MARIO WAGNER

NEUROBIOLOGY

Rise of resilience

Stress can have a negative influence on the human brain, but increasingly it is the ability to withstand severe stress that is the focus of research.

BY ANTHONY KING

Daniela Kaufer has a personal interest in the effects of stress. "My mum's family had a very traumatic experience when their mother died in childbirth," she explains. The three children grew up motherless, in 1950s war-torn Israel, but there was a marked difference in how well the siblings coped. "My mum had an extremely difficult early life," she says. "Yet she is extremely resilient." Kaufer, who is a neuroscientist at the University of California, Berkeley, says that why her mother in particular coped so well has fascinated her.

Research into how people react to early trauma began in earnest after the Second World War. Distressing events such as the death of a parent have been found to increase children's short-term risk of major depression, anxiety disorders and post-traumatic stress disorder (PTSD). With advances in techniques to study genes and to explore the brain, the neurobiological study of stress is undergoing a revolution — and our view of the stress response is changing. Until about 20 years ago, the absence of a severe negative reaction such as PTSD was thought to be a lack of response. Instead, "resilience is now viewed as a reactive response", says Kaufer.

What resilience means in terms of gene expression, numbers of cells and brain networks is now the focus of research. "Years ago, most would have thought that resilient individuals escape some of the bad things that stress induces in the brains of more susceptible individuals," explains neurobiologist Eric Nestler at Mount Sinai School of Medicine, New York. "Now we believe susceptible individuals lack some of the more adaptive changes that occur in the resilient brain."

Stress is an unavoidable component of life, and the stress response is a crucial survival mechanism. "The brain is a detector of threatening information," says neuropsychologist Sonia Lupien at the University of Montreal, Canada. "This is its most important job if you want to survive." Acute stress readies us for action, but chronic stress wears us down, altering the brain genetically and neurologically and priming us for mental health problems. Whether a person is resilient to stress depends heavily on their life history. Understanding the effects of early-life difficulties could provide new ways to treat or prevent mental illnesses such as severe depression or PTSD in susceptible individuals.

STRESS IN THE BRAIN

Confronted with a life-threatening situation, hormones and neurotransmitters prep us for action. Specific stress hormones — cortisol in primates, corticosterone in most rodents — are released, some of which surge across the blood–brain barrier. Stress gets everywhere: all our cells host receptors for the hormone. "Every brain area has something happen to it," says Kaufer. The human brain has two types of receptor for cortisol. One has a six to tenfold higher affinity for the molecule than the other, and so is activated earlier, by smaller amounts of cortisol.

The hippocampus (which is pivotal for memory) and the amygdala (the centre for emotions) contain lots of the high-affinity receptors, and are, therefore, activated by slight rises in the hormone. The frontal lobe, which is involved in executive planning and control, has only the low-affinity receptor, and is activated later, after the tide has risen. And, as Lupien and colleagues found, both memory formation and recall in adults can be influenced by cortisol[1].

The existence of two receptor types means that response to stress is not linear. "The relationship between circulating stress hormone and memory is an inverted U-shape function," Lupien explains. "Up to a certain level, stress hormones are good for your memory" — when the cortisol binds only to the high-affinity receptors, the ability to lay down and retrieve memory is enhanced. When the low-affinity receptors are activated, the relationship enters the right-hand side of the U-shape and the response shifts, she adds.

The duration of stress is also important. A transient bout of stress causes a proliferation of neural stem cells and a spike in numbers of new neurons, which take at least two weeks to mature. The brain seems to be preparing itself in case a second stressor comes calling. Chronic stress is not so beneficial. It slashes investment in new neurons, prunes the tree-like shape of existing ones, and suppresses new connections.

If stress hormones remain elevated for

months or years, they can stimulate physiological changes: the hippocampus shrinks and the amygdala grows, for example. Eventually, the complex feedback system that suppresses the excess secretion of cortisol is disturbed. Once this happens, the capacity to discriminate between threat levels falls away. Either everything seems threatening (anxiety) or else nothing does (depression or burnout).

GEORGIA HODES/SCOTT RUSSO

A white 'bully mouse' intimidates a smaller mouse, which then develops signs of social withdrawal.

EARLY INFLUENCES

Old ideas that certain individuals have an inherent 'hardiness' or an innate ability to bounce back from severe stress have fallen by the wayside. Instead, resilience and our response to trauma are recognized as being more dynamic, changing throughout life. It's a complicated milieu, but one of the main ways that stress marks the brain is through epigenetics. This does not change genes, but it can change their expression by attaching methyl groups to DNA or associated proteins.

