

### II.III EARLY CHILD DEVELOPMENT: FINDINGS AND PERSPECTIVES FROM BIRTH COHORTS IN BRAZIL

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We aimed to compare the rates of early developmental delay, between epochs and geographical regions, among children participating in three population-based birth cohort studies (BCSs) in Brazil: MINA-Brazil (2015–2016),<sup>1</sup> the 1993 Pelotas BCS and the 2004 Pelotas BCS.

MINA-Brazil is a population-based cohort study examining maternal and child health and nutrition in the city of Cruzeiro do Sul, Acre, in the northern region of Brazil. The cohort consists of 1246 children born between July 2015 and June 2016 of women resident in the urban area of Cruzeiro do Sul. The two Pelotas BCS are based in the city of Pelotas, in the Southern state of Rio Grande do Sul. All women delivering during the years of 1993 and 2004 in one of the five maternity hospitals of Pelotas, and who were resident in the urban area of the city were invited to participate in the studies (5249 and 4231 live newborns from the 1993 and 2004 cohort, respectively). The Denver II Screening Test was used to characterize neurodevelopmental delay, at 12 months in the three cohorts and at 24 months in the MINA-Brazil study. Suspected delay was defined as  $\geq 2$  items of concern and/or  $\geq 1$  delayed items. In the 2004 Pelotas BCS, children's exposure to cognitive stimulation was assessed at 24 months, using measures of parent-child and interpersonal interactions, and attention-related executive functions were assessed at age 11 years using the adapted Test-of-Everyday-Attention-for-Children.

In our comparisons, the prevalence of suspected neuro-psychomotor delay at 12 months was 37% in the 1993 Pelotas cohort, 21% in 2004 Pelotas cohort<sup>2</sup> and 29% in MINA-Brazil. At age 24 months nearly half of the children of MINA-Brazil had suspected developmental delay, with highest rates of delay reported for the language domain. In the 2004 Pelotas cohort, levels of stimulation were inversely proportional to developmental scores. Just <3% of the more stimulated children presented low performance compared with 41 and 24% in the bottom groups of stimulation. Higher stimulation scores were also associated with fewer impairments in attentional-control and attentional-switching at 11 years.<sup>3</sup>

Overall, we observed an improvement in child development between 1993 and 2004 in the Pelotas cohorts. However, children from the MINA-Brazil study had higher rates of developmental delay than those born more than a decade earlier in the Pelotas cohorts. It is possible that these observed differences may be accounted for by the high levels of social vulnerability present in the MINA-Brazil study population compared with the Pelotas population. Our finding of the highest rates of language delay in this population is consistent with previous evidence that language is the developmental domain that is most sensitive to the negative impacts of socioeconomic adversity. Our findings also show that early child stimulation may provide protective effects against cognitive impairments.

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### III EARLY CHILD GROWTH AND DEVELOPMENT: SIMILARITIES ACROSS POPULATIONS; DIFFERENCES ACROSS PHENOTYPES AND EXPOSOTYPES

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The INTERGROWTH-21st Project has primarily addressed: 1) whether the variability in skeletal growth and early child development (ECD) within a population is larger than that among populations when health and nutritional needs are met, and 2) whether phenotypes and exposotypes of fetal and newborn growth are associated with differential growth and development during early childhood.

Between 2009 and 2016, we first conducted serial standardised measurements of fetal and postnatal growth, and a standardised, comprehensive 24-months ECD assessment, in 4607 mothers and their infants from geographically delimited populations in Brazil, China, India, Kenya, Oman, the UK, and USA, that had low-risk indicators for perinatal and postnatal morbidity and mortality at population and individual levels.

This allowed the construction of the first international standards of: (1) fetal growth (n=4321 fetuses from all participating sites) and (2) ECD, as measured on the INTER-NDA test at age 2 (n=1181 infants from five of the participating sites). The cohort's prescriptive nature was confirmed at age 2 years by demonstrating satisfactory postnatal growth and development, i.e. the infants overlapped at the 49th, 50th and 58th centiles for length, head circumference and weight, respectively, of the WHO Child Growth Standards, and between the 3rd and 97th centiles of the WHO motor development milestones. Using variance component analysis, the percentage of the total variance explained by *among-site* differences (as opposed to *within-individuals* in a population) ranged from 1.9% to 3.9% for skeletal growth (fetal, newborn and infant length) and 1.3% to 9.2% for neurocognitive outcomes measured on the INTER-NDA.<sup>1 2</sup>

