher wellbeing,
8. More inclusive school syllabi that represent diverse perspectives, and
9. Anti-bullying programmes at schools, especially ones that are designed to tackle social prejudice.

5.3.1.3 Inclusion objectives at the school level

One major goal of the Diverse Trajectories to Good Developmental Outcomes Workshop was the identification of needs at the national- and school-level, and the selection of what might be relevant to addressing those needs. After identifying key barriers to learning and wellbeing, workshop attendees discussed measures that could improve inclusive practices at the national and school levels. Again, many attendees argued that better national policies are needed in order to tackle poverty and inequalities in opportunity. We agreed with this sentiment. However, as discussed previously, it was not possible to create a policy brief that could address these broad systemic challenges. If we wanted to facilitate as much positive change as possible, we needed to determine the specific level at which we were best positioned to do so. In writing our initial policy brief, we therefore focused on *school-level recommendations* for promoting inclusion and reducing inequity. Some of the recommendations put forward for schools, and examples of associated actions, are summarised in Table 5.1.

Table 5.1: Here, we list several school-level inclusion measures that were proposed during the Diverse Trajectories to Good Developmental Outcomes Workshop.

Inclusion Objective	*Example actions*

Normalise the existence of neurodevelopmental diversity	• Implement the Universal Design by Learning (UDL) framework, which focuses on multiple means of representation, action and expression, and engagement, such as:
	  ○ presenting information and content in different ways;
	  ○ offering different options for students to show what they know; and
	  ○ providing different modes of classroom engagement that align with students' interests and challenge them appropriately.
	• Make schools more inclusive to a broader range of sensory needs—if possible, reduce harsh/artificial lighting and plan fewer activities in which students have to switch between sensory extremes.
	• Be more forgiving in cases where uniform policies not being followed perfectly—for example, child wearing black trainers instead of black dress shoes, or wearing clothes made from more comfortable fabrics.

Equip the workforce for inclusive practices	• Raise awareness among all staff about mental health challenges, neurodiversity, and inclusive practices through posters, seminars, workshops, etc. • Ensure comprehensive and consistent continuing professional development (CPD) on neurodiversity and inclusive practices. • Identify external partners, such as academics or local experts, to help with CPD.
Promote acceptance and empathy	• Teach students about neurodiversity both explicitly and by weaving it into the curriculum (for example, by highlighting the contributions of neurodivergent individuals to the sciences, arts, and other areas of human knowledge). • Host assemblies dedicated to informing students about neurodevelopmental differences, and talk about how to be understanding of diverse needs. • Educate students from an early age about sensory needs, and introduce them to words that describe different types of sensory needs so that they can advocate for themselves. • Set clear school rules about acknowledging and valuing individual differences. • Intervene in instances of bullying or peer exclusion in a way that teaches collaboration, understanding, and inclusion.
Eliminate unfair incentives	• Offer more flexible arrival and departure times for students who may need them. • Offer online resources for learning that students can access regardless of whether they are physically present in the classroom. • Reduce expulsion, suspension, and isolation by using alternative strategies to support students.

	• Limit rewards and punishments relating to school attendance (including the attendance of events like assemblies or Sports Day).
Include families and communities of support	• Set up support groups for parents to facilitate discussions about neurodiversity, promote a sense of belonging, and gather feedback. • Support families who lack the time to participate in co-production efforts, and/or who might not speak English fluently, by ensuring that information about inclusion efforts is communicated through multiple channels (i.e. via email, in the school newsletter, and on the school website).

The theme of context-dependence emerged regularly throughout discussions at the workshop. Inclusion does not look the same across all schools, because every locality in the UK has its own cultural and socioeconomic profile. Therefore, recommending a set of pre-defined inclusion policies may prove ineffective and short-lived. In embarking upon our next project, our team took these issues into account by focusing on the *creation* of inclusive school policies.

5.3.2 Belonging in School: a practical guide to creating inclusive policies in primary schools

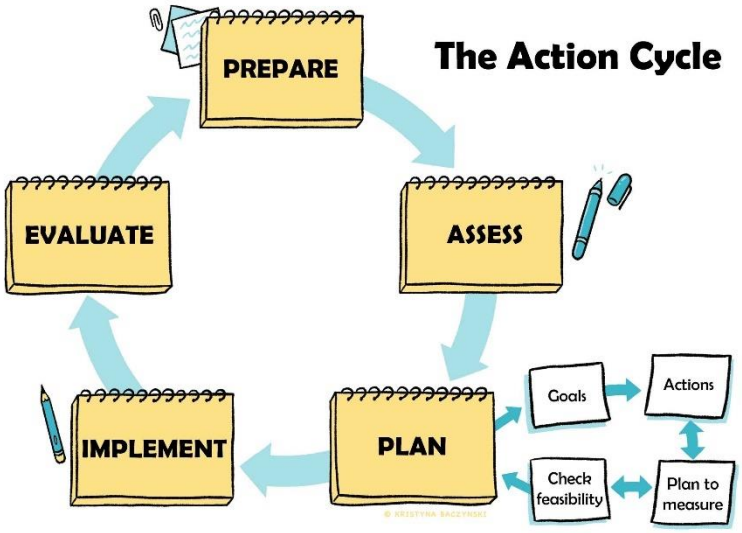
The *Belonging in School* initiative involved the creation of multiple freely-available online resources that were released to the public in September 2023. Importantly, these resources were created with self-sufficiency and free accessibility in mind. One concern we discussed early on in the process of creating these resources was that financial and staffing limitations would make it difficult for schools to incorporate a new, costly set of tools into their regular practices. Additionally, we wanted to give schools all the tools and strategies that they need in order to produce inclusion policies with their pupils, without having to dispatch members of our team to give instructional sessions and additional guidance. Clarifications about differences in inclusion provision across the nations of the UK are also provided on the website—while we designed these resources with all students and nations in mind, it is valuable to explicitly articulate these distinctions. The resources will become available through the following link on September 20th, 2023: https://inclusion.mrc-cbu.cam.ac.uk/

5.3.2.1 Practical guide and overview document

To introduce educators to themes surrounding neurodiversity and inclusion, we created a practical guide that provides schools with clear recommendations that they can select in order to begin improving their inclusion practices. We defined four primary characteristics of inclusive school policies. For a school policy to be inclusive, it must have: (1) a clear identification of goals and values, (2) a holistic conceptialisation of what inclusion means, (3) an ongoing process of planning and evaluation, and (4) a broad conceptualisation of which people and policies can create a school (for instance, activities outside of school, and interactions with school staff outside of the classroom).

The practical guide includes twelve practical recommendations for inclusion and four different strategies that allow schools to engage in the process of assessing pupils' needs (and instances where they are not being met), plan for action, implement inclusion policies, and evaluate the efficacy of inclusion efforts (see Figure 5.2). It also gives specific guidance about the tools and methods that can be used to engage in monitoring and evaluation. We describe policy production as a cyclical process where policies are constantly re-appraised, such that inclusion strategies remain aligned with pupils' needs and schools' local contexts.

Figure 5.2: Here, we illustrate the cyclical process of creating inclusive school policies. Illustration by Kristyna Baczynski.



The twelve practical recommendations we propose are framed as 'ideas to build on': concepts that could be acted upon continuously and in multiple different ways, depending on the local needs and values of the school. We recommend that schools:

1. Adopt a definition of educational inclusion that focuses on, or at least considers, pupils' sense of belonging in their school community.
2. Take a transdiagnostic approach to providing support.
3. Talk and teach about neurodiversity as an aspect of human diversity.
4. Talk and teach about the differences between equity and equality.
5. Improve staff awareness of sensory issues and their effects, and equip pupils with the knowledge and vocabulary that they need to talk about them.
6. Review school sensory environments (i.e. bright lights, visually overwhelming and distracting spaces, etc.), and potentially seek direct feedback about what could be improved.
7. Remove public rewards and punishments surrounding attendance.
8. Offer more flexibility about pupils' arrival to and departure from school.
9. Reduce barriers and sensory distress around school uniforms by making policies more flexible for all pupils.
10. Help staff feel equipped to support learners by investing in awareness and training related to inclusion.
11. Give all staff the opportunity to play a role in making their school inclusive.
12. Learn from neurodivergent staff members.

While the twelve recommendations listed above centred on *what* to do, the four strategies proposed in the executive document act as guides for *how* schools could begin to implement inclusive policies. These strategies, framed in terms of 'action cycles', give guidance on a process, rather than serving as step-by-step recipes for creating a certain results. The four strategies are:

1. Commitment to 'inclusion-as-belonging',
2. Participatory policy design,
3. Inclusion by design, and
4. Commitment to be a neurodiversity-affirming school.

To accompany the practical guide, we also wrote an 'overview' document which introduces relevant topics in inclusion and provides an explanation of how schools

might choose to engage with practical recommendations and inclusion strategies. Taken together, the practical guide and overview document give details about each of the strategies, provide a set of reflective questions for each stage in the action cycle, and link to further resources.

5.3.2.2 Slide decks

Lastly, in order to help schools facilitate teacher training and awareness sessions, we created slide decks that discuss neurodiversity, inclusion, and policy production strategies. These enable educators to gather and discuss their views on how to best begin the process of inclusive policy creation in their respective schools.

