WES FERNANDES/*NATURE*

A London lab is deploying every technology it can to understand infant brains, and what happens when development goes awry.

Baby Ezra is sitting on his mother's lap and staring at the computer screen with the amazement of someone still new to the world. The five-month-old's eyes rest on a series of pictures: three dancing women, four black circles, then a face among random objects. Ezra studies the screen with fascination — although now and then, his attention wanders. He lets out a gurgle, and moments later, a short cry. He is chewing a sock.

Below the screen, a box is shining infrared light at his cornea, and then capturing and processing the reflected light to work out the direction of his gaze. Behind a curtain, postdoc Jannath Begum Ali checks the data streaming in on her monitor. This set-up is part of a sophisticated experiment to understand the early development of the human mind in the Babylab at Birkbeck, University of London. The scientists here will closely monitor Ezra's brain and behaviour at visits over the next two and a half years.

Oblivious to his important role in science, Ezra furrows his brow into a frown. What happens next is apparent only to his mother, who turns him around and checks his behind. With just half of a planned 15-minute observation complete, Ezra has defecated. At that point, everyone takes a break.

At Babylab, a 6-month-old has her brain's electrical activity monitored.

How do you get into the mind of a human being who cannot speak, does not follow instructions and rudely interrupts your experiments? That is the challenge embraced by scientists at the Babylab. The brain undergoes more change during the first two years of life than at any other time: consciousness, traits of personality, temperament and ability all become apparent, as do the first signs that development could be drifting off course. But this period is also the most difficult to explore, because many of the standard tools of human neuroscience are useless: babies will not lie awake and still in an imaging machine, and they cannot answer questions or do as they are told. Researchers have measured infants' interest and attention mostly by tracking their gaze — but even this method has been criticized as crude.

"There are many studies where someone tries to prove that the baby understands goals, causality, number — and in 99% of those studies the only measure they look at is a change in looking time," says Jerome Kagan, a psychologist at Harvard University in Cambridge, Massachusetts.

The field is now becoming more sophisticated, thanks in part to the Birkbeck lab. Scientists there have pioneered techniques such as infant near-infrared spectrometry (NIRS), which measures brain activity by recording the colour, and therefore the oxygenation, of blood. They are also trying to strengthen conclusions by combining multiple techniques. Among the handful of baby labs around the world, this makes the London one stand out. "They are doing research on babies using every single technique you could imagine," says Richard Aslin, an infant-behaviour researcher and director of the Rochester Center for Brain Imaging in New York.

The lab has used such tools to reveal a series of 'firsts' about the infant mind: that babies prefer to look at faces that are looking directly at them, rather than away from them; that they respond to such direct gaze with enhanced neural processing[1]; and that changes in this brain response may be associated with the later emergence of autism — the first evidence that a measure of brain function might be used to predict the condition[2]. In 2013, the Babylab started the flagship project of which Ezra is part: an effort to study infants from 12 weeks old who are at high risk of autism spectrum disorder or attention deficit hyperactivity disorder (ADHD), alongside a control group, in order to detect more early signs of these conditions and find behavioural therapies that might help. "It's an exciting, and emerging, field," says Mark Johnson, director of the Babylab.

And, like its subjects, the London lab is growing up. In 2014, Johnson received £2.3 million (US$3.5 million) from a trio of foundations to establish a toddler lab at Birkbeck, in which children aged 18 months to 3 or 4 years old will be attached to wireless forms of electroencephalography (EEG), NIRS and eye-tracking technology as they walk around, play and interact with other children. The aim is to understand the brain during toddlerhood, the time when children start to appreciate the difference between self and other, complex language develops and long-term memories are first laid down. "In child development in general, but also in our brain-development work, the terrible twos are a major black hole," Johnson says.

LOOK AND LEARN

There is a well-worn adage in show business that you should never work with children or animals. Johnson built his career doing both. For his PhD project in the 1980s, he investigated whether day-old chicks formed social attachments to any object placed in their pen, or if they preferred ones that resembled a mother hen. (The chicks were particularly drawn to objects with hen-like necks and faces, but weren't too fussy about the rest of their looks[3].) But Johnson was more interested in human development, so after his PhD he took a research-scientist position in London to begin studying infants. "In some ways that's not as big a jump as it sounds," he says. "In both cases you're trying to develop tasks and get information from non-verbal creatures."

