Hence TRN burst are indeed absolutely ideal for timing TC output.

What, then, governs TRN activity? TRN is innervated both by TC and by cortical cells (Fig. 1). McCafferty et al.[7] conclude that cortical, not thalamic, impact on the TRN will frame the SWD oscillations via the feedforward inhibition of TC cells. They robustly support this conclusion by providing sophisticated cross-correlograms of the respective cell populations and the reduction of seizures after blocking T-channels in the cortex. Notably, both the importance of TRN bursts and the role of cortex–TRN connection are at odds with earlier studies[11,12].

Two things may help one keep track of these often conflicting studies. First, the entire interconnected thalamocortical system (Fig. 1) is wired to produce oscillatory (resonant) activity at various frequencies in a state-dependent manner. Each component of the reverberating loop is required for these activities. Seizures clearly hijack the circuit[13], including all of its elements, albeit probably not all to the same degree. Clarifying which connection(s) are the main culprits in cases of epileptic activity has obvious importance in drug development. Second, both the animal models (pharmacological or genetic) and the types of experimental manipulations (chronic, acute, genetic knockout, pharmacology) differed in the studies listed above. This can result in emphasizing the role of one or the other connection within the circuit.

All approaches bring us closer to a final understanding of seizure dynamics, but many questions remain. Very few data are available about the cellular background of the initiation of seizures, and nearly none about their termination. A recent study demonstrated a decrease in TRN bursting toward the end of a normal oscillatory electroencephalographic transient, the sleep spindle[14]. This suggests a causative role of dwindling TRN bursts in the termination of oscillatory activity. Whether the same holds true for seizures remains to be seen. Thalamic neurons in different nuclei have widely different input–output characteristics. TC cells with long-range connections, strongly driven by cortex, probably have different roles in seizures from TC cells with compact, focal axon arbors and weaker cortical inputs. Indeed, early loss of consciousness correlates with synchrony between temporal lobe activity and medial pulvinar (a cortically driven nucleus with widespread connections)[15]. Cortical cells are similarly heterogeneous, and only deep layers project to the thalamus. Layer-selective recording of their activity is still missing in animal models during seizures. Finally, how long-term or short-term plasticity is altered at the nodes of the circuit (Fig. 1) is not known.

Regardless of any future, potentially better, animal models, McCafferty et al.[7] clearly set the stage and demonstrate the level of analysis required for the next generation of experiments. Identification of the activity in representative sets of individual neurons at multiple levels of the circuit before and after an acute experimental intervention in freely moving animals is clearly the optimal approach to identifying key elements in the network responsible for the seizures. Whether or not we need the heartless beat of T-channel-mediated TC bursts in every model and, most importantly, in the human condition remains to be seen, but we now have a route forward. ❐

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Competing interests

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PRENATAL EXPERIENCE

Baby brains reflect maternal inflammation

Epidemiology and animal research have shown that the offspring of mothers who experience inflammation during pregnancy are at increased risk for psychopathology. A human study links a mother's inflammation during pregnancy to her newborn's functional brain organization and the child's working memory two years later.

Monica D. Rosenberg

What makes us who we are? The answer is, on the surface, straightforward: who we are—how we look, think, perceive, feel, and act—is shaped by reciprocal interactions between genetic variation and experience. But what are these genes and experiences, and how do they interact across development to affect our bodies, brains, and minds?

Although an exhaustive set of answers to these questions (a holy grail in social and biological science) remains elusive, a picture of the types of experiences that influence our development has emerged. We know, for example, that our physical, social, cultural, and economic environments influence our practices, preferences, and personalities. What is remarkable, however, is that the groundwork for some aspects of our lives, from the foods we like[1] to the language sounds we can distinguish[2], is laid in our gestational environment before we are even born.

In this issue of *Nature Neuroscience*, Rudolph et al. demonstrate new associations between our experiences in utero, functional brain architecture, and cognitive abilities[3]. Following a longitudinal cohort of women from early pregnancy through motherhood, they show that the degree to which women experience inflammation while pregnant is related to their children's functional brain organization immediately after birth and working memory abilities at age two.

Although this study does not establish causal relationships between maternal inflammation, altered brain function, and working memory, it corroborates findings from preclinical and public health research to underscore the importance of maternal inflammation during pregnancy for the developing brain and mind.