5.4 Discussion

In this final thesis chapter, I outlined two projects that I completed during my PhD. The first, which I completed alongside Duncan Astle, involved the organisation of a workshop that brought together academics and charity leaders, policymakers, educators, clinical practitioners, and individuals with lived experiences of neurodivergence to discuss barriers to learning and wellbeing in the UK. The second project, which I completed with Duncan Astle and Alyssa Alcorn, involved the creation of a set of online resources for schools. These resources help educators engage in cycles of learning, planning, implementing, and measuring the efficacy of inclusion-oriented school policies.

The Diverse Trajectories to Good Developmental Outcomes Workshop saw many productive discussions about the future of inclusion policies at the national and school levels. Following the event, we received a breadth of positive feedback for our attendees, who described the workshop as a chance to build cross-disciplinary connections and share their work with other stakeholders in education and social care. Throughout the workshop, attendees continually pushed for the importance of viewing socioeconomic deprivation as a primary cause of disparities in learning and wellbeing across the UK. This echoes contemporary research, which highlights the impacts of socioeconomic inequity on childhood educational attainment and later life outcomes (Morris et al., 2015; Volante et al., 2019). While school-level policy recommendations aid inclusion efforts at the local level, it is therefore essential to consider how more

primary resource constraints—including those that would be best targeted through national-level policies—might be limiting children's opportunities to cultivate wellbeing and engage in learning throughout school.

In starting the *Belonging in School* initiative, our aim was to create a comprehensive, actionable set of strategies that would enable schools to understand and implement inclusion policies at the local level. Previous studies indicate that engaging in the process of developing inclusive school policies has the capacity to yield positive results, even in socioeconomically-deprived contexts. These include improvements in teacher-parent relations, increased parental involvement in children's learning, and better learning outcomes (see Honingh et al., 2020 for review). Teacher training holds an important role in ensuring the long-term success of inclusive practices, which is why we made resources that provide thorough, practical descriptions of policy production strategies alongside existing use-cases in schools. Without imposing any specific rules about what inclusion *should* look like, *Belonging in School* empowers educators to construct inclusion policies that are directly informed by the needs of their students and the unique features of their local communities. We hope that, with time, many more educators make use of our resources, and that more children develop a sense of belongingness at school. This is, in our view, a strong first step to ensuring good developmental outcomes.

6 General Discussion

6.1 Overview

The title of this thesis, 'Reality Resists Classification', describes a theme that permeates the empirical chapters of this work. Neurodevelopment, in particular, seems to evade our efforts to create stark delineations, draw straightforward conclusions, and form sweeping generalisations. From the very beginning of development, each of us is deeply entangled with our surroundings—armed with our unique genetic profiles and life circumstances, we embark upon trajectories through which we mould, and are moulded by, our worlds. As we progress through time, so too do we encounter, and refine, different versions of ourselves. Each developmental trajectory is a testament to the labyrinthine complexity of biological phenomena, which never fail to humble us with elaborate motifs whenever we seek out simple, first-order explanations. Although we all possess some awareness of the fact that biological processes are informational, we are often surprised by the multiplicity of mechanisms that allow information to be transformed and adapted to different contexts. A grand challenge within developmental cognitive neuroscience, then, is to develop predictive frameworks that embrace complexity and multidimensionality, rather than ignoring the many counterfactuals that arise when we attempt to classify reality.

Identifying the specific attributes of a child's neurology that contribute to differences in cognition and behaviour presents a significant methodological challenge, but one of critical importance. Firstly, theoretical models that explain relationships between these features could be used to formulate fundamental principles of development itself, thus enabling us to grapple with some of the more difficult and foundational problems in biology. Perhaps even more importantly, studying behavioural, cognitive, and neurological development lends itself to our understanding of neurodevelopmental diversity, a primary characteristic of human populations with many societal implications. An estimated 15-20% of children fulfil the DSM-5's criteria for being diagnosed with neurodevelopmental conditions, which are clinically-defined profiles of cognition and behaviour that deviate significantly from those exhibited across the general population (Francés et al., 2022). For a variety of social and

systemic reasons, neurodevelopmental conditions are broadly linked to negative life outcomes, including worse physical wellbeing, lower educational attainment, and a higher risk of developing mental health difficulties (Warrilow et al., 2021; Heady et al., 2022). Studying neurodevelopmental conditions, as well as neurodevelopmental diversity as a whole, has a role to play in the cultivation of better scientific, educational, and social care frameworks. In the past, developmental cognitive neuroscientists have largely focused their efforts on studying the differences between those with neurodevelopmental conditions of interest and typically-developing controls. However, this is made difficult by the significant cognitive and behavioural heterogeneity that exists within, and between, diagnostic categories (Astle et al., 2022). Additionally, past methodological constraints have limited progress in the study how neuronal assemblies are shaped by their complex interactions with one another, and with the world, across development.

A number of recent theoretical and methodological advancements seek to overcome these challenges. Transdiagnostic research, as discussed in previous chapters, aims to overhaul the procedures by which data are collected, analysed, and interpreted in developmental cognitive neuroscience. Instead of relying on recruitment by diagnosis and case-control designs, transdiagnostic approaches can use diagnosis-agnostic recruitment strategies, broad, high-dimensional datasets, and bottom-up data analysis approaches to look for underlying relationships between cognition, behaviour, and the brain. Additionally, neuroconstructivist perspectives on development provide a new set of foundational principles on which more robust scientific theories can be established. In contrast to more traditional views, neuroconstructivism posits that neurological development is best described as probabilistic, rather than as something fully determined by genes that 'code for' different neuroanatomical functions (Astle et al., 2023). The interactions between the individual and the environment guide the functional organisation of the brain, and developmental processes are sensitive to ongoing changes across and within different phenomenological levels (genes, neurology, cognition, behaviour, environmental factors, etc.). As a result, neurodevelopment is characterised by multifinality and equifinality, whereby multiple similar trajectories can converge on different outcomes, and different trajectories can converge on similar outcomes, respectively. Small initial differences between individuals act as probabilistic anchors, which produce

progressively more path-dependent outcomes as development unfolds. Transdiagnostic approaches, which are concerned with studying subtle differences between individuals, therefore provide a set of methods which are consistent with the theoretical demands of neuroconstructivism.

The studies described in this thesis built on these theoretical and methodological trends by applying a transdiagnostic, complex systems approach to investigating the relationships between cognition, behaviour, and the brain. Methods from connectomics allowed us to characterise the topological properties of structural and functional brain networks. Additionally, Hidden Markov Modelling enabled us to infer features of spontaneous, transient neural dynamics in a developmental sample. Using these techniques, we addressed three key research questions:

1. Do the topological features of structural brain network connectivity differentiate children with elevated inattention and hyperactivity?
2. Do patterns of functional brain network connectivity differentiate the brains of children with elevated inattention and hyperactivity?
3. How are resting-state neural dynamics related to individual differences in behaviour and cognition?

Using data from the Centre for Attention, Learning, and Memory, we demonstrated the value of applying a connectomics approach to studying how neurological equifinality emerges in subgroups of highly inattentive and hyperactive children (n = 232). Additionally, using MEG data from a sample of children aged 8-13 (n = 46), we showed that it is possible to study individual differences in the spontaneous, transient neural dynamics that emerge at rest. Finally, to help improve the state of inclusive educational practices in the UK, I described ongoing work as part of a multidisciplinary team of researchers, charity leaders, educators, policymakers, and neurodivergent community partners, aimed at developing a set of freely-available online resources. In the following sections, I briefly outline the findings and outputs that enabled us to answer our key research questions. These results build on the current literature by providing further insight into how structural and functional brain networks differ along important dimensions of behaviour and cognition in childhood.

6.2 Do topological features of the structural connectome differentiate children with elevated inattention and hyperactivity?

We first investigated how differences in structural brain organisation, defined along three graph theoretic measures of network topology, related to features of behaviour and cognition in children with neurodevelopmental difficulties. Using EFA, we found that inattention and hyperactivity are best captured by one latent factor. PLS regression did not reveal any linear components that explained variability in measures of structural topology and behaviour. However, a further k-means clustering analysis indicated that there were two neural subtypes that characterised children with clinically-elevated levels of inattention and hyperactivity (n = 232). These subtypes, or clusters, were differentiated by their node-wise degree, clustering coefficient, and communicability values, suggesting that their brains differed in their modular structures and the general efficiency with which they could process information. While the clusters were comparable across behavioural measures, and not distinguished by gender, they differed in their cognitive abilities. Those in the lower-communicability group, Cluster 2, performed comparatively worse on tests of executive function and visuospatial reasoning.

