The potential and translational application of infant genetic research

Angelica Ronald[1*], Anna Gui[2]

[1] School of Psychology, Faculty of Health and Medical Sciences, University of Surrey, United Kingdom.

[2] Department of Psychology, University of Essex, United Kingdom.

*Corresponding author: a.ronald@surrey.ac.uk, ORCID: 0000-0002-9576-2176

Abstract

In the current genomic revolution, the infancy life stage is the most neglected. Although clinical genetics recognizes the value of early identification in infancy of rare genetic causes of disorders and delay, common genetic variation is almost completely ignored in research on infant behavioral and neurodevelopmental traits. In this Perspective, we argue for a much-needed surge in research on common genetic variation influencing infant neurodevelopment and behavior, findings that would be relevant for all children. We now see convincing evidence from different research designs to suggest that developmental milestones, skills and behaviors of infants are heritable and thus are suitable candidates for gene discovery research. We highlight the resources available to the field, including genotyped infant cohorts and we outline, with recommendations, special considerations needed for infant data. Therefore, infant genetic research has the potential to impact basic science and to affect educational policy, public health and clinical practice.

Keywords

Infancy, genetics, behavioral genomics, neurodevelopment.

Main

Infancy is defined as "the earliest period of human life, early childhood"[1]; here, we refer to infancy as from birth to 36 months. Infancy is a time of many important, time-specific developments in perception, cognition, mobility, language, self-care, sociality, sleep, and laterality. There is a rapid onset of developmental milestones unsurpassed by any other stage in the human lifespan. For example, in the motor domain, rolling over, sitting, crawling, standing and walking are all typically achieved within an approximate 5-10-month window in the first and second year[2]. In terms of brain growth, the infant brain changes from being 36% of its adult volume 2 to 4 weeks after birth to 72% of its adult volume at 12 months and 83% by 24 months of age[3]. Subcortical and gray matter volume have been estimated to grow at a maximal velocity between 5 to 6 months of age, and white matter volume grows maximally around 2.4 years[4]. These structural brain changes are accompanied by a cascade of psychological milestones. In sum, a wide range of critical brain and behavioral development occurs in infancy.

We first review the evidence that common genetic variation influences infant behavioral and neurodevelopmental traits. We then articulate how we can harness new findings on the genetics of infancy, obtained with emerging methodological tools, to improve societal outcomes for all children through translational application[5]. We then focus on the practical steps needed to enact research on common genetic variation in infants. We outline the resources available to researchers and highlight special considerations when working with infant data. While this article primarily focuses on behavioral and neurodevelopmental phenotypes within infancy, our perspective can also be applied to other infant phenotypes, for which there is only modest research on common genetic architecture relative to outcomes in later life.

Evidence for common genetic variation influencing infant behavioral and neurodevelopmental traits

In behavior genetic research on infancy, the most used study design to estimate the relative role of genetic and environmental influences on 'complex traits' (i.e., traits that are influenced by multiple genetics and environmental factors) has been the twin design[6]. A second powerful design for distinguishing genetic and environmental effects is the adoption design, but it is less feasible to conduct large adoption studies of infancy because placement

with adoptive families often occurs later in childhood. Finally, the sibling design can be used but is limited because sibling data alone cannot disentangle genetic and shared environment. Additionally, researchers need to rely on families having a second child within the timeframe of their research project to capture the infancy period of both siblings.

Table 1 provides an overview of infant behavioral and neurodevelopmental phenotypes based on definitions from the World Health Organization International Classification of Functioning, Disability and Health (ICF)[78].

Twin heritability in infancy

The first meta-analysis of infant twin studies reported on the meta-analyzed heritability and environmental estimates across infant traits[8] and identified 139 publications with 377 psychological and developmental phenotypes measured in a pooled sample of 79,044 twin pairs (31,053 monozygotic, 47,991 dizygotic). Phenotypes were categorized using the ICF[7], and estimates of heritability, shared and non-shared environment were calculated in meta-analytic structural equation models. These estimates indicate the proportion of the phenotypic variance attributable to genetic and environmental influences. Non-shared environmental influences operate to make children growing up in the same family different, whereas shared environmental influences make children growing up in the same family similar. This meta-analysis revealed moderate to high twin heritability and significant non-shared environmental influences. Results were found across key domains of infant behavior including attention (pooled heritability or h^2 = 48%, shared environmental effect or c^2 = 12%, nonshared environmental effect or e^2 = 40%), psychomotor skills (h^2 = 59%, c^2= 7%, e^2 = 33%), emotional (h^2= 40%, c^2 = 18%, e^2 = 42%), and social behaviors (h^2 = 38-44%, c^2 = 17-27%, e^2 = 29-42%) (Fig. 1).

Findings from adoption studies that include the infancy stage, such as the Early Growth and Development Study[9] and the Colorado Adoption Project[10], concur with infant twin studies in reporting heritability of behavioral and neurodevelopmental traits in the first years of postnatal life, including cognitive ability[11] and externalizing behaviors[12].

However, deducing heritability from twin and adoption designs does not specify, which form of genetic variation is involved. In order to assess whether some of this family-

based heritability is explained by common genetic variation, the next step is to apply molecular genetic methodologies to test for associations of common genetic variants with individual differences in infant development.

Genetic associations in infancy using polygenic scores

In support of the hypothesis that common genetic influences play a role in infant traits, recent studies report significant associations between a polygenic score (PGS) derived from a genome-wide association study (GWAS) of psychiatric or neurodevelopmental conditions in older participants and infant behavioral phenotypes. A PGS represents an individual's genetic propensity for a trait based on common genetic variation and is calculated as the sum of alleles associated with the trait the individual carries weighted by their effect sizes estimated from a genome-wide association study of that trait[13]. In terms of recent findings in infancy, the attention deficit hyperactivity disorder (ADHD) and autism PGSs were both found to be associated with neuromotor development in 1,174 3- to 5-month-olds[14] and with age at first independent steps in a sample of over 20,000 infants[15]. Notably, the schizophrenia PGS and the neurodevelopmental PGSs were not associated with age at first word, first sentences, or language delay [15]. However, in a longitudinal analysis on a partly overlapping sample (N = 15,205), the autism PGS was associated with language difficulties at 18 months and motor difficulties at 3 years[16]. Further, an association between the ADHD PGS and hyperactivity and inattention at age 18 months was reported. No associations between PGSs and parent-reported social communication and repetitive behaviors at 6, 18 or 36 months were found to be significant after multiple testing corrections [16].