Scientists have been attempting practical research with babies since the middle of the twentieth century. One of the first to do so was Jean Piaget, a Swiss psychologist who used detailed observations of infants and older children to gain insight into how they understand the world — including, famously, by hiding an object to see whether infants try to find it. He concluded that babies cannot grasp the concept that an object still exists when it is out of sight until they are around eight months old. Piaget went on to develop the theory that babies are essentially born as blank slates, but possess the machinery that motivates them to explore the world and allows them to assimilate knowledge.

Infant neuroscience leapt forward in the early 1960s, when the US developmental psychologist Robert Fantz started measuring the amount of time babies spent looking at something as a way to gauge how interested in it they were. Fantz reported that a two-month-old baby spent twice as long looking at a sketch of the human face as at a bullseye, for instance. Experiments based on gaze measurements have been the field's workhorse ever since. "It is no exaggeration to say that without looking-time measures, we would know very little about nearly any aspect of infant development," says Aslin. Gaze experiments have led some researchers to conclude that, far from being blank slates, babies are born with an innate appreciation of number and human faces, as well as the ability to recognize when their mother's native language is being spoken — a familiarity proposed to develop through hearing speech while in the womb.

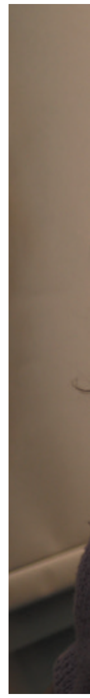
> "They are doing research on babies using every single technique you could imagine."

"There have been literally thousands of experiments done with these looking-time methods," Aslin says, "and by and large it is a pretty reliable technique; you can have two labs running the same experiment and you get the same results." But Aslin and Kagan are two of a growing number of researchers who think that such infant studies should be viewed with caution: it can be dangerous to infer too much about the workings of a baby's mind from just their fleeting glance — and they worry that some labs do not control for confounding factors as well as they should. "Looking time is under the control of so many conditions," Kagan says. "What are the physical features of the stimulus? Are its lines mainly curved or straight? What colours are present? How much contrast in lighting is there?"

Babies' brains are growing and developing at an extraordinary pace, which makes comparisons between different ages difficult: a newborn's gaze might reflect innate abilities, but a seven-month-old's will also be influenced by what he or she is starting to learn and remember about the world. "An infant may look longer in order to relate the event to what it already knows," says Kagan. "The main point is that no single measure is able to supply all the evidence required for conclusions about what infants know."

That was the opinion that Johnson quickly reached when he began infant research: the reliance on looking time and observations alone were unsatisfying. He established a baby lab at University College London (UCL) in 1993, and it moved to more spacious premises at Birkbeck in 1998. From the start, Johnson wanted to take a more high-tech approach to investigating brain development than were the handful of other similar labs.

In 2005, Johnson and his colleagues combined observations of looking time with electrical measurements of brain activity to investigate



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Piaget's claim that infants younger than nine months do not understand the permanence of an object that has vanished. When adults view an object disappearing, they tend to show an increase in a particular type of neural oscillation over the right temporal cortex. Johnson, working with colleagues Gergely Csibra and Jordy Kaufman, showed that six-month-old babies show a similar pattern — suggesting that they do keep hidden objects in mind. The same pattern was not observed when the object disintegrated instead of being hidden[4].

Studies such as these have convinced Johnson that babies are not born blank slates, but neither do they possess adult-like concepts about things like number. "My work, I think, goes for a middle ground," he says. He argues that the newborn has basic attention preferences for things such as faces and speech, and that these preferences shape the brain as it develops[5]. Johnson's observation that young babies prefer direct eye contact is one such example; this sets them up to focus on socially relevant parts of their surroundings, which in turn enables them to learn about language and other social cues such as facial expressions.

HAPPY BABY

Working with babies requires specialized kit — particularly for a laboratory that can see as many as 14 in a day. The Babylab kitchen hosts a bottle-warmer, and bathrooms are well stocked with wet-wipes. The waiting room is brightly decorated and scattered with easy-to-clean toys. The laboratories, however, are largely empty and painted a dull battleship grey — a deliberate choice, because babies are easily distracted. "We try to make it as boring as possible, except for the thing we need them to focus on," says Leslie Tucker, coordinator of the Centre for Brain and Cognitive Development, of which the Babylab is part.