This first study represented a significant step towards the use of transdiagnostic approaches in the study of structural brain differences among children with developmental difficulties. Interestingly, inattention and hyperactivity formed one common factor in our sample; while the literature remains divided about the separability of these constructs, some studies have argued that inattention and hyperactivity are often highly correlated among those with developmental difficulties (Toplak et al., 2009; Sokolova et al., 2016). These findings stand in contrast to clinical accounts of ADHD, which classify the condition into behavioural 'subtypes' (August & Garfinkel, 1989). However, using a transdiagnostic approach meant that we could perform analyses that were data-driven, rather than diagnosis-driven, thereby avoiding the issue of assuming anything about the separability of inattention and hyperactivity in our sample. However, something that limits the interpretability of this result is the fact that our single inattention/hyperactivity factor may, at least in part,

represent a more general dimension of behavioural difficulty. Holmes et al. (2021) previously found that the behavioural questionnaires in the CALM sample are characterised by a broad, general dimension ('P factor'), in addition to a more specific neurodevelopmental dimension which represents symptoms of inattention, hyperactivity, and executive function. Due to the intercorrelation of behavioural features in CALM, it is unlikely that our latent inattention/hyperactivity factor was limited to these two constructs. Although it is possible to partition the variance between factors in a multivariate model (hence the hierarchical structure of the 'P factor' model described previously), the model described in the first empirical chapter only examined whether there is a strong delineation between inattention and hyperactivity. As a result, the granularity of our model was limited.

Our findings about the demonstration of structural connectivity differences between the two clusters in our sample echoed trends previously observed in developmental connectomics. Although the study of communicability in relation to individual differences is relatively novel, our results corresponded to those from previous studies, which showed that cognitive difficulties may be associated with lower brain network communicability (Gilson et al., 2020; Lella & Vessio, 2021). Lower widespread communicability values could reflect the formation of fewer short paths between brain areas, which can act as a limitation on the flexibility with which brain network modules are able to communicate (Giedd & Rapoport, 2010; Park & Friston, 2016; Gallen et al., 2016; Hilger et al., 2017; Chaddock & Heyman, 2020). It is possible that communicability, as a measure of connectome organisation, serves as a good proxy measure for a variety of biologically-relevant features: for instance, the small-worldedness, rich-club organisation, and modularity of the brain (Rubinov & Sporns, 2010).

Neurological development is characterised by the gradual maximisation of efficient information transfer within a system that is energetically and spatially constrained (Bullmore and Sporns, 2012). As children engage with their environment over time, they form unique developmental trajectories that reflect trade-offs between the energy economy and computational capacity of the brain. Gradually, these trade-offs manifest into patterns of neurological, cognitive, and behavioural diversity across the population. In the first empirical chapter of this thesis, we demonstrated that there

are multiple potential 'paths' towards exhibiting elevated inattention and hyperactivity. Different profiles of structural brain organisation can nonetheless yield similar profiles of behaviour, suggesting the existence of neural-behavioural equifinality across development.

6.3 Does functional connectivity differentiate the brains of children with elevated inattention and hyperactivity?

In the next chapter of this thesis, we investigated differences in functional connectivity between two clusters of inattentive and hyperactive children identified in the first empirical chapter. Having found structural connectome differences between the two clusters, our aim was to uncover whether or not this translated into differences between the clusters' functional connectomes. We also tested whether the clusters differed on measures of internetwork connectivity between the default-mode, salience, and central executive networks, which had previously been implicated in the Triple Network Model of Neurodevelopmental Psychopathology (Menon, 2011). We did not detect any node-wise differences between the clusters' functional connectomes, despite finding that Cluster 1 has a higher average clustering coefficient at a global level. However, we did find a higher degree of functional connectivity between the default-mode and salience networks in Cluster 2.

Previous studies have highlighted the differences between structural and functional brain networks. Even though functional networks are constrained by their structural underpinnings, they exhibit a flexible divergence from structural networks when processing context-specific information. This makes behavioural adaptation possible (Park & Friston, 2013). Since the inattentive and hyperactive clusters identified in the first empirical chapter were differentiated by their cognitive ability and patterns of structural connectivity, rather than by their behaviour, then between-groups differences might be captured more robustly by structural, rather than functional, brain network characteristics. We did, however, find that Cluster 1 (which demonstrated higher cognitive ability than Cluster 2) had comparatively higher global clustering coefficient values. We had previously uncovered the same trend in the first empirical chapter. In the context of the functional connectome, nodal clustering coefficients reflect localised patterns of activation within interconnected groups of

brain regions. A global clustering coefficient represents a higher degree of local information processing across the brain, pointing to patterns of increased functional segregation.

Throughout development, the human connectome undergoes a process of gradual functional modularisation, described as a process that optimises for segregation/integration balance between brain networks (Solé-Padullés et al., 2016; Bruchhage et al., 2020). This process of functional segregation is characterised by substantial individual variability, with implications for the emergence of cognitive and behavioural diversity (Cortese et al., 2012; Sripada et al., 2014; Francx et al., 2015; Jones et al., 2022; Kardan et al., 2022). In particular, over-connectivity between the default-mode network and task-positive networks, like the central executive and salience networks, has been associated with a range of cognitive and behavioural difficulties (Choi et al., 2013; Sripada et al., 2014; Kessler et al., 2016; Abbott et al., 2016; Mills et al., 2018; Hilger et al., 2019; Wang et al., 2021). In this chapter, we found that Cluster 2, which demonstrated lower cognitive ability compared to Cluster 1, also had comparatively higher levels of connectivity between the DMN and SN. As discussed previously, this finding aligns with and contributes to the literature surrounding the so-called Triple Network Model of Developmental Psychopathology. However, it is important to note that divergent patterns of functional brain network development could emerge as a result of numerous different underlying processes, and little work has been done to investigate the causal paths that could lead to over-connectivity between the default-mode and task-positive networks.

6.4 How are resting-state neural dynamics related to individual differences in behaviour and cognition?

One limitation of the methods used in the first empirical chapter the fact that time-averaged functional connectome models only provide a static representation of neural activity. However, a broad range of studies indicate that the spontaneous, transient dynamics of neural activity capture important features of information processing, thus making them relevant to the study of behavioural and cognitive differences (Rabinovich et al., 2008; Nachstedt & Tetzlaff, 2017; Greene et al., 2023). In the third empirical chapter, our aim was to investigate how properties of resting-state neural

dynamics varied with measures of cognitive ability and behavioural difficulty. Using a multivariate Gaussian Hidden Markov Model, we inferred a seven-state model of neural dynamics in a developmental sample aged 8-13 (n = 46). The spatial topographies of multiple prominent resting-state networks—including the DMN, fronto-parietal, and multiple sensory and somatomotor networks—were represented across the HMM. These states differed in their temporal properties. Additionally, we found that cognitive ability was positively related to entropy rates and switching rates, which represented the complexity of participants' state time-courses. Moreover, we found specific relationships between cognitive ability and certain states. Transitions into, and time spent within DMN-heavy states, was associated with lower cognitive ability, whereas the opposite was true of states with more fronto-parietal and sensory network activation profiles. We did not, however, find any relationships between resting-state dynamics and other neurodevelopmental features of interest.

A number of previous studies have highlighted the positive associations between state switching, time-course entropy, and cognitive ability (Medaglia et al., 2018; Taghia et al. 2018; Reddy et al., 2018; Saxe et al., 2018; Wang, 2021; Thiele et al., 2023). Additionally, there have been a number of links established between cognitive ability and certain states of brain activity. Previous research indicates that the activation and spatiotemporal segregation of fronto-parietal networks enables the enhancement of executive function across childhood (Keller et al., 2023), whereas the over-activation and hyper-integrated spatiotemporal patterning of the DMN is related to cognitive and behavioural difficulties (Cortese et al., 2012). Our findings echo these previous results while putting them into the context of neural dynamics: DMN states were negatively associated, and fronto-parietal states were positively associated, with cognitive ability in our sample. Additionally, our findings across Chapters 2 and 3 complement each other, with the DMN implicated in group-level differences in cognitive ability. More work is needed to create coherent models of how DMN connectivity, as well as the activation of dynamical states that involve the DMN, contribute to differences in childhood cognitive development.

We were surprised to find no significant effects between age, gender, behaviour, and HMM state measures. It is possible that this was due to the limited age range of our sample. Little is currently known about how resting-state neural dynamics change

across the human lifespan, and it is therefore difficult to draw conclusions about what kinds of age-related effects should be expected in a developmental sample. Since we believe this is the first study to use HMMs to infer neural dynamics in a sample of children, more research—with larger samples that include broader age ranges—would be a useful next step for the field.

Across the first three empirical chapters of this thesis, we found significant relationships between cognition and elements of brain structure, function, and dynamics. We did not find any robust brain-behaviour relationships. Previous work has highlighted the seemingly elusive nature of brain-behaviour associations, arguing that variations between contexts, people, and studies are the result of small sample sizes (e.g. Marek et al., 2020), irreproducible methodological reporting (Guo et al., 2014), and variability in data preprocessing techniques (Botvinik-Nezer et al., 2020). However, it is possible that the variability of brain-behaviour findings emerges from a much more fundamental limitation of research in cognitive neuroscience: the fact that the psychological phenomena, themselves, are ill-defined. Westlin et al. (2023) argue that three primary assumptions about behaviour drive theoretical misconceptions in cognitive neuroscience. The first is that a category of behavioural events (e.g. hyperactivity) is caused by a single psychological process that is implemented by a dedicated neural process. The second is that the dedicated neural process in question *uniquely* maps onto the psychological category, and that this mapping generalises across people and contexts. The third is the 'independence assumption', which leads researchers to act as if neural processes function independently of contextual factors, including the body. Despite the concession that contextual factors moderate certain brain-behaviour relationships, many studies are conducted on the assumption that the mapping between psychological categories and their respective neural processes is the same across individuals.