In smaller infant cohorts, associations have been reported between the ADHD PGS and 'face looking' at 14 months[17], the schizophrenia PGS and the pupillary light reflex at 5 months[18], between a PGS capturing a range of psychiatric conditions and neural sensitivity [19] to faces at 8 months [19], and finally between the autism PGS and developmental change in latency of the pupillary light reflex between 9 and 14 months[20]. Although there is a risk of false positives with such association analyses due to the large numbers of possible PGS on offer to authors, p-value correction for multiple testing greatly reduces the likelihood of false positives.

In sum, PGS can be used to test for genetic associations with infant complex traits. There is alignment of this PGS evidence with past longitudinal twin studies that have reported stable genetic effects between infant phenotypes and later outcomes (e.g., [21]). However, creating PGS of infant phenotypes themselves would allow the estimation of infants' common genetic propensity for concurrent behavioral and neurodevelopmental phenotypes. This could be achieved through discovery GWAS of infant complex traits. Although the evidence base is still growing, existing PGS studies indicate that polygenic influences can be detected on infant motor skills and neuromotor functioning, as well as on early behavioral signs of ADHD, suggesting that these traits may be suitable for future infant GWASs.

Scoping review of existing genome-wide association studies of infant behavior

Most molecular genetic studies of psychological traits in infancy have used candidate-gene association methods (reviewed by [22]), but these have produced non-replicable findings. The preferred common gene-discovery approach has thus become GWAS, which allows simultaneous and systematic tests for association between a large number of single nucleotide polymorphisms (SNPs) with a phenotype. To quantify the number and type of published GWAS focusing on common genetic variants on infant behavioral and neurodevelopmental phenotypes, we conducted a scoping review following the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2020 checklist[23]. The protocol was preregistered on Open Science Framework (DOI: 10.17605/OSF.IO/PWF57) (see Supplementary Information, Supplementary Table 1 and 2 for methods).

Our systematic search revealed a limited existing literature (Supplementary Fig.1). While we observed some GWAS that merged samples aged approximately 36 months with older ages[24–27], we only found three GWAS, all with samples of N>1,000, conducted on behavioral and neurodevelopmental phenotypes in infants. Two studies[28,29] examined common genetic influences on infants' vocabulary in two developmental periods (15-18-months and 24-30[29] or 38[28] months of age) in overlapping samples. One of the two studies identified one genome-wide significant locus associated with expressive vocabulary ($p<5 \times 10^{-8}$)[28]. Another study investigated common genetic variants associated with preschool

internalizing problems in 2- and 3-year-olds[30] and found no genome-wide significant associations (see Supplementary Information).

Taken together, twin studies, adoption studies and recent polygenic score analyses on infant samples support the hypothesis that there are significant genetic influences on infant behavioral and neurodevelopmental phenotypes. Our scoping review showed that there is some gene discovery research focusing on infant anthropometric measures and a small number of infant medical conditions concerning body structures as defined by ICF[7] (see Results in Supplementary Information), but GWAS has not yet been exploited at scale or with adequately powered samples to identify the common genetic variation associated with infant behavioral and neurodevelopmental traits.

There are likely multiple reasons for the lack of well-powered GWAS studies on infant phenotypes, including the absence – until relatively recently (see Data Resources section below) – of available large-scale genotyped cohorts with waves of data collection in infancy. A second interrelated reason is a priority of funders for research on later life phenotypes (e.g., education, later life health) and there is greater advocacy/ stakeholder involvement for these later-life phenotypes (c.f. infants, who cannot advocate for themselves).

Next, we reflect on why infant genetic research is worthwhile and its translational applications.

The potential of infant genetic research for improving societal outcomes

An understanding of heritability, and subsequent gene discovery work on infant behavioral and neurodevelopmental traits, will advance basic science. Furthermore, while genetic research on phenotypes from later ages can in theory be applied to infant public health and medicine, we suggest that the new field of infant research on common genetic variation also has potential, in combination with other known modifying factors, for translational application and can feed into research on early intervention to optimally support infant development.

Public health policy

Clinical medicine allocates significant time and resources to identifying known genetic syndromes and rare causes of developmental delay in infants. For example, newborn population-based screening programs attempt to screen every newborn within the first few days of life for a small number of rare diseases worldwide, including almost all European countries, North America, Australia, Latin America, sub-Saharan Africa, China and India[31–34]. The importance of checks carried out by health visitors on all infants with the aim to pick up on developmental delay is now internationally recognized, and multiple programs have been launched to obtain global coverage of early developmental screenings[35]. Many causes of severe developmental delay involve rare genetic effects. However, these population-wide policies completely ignore the common genetic background of individual children. From other fields, there is evidence that rare and common genetic variation operate together. For example, common genetic variants have been shown to add to the likelihood of neurodevelopmental problems in individuals carrying a rare deleterious protein-coding variant[36].

With the arrival of reliable PGS for infant phenotypes, such as age at learning to walk or activity level, this genetic information could in theory be used to enhance predictive accuracy in terms of the needs of infants with known genetic syndromes and other rare causes of developmental delay, as well as the needs of children without known risk factors for developmental delay. For phenotypes for which well-powered GWAS and PGS exist, such as coronary heart disease, the clinical use of PGS is promising, but several important further steps need to be taken first, such as clinical trials, assessment of the precise clinical utility of the PGS[37] and careful assessment of the bioethical issues[38].

