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Critical connectivity:

Assessing and supporting the development of brain and behaviour

The Wyeth Nutrition Science Center (Hong Kong) recently brought together neurological and paediatric specialists from Hong Kong and the USA for the Critical Connectivity Symposium. The experts reviewed the clinical implications of advances in neuroimaging and neurochemistry on our understanding of neurodevelopment, child nutrition and developmental assessment and intervention.

Neuroscience in Hong Kong primary care settings

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The human brain undergoes extensive transformation throughout life, but the late stages of pregnancy and first 3 years of life are critical for brain growth and development.[1,2] During the first 3 years, the overall increase in brain volume is characterized by a gradual reduction in grey matter volume and increasing total white matter.[3] At the cellular level, 3 intersecting processes occur during early brain development:

- **Proliferation:** New synapses form between neurons, leading to an overproduction of neural connections.[2]
- **Myelination:** The myelin sheath surrounding each neuron's axon develops and thickens, facilitating rapid signalling through neural circuits.[2-4]
- **Pruning:** Redundant or unused connections are eliminated resulting in a more efficient, streamlined, mature system.[2]

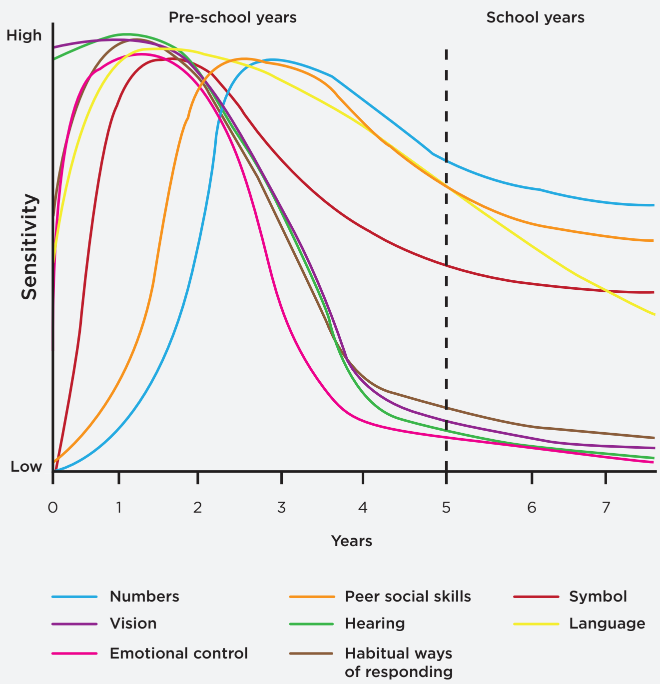
The timing and rate of these processes differ across various brain areas and functions.[2] Which synaptic connections are maintained and strengthened, and which are eliminated, is largely dictated by early experiences and stimuli.[1,2] This synaptic plasticity is necessary for both learning and the development of efficient, stable and adaptive neural networks.[5]

Brain structure and function is influenced by external stimuli

'Sensitive periods' of brain development are phases when synaptic plasticity is pronounced and the brain is particularly influenced by – and vulnerable to – environmental factors and experiences (**Figure 1**).[1,2,5]

While the first few years of life is a developmentally sensitive period, brain maturation continues well into adolescence and young adulthood, when further extensive synaptic pruning and myelination occur.[1,8] Hence, the developing brain remains sensitive to environmental influences from childhood through adolescence (**Figure 2**).[1,8,9]

Figure 1. Sensitive periods in early brain development[2,6,7]



Nutrition, sleep and substance abuse are examples of environmental factors that can potentially influence brain development during this period.[1,8,9]

Figure 2. Environmental factors affecting brain development

Infant · **Child** · **Teen**

Nutrition[1]

Nutrition contributes to neurodevelopment by:
- Meeting the high metabolic demands of a growing brain
- Providing necessary nutrients for critical cellular processes
- Modulating genes that regulate synaptic plasticity

Nutrient deprivation can result in chronic, irreversible brain and behavioural deficits

Sleep[9,10]

Poor sleep or sleep deprivation has long-term effects on brain development:
- ▼ Neurogenesis and synaptic plasticity
- ▼ Grey matter volume and white matter development
- ▼ Memory formation and learning

Short-term sleep deprivation produces cognitive psychomotor impairment similar to alcohol intoxication

Substance abuse[8,11]