As mentioned in the General Introduction, this set of assumptions fails to recognise the fact that equifinality and multifinality characterise the relationships between different levels of analysis in cognitive neuroscience. Although it is tempting to assume that there is a consistent neural process that underpins every behavioural tendency, this is far from the case. It would be similarly outrageous to assume that every *external* stimulus has a corresponding behavioural response that is invariant between

individuals. Rather, behaviour emerges as a complex ensemble of signals from the brain, body, and world. This is also true of cognition (Hedge et al., 2016); however, there are multiple reasons why measures of cognitive ability more reliably track neurological differences between individuals.

Throughout the General Introduction, as well as the first two empirical chapters, the reader will have become acquainted with the idea that general measures of behaviour are noisy. This is particularly true in the case of children, for whom behavioural inventories are completed by parents and/or teachers (who often have very different experiences with, and views concerning, a child's behavioural tendencies). Measures of cognitive ability, despite appearing more 'abstract' and removed from everyday experiences than behavioural meausres, are more conducive to assessing consistent differences between individuals, since they can measure more clearly-defined traits through testing (Boogert et al., 2018). Behavioural questionnaires provide a coarse, second-order measure of how a child might act in a particular environment, whereas cognitive assessments completed by the child allow for a more reliable and precise understanding of general cognitive ability. Moreover, general cognitive ability (commonly summarised as the 'g factor') persists across the lifespan and generalises across contexts and stimuli (Ree & Carretta, 2022). Cognitive measures are therefore more stable than behavioural measures—they are more reliable, less noisy, and they capture psychological processes with greater context-invariance. While a more precise line of research is needed to determine whether the neural processes that support behaviour are fundamentally more heterogeneous than those which support cognitive ability, variability in brain-behaviour relationships—along with the relative noisiness of behavioural data—could help explain why we found brain-cognition, but not brain-behaviour, associations in this thesis.

6.5 Bridging the evidence-policy gap: creating inclusive educational frameworks in schools

The final component of this thesis was dedicated to outlining a project that focused on improving inclusive education practices in UK schools. First, we organised the Diverse Trajectories to Good Developmental Outcomes Workshop, which brought together leaders from a variety of disciplines in order to outline the barriers to learning and

wellbeing in the UK's educational and social care systems. Throughout the workshop, attendees highlighted the importance of challenging norms surrounding diagnosis-dependent inclusion measures and recalibrating school policies to feature universally-beneficial practices. Although systemic problems surrounding economic precarity were identified as primary barriers to both learning and wellbeing, workshop attendees also discussed ways in which schools could implement better practices at the local level. After collecting feedback from this workshop, we then created a set of resources for schools called 'Belonging in School: a practical guide to creating inclusive policies in primary schools', which will be freely-available online in late September 2023. These resources—which come in the form of an informational document, practical guide, and slide decks—were designed to help schools engage in the process of creating inclusive policies alongside pupils, families, and wider school communities. Rather than being prescriptive about what inclusion should look like, we wanted to empower educators to construct inclusion policies that are directly informed by the needs of their students and the unique attributes of their local communities. We believe that efforts such as these represent an important contribution developmental scientists can make to the improvement of children's learning and wellbeing outcomes.

6.6 Limitations

There are a number of constraints that limit the generalisability of the studies described in this thesis.

Firstly, these studies relied on data that were collected at one timepoint, meaning that longitudinal effects could not be captured. While these more 'static' data are valuable for capturing effects between individuals, we could not track how development unfolds *across* individuals' lifespans. Therefore, we could not make any concrete inferences about developmental trajectories as a whole. Another potential limitation of our dataset was its sample size; a growing number of methodological reviews recommend the use of datasets with hundreds, if not thousands, of participants (e.g. Marek et al., 2022). Although having a larger sample would have enabled us to generalise our findings with greater confidence, we believe that all of our studies were focused enough in their scope that they could capture important neurodevelopmental effects.

Secondly, the empirical studies presented in this thesis had inattention and hyperactivity as their primary behavioural features of interest. However, high inattention and hyperactivity levels are associated with a lower quality of neuroimaging data due to high levels of movement (Kong et al., 2014; Thompson et al., 2021; Tansey et al., 2022). Therefore, it is possible that children with the highest levels of inattention and hyperactivity were excluded early on in our preprocessing pipelines. This factor reduces the generalisability of our findings to children who can remain still enough to undergo a brain scan.

Thirdly, studying behavioural inattention and hyperactivity is made difficult by the fact that parent-report questionnaires for these measures, such as the Strengths and Difficulties Questionnaire, can be unreliable, and are often inconsistent with teacher reports (Hartman et al., 2007; Murray et al., 2018; Murray et al., 2019). Indeed, inattention and hyperactivity behaviours are extremely context-dependent, and parent-reports only provide a snapshot of what a child's behaviour is like in the home environment (Kofler et al. 2016). There are differences between every parent's idea of what high inattention and hyperactivity look like, meaning that it is challenging to extract an objective picture of children's behavioural difficulties. Our research, like other research investigating brain-behavioural relationships, must be appraised with this in mind.

Fourthly, it is worth noting that brain network models, such as connectomes, are heavily simplified summaries of structural and functional connectivity patterns in the brain. To study something as complex as the brain, it is necessary to achieve a balance pragmatic reductionism and the representation of salient neurological features. In the studies described throughout this thesis, we used binarised 100-node and 38-node connectomes to represent features of brain network topology and dynamical state activity, respectively. Binarised connectomes, while useful for capturing the topological features of brain networks, are limited by their inability to represent the strength of connections between regions. In a recent study, Akarca et al. (2023b) demonstrated that weighted generative network models can be used to capture the dynamic strengthening or weakening of connections over time, and therefore simulate critical neurodevelopmental processes in greater detail. Additionally, using a 38-node parcellation to represent spatial patterns of activation in HMM states in the third

empirical chapter meant that the spatial resolution of these states was relatively coarse. Although a low-rank parcellation enabled us to perform corrections for MEG signal leakage, there are certainly advantages to being able to use a finer-grained parcellation. Inevitably, the use of models in developmental cognitive neuroscience allows us to reduce the dimensionality of our subject matter so that we can build testable and interpretable theoretical frameworks. However, we must acknowledge that in creating simplified models of the brain—for instance, through parcellation and binarisation—we lose information that is relevant to the study of neurological development.

Lastly, one of the biggest constraints on the interpretability of our findings is the fact that they are associational—we cannot assume causality across any of the relationships found. Thus, it is not clear how concurrent neurological, cognitive, and behavioural differences emerge. This problem is related to our previous point about not being able to make longitudinal inferences about the effects mentioned in this thesis. While it is likely that neurology, cognition, and behaviour all exert a causal influence one another over time, the dynamics of these influences across time is something that would best be captured on an individual level and compared across individuals. Longitudinal studies and the construction of more refined, causally-tractable computational models will enable researchers to investigate how specific levels of analysis (e.g. brain function and cognitive ability) interact across time, or in response to perturbation. Some suggestions for addressing this perennial issue in developmental cognitive neuroscience are discussed in the next section.

6.7 Future Directions

Developmental cognitive neuroscience is in its infancy. The research available to date has primarily taken a diagnosis-informed view of childhood neurodevelopmental differences. As transdiagnostic approaches become more widely used, and larger developmental samples are made available for analysis, it is likely that the field will gain a more refined understanding of the relationships between dimensions of cognition, behaviour, and neurobiology. Additionally, the collection of longitudinal data will allow researchers to study how biological and environmental factors interact to produce unique trajectories of neurodevelopment. Going forward, it is vital that

associations between these factors are interrogated on a causal basis, such that we can begin to understand the directionality of developmental effects.

Crucial to this process will be the application of more advanced computational models to the study of the developing brain. For instance, neural networks can be initialised and trained to perform cognitive tasks, enabling researchers to study the causal effects of model adjustments and perturbations. A wide range of neural network architectures can be applied to the challenges of extracting fundamental features of neurodevelopment from large, multidimensional datasets (Goodhill, 2018; Zhao et al., 2022) and modelling the relationships between different levels of analysis (Achterberg et al., 2022). By using neural network models, developmental cognitive neuroscientists can target all three levels of analysis famously put forward by David Marr in 1982: representations at the 'implementation' level can be achieved through the study of neurobiology itself, whereas representations at the 'algorithmic' and 'computational' levels can be reached through the manipulation of neural network learning rules and architectures. There is no doubt that recent innovations in machine learning techniques, as well as the expansion of computational resources, jointly represent a critical opportunity to build developmental theories that bridge the gaps between cognition, behaviour, and the brain.

Lastly, and perhaps most importantly, developmental cognitive neuroscientists should strive to translate their findings for policymakers, clinical practitioners, and educators. This can be achieved through scientific communication, but as we demonstrated in the final chapter of this thesis, it is also possible for neuroscientists to participate directly in the creation of resources and policies that promote inclusive, neurodiversity-informed practices. Developmentalists should embrace their advantageous epistemic positions, share their knowledge widely, and aim to give back to the communities whose experiences they study.