Hungry or tired babies do not make for good experiments, so everything is carefully planned around meals and naps. In the waiting room, Caitlin — a four-month-old in stripy blue dungarees — is receiving a last-minute breastfeed before being ushered into a lab. She is participating in a study to assess the development of mimicry in babies: the unconscious tendency of people to frown when someone else frowns, or smile when they smile.

"Mimicry serves important social functions in adults and has even been suggested to be the 'social glue' that binds us together," says Carina de Klerk, who is leading that study at Birkbeck. But very little is known about how, and when, it develops. Some researchers think that it is something babies are born with — newborns have been observed to stick their tongues out in response to an adult doing the same[6]. But "it's not clear if the baby is actually copying, or perhaps they just stick out their tongue whenever something exciting happens", de Klerk says.

She sings to baby Caitlin while sticking electrodes on her temples, cheeks and under her chin. The baby seems unsure, so a research assistant appears, brandishing a garish musical telephone. The art of distraction is a fundamental skill that anyone working in a baby lab must quickly master. "Researchers from other fields come down here and are often horrified at the lack of controls," says Tucker. "You're going to interrupt the experiment if you have to, or make noises to distract them if they look like they're going to cry."

It works: Caitlin is now cooing and smiling. The researchers pause for a moment, while Caitlin's mother takes a photo of her "science baby" on her phone. Then Caitlin is shown a series of video sequences of a woman raising her eyebrows or opening and closing her mouth, interspersed with static pictures of farm animals.

The mimicry experiment is a prime example of the Babylab's mixed-methods approach. Baby Caitlin stares intently at the screen; she does not seem to be copying the woman's actions. But the electrodes on her face may tell a different story: the technique, called electromyography (EMG), picks up electrical activity in her facial muscles, which will indicate if Caitlin is activating her eyebrow area — even if she is not overtly moving it — in response to the woman raising hers. Later in the day, Caitlin is shown the same video sequence while hooked up to NIRS.

NIRS is transforming the ability of researchers to peer into the minds of babies. It was originally adopted by medical physicists at UCL as a technique to help predict the risk of stroke in premature babies. They then began working with Birkbeck researchers to adapt it to answer more fundamental questions[7]. By tracking the flow of oxygenated blood, NIRS allows scientists to see which brain areas become more active in response to external events. For instance, a 2009 study from the Babylab revealed that the brains of five-month-olds already show an adult-like pattern of activation in response to social stimuli, such as a woman playing peek-a-boo with them[8]. In the mimicry study, the researchers want to see if the babies' brains show a similar pattern to those of adults who are mimicking others, which should help to explain if mimicry is partly innate.

But NIRS is not perfect, in part because it cannot measure what is happening in important inner brain regions such as the hippocampus or the amygdala. "The brain is a complex connected circuit. If you only measure a superficial part of that circuit, you can come to the wrong conclusions," Kagan says. To assess these deeper areas, researchers need a technique such as functional magnetic resonance imaging (fMRI),

Not your average lab: the Babylab (left) is designed for infants; a row of EEG 'hairnets' (middle); and an eye-tracking experiment under way (right).

"You're going to interrupt the experiment if you have to, or make noises to distract them."

which has yielded huge insight into the adult brain. But fMRI is highly sensitive to movement, so babies can be scanned only if they are sedated or asleep, which has severely limited the technique's use.

AN EYE ON AUTISM

Looking time remains an important tool at Birkbeck and elsewhere — although these days, it is assessed not by human observation but by precise eye-tracking technology, such as that being used on baby Ezra. Ezra is a control for the autism and ADHD study: he does not have an older sibling with one of the disorders, so is not considered at high risk. As his attention flits between the apparently random objects on the screen, the reflected infrared light allows psychologist Emily Jones — who directs the project — to gauge precisely what he is looking at, and in which order. "What we tend to find is that typically developing babies will always look first, and longer, at the face, before looking at the other objects," she says.