Substance abuse in adolescents is linked to:
- ▼ Decreased grey matter volume and abnormal white matter microstructure
- ▼ Verbal memory, working memory and attention
- ▼ Visuospatial functioning

Table 1. Brain structural and functional changes in developmental disorders

Developmental disorder	Underlying brain structural-functional changes
ADHD	• Frontal, striatal, cerebral and temporoparietal brain regions exhibit structural and functional abnormalities.[12] • Some structural changes are linked to dopamine genotypes, and drugs that inhibit dopamine reuptake (eg, methylphenidate) can be used to control the symptoms of ADHD.[12]
Autism	• Irregular brain activity correlates with behavioural symptom severity.[13] • Functional magnetic resonance imaging (fMRI) suggests dysfunction in the mirror neuron system located in the inferior frontal gyrus is responsible for impaired social communication skills.[13]

ADHD, attention deficit-hyperactivity disorder

Discovering a biological basis for neurological disorders

Neuroimaging studies revealed differences in brain development and activation among individuals with neurological disorders. These differences provide a biological basis for observed behaviours (**Table 1**), and present an opportunity for early intervention when synaptic plasticity is at its greatest.

Early intervention and training strategies can help to restore brain function and improve the skills and abilities of individuals with developmental disorders. For example, an intensive 10-week reading intervention was shown to strengthen functional connectivity in children with autism spectrum disorders.[14] In addition to domain-specific abilities and skills training, stem cell therapy has been proposed as a mechanism for regenerating damaged neural tissue in autism and other central nervous system disorders.[15]

Conclusion

Overall, a greater understanding of brain development and how it is influenced by environmental factors has practical implications for primary care settings, for educating patients and families, and developing innovative, integrated intervention strategies.[16]

Longitudinal evaluation of child brain development and behaviour in Hong Kong

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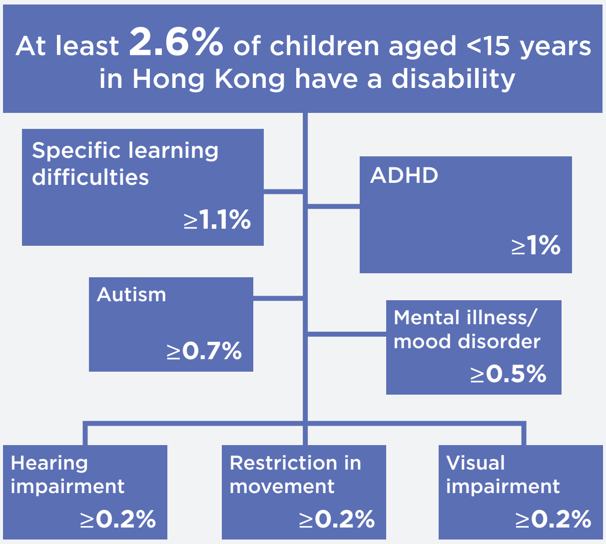
Developmental problems are relatively common in Hong Kong, with approximately 15% of preschool children affected by developmental conditions# and at least 2.6% of children under 15 years of age experiencing some form of mental or physical disability (**Figure 3**).[17,18]

Early identification of developmental conditions is key for successful intervention and habilitation as the brain's ability to respond and adapt to stimuli is greatest in the first few years of life, whereas the effort demanded to generate change increases exponentially with age.[19] Furthermore, early intervention also enables appropriate holistic care of other comorbid conditions (**Figure 4**).[19]

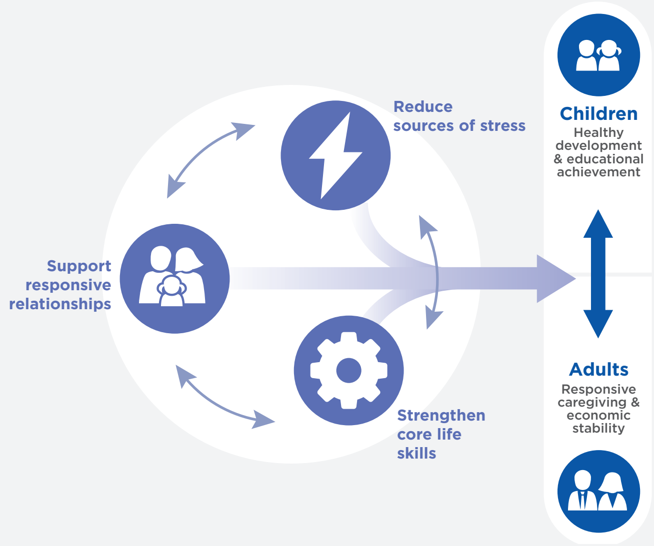
#Personal communication with The University of Hong Kong, Department of Paediatrics and Adolescent Medicine

Figure 3. Minimum prevalence of developmental disorders among children in Hong Kong[17,18]



ADHD, attention deficit–hyperactivity disorder

Figure 4. Improving outcomes for children with developmental disorders[20]



How are developmental disorders detected in children?