Educational policy

Governments create policies for infants and young children by providing guidelines and frameworks to ensure high-quality early childhood education and care that support children's learning and development in the first five years of age (e.g., [39,40]). Yet there is weak scientific evidence for the relative importance of different skills and behaviors in the early years regarding their effect on later outcomes due to the known challenges in

establishing causality from epidemiological data alone. However, a method that 'uses' GWAS summary statistics without focusing on genetic influence *per se*, can derive evidence for causality between two phenotypes. Mendelian randomization (MR) [41] of well-powered GWAS of infant milestones, behaviors and skills, could be used to test for the causal role of infant phenotypes on later educational outcomes. For example, MR has been used to demonstrate that childhood obesity and high body-mass index increase the odds of developing a major depressive disorder in adulthood, suggesting that interventions targeting obesity early in life can be beneficial for preventing major depression later in life [42]. Obtaining causal evidence concerning infant behavioral and neurodevelopmental traits on later educational outcomes would empower early years educational policies and intervention strategies. Policies and intervention strategies could offer resources for those infant skills that are shown to impact children's outcomes.

Parents and parenting

This new field of research on common genetic architecture in infants has the potential to reveal the extent and type of influence parents have on their infants. Without any information on genetics, a research design that studies parents and infants cannot disentangle effects of parents on infants that operate via the environment, via the shared genetics between them, and effects of parents on infants that are due to the genes of the parent that are not shared with the infant ("genetic nurture")[43]. However, once our field conducts well-powered GWAS of infant milestones, behaviors and skills, these three processes can be disentangled and their relative effects estimated. A disentanglement of these three processes will also offer realistic estimates of the size of their relative contributions to individual differences in the phenotype. This would then help to identify which process(es) early interventions and policies could aim to target in order to support infant development (e.g., the behavior itself, the infant's environment, parenting or more distal factors).

Methods to dissect a polygenic signal into direct genetic effects (in which family-wide effects are controlled for) and indirect effects, such as assortative mating, dynastic effects or population stratification, are available, such as comparing the association of a polygenic score in within- versus between-sibling (or dizygotic twin) analyses[44,45]. Second,

242 "genetic nurture" effects on an infant's phenotype can be quantified in samples where
243 genotype data from an infant and at least one parent are available[43]. Third, a new method
244 for genetic sensitivity analyses (Gsens[46]) enables associations between exposures and
245 outcomes in epidemiology to be adjusted for genetic confounding. Gsens could be
246 employed to assess the extent of associations between exposures and outcomes after
247 controlling for genetic confounding using PGS for infant traits. Therefore, application of the
248 above approaches using GWAS summary data for infant traits would open new possibilities
249 to explore to what degree direct genetic effects compared to parental and environmental
250 influences contribute to individual differences in infants, providing evidence that can be
251 used to design early interventions and policies.

252 To sum up, the availability of GWAS summary statistics for infant traits will open up
253 new avenues for translation beyond the primary aims of GWAS, such as investigating
254 parental effects and environmental influences on infant traits and their causal role on later
255 outcomes. It is possible that the polygenic contribution from common genetic variation for
256 early development is found to play a role in phenotypic presentation for young children with
257 rare disorders. New forms of evidence that would result from well-powered GWAS of infant
258 behavioral and neurodevelopmental traits will be directly relevant to evidence-based
259 policies for the first years of postnatal life and may have the potential to influence the
260 development of early interventions.[47].

261

262 **Data resources to advance infant genetics**

263 Here, we highlight the recent large samples and consortia that focus on early
264 childhood that offer new opportunities to identify common genetic effects on infant
265 behavioral and neurodevelopmental traits.

266 The relatively recent availability of a range of large, genotyped cohorts that include infant
267 assessments now allows well-powered gene-discovery investigations into the common
268 genetic architecture underlying infant traits. There are some organized efforts to bring
269 together genotyped cohorts from the early years, including the Early Growth Genetics (EGG)
270 Consortium which focuses on early growth, the EArly Genetics and Lifecourse Epidemiology
271 (EAGLE) consortium[48] and other curated lists of cohorts, including some of non-European

ancestry (see Table 2)**.** Most recently, the ongoing genotyping of multi-generation cohort studies, such as the Norwegian Mother, Father and Child (MoBa)[49] and the Japanese Tohoku Medical Megabank Project Birth and Three-Generation (TMM BirThree)[50] cohorts, constitute rich resources for gene discovery in infant research due to their size and extent of phenotyping. Cohorts that include genotyped relatives, such as siblings and parents, enable additional hypotheses to be tested, as articulated in the previous section. Projects are ongoing to deliver even larger sample sizes than those currently available, such as the USA All of Us research program[51].

Target infant samples, by which we mean genotyped infant samples that are independent of the samples used in discovery GWAS, can be used to test PGS associations. Target samples do not need to be as large as discovery GWAS samples to have the statistical power to detect associations between polygenic scores and phenotypes. Within infant genetic research, the field is in a strong position because a range of richly phenotyped target infant samples have been established and many have data access options for new collaborations e.g., the developing Human Connectome Project[52]. Furthermore, the explosion of multi-disciplinary, high-quality research within developmental cognitive neuroscience means that there are now infant samples that are sufficiently large to act as target samples and that have been assessed on a multitude of measurements, including neuroimaging, EEG, physiological assessments, eye tracking, behavioral observations and parental reports (see Supplementary Table 3). Therefore, there is considerable potential to test to what degree known common genetic architecture underlying complex traits influences infant physiology, behavior and brain structure and function. GWAS of infant phenotypes are likely to rely on phenotype measurements that are relatively efficient and inexpensive to collect, since timely or expensive measurement is often not feasible with large samples in the tens of thousands. In contrast, as target samples can be smaller, it is feasible to deeply phenotype them by inviting children to participate at multiple ages across their development and to include neurophysiological and neurocognitive assessments.

Considerations and challenges when working with infant data

Here, we consider infant phenotypic measurement, gestational age and other potential infant-specific factors, before highlighting participation and attrition biases that may be relevant for infant data.

