$45M Wellcome Leap Program
The First 1000 Days: Promoting Healthy Brain Networks

We all know what a difference a day makes. The first 1000 days can make *all* the difference to a child's start in life, perhaps more so than we ever understood before. In this early period, we develop critical cognitive abilities, such as executive function (EF) and self-regulation. By the end of the first 1000 days, a child's individual EF performance changes their odds of dealing successfully with opportunities and obstacles they face in life. Well-developed EF improves a child's chances for lifelong physical, neural, and mental health; reduces the pace of aging; and underpins greater productivity and prosperity.[i] [ii] Indeed, if EF is underdeveloped it has significant consequences. We know that children with underdeveloped EF at age 3 represent about 20 percent of the population, but make up nearly 80 percent of adults who are likely to require some form of societal or economic assistance.[iii] So how do we assess and promote healthy development in the first 1000 days?

We routinely measure height and weight to assess a child's physical health. We also need objective, scalable ways to assess a child's cognitive health.

During the first 1000 days, the brain undergoes extensive network construction and remodeling in response to interactions with the environment, that in turn endows the capacity to successfully live in that environment. For example: a child's postnatal nutrition influences the health of circuit formation; their physical exploration is key to development of sensorimotor skills; and their social interactions with caregivers are central to language and emotional development. But we lack tools and models that are predictive of the influence and dependency of these factors on individual network development. Without them, we cannot optimise the key ingredients necessary for promoting healthy brain development, nor identify those at risk of being underdeveloped. Timing is critical – because developmental windows are narrow. For example, previously neglected children admitted into foster care before 24 months old versus those admitted after 26 months show significant differences in their ability to regain aspects of cognitive function by adolescence.[iv] [v] And the results can be dramatic – if we could accurately predict and improve EF outcomes by 20% in 80% of children before age 3, we could reduce the risk of childhood obesity by nearly 20%, reduce the risk of accelerated ageing by about 12% and potentially reduce the risk of encounters of crime by over 20%.

If we could develop accurate, scalable, early screening methods to predict EF outcomes, risk-stratify children, and predict responses to interventions in the first 1000 days, we could help ensure a healthy and productive life for millions globally. Importantly, this goal may now be within our reach.

Why now?

To date, our primary window into the developing brain has been neuroimaging techniques and animal models, which can help identify quantitative biomarkers of network health and characterise network differences underlying behaviours. Advances in EEG, processing, and other lab-based systems are opening additional possibilities in young infants. But these are limited by difficult set ups and therefore require short data collection windows in unnatural environments. While opportunities remain, so far, these methods have not yielded the scale for broader use in more natural environments, nor the density of data needed to model critical features of network development. The sampling frequency, duration and volume of data required in these early, highly dynamic developmental periods, calls for another approach.

Advances in *in vitro* 3D brain models over the last five years demonstrates the viability of modeling network formation and functional connections in much the same way as we see in the infant brain. Progress has been made in at least three key areas: 1) the diversity and maturation of brain regions that can be sustained in long-term cultures and that mirror the timeline of human development; 2) the formation of microcircuits, synapses, and functional connections between two brain organoids into brain assembloid structures; and, 3) the ability to record and manipulate synapse activity and functional connectivity across these assembloid networks.

At the same time, advances in artificial neural networks (ANNs) have demonstrated the viability of modeling network pruning processes and the acquisition of complex behaviours in much the same way as a developing brain. For example, deep language and face recognition models have acquired human-level prediction performance by optimising millions of synaptic weights over millions of real-world observations. Moreover, connecting visual, auditory, and motor networks and allowing them to learn from each other has led to: multi-agent ANNs that can play hide and seek[vi] and; cognitive robotics models that can replicate altruistic behaviours, recognise emotional states, and reproduce drawing behaviours typically observed in a child aged 1-2 years. These ANNs are beginning to help us understand the brain and behaviour in new ways.

Meanwhile, advances in data analytics coupled with the diversity of data available on childhood development are presenting options for validating new approaches. Improvements in machine learning (ML), are enabling extraction of meaningful signals from single neuroimaging trials. And longitudinal cohorts are presenting psychological, neurological and environmental measures for thousands of children between ages 0-10 years and their families. This has made it possible to distinguish sex dependent network differences underlying emotional outcomes in children, as predicted by maternal mental health.[vii]

Finally, the proliferation of low-cost mobile sensors, wearables, and home-based systems are providing a new opportunity to assess the influence and dependency of brain development on natural physical and social interactions. For example, relatively unobtrusive, scalable electronic badges that collect visual, auditory, and motion data, as well as interactive features (such as turn-taking, pacing, and reaction times) can assess the richness of interactions and predict social and emotional outcomes in a variety of everyday situations with near 100% accuracy. Continuous visual and audio recordings in the home have collected millions of data points on a child's development and identified sensorimotor interactions predictive of language development in a 2-year-old.[viii]

Together, these advances suggest we are at an inflection point. Modeling and predicting EF outcomes and responses to interventions during the first 1000 days—more reflective of how the infant brain develops *in vivo* and how cognition is acquired in the real world— is now a possibility. This will enable the promotion of healthy brain network development at the individual level based on developmental and environmental experiences.