Periodic surveillance, developmental screening and assessment is crucial to identify developmental disorders in children and facilitate early intervention.[21] A developmental surveillance program is carried out through a combination of observing childhood behaviours, gathering perinatal and parental concerns, developmental history and other contributing factors, such as vision or hearing problems. If developmental problems are suspected, screening is performed, additional follow-up surveillance is scheduled, and parents are educated on the condition to facilitate better monitoring of child development (**Figure 5**).[22] In Hong Kong, the Maternal and Child Health Centres (MCHCs) provide routine developmental surveillance for all children, scheduled at 6, 12, and 18 months of age.[23,24] At the same time, preschool teachers and general practitioners may also refer children with suspected developmental problems to MCHCs or Integrated Family Service Centres (IFSCs)/Integrated Services Centres (ISCs) through the Comprehensive Child Developmental Service Program (CCDS).[24,25] The CCDS was launched in Hong Kong to improve early identification and support for children through facilitating interdisciplinary collaboration between multiple providers: the Education Bureau, Department of Health, Hospital Authority and the Social Welfare Department.[25] This service model utilizes the close contact preschool teachers have with children and facilitates teacher referral of parents and children to support services.

Developmental screening comprises a brief assessment procedure to identify whether further assessment and diagnosis is advised, using standard screening tools, such as the Modified Checklist for Autism in Toddlers (M-CHAT).[23,24] Beyond standard screening, a wide range of screening tools are used by hospitals and specialist services for high-risk groups, such as infants born prematurely or with perinatal complications, hypoxic ischaemic injury or maternal drug abuse. Despite international policies designed to improve developmental screening efforts, the accuracy of screening tools is limited.[26] Therefore, re-testing over multiple sessions, or using a more accurate and specific test, is often necessary.[21,26] Furthermore, several studies have suggested that only a small proportion of healthcare professionals use standardized screening tools routinely.[27,28] Therefore, repeated screening may be necessary in conjunction with ongoing surveillance.