7 Conclusion

In conclusion, we highlight the importance of using a transdiagnostic, complex-systems oriented approach to studying neurodevelopmental differences in childhood. We illustrate our use of data-driven methods like exploratory factor analysis, PLS regression, k-means clustering, and Hidden Markov Modelling, combined with connectomic models, in the process of uncovering the underlying relationships between behaviour, cognition, and multiple features of neurological structure and function. Structural and functional brain network organisation, as well as spontaneous, transient patterns of resting-state neural activity, were primarily related to individual differences in cognitive ability. This work lays the foundation for future investigations into how neurological heterogeneity translates into the emergence of cognitive and behavioural diversity. We believe that the use of larger samples, longitudinal approaches, and more refined computational methods will help developmental cognitive neuroscientists reach a better understanding of the relationships between cognitive, behavioural, and neurological phenomena. Additionally, we urge members of the scientific community to engage in more collaborative projects with educators, practitioners, and policymakers, which will enable the creation of more inclusive educational and social care policies.

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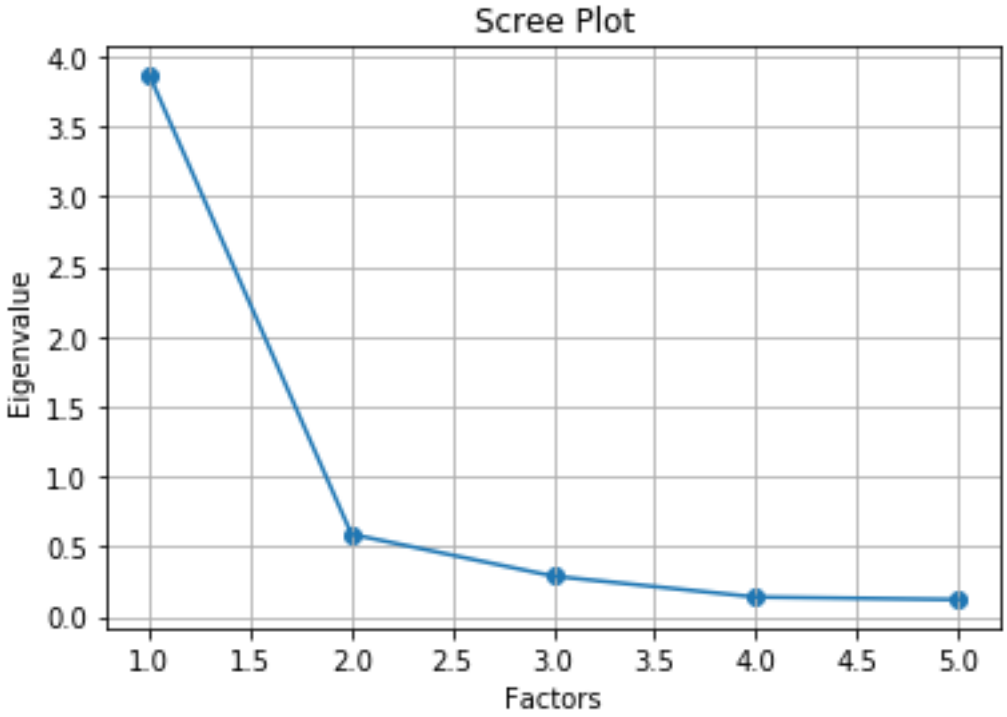
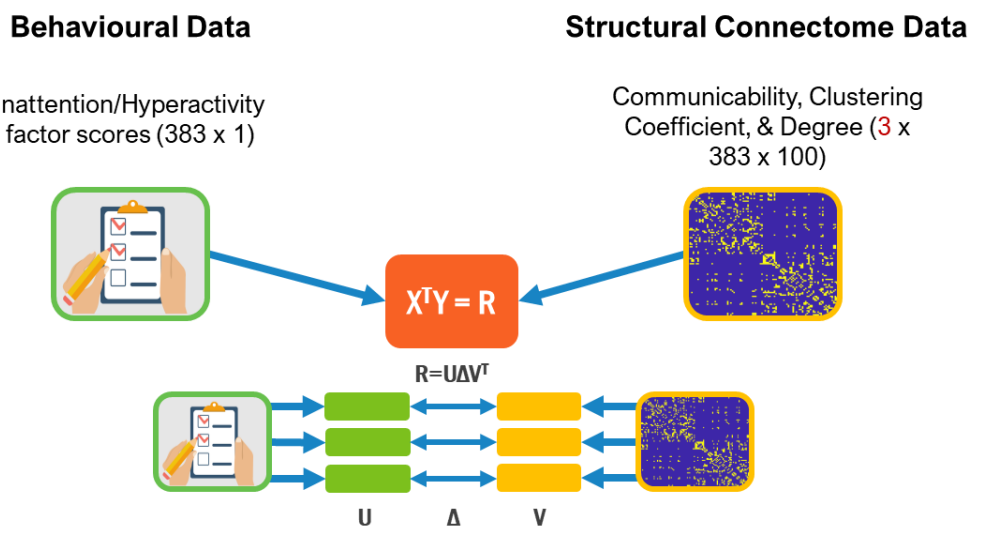
Appendix A

Scree plot displaying eigenvalues corresponding to n-factor solutions from our Exploratory Factor Analysis.



Appendix B

Schematic representation of Partial Least Squares (PLS) Regression analysis used to compare inattention/hyperactivity factor scores and nodal degree, clustering coefficient, and communicability values across the entire sample (n = 383).



Schematic of Partial Least Squares Regression (PLS) Technique

Appendix C

Correlations between behavioural questionnaire subscales included in our Exploratory Factor Analysis (EFA).

	SDQ Hyperactivity	Conners Inattention	Conners H/I	Brief WM	Brief Monitor
SDQ Hyperactivity					
Conners Inattention	0.84655				
Conners H/I	0.85327	0.70585			
Brief WM	0.79683	0.88146	0.61670		
Brief Monitor	0.76375	0.77777	0.70352	0.77608	

Appendix D

Alternative Exploratory Factor Analysis (EFA) solutions based on the specification of 1 versus 2 factors, oblique rotation vs. no rotation, and the inclusion vs. exclusion of BRIEF subscales.

One factor, no rotation, all questionnaires included (ORIGINAL)

Variance explained by each factor: **77.60%**

Factor loadings for questionnaires

Questionnaire	*Factor 1*	*Factor 2*	*Uniquenesses*
SDQ	-0.94185013	N/A	0.112918
Conners I	-0.9262791	N/A	0.142007
Conners H/I	-0.80319169	N/A	0.354883
BRIEF WM	-0.87529597	N/A	0.233857
BRIEF Monitor	-0.85172229	N/A	0.274569

Two factors, no rotation, all questionnaires included

Variance explained by each factor: **79.41%, 7.88%**

Factor loadings for questionnaires

Questionnaire	*Factor 1*	*Factor 2*	*Uniquenesses*
SDQ	0.928529	0.0936231	0.129069
Conners I	0.92021	-0.181796	0.120164
Conners H/I	0.869468	0.489792	0.00412894
BRIEF WM	0.896368	-0.330074	0.0875766
BRIEF Monitor	0.838152	-0.059217	0.293995

Two factors, oblique rotation, all questionnaires included

Variance explained by each factor: **50.93%, 25.54%**

Factor loadings for questionnaires

Questionnaire	*Factor 1*	*Factor 2*	*Uniquenesses*
SDQ	0.538	0.472682	0.487127
Conners I	0.868253	0.095573	0.237002
Conners H/I	0.0130637	0.988693	0.0223147
BRIEF WM	1.03245	-0.114659	-0.079101
BRIEF Monitor	0.661027	0.231495	0.509453

One factor, no rotation, BRIEF Working Memory excluded

Variance explained by each factor: **77.93%**

Factor loadings for questionnaires

Questionnaire	*Factor 1*	*Factor 2*	*Uniquenesses*
SDQ	-0.962216	N/A	0.0741402
Conners I	-0.882211	N/A	0.221704
Conners H/I	-0.846902	N/A	0.282758
BRIEF Monitor	-0.834165	N/A	0.304169

Two factors, no rotation, BRIEF Working Memory excluded

Variance explained by each factor: **79.88%, 5.90%**

Factor loadings for questionnaires

Questionnaire	*Factor 1*	*Factor 2*	*Uniquenesses*
SDQ	0.939925	0.0830465	0.109644
Conners I	0.932214	-0.348953	0.00920888
Conners H/I	0.879542	0.324247	0.121269
BRIEF Monitor	0.818061	-0.0463878	0.328624

Two factors, oblique rotation, BRIEF Working Memory excluded

Variance explained by each factor: **38.62%, 33.40%**

Factor loadings for questionnaires

Questionnaire	*Factor 1*	*Factor 2*	*Uniquenesses*
SDQ	0.653835	0.339759	0.457064
Conners I	0.000497087	0.994996	0.00998239
Conners H/I	0.982204	-0.0581863	0.0318894
BRIEF Monitor	0.390788	0.476748	0.619995