Previous work has established that experiences during fetal development can have profound effects on mental and physical health. At one end of the spectrum, prenatal care can improve infant outcomes[4], whereas at the other, malnutrition or alcohol use during pregnancy can cause mental and physical disabilities in children[5]. Research characterizing the effects of gestational environment on neurodevelopment has emphasized, in particular, the impact of maternal inflammation on the fetal brain. Birth cohort studies have observed elevated risk for schizophrenia following maternal bacterial or flu infection during pregnancy[6], and historical analyses suggest that neurodevelopmental disorders became more common after viral pandemics[7]. Notably, it appears that maternal inflammation itself, rather than infection or injury per se, increases risks for developmental disorders: in mice, administering a protein to pregnant females that stimulates immune responses is enough to cause autism spectrum-like and schizophrenia-like behaviors in offspring[8]. Although epidemiology and animal work provide converging evidence that maternal inflammation during pregnancy alters offspring brain function and behavior[7], methodological constraints have limited our ability to directly observe these relationships in humans.

To overcome this challenge, Rudolph et al.[3] first quantified how much inflammation women experienced during pregnancy. They did so by measuring interleukin-6 (IL-6) concentrations with blood draws during early, middle, and late pregnancy in a cohort of 84 women drawn from the general population in Irvine, California, USA[9]. IL-6 is an inflammatory cytokine—a protein that facilitates cell signaling and stimulates immune responses[10]. Although IL-6 can also have anti-inflammatory effects[10], in clinical work it is considered an overall marker of systemic inflammation due to factors including infection, injury, and stress.

Rudolph et al.[3] hypothesized that, because inflammation has broad deleterious consequences for neurodevelopment, the effects of maternal IL-6 on the neonate's brain would not be localized to a single structure, but rather would span multiple regions and circuits. To test this hypothesis, they used functional magnetic resonance imaging (fMRI) to characterize the functional brain architecture of each woman's baby about 4 weeks after birth. Specifically, they calculated each newborn's unique pattern of whole-brain functional connectivity—the synchronous activity observed across different parts of the brain—from data collected while the infant was sleeping in the MRI scanner. Functional connectivity, distinct from structural connectivity, is thought to provide an overall picture of brain organization by summarizing the degree to which different brain regions engage common or related processing. If maternal inflammation affects newborns' functional brain architecture, functional connectivity patterns in babies exposed to more maternal IL-6 in utero should look distinct from patterns in babies exposed to less.

That's in fact what the scientists observed: neonates' functional connectivity patterns differed as a function of their mother's IL-6 levels during pregnancy. Remarkably, this relationship was reliable enough that Rudolph et al.[3] could use a baby's functional connectivity pattern to predict its mother's IL-6 level. Using an algorithm known as partial least squares regression, the authors defined a model relating connectivity data from 68 infants to their mother's average IL-6 value. They then applied this model to connectivity data from the remaining 16 babies to generate a predicted maternal IL-6 level for each. Repeating this process thousands of times, they found that these predicted levels were more strongly related to true maternal IL-6 values than would be expected by chance when models were trained and tested on functional connections within and between large-scale cortical and subcortical brain networks related to attention and executive control. In other words, infants' functional connectomes contained signatures of the degree to which their mothers experienced systemic inflammation during gestation.

A specific set of infant functional connections is related to maternal inflammation, but do these connections have consequences for later behavior? To get initial traction on this question, Rudolph et al.[3] compared the brain regions whose connections most strongly predicted maternal IL-6 to brain regions associated with working memory in a large meta-analysis conducted with the online software tool Neurosynth[11]. Working memory is a central component of the cognitive abilities supporting goal-directed behavior, which they expected to relate to maternal inflammation. Rudolph et al.[3] found significant overlap between these two sets of