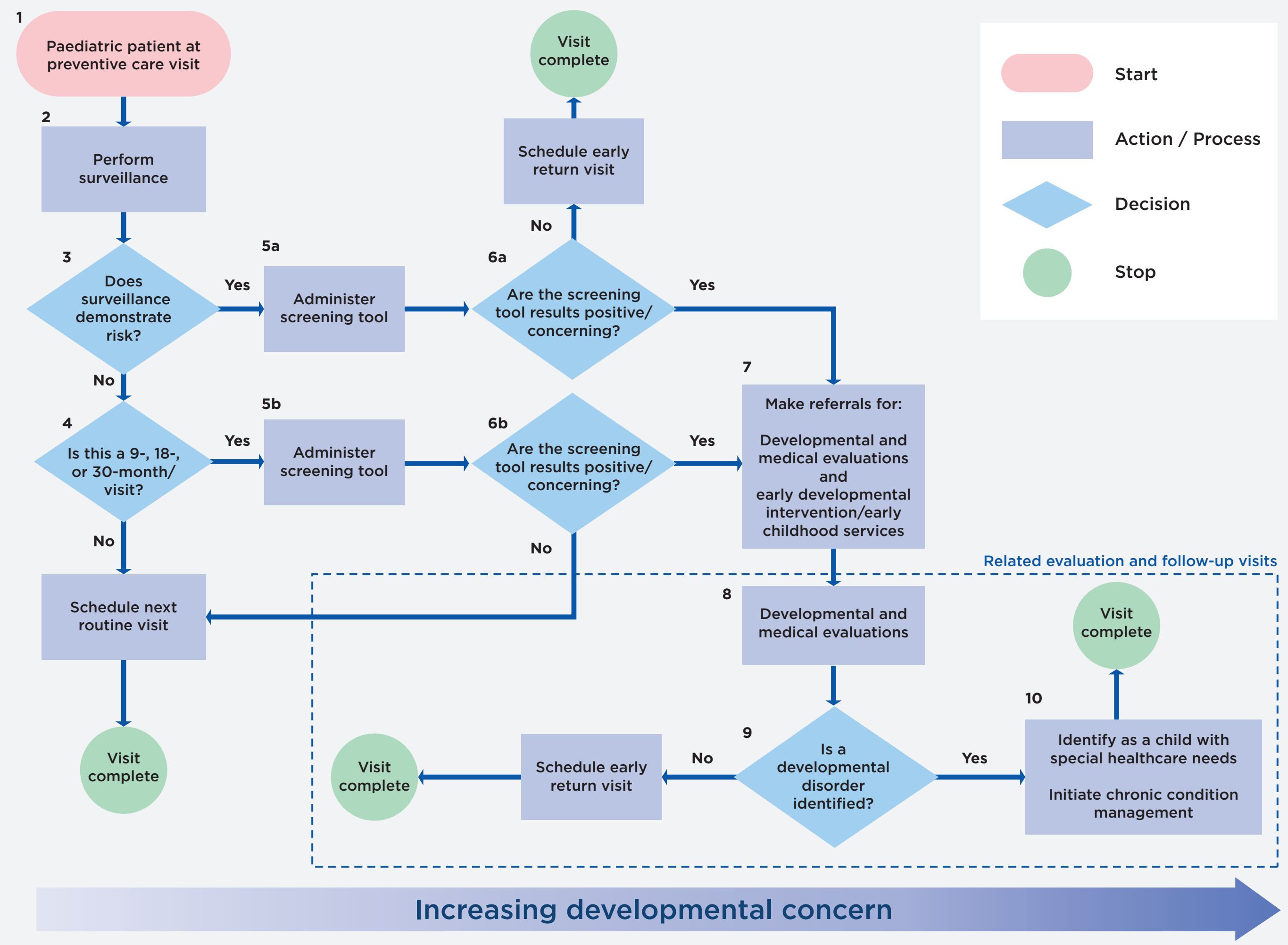
What happens following a positive screening assessment?

Following a positive or concerning screening result at the MCHCs, children are referred to the Child Assessment Service (CAS), where a multidisciplinary team of paediatricians, clinical psychologists, registered nurses and other healthcare professionals provide developmental assessment, diagnosis and holistic rehabilitation services.[29,30] After an initial interview and clinical observation to gather information regarding the child's physical, intellectual and behavioural issues, a range of standardized tests can be used to identify any developmental disorder (see **Table 2**).[31]

It is critical that locally validated assessment tools are used so children are assessed against benchmarks appropriate to their sociocultural environment.[38,49] In recognition of this, the CAS has launched locally developed, validated and standardized tests, including:

- Hong Kong Comprehensive Assessment Scales for Preschool Children (HKCAS-P)[39]
- Hong Kong Cantonese Oral Language Assessment Scale (HKCOLAS)[50]
- Hong Kong Cantonese Articulation Test (HKCAT)[52]
- Hong Kong Cantonese Receptive Vocabulary Test (HKCRVT)[53]
- Hong Kong Dyslexia Early Screening Scale (HKDESS)[54]
- Children Reading Acuity Test (CRAT)[55]

Figure 5. Surveillance, screening and assessment for detecting developmental disorders[22]



What happens after the diagnosis of developmental conditions?

Multidisciplinary intervention for developmental needs may then be provided by the Early Education and Training Centre (EETC),[56] Integrated Programme in Kindergarten-cum-Child Care Center (IP in KG-cum-CCC),[56] Special Child Care Center (SCCC)[56] or On-site Pre-School Rehabilitation Services (OPRS),[57] depending on the child's needs. As children enrol in government-funded primary schools, the Student Health Service or Early Identification and Intervention Programme for Primary One Students with Learning Difficulties (EII) of the Education Bureau provide teachers with an Observation Checklist for Teachers (OCT) for students suspected to have Specific Learning Difficulties (SLD).[58] Through consultation with the school's Student Support Team (SST) and educational psychologists, a support programme is developed and monitored over time.[58] Students with severe or comorbid learning difficulties are referred to CAS for further assessment, and are placed in special schools that cater to their needs and have smaller class sizes.[59] Students with less severe learning difficulties may continue to attend mainstream school, but receive additional, individualized support.[59,60]

Challenges for children with developmental disorders

There are several limitations to the current child developmental assessment and intervention model in Hong Kong given its highly complex nature, spanning multiple medical, educational, social and vocational services offered by various governmental departments, and non-governmental and private sector agencies.[61] Such complexity is challenging for parents and children to navigate and can lead to long waiting times. Furthermore, to be effective, successful collaboration and coordination between different services is imperative. However, this close networking is further complicated by the absence of dedicated case managers and a shortage of social workers for children with developmental disorders.