One factor, no rotation, BRIEF Monitor excluded

Variance explained by each factor: **79.01%**

Factor loadings for questionnaires

Questionnaire	*Factor 1*	*Factor 2*	*Uniquenesses*
SDQ	-0.963606	N/A	0.0714644
Conners I	-0.929649	N/A	0.135753
Conners H/I	-0.794772	N/A	0.368337
BRIEF WM	-0.857936	N/A	0.263946

Two factors, no rotation, BRIEF Monitor excluded

Variance explained by each factor: **81.30%, 7.93%**

Factor loadings for questionnaires

Questionnaire	*Factor 1*	*Factor 2*	*Uniquenesses*
SDQ	0.950288	0.157984	0.0719942
Conners I	0.918348	-0.161175	0.130659
Conners H/I	0.835694	0.376507	0.159858
BRIEF WM	0.898399	-0.352583	0.0685649

Two factors, oblique rotation, BRIEF Monitor excluded

Variance explained by each factor: **41.59%, 37.05%**

Factor loadings for questionnaires

Questionnaire	*Factor 1*	*Factor 2*	*Uniquenesses*
SDQ	0.3115	0.706538	0.403772
Conners I	0.74474	0.232262	0.391417
Conners H/I	-0.0619382	0.962374	0.0699996
BRIEF WM	1.00412	-0.052574	-0.0110162

Appendix E

Silhouette values for n-cluster solutions from k-means clustering performed on the entire sample (n = 383). Multivariate outliers were identified using MATLAB's robustcov function. After these outliers were excluded, nodewise graph measure data from n = 379 participants were included in the k-means clustering procedure.

Number of Clusters	***Silhouette Coefficient***	***Cluster sizes***
2	0.6028	n = 216, 163
3	0.5673	n = 141, 139, 99
4	0.5262	n = 98, 70, 100, 111
5	0.4745	n = 64, 70, 81, 93, 71
6	0.5031	n = 70, 77, 63, 85, 25, 59
7	0.5032	n = 65, 56, 24, 66, 59, 70, 39
8	0.4719	n = 40, 64, 63, 75, 28, 56, 28, 25
9	0.5141	n = 61, 26, 15, 47, 42, 42, 51, 53, 42

Appendix F

Silhouette values for alternative n-cluster solutions for inattentive/hyperactive sample (n = 232).

Number of Clusters	*Silhouette Coefficient*	*Cluster sizes*
2	**0.6808**	**n = 109, 123**
3	0.5860	n = 89, 84, 59
4	0.5175	n = 67, 90, 45, 30
5	0.4716	n = 44, 63, 45, 37, 43
6	0.4699	n = 42, 38, 39, 40, 39, 34
7	0.5167	n = 35, 15, 38, 27, 41, 50, 26
8	0.4594	n = 19, 32, 42, 30, 30, 32, 17, 30
9	0.4997	n = 18, 29, 11, 48, 33, 25, 25, 35, 8

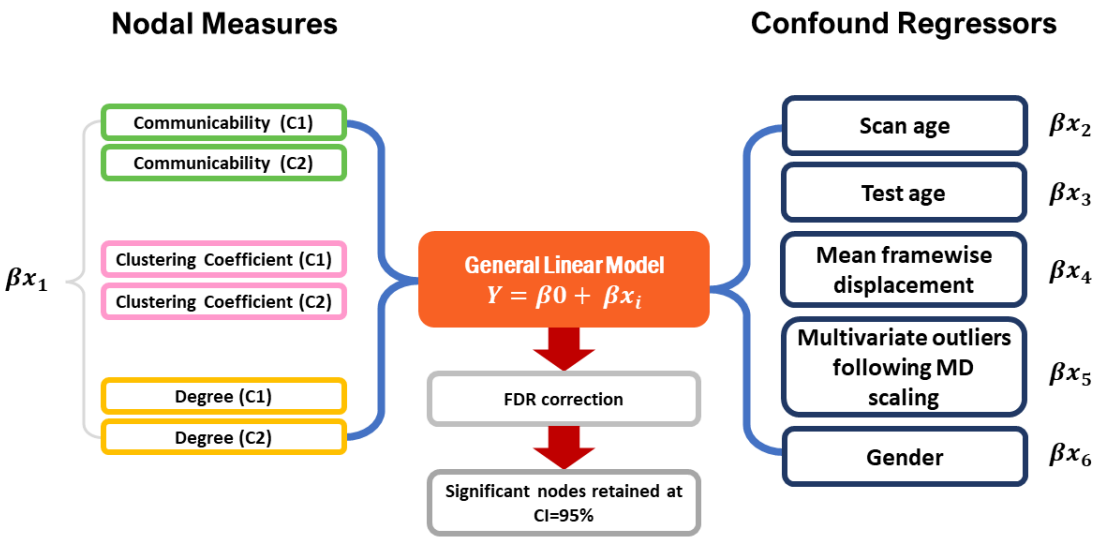
Appendix G

Behavioural (in blue) and cognitive (in red) characteristics of inattentive/hyperactive children (Conners Questionnaire scores >60; n = 232) compared to children without elevated inattention and hyperactivity (Conners Questionnaire scores <60; n = 151), in addition to the full sample (n = 383). Values are displayed in 'Mean (SD)' format. ANOVAs were performed to compare the three groups on 19 measures of behaviour and cognition.

Measure	*Total sample (n = 383)*	*I/H subsample (n = 232)*	*Discarded sample (n = 151)*	*F*	*p*
SDQ (Total)	15.87 *(8.66)*	20.30 *(6.92)*	6.14 *(5.21)*	95.432	**1.148×10^{-37}**
SDQ (Emotion Regulation)	3.71 *(2.84)*	4.48 *(2.80)*	1.87 *(2.15)*	22.863	**2.294×10^{-10}**
SDQ (Conduct)	2.80 *(2.38)*	3.73 *(2.38)*	1.14 *(1.35)*	50.060	**3.871×10^{-21}**
SDQ (Hyperactivity)	6.49 *(3.19)*	8.49 *(1.72)*	1.96 *(1.93)*	163.207	**1.313×10^{-59}**
SDQ (Peer Problems)	2.87 *(2.67)*	3.61 (2.70)	1.18 *(1.58)*	23.443	**1.329×10^{-10}**
SDQ (Prosocial)	7.31 *(2.22)*	6.80 *(2.22)*	8.61 *(1.71)*	16.753	**7.609×10^{-08}**
Conners (Inattention)	75.00 *(16.30)*	83.82 *(7.46)*	47.73 *(6.58)*	114.137	**5.401×10^{-44}**
Conners (Hyperactivity/Impulsivity)	69.71 *(17.23)*	81.38 *(9.64)*	48.21 *(5.85)*	212.225	**8.005×10^{-74}**
Conners (Learning Problems)	70.31 *(15.91)*	75.96 *(12.21)*	52.79 *(13.11)*	41.0102	**1.243×10^{-17}**
Conners (Executive Function)	70.27 *(15.70)*	77.58 *(10.45)*	48.57 *(9.04)*	77.094	**3.587×10^{-31}**
Conners (Aggression)	59.85 *(16.48)*	65.61 *(17.21)*	49.25 *(7.38)*	40.432	**2.104×10^{-17}**
Conners (Peer Relations)	68.91 *(18.67)*	74.96 *(17.36)*	53.72 *(13.22)*	32.527	**2.863×10^{-14}**
WASI-II	46.01 *(10.14)*	44.23 *(9.46)*	51.42 *(10.52)*	10.249	**4.050×10^{-5}**
Peabody Picture Vocabulary Test	93.65 *(16.67)*	92.68 *(9.37)*	109.81 *(16.65)*	0.724	0.485
PhAB (Alliteration)	103.59 *(9.50)*	101.64 *(16.21)*	97.26 *(8.22)*	10.842	**2.278×10^{-5}**
AWMA (Digit Recall)	96.58 *(17.28)*	88.75 *(14.00)*	104.49 *(17.02)*	8.921	**0.0001**
AWMA (Dot Matrix)	94.60 *(16.23)*	93.18 *(15.98)*	102.75 *(15.22)*	4.163	**0.0159**
AWMA (Digit Back)	95.77 *(14.30)*	91.63 *(15.88)*	104.68 *(14.61)*	18.174	**1.963×10^{-8}**
AWMA (Mr X)	99.85 *(16.06)*	92.75 *(12.86)*	105.71 *(16.67)*	13.049	**2.685×10^{-6}**