Autism and ADHD have become a major focus of the Babylab as the prevalence and awareness of the conditions have risen in the past two decades — they are now believed to affect around 4% of the UK population. Last year, in a study of 104 infants, the Birkbeck team showed that infants at high risk of autism were drawn towards the face first, but they seemed to spend less time overall than 'neurotypical' babies in looking at any of the objects — and those that went on to develop autism had the shortest looking time of all[9]. A separate eye-tracking study published by the group earlier this year revealed that nine-month-olds who went on to develop symptoms of autism were more likely to spot the odd-one-out among a group of letters on a screen[10].

It is not completely clear why this is, but the working hypothesis is that these infants are more attentive to the details of what they see, says Teodora Gliga, who led the odd-one-out study. The downside of this could be that children who go on to develop autism find it harder to draw general conclusions about what they are seeing, she says. The study of which Ezra is part aims to extend this work by collecting more-detailed measures from over 400 families — and to identify those features that are strongly associated with the later onset of a developmental disorder. During the five visits that Ezra will make to the Babylab as he grows up, he will be tested using EEG, NIRS and EMG, and his parents will be given extensive questionnaires to assess his language skills, social development, temperament and sleeping patterns.

The team hopes that early brain differences could some day provide indicators — or biomarkers — of autism, which isn't usually diagnosed until close to a child's third birthday. They also hope to find ways to steer brain development back towards a more typical course.

One clinical trial at the Babylab already suggests that early intervention can have an effect. Babies in 28 families with an older sibling with autism were randomly assigned to a group in which they were visited by a therapist at least six times between the ages of seven and ten months, and were compared with a group of high-risk babies who received no therapy. The therapist showed parents videos of them interacting with their child to help understand how their baby was trying to communicate with them, and how to respond. After five months, the team saw hints of improvements in the babies' engagement, attention and social behaviour, compared with controls. But the team acknowledged that many of the results had wide confidence intervals and that it is too early to say whether the intervention will have long-term effects[11].

Johnson hopes that investigations in the toddler lab, when they start, might also eventually find a practical use, helping researchers to devise ways to boost cognitive, attention and memory skills. "I believe we are now at a unique point of convergence between this basic science and the clinical science," he says.

Meanwhile, the techniques continue to evolve. Jones is currently piloting 'gaze-contingent' tasks, which enable babies to become active participants in experiments. "If they can focus their attention on a butterfly flying across the screen, and not get distracted by other things that are happening, then the butterfly keeps flying, so they get rewarded for controlling their attention," Jones says. A more distant goal is to develop ways of using fMRI so that it could be used on awake babies. And there are still so many questions that demand answers. How do differences in the temperaments of babies develop into more complex personality traits as children age? And why can't people remember their earliest months and years?

Baby Ezra will certainly not remember his day in the lab. By late afternoon, his mother is tucking him into the pushchair for his journey home — a 1-hour 45-minute journey to Bristol by train. The trip was worth it, she says, because she was curious to learn what goes on at the Babylab. "I was interested in how Ezra would respond, but also in why those tasks were being done," she says.

Ezra and his mother now have souvenirs of their day: some photos, a certificate of participation and a baby-sized T-shirt. "I'm an infant scientist," it reads. ■

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1. Farroni, T., Csibra, G., Simion, F. & Johnson, M. H. *Proc. Natl Acad. Sci. USA* **99,** 9602–9605 (2002).
2. Elsabbagh, M. *et al. Curr. Biol.* **22,** 338–342 (2012).
3. Johnson, M. H. & Horn, G. *Anim. Behav.* **36,** 675–683 (1988).
4. Kaufman, J., Csibra, G. & Johnson, M. H. *Proc. Natl Acad. Sci. USA* **102,** 15271–15274 (2005).
5. Johnson, M. H. *Dev. Cogn. Neurosci.* **1,** 7–21 (2011).
6. Meltzoff, A. N. & Moore, M. K. *Child Dev.* **54,** 702–709 (1983).
7. Blasi, A. *et al. Phys. Med. Biol.* **52,** 6849–6864 (2007).
8. Lloyd-Fox, S. *et al. Child Dev.* **80,** 986–989 (2009).
9. Wass, S. V. *et al. Sci. Rep.* **5,** 8284 (2015).
10. Gliga, T. *et al. Curr. Biol.* **25,** 1727–1730 (2015).
11. Green, J. *et al. Lancet Psychiatry* **2,** 133–140 (2015).