Conclusion

Paediatricians play a key role in overcoming the challenges associated with identifying and managing children with developmental disorders by collaborating with other healthcare professionals and by using standardized screening tools during children's regular visits or during their intermittent illnesses.[61]

Following screening, developmental paediatricians use locally validated and culturally appropriate assessment tools to diagnose childhood developmental disorders, allowing tailored early intervention to optimize outcomes. Timely diagnosis and intervention is essential for improving child developmental outcomes.

Table 2. Commonly used paediatric physical, intellectual and behavioural assessment tools[32]

Test function	Test	Description
Standardized questionnaires	Achenbach System of Empirically Based Assessment (ASEBA)	Assesses emotional, behavioural and social problems, competencies and strengths[33]
	Strengths and Difficulties Questionnaire (SDQ)	Measures emotional, social, peer and conduct problems, hyperactivity–inattention, and pro-social behaviours[34]
	Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour (SWAN) rating scale	Measures behavioural characteristics and attention skills (controlling anxiety; focusing attention; inhibiting impulsive behaviour)[35]
	Spence Anxiety Scale	Evaluates anxiety, panic/agoraphobia and physical injury fears[36]
	Cambridge University Behaviour and Personality Questionnaire for Children (AQ-Child)	Measures social skills, communication, imagination, attention to detail, and attention switching[37]
Comprehensive mental assessment	Griffiths Developmental Scales-Chinese (GDS-C)	Assesses child development behaviour across several domains, including locomotor skills, personal–social skills, language, hand–eye coordination, performance and practical reasoning[38]
	Hong Kong Comprehensive Assessment Scales for Preschool Children (HKCAS-P)	Assesses a wide range of preschool children's functions, including cognition, language, social cognition, fine and gross motor functions, perceptual function and ability, and literacy and numeracy skills[39]
IQ tests	Wechsler Preschool and Primary Scale of Intelligence (WPPSI)	Measures overall cognitive ability, including reasoning, visual–spatial processing and working memory[40,41]
	Weschler Intelligence Scale for Children (WISC)	Generates a full-scale IQ assessment that represents a child's general intellectual ability.[42] Also used to diagnose ADHD and learning disabilities
Diagnostic tests for social interaction and communication	Happe Strange Stories Test	Assesses theory of mind and social communication using stories about everyday situations. May be used to detect autism spectrum disorder[43]
	Autism Diagnostic Interview-Revised (ADI-R)	Assesses the quality of social interaction and stereotyped utterances, as well as assessing repetitive or aggressive behaviours[44]
	Autism Diagnostic Observation-Schedule (ADOS)	Measures social affect and restrictive and repetitive behaviour to identify autism and autism spectrum disorder.[45] Currently the gold standard test for autism spectrum diagnosis[45]
Diagnostic tests for executive function	Conners' Continuous Performance Test	Measures attentiveness, impulsivity and sustained attention to detect ADHD[46]
	Test of Everyday Attention for Children (TEA-Ch)	A game-like test that assesses selective and sustained attention and attention switching to detect ADHD[47]
Diagnostic tests for language	Symbolic Play Test	Assesses children's play with miniature objects to evaluate conceptual skill development necessary for language development[48,49]
	Hong Kong Cantonese Oral Language Assessment Scale (HKCOLAS)	Assesses Cantonese-speaking school age children with language problems, with reference to the understanding of Cantonese linguistics and language acquisition[50]
	Reynell Developmental Language Scale (RDLS)	Assesses the language age of children by measuring language comprehension and language expression[48]
	Clinical Evaluation of Language Fundamentals® - Fifth Edition (CELF®-5)	Assesses a student's language and communication skills in a variety of contexts.[51] Determines the presence of a language disorder, describes the nature of the language disorder and provides a plan for intervention or treatment[51]

Note: Many of the above tests have been translated and validated for the Chinese population.
ADHD, attention deficit–hyperactivity disorder

The brain connectome: Mapping structural and functional connectivity from infancy to early childhood