Appendix H

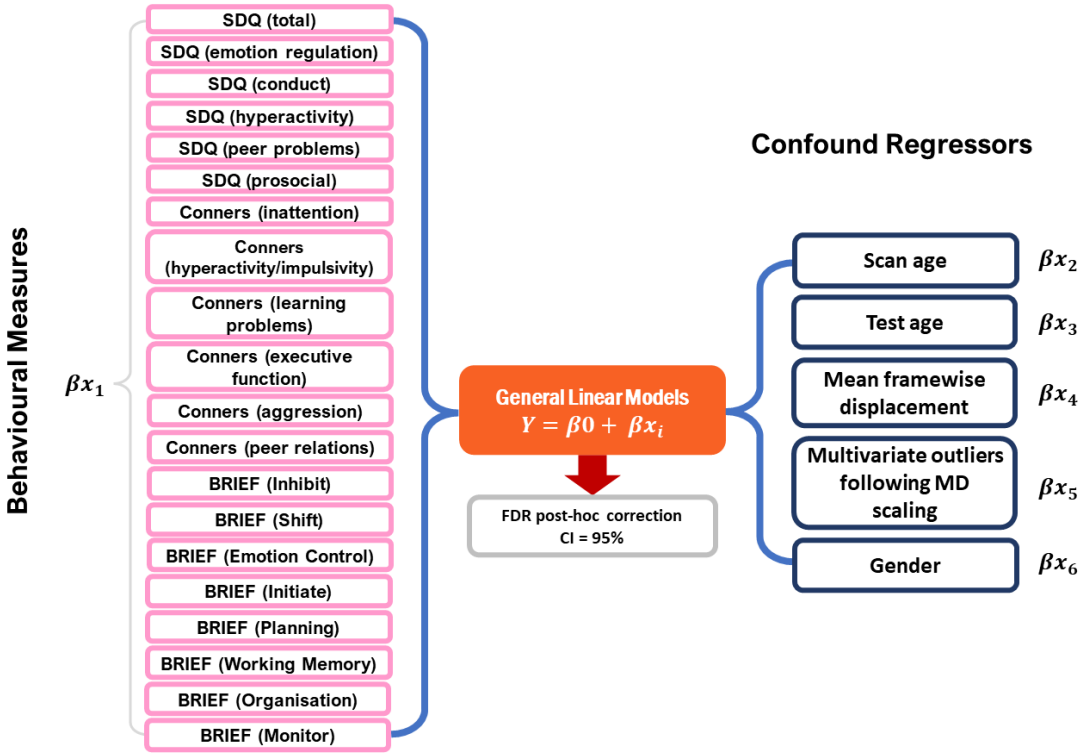
Schematic representation of General Linear Model (GLM) analyses comparing behavioural questionnaire scores between the inattentive/hyperactive clusters.



Schematic of GLMs assessing nodewise measure differences between clusters of inattentive and hyperactive children

Appendix I

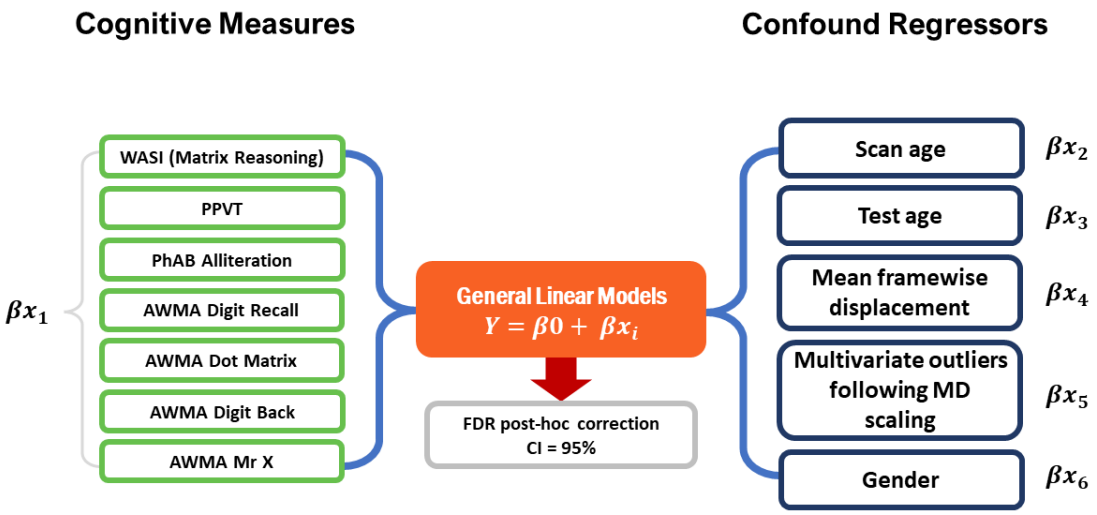
Schematic representation of General Linear Model (GLM) analyses comparing behavioural questionnaire scores between the inattentive/hyperactive clusters.



Schematic of GLMs assessing behavioural differences between clusters of inattentive and hyperactive children

Appendix J

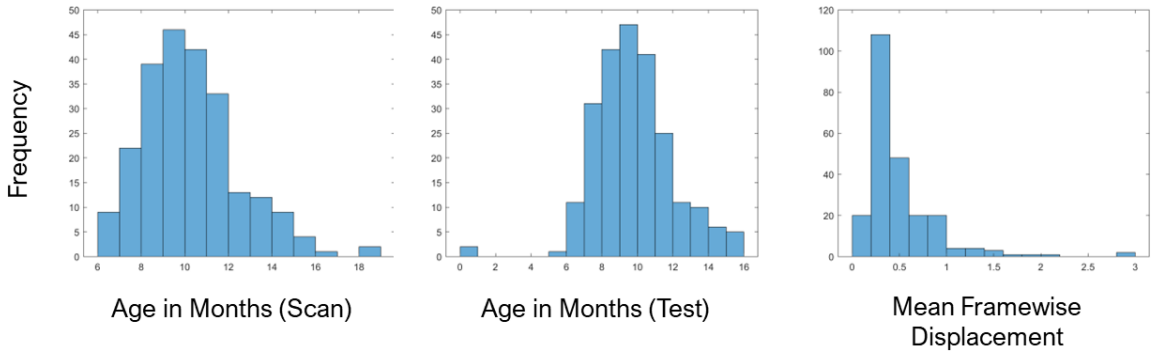
Schematic representation of General Linear Model (GLM) analyses comparing cognitive test scores between the inattentive/hyperactive clusters.



Schematic of GLMs assessing cognitive differences between clusters of inattentive and hyperactive children

Appendix K

Histograms displaying distributions of confound regressor values (mean framewise displacement and age) across the inattentive/hyperactive sample (n = 232).



Frequency distributions of Age and Mean Framewise Displacement across inattentive and hyperactive children (n = 232)

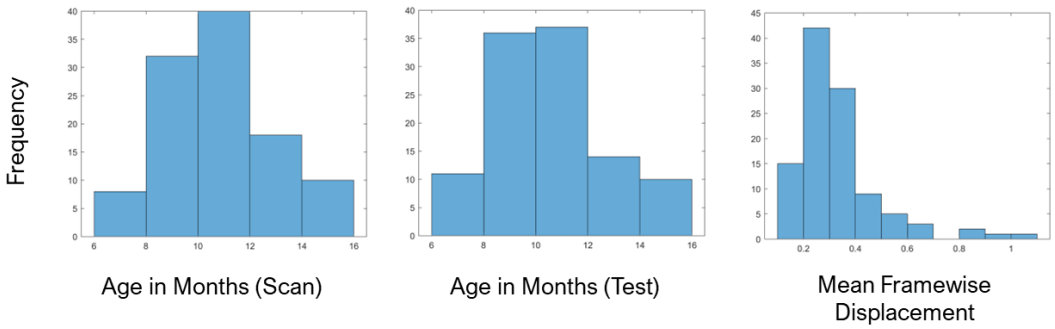
Appendix L

Incidence of neurodevelopmental and mental health diagnoses in Clusters 1 (n = 109) and 2 (n = 123).

Diagnosis	*Cluster 1*	*Cluster 2*
Diagnosis present	49 (44.95%)	49 (39.84%)
ADHD (Inattentive)	0	0
ADHD (Combined)	30 (27.5%)	30 (24.39%)
ADHD (Hyperactive)	1 (0.92%)	1 (0.8%)
ADHD (Medicated)	19 (17.43%)	19 (15.45%)
Possible ADHD	13 (11.93%)	13 (10.57%)
Dyslexia	10 (9.17%)	10 (8.13%)
Dyspraxia	4 (3.67%)	4 (3.25%)
Dysgraphia	0	0
Dyscalculia	0	0
FASD	0	0
GGD	1 (0.92%)	1 (0.8%)
SAD	0	0
Depression	0	0
Autism	8 (7.34%)	8 (6.5%)
PDA	0	0
Tourette Syndrome	2 (1.83%)	2 (1.6%)
DAMP	0	0
Anxiety	1 (0.92%)	1 (0.8%)
OCD	0	0
SPD	0	0
Language Disorder	0	0
Conduct Disorder	1 (0.92%)	0
ODD	0	0
Epilepsy	0	0
Anorexia Nervosa	0	0

Appendix M

Histograms displaying distributions of confound regressor values (mean framewise displacement and age) across the inattentive/hyperactive sample (n = 110).