Phenotypic measurement

We highlight four important considerations with respect to phenotypic measurement in infant genetic research. The first is that parental report from the primary caregiver (often the mother) is typically relied on when data are collected at large scale (unless national registers are accessed), because it is often unfeasible (due to cost, time or practicalities) with large research samples (N>1000) to employ home-based or lab-based assessments that are conducted in person by researchers. Parental ratings of phenotypes will include some rater bias, including potentially the parent's own traits and perceptions, which will be partly influenced by genetics[53]. In addition, parental ratings can include sibling contrast effects for some phenotypes, such as activity level, which inflate the variance[54]. It has long been known that different raters provide different sources of information about children[55], and for this reason an optimal solution is to employ multiple raters. However, it is less feasible to collect multiple ratings for infants, since infants do not yet have school teachers, and self or "peer" ratings are evidently not possible at a young age. Many infants may have a second caregiver, and some cohorts collect father/ second caregiver ratings, as well as mother ratings, but in our experience, paternal/ second caregiver ratings have far higher rates of missingness. We are not aware of large infant cohorts with ratings from day-care staff or grandparents, and again, there would be high rates of missingness since not all parents employ day-care for their infants or have their own parents involved. High reliance on the primary caregivers' report is evidently a challenge facing large infant cohorts. Nevertheless, there are reasons to believe that parents provide a realistic account of their children's general behavior, compared with assessments in an unusual laboratory setting or ratings by unfamiliar observers[56]. Parent reporting may be relatively more accurate for infants than for older children, given that older children spend less overall time with their parents[57,58]. Nevertheless, it is important to consider carefully the reliability of infant measures and where possible, ensure that parent-ratings have been validated against other forms of measurements (e.g. [59]). Looking to the future, a range of technology-enabled solutions for

obtaining objective measurements of infant behavior at a large scale are available, such as through actigraphy and content uploaded to apps[60]. Future research could consider further sources, including ratings from childcare providers, close relatives and linked registry data.

The second challenge in phenotypic measurement in infant genetic research is that instruments used to measure infant behavior are often specific to narrow developmental age ranges. For example, the Ages and Stages Questionnaire-3[61], a cost-effective tool widely used globally for developmental assessments[62], has 21 versions for specific ages between ages 2-60 months. As such, there can be heterogeneity of measurement across cohorts, depending on the age at which infants were assessed. When data are already collected, measurement heterogeneity can be handled by creating a reference panel in order to compare different measures[63]. Standardization of the scores for each of the studies included in a GWAS meta-analysis, where the sample mean equals 0 and standard deviation equals 1, is recommended to obtain consistency of the effect sizes and standard error units across studies. When scores are not on the same units because studies used varying measures, a sample size-weighted meta-analysis should be conducted, as opposed to a standard-error weighted meta-analysis[64]. With GWAS summary statistics, it is also possible to estimate the degree of genetic heterogeneity present across samples. For future large-scale efforts, consortia and collaborations could agree on standardized measures at set ages during infant development so that datasets are harmonized.

A third consideration is the special nature of infancy, which means that there is not always a direct mapping of phenotypic constructs in infancy to phenotypes in older ages. As an example, terms like reactivity and surgency are used uniquely to describe types of temperament in infancy. Conversely, at later ages, personality and behavior problems, rather than temperament, are terms used to refer to common types of behavior. These differences will partly reflect the different capabilities of infants versus older children and adults. For example, young infants cannot lie or steal so we do not measure 'conduct problems' in young infants.

Finally, in contrast to most complex traits in older ages[6], some key phenotypes in infancy may not show any significant heritability. Evidence from the recent twin meta-analysis suggests only a small and non-significant twin heritability for some infant phenotypes, including sleep problems (pooled twin heritability = 35%), cognitive ability

(34%) and language (24%)[8]. There is a risk that gene discovery research will be fruitless if carried out on phenotypes that either have low or zero heritability or a very high measurement error. It would be important to clarify whether there is a complete lack of SNP heritability for those traits with low twin heritability (see e.g., [28]).

Gestational age and other infant-specific factors

Gestational age is an infant-specific factor that needs to be considered when calculating infants' 'age'. For example, gestational age influences early motor development in the first two years of age in preterm infants, while it becomes less relevant from the third year[65]. As such, in a sample including infants born preterm, the rank distribution of 5-month-olds' ability to roll over is likely to be different if chronological age or gestational age is used. In addition, multiple births have an earlier average gestational age and lower average birth weight than singleton births. It is our view that chronological age is suitable in most instances but whenever possible, and particularly for research on ages 0-12 months, it would be important to conduct sensitivity analyses to test whether results are robust to individual differences in age at birth and singleton versus multiple births (that is, including these factors as covariates).

Furthermore, the behavior of an infant might be temporarily affected by age-related events, such as feeding issues, infantile colic and teething. Thus, events that occur during infancy and may be influenced by genetics might also be associated with the phenotype of interest.

Attrition biases

Infant cohorts will be subject to attrition and participation biases, and these may be the same or different to these biases present in older cohorts. At present, more research has been conducted on the biases in older-age samples than infant ones. In adult genotyped cohorts, samples are not always representative of the general population. For example, UK Biobank participants (aged approximately 40-70-year-olds) live in less socially deprived areas, are healthier, have fewer addictive behaviors and tend to live longer than the general population[66]. Thinking more generally, it is likely that subsections of society, including adults

who are marginalized or have died prematurely will not be part of adult genotyped cohorts. Furthermore, attrition occurs over time in longitudinal studies and often increases with the sample age[67,68]. It is known that this attrition is contingent on genetic influences[69].

What does this all mean for infant samples? For longitudinal samples established in infancy, including birth cohorts, we might assume that attrition is lower in the infant phenotype data collection phases compared to later phases when the attrition is higher. Indeed, in the MoBa cohort, the response rate for maternal questionnaires decreased from 85% at the children's 6 months of age, to 73% at 18 months, to 59% at 3 years and 47% at 8 years[70]. To minimize attrition biases in infant genetic research, studies should aim where possible to collect participant DNA samples early on within a longitudinal study in order to obtain DNA for as large and representative sample as possible. Nevertheless, it is likely that some attrition and participation biases are present in infant samples too. For example, self-selection into participating in a prospective longitudinal study and loss at follow-up in the first three years has been demonstrated in the MoBa cohort[71]. Additionally, higher PGS for schizophrenia were associated with questionnaire data missingness and drop out in the Avon Longitudinal Study of Parents and Children (ALSPAC). This was present even in the collection of the data at age 1, indicating that parents of individuals with higher genetic predisposition for schizophrenia were less likely to provide data about their children from the infancy stage of data collection, and not just from data collections at older ages[72]. Participation biases can now be handled constructively in GWAS using a statistical correction involving weighting[69] and it remains vital to invest resources to minimize attrition in longitudinal cohorts.