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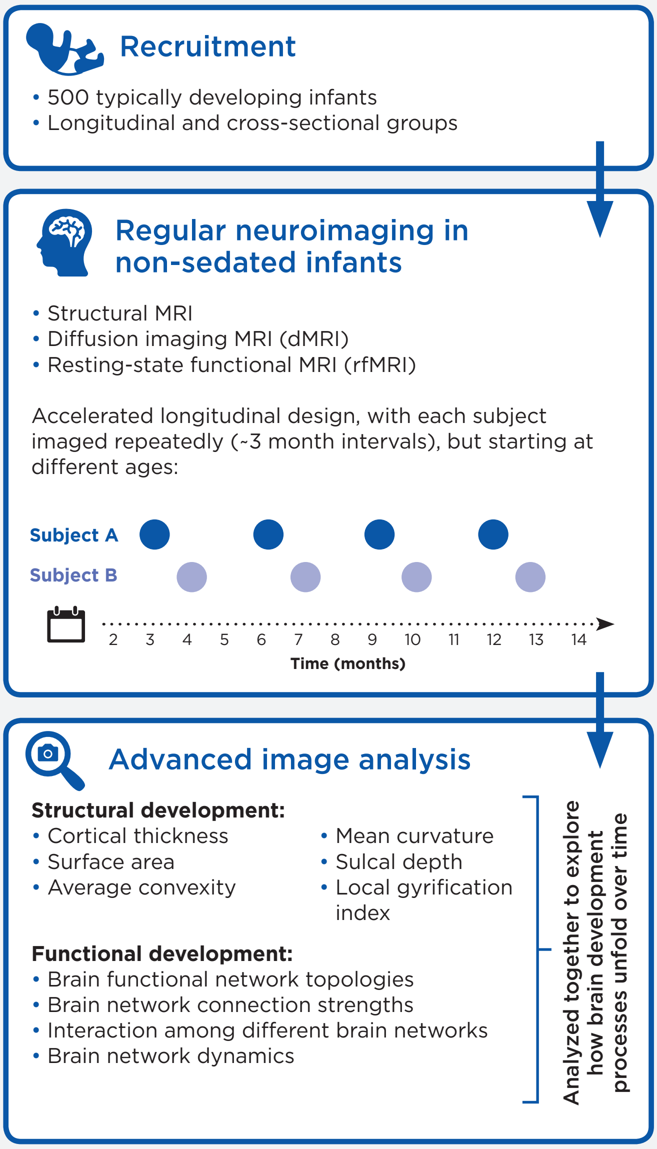
A series of ambitious projects are aiming to create a comprehensive map, or connectome, of the neural pathways of the human brain over a person's entire lifespan – the Lifespan Connectome Project. One such project is exploring brain development from infancy to 5 years of age – a period of rapid and extensive structural and functional change.[62] This connectome project is the first comprehensive imaging study of early brain development and uses a combination of neuroimaging data and behavioural assessments to evaluate and map brain structure–function–behaviour relationships (**Figure 6**).[62]

Figure 6. Connectome project study design[62]

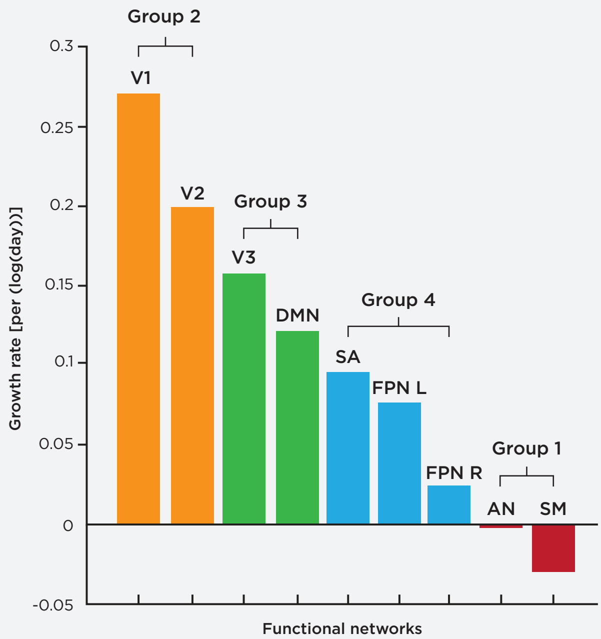


MRI, magnetic resonance imaging

How does the infant brain mature?