Frequency distributions of Age and Mean Framewise Displacement across inattentive and hyperactive children (n = 110)

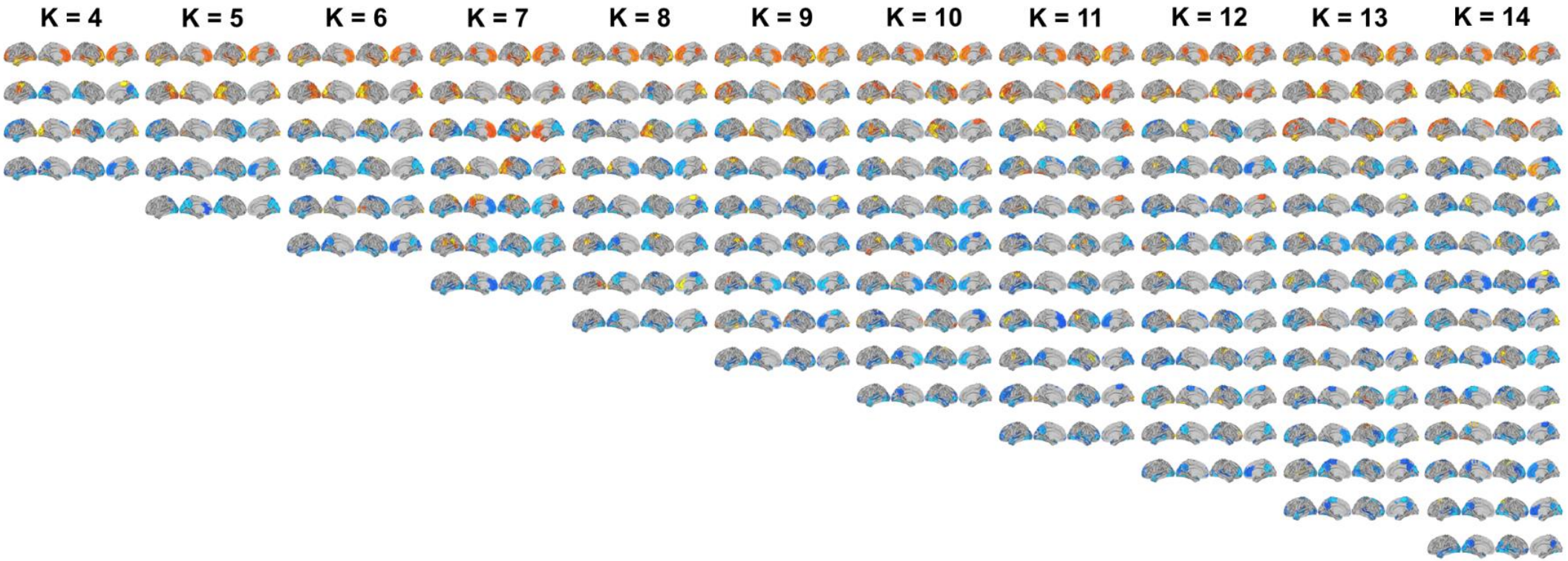
Appendix N

Incidence of neurodevelopmental and mental health diagnoses in Clusters 1 (n = 50) and 2 (n = 60).

Diagnosis	*Cluster 1*	*Cluster 2*
Diagnosis present	22 (44%)	22 (36.67%)
ADHD (Inattentive)	0	0
ADHD (Combined)	11 (22%)	11 (18.33%)
ADHD (Hyperactive)	1 (2%)	1 (1.67%)
ADHD (Medicated)	8 (16%)	8 (13.33%)
Possible ADHD	6 (12%)	6 (10%)
Dyslexia	6 (12%)	6 (10%)
Dyspraxia	2 (4%)	2 (3.33%)
Dysgraphia	0	0
Dyscalculia	0	0
FASD	0	0
GGD	1 (2%)	1 (1.67%)
SAD	0	0
Depression	0	0
Autism	6 (12%)	6 (10%)
PDA	0	0
Tourette Syndrome	0	0
DAMP	0	0
Anxiety	0	0
OCD	0	0
SPD	0	0
Language Disorder	0	0
Conduct Disorder	0	0
ODD	0	0
Epilepsy	0	0
Anorexia Nervosa	0	0

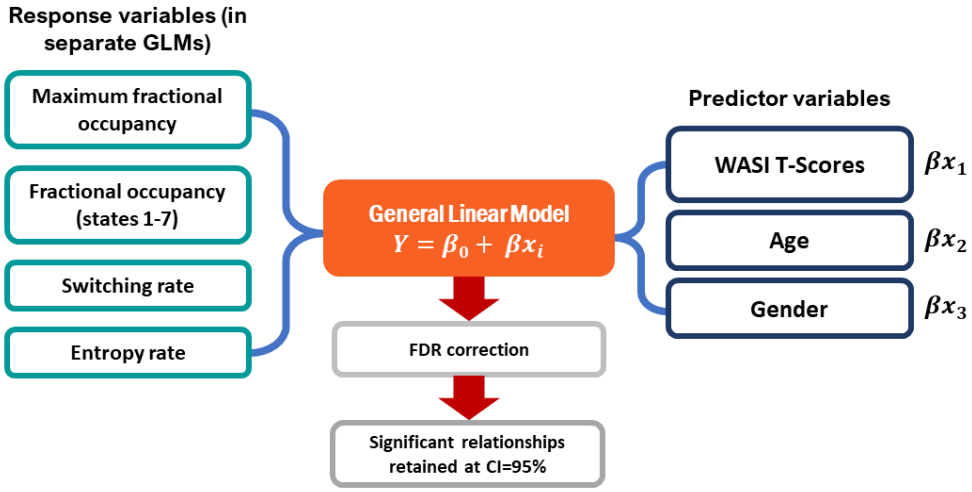
Appendix O

Results from HMMs with prespecified numbers of states ranging from 4-14.



Appendix P

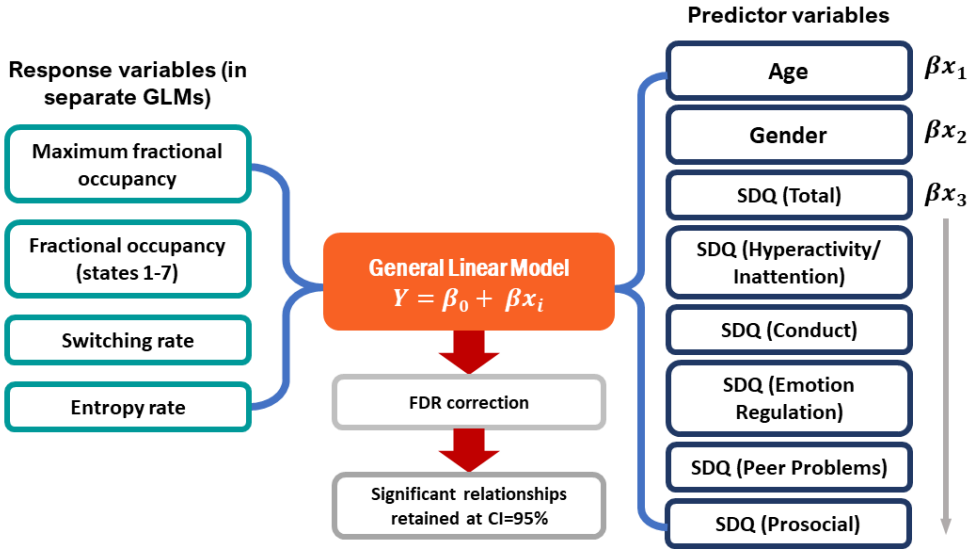
Schematic representation of General Linear Model (GLM) analyses investigating the relationships between state measures and cognitive ability.



GLMs between State Measures and WASI Matrix Reasoning

Appendix Q

Schematic representation of General Linear Model (GLM) analyses investigating the relationships between state measures and features of behaviour.



GLMs between State Measures and Behavioural Measures

Appendix R

Results from GLMs comparing temporal state properties and measures of behaviour.

Behavioural Comparison	*t-statistic*	$p_{adjusted}$
SDQ_{Total} x switching rate	-0.7861	0.4362
SDQ_{Total} x entropy rate	0.4378	-0.7834
SDQ_{Total} x state FOs	<|1.5107|	>0.2895
SDQ_{Total} x maximum FO	1.1055	0.2752
$SDQ_{Hyperactivity}$ x switching rate	-1.6618	0.1040
$SDQ_{Hyperactivity}$ x entropy rate	-1.6216	0.1124
$SDQ_{Hyperactivity}$ x state FOs	<|-2.1504|	0.0932
$SDQ_{Hyperactivity}$ x maximum FO	1.3194	0.1924
$SDQ_{Conduct}$ x switching rate	-1.3304	0.1906
$SDQ_{Conduct}$ x entropy rate	-1.3013	0.2002
$SDQ_{Conduct}$ x state FOs	<|-2.0747|	>0.1176
$SDQ_{Conduct}$ x maximum FO	1.3350	0.1891
$SDQ_{Emotion}$ x switching rate	-0.2668	0.7909
$SDQ_{Emotion}$ x entropy rate	-0.3016	0.7644
$SDQ_{Emotion}$ x state FOs	<|1.2939|	>0.6885
$SDQ_{Emotion}$ x maximum FO	0.8060	0.4248
$SDQ_{PeerProblems}$ x switching rate	-1.4177	0.1636
$SDQ_{PeerProblems}$ x entropy rate	-1.4162	0.1641
$SDQ_{PeerProblems}$ x state FOs	<|2.0321|	>0.1160
$SDQ_{PeerProblems}$ x maximum FO	1.3771	0.1758
$SDQ_{Prosocial}$ x switching rate	1.0982	0.2784
$SDQ_{Prosocial}$ x entropy rate	0.9619	0.3416
$SDQ_{Prosocial}$ x state FOs	<|1.4211|	>0.3909
$SDQ_{Prosocial}$ x maximum FO	-0.8401	0.4056