Concluding remarks

In this Perspective, we highlight the potential for much-needed progress in infant genetic research. Evidence from a twin meta-analysis, which concurs with findings from PGS analyses and adoption studies, shows that genetic influences are significant across a wide range of key infant complex traits (Fig. 1). However, genetic influences on infant behavioral phenotypes thus far remain almost completely undiscovered. A future goal, beyond

identifying genetic variation associated with individual infant phenotypes, will be to test for pleiotropic genetic effects across different infant phenotypes.

Knowledge about common genetic variation could potentially be used in combination with rare genetic variation to understand and better predict the phenotypic presentation of rare disorders and known genetic syndromes in early life, test causal links between infant traits and later outcomes and to shed light on the contribution of the parenting environment over and above genetics.

Genomic research on phenotypes measured in infancy within longitudinal studies has the potential to be more inclusive than genetic research on older individuals, as the earlier waves of data collection can be less affected by attrition biases compared to data collection on older participants. We anticipate that a surge in infant genetic research will complement the progress already made on the genetics of later life outcomes. However, more than that – and uniquely – a surge in infant genetic research has the potential to benefit all members of future generations from birth onwards by providing a clearer understanding of the early etiology of human brain and behavioral development.

Acknowledgements

This work was funded by the Simons Foundation to AR (Award ID: 724306).

Author contributions

AR conceived and designed the experiments, wrote the paper.

AG conceived and designed the experiments, analysed the data, wrote the paper.

Competing Interest Statement

The authors declare no competing interests.

Figure legend

Fig. 1. Infant phenotypes listed in the International Classification of Functioning, Disability and Health (ICF)[7] (see Table 1), for which pooled twin heritability has been estimated[8]. Behavioral and neurodevelopmental domains of the ICF (title of the boxes, in black bold font) belong to the Body Structures (light yellow box), Body Functions (light green box) and Activities and Participation (light blue boxes) components. Phenotypes in purple bold font are those for which there was enough data from twin studies to derive estimates from a meta-analysis of infant twin studies[8]. The resulting twin heritability (h^2), shared environment (c^2) and non-shared environment (e^2) estimates are shown in individual bar charts in dark purple, red and pink, respectively. For example, within the Mental Functions domain, the Psychomotor functions category was shown to have a pooled heritability of 59%, shared environment estimate of 7% and non-shared environment estimate of 33%[8]. The phenotypes are listed in the Mental functions and Interpersonal interactions and relationships domains boxes, but it is noted there is overlap with some other domains. Created with BioRender.com

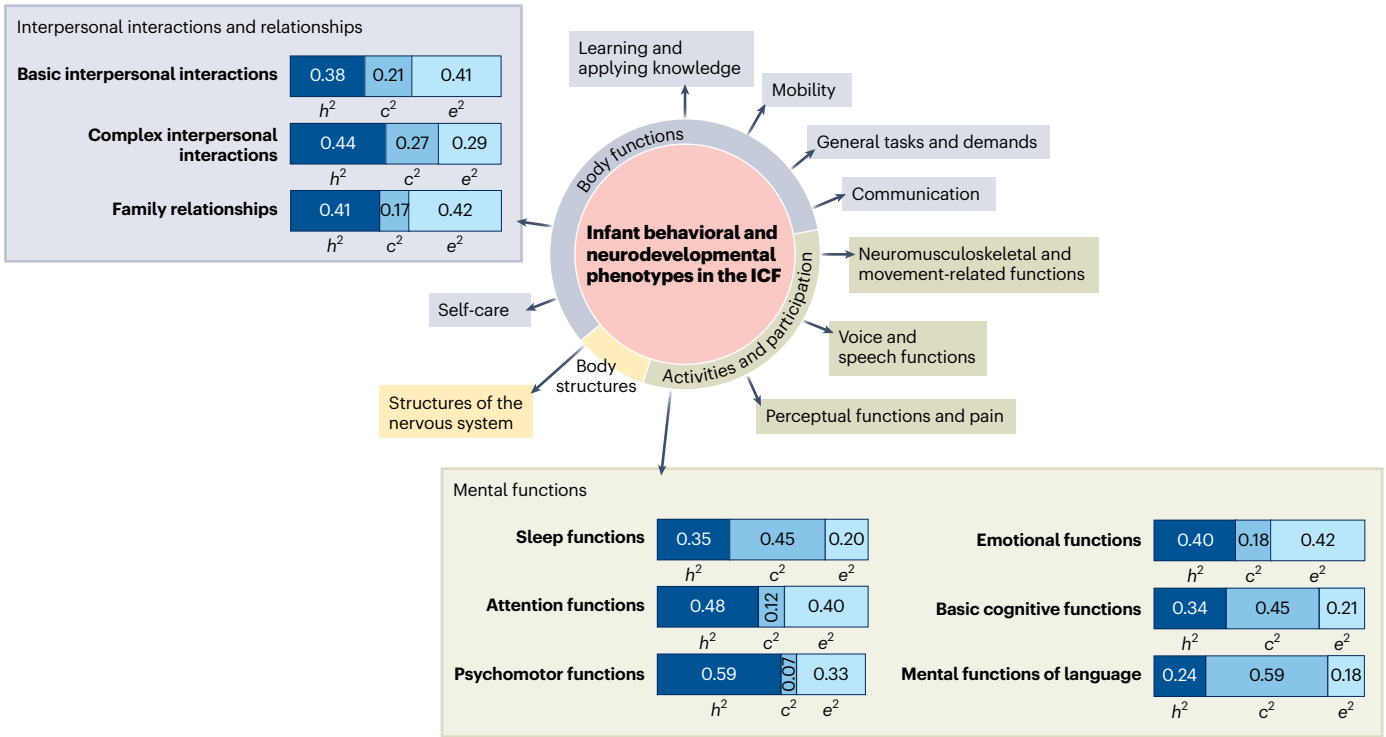

Table 1. Infant phenotypes listed in the International Classification of Functioning, Disability and Health (ICF)[7] that could be investigated in genomic research. For each component, the categories of that domain are listed relevant to children aged between 0 and 36 months. Of note, the categories defined as "[...] other specified, unspecified" traits in the ICF have not been included in this table.