Program goals.

1. Develop a fully integrated model and quantitative measurement tools of network development in the first 1000 days, sufficient to predict EF formation before a child's first birthday, with 80% predictive validity for EF outcomes at age 3.
    - The model and measures should capture critical windows of network development from sensorimotor to language and prefrontal networks and the connections established between them.
    - The integrated model should predict contributions of nutrition, the microbiome, and the genome on circuit formation, as well as,

sensorimotor and social interactions on network pruning processes, both in relation to EF outcomes at age 3.
    - Predictive validity should be verified against assessments of network differences and environmental influences in retrospective studies of a statistically relevant number of children.
2. Create scalable methods for optimising promotion, prevention, screening and therapeutic interventions to improve EF by at least 20% in 80% of children before age 3. Of interest are improvements from underdeveloped EF to normative or from normative to well-developed EF across the population to deliver the broadest impact. Techniques that improve EF by 80% or more in 20% of at-risk children are important, but they are not the sole focus of this program.

Advances across models and measures should inform each other to improve and validate predictive markers, environmental influences and optimise the key ingredients necessary for promoting healthy network development. It is not necessary to form a large consortium or team to do this. Synergies and integrated system demonstrations will be facilitated by Wellcome Leap on an annual basis as we make progress together towards the program goals.

Call for abstracts and proposals.

We are soliciting abstracts and proposals for work over 3 years (with a potential additional one-year option) in one or more of the following thrust areas. Proposers should clearly relate work in these thrust areas to one or more of the program goals.

Thrust Area 1: Data Collection, Measurement & Assessment in Infants

Test and validate neuroimaging/computational tools capable of assessing differences in network development and functional connectivity in children aged 3 months through to 3 years to predict EF outcomes and measure responses to interventions. Tools should be deployed in at least two different populations (across cultures and geographies) and should include children at risk for underdeveloped EF, normative and low risk children, representative of the general population.

Of interest are electroencephalogram (EEG) or functional near-infrared spectroscopy (fNIRS) techniques coupled with cognitive behavioural tasks that can be deployed in randomised control trials (RCTs) to measure the effect of: a) nutritional interventions in the first 12 months of postnatal development (e.g. focused on breastfeeding exposure and post-weaning food intake) and b) psychosocial interventions between an infant and

caregiver to improve subcomponents of EF (e.g. attention and novelty seeking in children under 12 months of age and language development for children over 18 months old). Proposers should have access to large-scale randomised control trials (n>100 children for each arm), directly or through established partnerships.

Deploy tools to quantitatively assess infant sensorimotor and social interactions in real world settings across the first 1000 days, to provide training data for the *in-silico* models (thrust 2). At home instrumentation devices or wearable/mobile sensors that can be used to generate video and audio recordings on up to 50 children (minimum of 5), for 8-10 hours a day, are of interest. Data collection should be focused between the ages of 4-12 months for visual, auditory and motor network development, 18-24 months for language and 24-36 months for prefrontal networks. Tools should also be capable of quantifying pacing, reaction times and turn-taking during interactions. Validating these tools against the neuroimaging/computational tools to determine if they could be used as a scalable way of assessing network development, is of interest.

Develop strategies for identifying candidate microbial metabolites or cytokines that affect EF outcomes and/or subcomponents of EF in children, to feed the *in vitro* model (thrust 2). Investigations should ideally be performed using existing child development cohorts or RCT data (e.g. children with Autism Spectrum Disorder, or Stunting) to ensure there is a significant relationship with cognitive outcomes and microbial differences that can be manipulated with nutritional interventions. Microbial candidates that affect cortico-thalamic-striatal networks and connections will be key.

All measures and assessments should be verified against individual child performance on standard EF cognitive behavioural tasks at age 3, to ascertain predictive validity. Prospective performers are expected to indicate the measures that will be used for this thrust. As part of the program, Leap will provide the infrastructure for managing large scale data collection efforts.

Thrust Area 2: Developing and Validating Models of Network Development

Develop an *in vitro* 3D brain assembloid that replicates the timed formation of networks, synapses and functional connections established between the cortex, thalamus, striatum and midbrain during the first 300 days of postnatal circuit formation. Network diversity should be verified via immunohistochemistry and transcriptomic methods. Synapse activity and functional connectivity should be verified via electrophysiology methods.