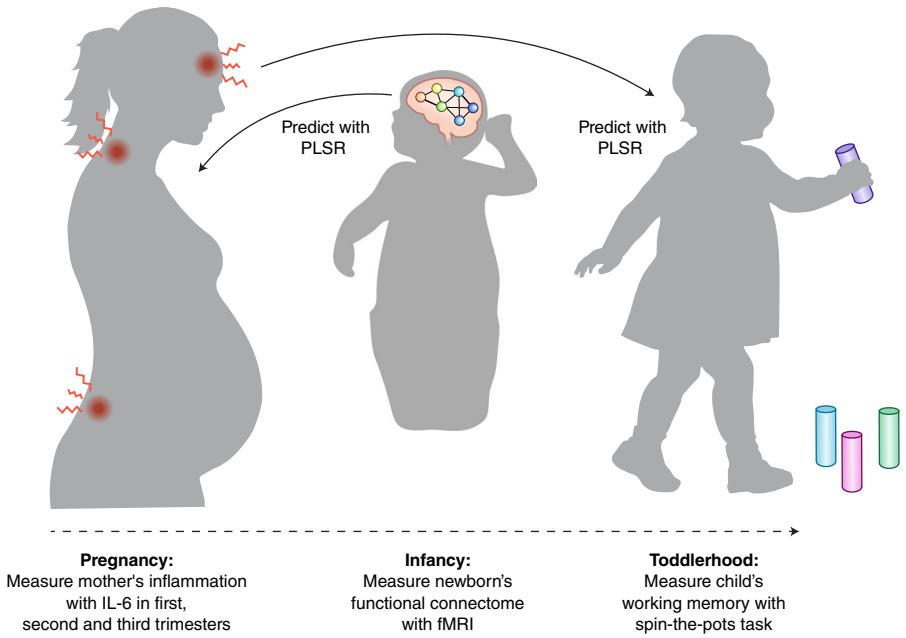

Fig. 1 | Links between maternal inflammation, neonatal functional brain organization, and toddler working memory. Neonates' functional connectivity patterns predicted the degree to which their mother experienced inflammation while pregnant. Systemic maternal inflammation during pregnancy, operationalized as IL-6 level, predicted these children's performance on a memory game at age two. Predictions of maternal IL-6 and toddler working memory were generated using partial least squares regression (PLSR) and fivefold cross-validation, meaning that predictive models were defined using data from 80% of participants and applied to data from the remaining 20%.Credit: Marina Corral Spence/ Springer Nature

regions, suggesting that brain areas relevant for working memory may be particularly susceptible to the influences of maternal inflammation during pregnancy. The critical question remained, however, whether there was a relationship between mothers' inflammation and children's behavior.

When the children scanned in infancy were 2 years old, the researchers invited them to return to the lab and play a variety of games designed to assess cognitive and emotional function. Rudolph et al.[3] had hypothesized links between maternal inflammation, large-scale brain networks, and executive function, so they focused on a task that tested working memory, an important aspect of executive function that can be measured reliably at age two. At the outset of this task—aptly known as 'spin-the-pots'[12]—children were presented with eight distinctive, covered containers on a spinning tray, and asked to place stickers inside six. The tray was obscured from their view and spun to change the spatial location of the containers. Children were then shown the tray and asked to choose a container that they thought held a sticker. The tray was covered, spun again, and the process was repeated until children found all six stickers or made 16 guesses. Working memory scores, available for 46 of the original 84 children in the study, could range from a high of 16 (no errors) to a low of 0 (16 incorrect guesses).

Now that they had measured children's working memory abilities, Rudolph et al.[3] could ask whether there was a direct link between a woman's inflammation during pregnancy and her toddler's memory function. To do so, they used mothers' IL-6 levels during the first, second, and third trimesters of pregnancy to predict children's scores on the spin-the-pots task. They found that maternal IL-6 reliably predicted working memory, such that higher IL-6 levels were associated with poorer memory. Furthermore, maternal IL-6 concentrations measured latest in pregnancy, when the rapidly maturing fetal brain is especially vulnerable to environmental stress[13], were most predictive of working memory.

The results of Rudolph et al.[3]—that the neonate functional connectome predicts maternal inflammation, which in turn predicts a toddler's working memory function (Fig. 1)—are consistent with aspects of results from another study published this year, although the findings differ in notable ways. In an independent study of 34 adolescent mothers and their newborns that tested 21 of the children a year later, Spann et al. found that maternal IL-6 level during the third trimester of pregnancy was related to neonatal functional connectivity patterns and cognitive function at 14 months[14]. However, unlike Rudolph et al.[3], Spann et al.[14] observed a positive relationship between maternal inflammation and later cognitive abilities, meaning that mothers with higher IL-6 levels in late pregnancy had children with better, rather than worse, developmental outcomes (including sensorimotor integration, concept formation, attention, habituation, and memory). Spann et al.[14] suggest that, if replicated, this result could point to an adaptive neurodevelopmental response to inflammation exposure. Interestingly, Spann et al.[14] did not find evidence that neonatal functional connectivity mediated the relationship between maternal IL-6 and toddler cognitive abilities, a key link in the causal chain untested by Rudolph et al.[3].

Rudolph et al.[3] provide unique evidence that what we experience before we are born is related to neural and cognitive processes fundamental to our life outcomes. Although, as they emphasize, their findings do not prove causal relationships (it's unclear, for example, whether other factors, such as genetic variants, could explain these associations) or show whether the relationship between maternal IL-6 and behavior is specific to working memory or whether it generalizes to other aspects of executive function, such as impulse control, measured in the same dataset[9], they support epidemiological and preclinical evidence that maternal inflammation during pregnancy influences offspring neurodevelopment. More broadly, the results of Rudolph et al.[3] highlight the power of combining experimental and analytical techniques—bridging fields such as immunology, obstetrics, neuroscience, and psychology; testing model-informed hypotheses with data-driven approaches; pairing longitudinal, dyadic samples with predictive modeling methods[15]—for understanding what shapes the developing brain and mind to make us who we are. ❐

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Competing interests

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