The maturation sequence of 9 brain functional networks have been established by analyzing patterns of synchronous brain activity captured during resting-state functional magnetic resonance imaging scans over the first year of life of typically developing infants.[63] These revealed that the sensorimotor and auditory/language networks resemble their adult topology and undergo only minor changes during the first year of life, suggesting that these are more mature networks. In contrast, the visual network undergoes rapid developmental processes and reaches an adult-like network topology at 1 year of age.[63] The default-mode, executive control and dorsal attention networks – higher brain function networks responsible for attention, self-awareness, self-control and mental flexibility – demonstrate some development in the first year, but overall remain relatively immature with topology distinct from the adult network.[63] Overall, these findings indicate that brain development follows a sequence of primary sensorimotor and auditory network maturation first, then visual networks, followed by the attention network or default-mode network, and lastly the salience and executive control networks (**Figure 7**).[63]

Figure 7. Network growth rates in the developing brain[63]



AN, auditory/language network; DMN, default mode network; FPN, frontoparietal network; L, left; R, right; SA, salience network; SM, sensorimotor network; V1, medial occipital network; V2, occipital pole network; V3, lateral visual parietal network

Adapted from Gao W, et al. *Cereb Cortex* 2015;25:2919–2928.[63]

It is not feasible to conduct extensive imaging of all newborns as part of routine clinical practice, but connectome projects may provide important insights into the developmental processes of essential brain functional networks, as well as the association among these networks, which in turn may enable the development of assessment tools for characterizing brain development during the early postnatal years. In particular, while higher-order brain functional networks start to emerge during the first years of life, widely accepted tools with a sufficiently high sensitivity and specificity to assess/monitor maturation processes of higher-order brain functions are currently lacking. The early maturation of the visual system is particularly notable, given this key sensory channel for newborns also appears to influence the development of the motor, attention and higher-cognition networks.[64] When combined with the early maturation of the visual system relative to higher-order brain function networks,[63] the apparent interconnectedness of visual and cognition networks and concurrent growth trajectories for the visual cortex and corpus callosum,[65] an assessment of visual function could act as a surrogate for higher-order brain function. Indeed, encouraging preliminary results have recently indicated that the degree of functional connectivity in the visual network is correlated with functional connectivity in higher-order cognition up to 9 months of age, suggesting that early assessments of visual function may predict cognitive ability later in development.

The interaction between the infant microbiome and brain development

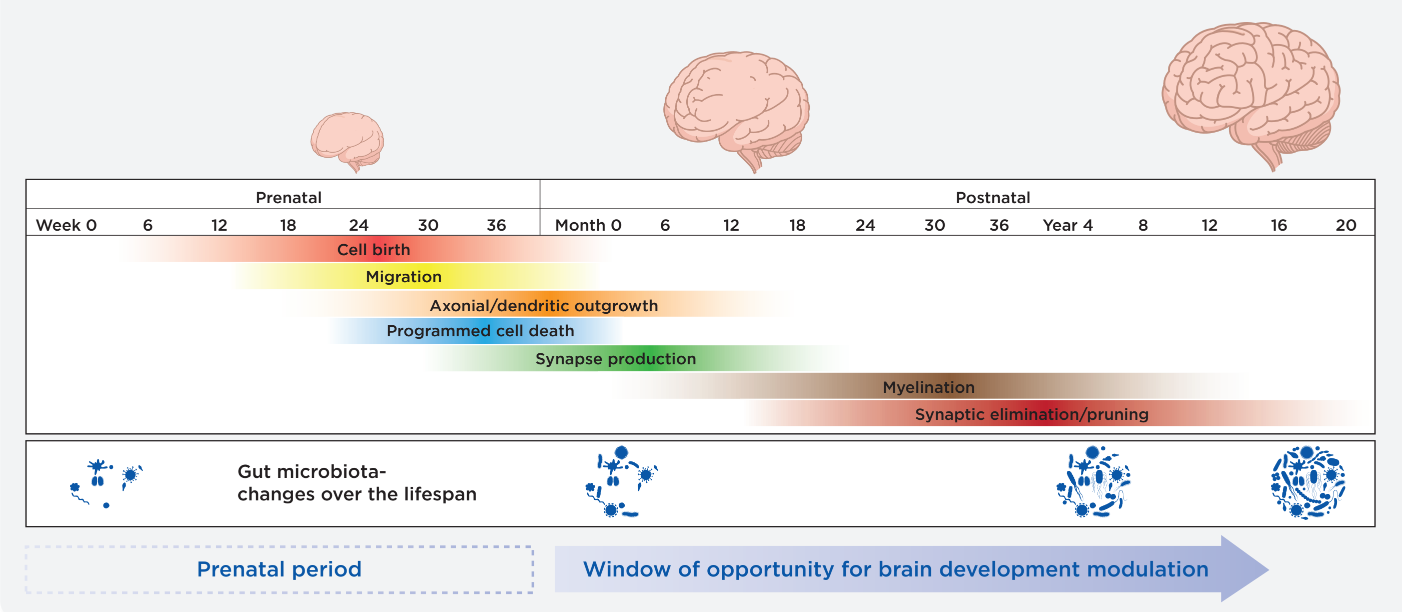
The infant microbiome is one of the many factors influencing early neurodevelopment. The gut microbiota is the most diverse and abundant collection of microorganisms in the human body, and plays a significant role in immune system function, digestion, metabolism and intestinal homeostasis.[66,67] In particular, microbial imbalances (ie, dysbiosis) have been associated with a range of immune, intestinal and metabolic diseases, such as asthma, inflammatory bowel disease and diabetes.[67]