Once verified, models should be used to test and predict the impact of: genetic variants associated with conditions in which EF is underdeveloped (e.g. Attention Deficit Hyperactivity Disorder); candidate microbial metabolites and cytokines identified

in thrust 1; and the joint contribution of genetic and microbial variants, on the rate, quantity and quality of circuit formation and connectivity. Advances in this model should inform different starting points for the *in-silico* models.

Develop *in-silico,* computational models that recapitulate network pruning processes and connections established between sensorimotor/language networks and prefrontal networks during critical windows of postnatal development. Model performance should be verified on relevant cognitive behavioural tasks and demonstrate equivalent proficiency to a developing child.

We are particularly interested in predictive coding models that can predict the impact of sensorimotor and social interactions on the development of: a) infant attention or novelty seeking as it relates to EF formation by modeling a subset of data collected between 4-12 months and 24-36 months (thrust 1); and b) language development as it relates to EF formation by modeling data collected between 18-24 months and 24-36 months (thrust 1). Embodied robotic models that can learn in the real world based on sensorimotor activity and acquire subcomponents of EF, are also of interest. Determining the impact of interactions on the rate of network pruning, acquisition of cognition and the degree of pruning needed in earlier networks before new behaviours can be learned, will be key.

Deploy state of the art ML methods to mine existing longitudinal data (such as, but not limited to the FinnBrain cohort and Growing Up In Singapore Towards Healthy Outcomes study) to validate models by: a) characterising typical and atypical network differences and functional connections underlying childhood EF outcomes; b) identify predictive network markers and subcomponents of EF present before 12 months old and; c) identify and validate key environmental factors (such as postnatal nutrition, microbial variants and caregiver mental health as it relates to caregiver interactions) predictive of network differences and individual EF outcomes. Network markers and environmental factors should predict EF cognitive outcomes reported in children at age 3-5 with 80% accuracy. Such insights shall underpin the creation of a fully integrated predictive model and validate measures collected in thrust 1.

Thrust Area 3: Methods for Scalable Screening, Promotion, Prevention & Intervention

Develop novel scalable measurement tools for assessing network development and quantifying the health of a child's interactions, from 3 months through to 3 years of age. Predictive markers should be verified against network and cognitive behavioural assessments performed in children (thrust 1) and EF behavioural outcomes at age 3, as verified through standard cognitive tasks.

Of interest are: tools that assess infant microbiome health as a predictor of circuit formation; instrumented toys, games or reading books to assess the health of sensorimotor, language and social interactions; wearable sensors that assess physiological measures predictive of brain health (e.g. electrodermal activity, respiratory rate and heart rate) and wireless, wearable EEG or eye tracking technology.

REFERENCES:

[i] Moffit, T.E., Arseneault, L., Belsky, D., *et al*. A gradient of childhood self-control predicts health, wealth and public safety. *PNAS*. 108: 2693-2698 (2011).

[ii] Richmond-Rakerd, L.S., Caspi, A., Ambler, A., *et al*. Childhood self-control forecasts the pace of midlife aging and preparedness for old age. *PNAS*. 118: (2021). https://doi.org/10.1073/pnas.2010211118

[iii] Caspi, A., Houts, R.M., Belsky, D.W., *et al*. Childhood forecasting of a small segment of the population with large economic burden. *Nat Hum Behav*. 1: (2016). doi:10.1038/s41562-016-0005.

[iv] Wade, M., Fox, N. A., Zeanah, C.H., and Nelson, C. A. Long-term effects of institutional rearing, foster care and brain activity on memory and executive functioning. *PNAS*. 116: (5) 1808-1813 (2019). https://doi.org/10.1073/pnas.1809145116

[v] Fox, N.A., Almas, A.N., Degnan, K.A., *et al*. The effects of severe psychosocial deprivation and foster care intervention on cognitive development at 8 years of age: findings from the Bucharest Early Intervention Project. *Journal of Child Psychology and Psychiatry*. 52:9: 919–928 (2011).

[vi] https://openai.com/blog/emergent-tool-use/

[vii] Wang, Q., Zhang, H., Poh, J.S., *et al*. Sex-Dependent Associations among Maternal Depressive Symptoms, Child Reward Network, and Behaviors in Early Childhood. *Cerebral Cortex. 30 (3): 901-912* (2020). doi: 10.1093/cercor/bhz135.

[viii] Roy, B.C., Frank, M.C., DeCamp, P., Miller, M., and Roy, D. Predicting the birth of a spoken word. *PNAS*. 112: 12663–12668 (2015). https://doi.org/10.1073/pnas.1419773112