Components	**Domains**	**Categories**
Body Structures	Structures of the nervous system	Structure of brain Spinal cord and related structures Structure of meninges Structure of sympathetic nervous system Structure of parasympathetic nervous system
Body Functions	Interpersonal interactions and relationships	Basic interpersonal interactions Complex interpersonal interactions Relating with strangers Formal relationships Informal social relationships Family relationships Particular interpersonal relationships
	Self-care	Washing oneself Caring for body parts Toileting Dressing Eating Drinking
	Learning and applying knowledge	Watching Listening Other purposeful sensing Copying Learning through actions with objects Acquiring information Acquiring language Acquiring additional language Focusing attention Directing attention Solving problems Making decisions
	Communication	Communicating with (receiving) spoken messages Communicating with (receiving) nonverbal messages Communicating with (receiving) formal sign language messages Speaking Pre-talking Singing Producing nonverbal messages Producing messages in formal sign language Conversation Discussion Using communication devices and techniques

	General tasks and demands	Undertaking a single task Undertaking multiple tasks Carrying out daily routine Handling stress and other psychological demands Managing one's own behaviour
Activities and Participation	Perceptual functions and pain	Seeing functions Hearing functions Vestibular functions Taste function Smell function Proprioceptive function Touch function Sensation of pain
	Voice and speech functions	Voice functions Articulation functions Fluency and rhythm of speech functions Alternative vocalization functions
	Neuromusculoskeletal and movement-related functions	Muscle tone functions Control of voluntary movement functions Involuntary movement functions Gait pattern functions Sensations related to muscles and movement functions
	Mental functions	Consciousness functions Orientation functions Intellectual functions Global psychosocial functions Dispositions and intra-personal functions Temperament and personality functions Energy and drive functions Sleep functions Attention functions Memory functions Psychomotor functions Emotional functions Perceptual functions Thought functions Basic cognitive functions Higher-level cognitive functions Mental functions of language Calculation functions Mental function of sequencing complex movements Experience of self and time functions

469

470

471 *Table 2.* Resources for finding cohorts with genetic and phenotypic infant data.

472

Name	Short description	Website
Birthcohorts.net	List of birth cohorts together with key information such as number of participants and contact names.	https://www.birthcohorts.net
COllaborative project of Development of Anthropometrical measures in Twins (CODATwins) project	Consortium of twin projects including both monozygotic and dizygotic twins to study macro-environmental variation in genetic and environmental effects on anthropometric traits	
Cohort and Longitudinal Studies Enhancement Resources (CLOSER)	Interdisciplinary partnership of leading social and biomedical longitudinal population studies, the UK data service and the British Library. It aims to increase the visibility, use and impact of longitudinal population studies, data and research.	https://www.closer.ac.uk/
Developing a Child Cohort Research Strategy for Europe (CHICOS)	Project to improve child health across Europe by developing an integrated strategy for mother-child cohort research in Europe.	https://www.cpo.it/chicosproject/
Early Genetics and Lifecourse Epidemiology (EAGLE) consortium	Consortium of pregnancy and birth cohorts that aims to collaborate to investigate the genetic basis of phenotypes in antenatal and early life and childhood.	https://www.eagle-consortium.org/
Early Growth Genetics (EGG) consortium	Collaborative effort to combine data from multiple genome-wide association studies (GWAS) in order to identify additional human genome loci that have an impact on traits related to early growth.	http://egg-consortium.org/

Landscaping International Longitudinal Datasets	List of longitudinal datasets to conduct transformative mental health research and work on early intervention in anxiety, depression and psychosis.	https://www.landscaping-longitudinal-research.com/
LifeCycle	Network of European cohorts with data collection beginning in pregnancy or childhood to conduct research on the role of markers of early-life stressors that influence health across the lifecycle.	https://lifecycle-project.eu
Twin family registries worldwide: An important resource for scientific research	Special Issue published on Twin Research and Human Genetics (Volume 22, 2019) that includes 61 papers on twin family registries from 25 countries.	https://www.cambridge.org/core/journals/twin-research-and-human-genetics/issue/AD90E6C75274A5A39DE9847B304414B9
UK Research and Innovation Medical Research Council	Collection of UK population cohorts to signpost users to individual cohorts with the aim to maximize the use and translation of findings of these UK assets.	https://mrc.ukri.org/research/facilities-and-resources-for-researchers/cohort-directory/