The composition of the developing infant microbiota is affected by a range of factors, including the maternal microbiome, mode of birth delivery (vaginal or caesarean section), feeding patterns (breast-fed or formula-fed), and antibiotic and environmental exposure.[66,67] Extensive and complete colonization of the infant gut occurs in the first 3 years of life, transforming the newborn microbiome from a relatively sparse environment into a rich and stable ecosystem.[66]

This period of microbiome development coincides with rapid neurodevelopment and these 2 systems do not develop in isolation: a complex bidirectional communication system exists between the gut and brain (the gut–brain axis), integrating signals from neural, immunological and endocrine pathways.[66,68,69] This relationship means that the microbiome may impact neurodevelopment and maturation (Figure 8).[66,68,69]

Several studies using germ-free animals suggest the microbiome regulates brain development through modulation of neurotransmitter gene expression, synthesis and transport, and alteration of the hypothalamic–pituitary–adrenal axis, contributing to memory dysfunction and anxiety behaviours.[68,69] While these results suggest a crucial role for the microbiome during critical periods of neurodevelopment, this has yet to be replicated in human studies.[68] The ongoing 3-year BCP-Enriched study aims to shed light on the role of gut microbiota in regulating early brain development and function. This study expands the scope of the connectome project by exploring the interaction between nutrient intake, feeding practices, microbiota, environmental exposure, sleep quality, brain structure and function, and cognitive and behavioural outcomes in infants aged 0 to 3 years.[70]

Figure 8. Potential interaction between brain and microbiome development[69]



Although results from the BCP-Enriched study are yet to be published, an earlier study had already identified associations between bacterial composition at 1 year of age and subsequent cognition at 2 years of age among typically developing infants.[71] Specifically, 89 infants could be sorted into 1 of 3 groups based on microbial composition profile, and while infant microbiome had minimal effects on regional brain volume, higher alpha diversity (mean species diversity) was associated with lower overall composite, visual reception and expressive language scores assessed using the Mullen Scales of Early Learning.[71] The finding that infant gut microbiome composition predicts cognitive performance at 2 years of age hints at potential targeted interventions to manipulate the microbiome and cognitive development.

Conclusion

Contemporary neuroimaging techniques are enabling the creation of a connectome of the developing human brain,[62] yielding new insights into the timing of critical developmental processes and the role of the microbiome–gut–brain axis in contributing to early brain development.[63,71]

Questions and answers

Q: Can you predict or investigate intelligence from neurodevelopmental brain metrics?

A (Professor Weili Lin): Intelligence is a complex topic, but has some associations with structural and functional neuroimaging measures. Typically, assessments of intelligence include components that have some strong neural correlates, such as cognitive flexibility. For measures of intelligence that include such components, brain imaging metrics could be used. For example, assessments of prefrontal cortex functional integration during infancy are associated with cognitive development at a later age.

Q: Caesarean section delivery produces a different microbiota in infants, is there any effect on neurodevelopment of infants delivered by Caesarean section, and is there any compensatory effect of breastfeeding or any other intervention?

A (Professor Weili Lin): There is evidence to suggest that delivery mode affects the infant gut microbiota,[66,67] but the jury is still out on how this affects infant brain development and immunity. Likewise, most of these studies have been performed in Western populations, so it is not clear how they may apply to Asian populations, which could reasonably be expected to have different gut microbiota, so more research is required in this field before definitive conclusions can be drawn.

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