Secondly, the characterisation of phenotypes and exposotypes associated with differential early growth and development was examined in a cohort of 7311 preterm and term singleton newborns enrolled between 2012 and 2018 in maternity hospitals in Brazil, Kenya, Pakistan, South Africa, Thailand, and the UK. Using repeated ultrasound scans of

fetal cranial growth measures from <14 weeks' gestation, five fetal trajectories were identified, subsequently associated with specific neurodevelopmental, behavioural, visual, postnatal morbidity and anthropometric measures at birth and at age 2 years (n=3598). Trajectories reflecting *early faltering* or *accelerating* fetal head circumference growth changed within a 20–25 week gestational age window and were associated with developmental scores at 2 years in a mirror (positive/negative) pattern, mostly focused on maturation of cognitive, language and visual skills.<sup>3</sup> Additionally, analysis of the 1381 preterm infants born within this cohort identified eight aetiologically-based preterm phenotypes, which were associated with markedly different neonatal morbidity, child growth and developmental profiles at age 2.

These findings confirm that in early life: (1) within-population variability for skeletal growth and neurodevelopment is far greater than that among-populations when health and nutritional needs are met, and (2) epidemiological patterns between un-selected populations are largely environment-driven, expressed by phenotypes and exposotypes with differential risk profiles. The Project has also constructed, for the first time, a set of international standards to monitor human growth and development from early pregnancy to age 2, to facilitate unified clinical care and research (<https://intergrowth21.tghn.org/standards-tools/>).

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## IV. Rescuing child development: from science to interventions

### IV.1 THE NEUROBIOLOGY OF EARLY PARENTING: FROM BASIC SCIENCE TO INTERVENTIONS

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Parents' early interactions with their infants have been shown to shape long-term child development. When interacting with an infant, adults intuitively enact a range of behaviours that support infant development, such as altering speech, establishing eye contact and mirroring infant expressions. Sensitive, contingent responsiveness from parent to infant involves the

parental capacity to detect, monitor and respond to infant social signals.

Our work has studied parental responses to infant signals using a range of methods, from magnetoencephalography and local field potential recordings, to observational studies of motor behavior and mother-infant interactions in depression. This work has provided converging evidence that infant communicative cues have a privileged status, and elicit highly selective responses in the human adult brain. We have demonstrated rapid differentiation of infant vocalisations from other sounds in both subcortical regions, such as the periaqueductal gray (PAG), and cortical regions, including the orbitofrontal (OFC), anterior cingulate and motor cortices. Before 100ms, we found a significant difference in activity recorded from the PAG in response to infant vocalizations compared with constructed control sounds and adult and animal affective vocalizations.<sup>1</sup> We propose that this rapid activity in response to infant vocalizations may reflect the initiation of a state of heightened alertness to support parenting responses.

Among cortical brain regions, we have reported several findings showing that the OFC rapidly responds to different infant communicative cues, such as faces and voices, which may support their efficient processing. OFC activity may thereby facilitate rapid orienting to infant cues, fundamental to intuitive parenting behaviour.<sup>2</sup> These neuroimaging findings of rapid processing of infant cues are further supported by experimental evidence showing that adults can move more rapidly, and with greater accuracy and effort after hearing infant cries, compared to other environmental sounds.

We have also shown that adults are highly attuned to subtle parameters communicating distress in infant cues, and that attunement can be enhanced via training. In adults with major depression, and no musical training, we found disrupted interpretation of infant vocal distress, but not in adults with music training.<sup>3</sup> This suggests that prior acoustic training might reduce depression-related disruptions in sensitivity to infant cues. Furthermore, we found that interpretation of infant vocal distress could be enhanced through short-term, perceptual acoustic discrimination training. Overall, our work suggests that adults can rapidly detect and preferentially orient to infant cues, processes supported by both subcortical and cortical brain responses. Interventions that can enhance parents' attention to infant cues, and the capacity to 'read', or interpret infant cues appropriately, may be useful in support of early caregiving. Such interventions may be of particular value in conditions where caregiving is disrupted, in for instance depression, where there are well-recognised biases in social and emotional processing.

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