473

474

475

476

References

1. Infancy. In Oxford English Dictionary. Retrieved November 2nd, 2023. Preprint at https://www.oed.com/ (2023).
2. WHO Multicentre Growth Reference Study Group. WHO Motor Development Study: Windows of achievement for six gross motor development milestones. *Acta Paediatr* **95**, 86–95 (2006).
3. Knickmeyer, R. C. *et al.* A structural MRI study of human brain development from birth to 2 years. *Journal of Neuroscience* **28**, 12176–12182 (2008).
4. Bethlehem, R. A. I. *et al.* Brain charts for the human lifespan. *Nature* **604**, 525–533 (2022).
5. Hagenbeek, F. A. *et al.* Maximizing the value of twin studies in health and behaviour. *Nat Hum Behav* **7**, 849–860 (2023).
6. Polderman, T. J. C. *et al.* Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat Genet* **47**, 702–709 (2015).
7. World Health Organization. *International Classification of Functioning, Disability and Health: ICF*. (Geneva, 2001).
8. Austerberry, C., Mateen, M., Fearon, P. & Ronald, A. Heritability of psychological traits and developmental milestones in infancy. *JAMA Netw Open* **5**, e2227887 (2022).
9. Leve, L. D. *et al.* The Early Growth and Development Study: A dual-family adoption study from birth through adolescence. *Twin Research and Human Genetics* **22**, 716–727 (2019).
10. Plomin, R. & DeFries, J. C. The Colorado Adoption Project. *Child Dev* **54**, 276–89 (1983).
11. Rhea, S.-A., Bricker, J. B., Wadsworth, S. J. & Corley, R. P. The Colorado Adoption Project. *Twin Research and Human Genetics* **16**, 358–365 (2013).
12. Leve, L. D. *et al.* The Early Growth and Development Study: A Prospective Adoption Study From Birth Through Middle Childhood. *Twin Research and Human Genetics* **16**, 412–423 (2013).
13. Wray, N. R. *et al.* Research Review: Polygenic methods and their application to psychiatric traits. *J Child Psychol Psychiatry* **55**, 1068–1087 (2014).
14. Serdarevic, F. *et al.* Polygenic risk scores for developmental disorders, neuromotor functioning during infancy, and autistic traits in childhood. *Biol Psychiatry* **87**, 132–138 (2020).
15. Hannigan, L. J. *et al.* Developmental milestones in early childhood and genetic liability to neurodevelopmental disorders. *Psychol Med* 1–9 (2021) doi:10.1017/S0033291721003330.
16. Askeland, R. B. *et al.* Early manifestations of genetic risk for neurodevelopmental disorders. *Journal of Child Psychology and Psychiatry* **63**, 810–819 (2022).
17. Gui, A. *et al.* Look duration at the face as a developmental endophenotype: Elucidating pathways to autism and ADHD. *Dev Psychopathol* **32**, 1303–1322 (2020).
18. Portugal, A. M. *et al.* Pupil size and pupillary light reflex in early infancy: heritability and link to genetic liability to schizophrenia. *Journal of Child Psychology and Psychiatry* (2021).
19. Gui, A. *et al.* Association of polygenic liability for autism with face-sensitive cortical responses from infancy. *JAMA Pediatr* **175**, 968–970 (2021).
20. Fish, L. A. *et al.* Development of the pupillary light reflex from 9 to 24 months: association with common ASD genetic liability and 3-year ASD diagnosis. *Journal of Child Psychology and Psychiatry* (2021).

21. Tucker-Drob, E. M. & Briley, D. A. Continuity of genetic and environmental influences on cognition across the life span: A meta-analysis of longitudinal twin and adoption studies. *Psychol Bull* **140**, 949–979 (2014).

22. Papageorgiou, K. A. & Ronald, A. The genetic basis of psychological traits in infancy. in *The Wiley Handbook of Developmental Psychopathology* 233–258 (Wiley Blackwell, 2017). doi:10.1002/9781118554470.ch11.

23. Page, M. J. *et al.* The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *The BMJ* vol. 372 Preprint at https://doi.org/10.1136/bmj.n71 (2021).

24. Middeldorp, C. M. *et al.* A Genome-Wide Association Meta-Analysis of Attention-Deficit/Hyperactivity Disorder Symptoms in Population-Based Pediatric Cohorts. *J Am Acad Child Adolesc Psychiatry* **55**, 896-905.e6 (2016).

25. Jami, E. S. *et al.* Genome-wide Association Meta-analysis of Childhood and Adolescent Internalizing Symptoms. *J Am Acad Child Adolesc Psychiatry* **61**, 934–945 (2022).

26. Ip, H. F. *et al.* Genetic association study of childhood aggression across raters, instruments, and age. *Transl Psychiatry* **11**, 413 (2021).

27. Pappa, I. *et al.* A genome-wide approach to children's aggressive behavior: The EAGLE consortium. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **171B**, 562–572 (2016).

28. Verhoef, E. *et al.* Genome-wide analyses of vocabulary size in infancy and toddlerhood: Associations with Attention-Deficit/Hyperactivity Disorder, literacy, and cognition-related traits. *Biol Psychiatry* (2023) doi:10.1016/j.biopsych.2023.11.025.

29. St Pourcain, B. *et al.* Common variation near ROBO2 is associated with expressive vocabulary in infancy. *Nat Commun* **5**, 1–9 (2014).

30. Benke, K. S. *et al. A Genome-Wide Association Meta-Analysis of Preschool Internalizing Problems*. *JOURNAL OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY* vol. 53 www.jaacap.org (2014).

31. Koracin, V. *et al.* Current Status of Newborn Screening in Southeastern Europe. *Front Pediatr* **9**, (2021).

32. Jansen, M. E., Metternick-Jones, S. C. & Lister, K. J. International differences in the evaluation of conditions for newborn bloodspot screening: A review of scientific literature and policy documents. in *European Journal of Human Genetics* vol. 25 10–16 (Nature Publishing Group, 2016).

33. Therrell, B. L. & Padilla, C. D. Newborn screening in the developing countries. *Curr Opin Pediatr* **30**, 734–739 (2018).

34. Borrajo, G. J. C. Newborn screening in Latin America: A brief overview of the state of the art. *Am J Med Genet C Semin Med Genet* **187**, 322–328 (2021).

35. The Global Research on Developmental Disabilities Collaborators. Accelerating progress on early childhood development for children under 5 years with disabilities by 2030. *The Lancet Global Health* vol. 10 e438–e444 Preprint at https://doi.org/10.1016/S2214-109X(21)00488-5 (2022).

36. Niemi, M. E. K. *et al.* Common genetic variants contribute to risk of rare severe neurodevelopmental disorders. *Nature* **562**, 268–271 (2018).

37. Patel, A. P. & Khera, A. V. Advances and applications of polygenic scores for coronary artery disease. *Annu Rev Med* **74**, 141–154 (2023).

38. de Hemptinne, M. C. & Posthuma, D. Addressing the ethical and societal challenges posed by genome-wide association studies of behavioral and brain-related traits. *Nat Neurosci* **26**, 932–941 (2023).

39. England's Department for Education. *Statutory Framework for the Early Years Foundation Stage*. (2021).

40. European Commission ET2020 Working Group. *Early Childhood Education and Care*. (2020).

41. Evans, D. M., Moen, G.-H., Hwang, L.-D., Lawlor, D. A. & Warrington, N. M. Elucidating the role of maternal environmental exposures on offspring health and disease using two-sample Mendelian randomization. *Int J Epidemiol* **48**, 861–875 (2019).

42. Yan, S. *et al.* Mendelian randomization analysis identified causal association of childhood obesity with adult major depressive disorder. *Pediatr Obes* **17**, (2022).

43. Kong, A. *et al.* The nature of nurture: Effects of parental genotypes. *Science (1979)* **428**, 424–428 (2018).

44. Chen, C. *et al.* Associations between psychiatric polygenic risk scores and general and specific psychopathology symptoms in childhood and adolescence between and within dizygotic twin pairs. *J Child Psychol Psychiatry* (2022) doi:10.1111/jcpp.13605.

45. Selzam, S. *et al.* Comparing Within- and Between-Family Polygenic Score Prediction. *Am J Hum Genet* **105**, 351–363 (2019).

46. Pingault, J. B. *et al.* Genetic sensitivity analysis: Adjusting for genetic confounding in epidemiological associations. *PLoS Genet* **17**, 1–22 (2021).

47. Ronald, A. Editorial: Polygenic scores in child and adolescent psychiatry – strengths, weaknesses, opportunities and threats. *Journal of Child Psychology and Psychiatry* **61**, 519–521 (2020).

48. Middeldorp, C. M., Felix, J. F., Mahajan, A. & McCarthy, M. I. The Early Growth Genetics (EGG) and EArly Genetics and Lifecourse Epidemiology (EAGLE) consortia: Design, results and future prospects. *Eur J Epidemiol* **34**, 279–300 (2019).

49. Magnus, P. *et al.* Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol* **45**, 382–388 (2016).

50. Kuriyama, S. *et al.* Cohort Profile: Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study (TMM BirThree Cohort Study): Rationale, progress and perspective. *Int J Epidemiol* **49**, 18-19M (2020).

51. https://allofus.nih.gov/news-events/press-kit/all-us-research-program-backgrounder.

52. Edwards, A. D. *et al.* The Developing Human Connectome Project Neonatal Data Release. *Front Neurosci* **16**, (2022).

53. Bartels, M., Boomsma, D. I., Hudziak, J. J., van Beijsterveldt, T. C. E. M. & van den Oord, E. J. C. G. Twins and the study of rater (dis)agreement. *Psychol Methods* **12**, 451–466 (2007).

54. Ronald, A., Edelson, L. R., Asherson, P. & Saudino, K. J. Exploring the relationship between autistic-like traits and ADHD behaviors in early childhood: findings from a community twin study of 2-year-olds. *J Abnorm Child Psychol* **38**, 185–96 (2010).

55. Achenbach, T. M., McConaughy, S. H. & Howell, C. T. Child/adolescent behavioral and emotional problems: implications of cross-informant correlations for situational specificity. *Psychol Bull* **101**, 213–32 (1987).

56. Diamond, K. E. & Squires, J. The Role of Parental Report in the Screening and Assessment of Young Children. *J Early Interv* **17**, 107–115 (1993).

57. Dotti Sani, G. M. & Treas, J. Educational Gradients in Parents' Child-Care Time Across Countries, 1965–2012. *Journal of Marriage and Family* **78**, 1083–1096 (2016).

58. Drago, R. The parenting of infants: A time-use study. *Mon Labor Rev* **132**, 33–43 (2009).

59. Langendonk, J. M. *et al.* Assessment of motor milestones in twins. *Twin Res Hum Genet* **10**, 835–9 (2007).

60. Daum, M. M. *et al.* The kleineWeltentdecker App - A smartphone-based developmental diary. *Behav Res Methods* **54**, 2522–2544 (2022).

61. Squires, J. & Bricker, D. *Ages and Stages Questionnaire (ASQ): A Parent Completed Child Monitoring System*. (MD: Brooks Publishing Company, Baltimore, 2009).

62. Filgueiras, A., Pires, P. & Landeira-Fernandez, J. Screening measures used in child daycare centers: A 15-years systematic review. *Psychology* **05**, 2109–2119 (2014).

63. Luningham, J. M. *et al.* Harmonizing behavioral outcomes across studies, raters, and countries: application to the genetic analysis of aggression in the ACTION Consortium. *Journal of Child Psychology and Psychiatry* **61**, 807–817 (2020).

64. Willer, C. J., Li, Y. & Abecasis, G. R. METAL: Fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26**, 2190–2191 (2010).

65. Harel-Gadassi, A. *et al.* Developmental assessment of preterm infants: Chronological or corrected age? *Res Dev Disabil* **80**, 35–43 (2018).

66. Fry, A. *et al.* Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol* **186**, 1026–1034 (2017).

67. Howe, L. D., Tilling, K., Galobardes, B. & Lawlor, D. A. Loss to follow-up in cohort studies. *Epidemiology* **24**, 1–9 (2013).

68. Young, A. F., Powers, J. R. & Bell, S. L. Attrition in longitudinal studies: Who do you lose? *Aust N Z J Public Health* **30**, 353–361 (2006).

69. Schoeler, T. *et al.* Participation bias in the UK Biobank distorts genetic associations and downstream analyses. *Nat Hum Behav* **7**, 1216–1227 (2023).

70. Vejrup, K., Magnus, P. & Magnus, M. Lost to follow-up in the Norwegian mother, father and child cohort study. *Paediatr Perinat Epidemiol* **36**, 300–309 (2022).

71. Biele, G. *et al.* Bias from self selection and loss to follow-up in prospective cohort studies. *Eur J Epidemiol* **34**, 927–938 (2019).

72. Martin, J. *et al.* Association of genetic risk for schizophrenia with nonparticipation over time in a population-based cohort study. *Am J Epidemiol* **183**, 1149–1158 (2016).