At McGill University in Montreal, neuroscientist Michael Meaney's group has been exploring the stress response in rats. It found that high-licking and low-licking grooming strategies in mother rats gave rise to different offspring[2]. The lesser-grooming mums produced pups with high anxiety, poor stress-recovery and low cognitive performance. The pups' brain circuits that switch off stress were sluggish, owing to higher DNA methylation and lower expression of the 'off' receptors in the hippocampus. Well-groomed pups showed the opposite.

People might be tempted to label high-groomers as better mothers, says Kaufer. "But it is not 'good mums' or 'bad mums', just a different parenting style." Parenting style can reflect the environment and prepare the offspring, she explains. Being a cautious, worried rat — the offspring of a less-thorough groomer — makes sense if you live in an alley full of cats.

"The stress response is one of the most conserved things in evolution," Kaufer says. This means that animal findings tend to be applicable to humans. However, what is good for avoiding predators may not be a healthy adaptation to the continued stress of modern life. Kieran O'Donnell, a neuroscientist in Meaney's lab, says that the epigenetic changes in the anxious rat brains seem to have human analogies. "We see the same sorts of changes in DNA methylation of the hormone receptor in people who suffered child maltreatment," he says. "The question is, can we intervene and do anything about this?" O'Donnell is currently investigating whether the children of vulnerable young mums who received regular nurse visits after they had given birth show changes in DNA methylation 27 years later.

Chronic stress in early life stamps an especially long-lasting mark on the brain. Some people carry an epigenetic signature of stress from exposure as a baby — or even as an embryo. Emotional stress in pregnant women, for example, can alter their children's epigenetics and the neural connections in their babies' amygdalas. Later exposure to severe trauma can activate this signature, explains neurobiologist Alon Chen, of the Weizmann Institute of Science in Rehovot, Israel. He was involved in a study that reported that chronic stress can reduce the number of hormone receptors in the hippocampus needed to shut off the stress response[3]. This means that individuals exposed to chronic stress early in life may be more susceptible to a stress-related disorder as an adult, owing to a disrupted feedback loop. "It is not healthy to stay in a stress situation for a long time," says Chen. "Returning to a normal level is an important part of the stress-response machinery."

"The stress response is one of the most conserved things in evolution."

BEATING THE BULLIES

Stress affects our relationships with others (and socializing is itself an agent in cognitive health; see page S14). Nestler has devised a 'bully mouse' scenario (pictured) in which, for 5 to 10 minutes a day over 10 days, a normal mouse is placed in a cage that is already occupied by a larger, more aggressive strain of mouse that intimidates the incomer. At all other times, the mice are kept close enough to see and smell one another, but they are separated by mesh. Nestler's team found that afterwards, some of the bullied mice avoid all social contact, even with smaller, non-aggressive mice.

As with memory, the way that sociability changes with stress is not linear. Kaufer's lab found that rats exposed to moderate stress — in this case, being immobilized in a bag — displayed more positive social behaviour, such as huddling, resource sharing and reduced aggression[4]. The researchers also saw an increase in the prosocial hormone oxytocin. But if the immobilized rats were exposed to fox odour, the addition of this high-level-stress inducer caused them to lose all pro-social behaviours. Oxytocin plummeted, as did its receptors. "This is really interesting because it can start to explain the social withdrawal that you can see in some psychopathologies like PTSD and depression," Kaufer says.

Yet even in these scenarios, some rodents did better than others. Nestler and his colleagues found that some of their mice were resilient to the bullying, and that these mice showed a greater number of gene-expression changes[5]. So resilience was a reaction, endowing the individuals with greater adaptability. "We don't know the underlying cause," says Nestler, adding that the search is on for genes with altered expression in the brains of resilient individuals. His lab is now planning to look at the role of individual messenger RNAs and proteins in mediating resilience to try and tease out what is different in the cells and neural circuits of resistant mice.

This research could deliver benefits for treating stress-related disorders such as depression. Most antidepressant drug-discovery efforts have focused on ways to undo the bad effects of stress. "Understanding resilience offers an additional approach," says Nestler, "to look for ways to induce mechanisms of natural resilience in those individuals who are inherently more susceptible."

Research into stress is changing how we view mental-health conditions. Epigenetic and brain-chemistry changes caused by life stresses can be reversed by activities such as exercise, yoga, meditation and mental stimulation. And soon these types of behavioural intervention might be complemented by pharmaceuticals. "We may learn the molecular mechanisms important for resilience," says O'Donnell. "And then use that to help those susceptible to stress or who have suffered ill treatment or trauma." ■

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1. Lupien, S. *et al. J. Neurosci.* **74,** 2893–2903 (1994).
2. Weaver, I. C. G. *et al. Nature Neurosci.* **7,** 847–854 (2004).
3. Taliaz, D. *et al. J. Neurosci.* **31,** 4475–4483 (2011).
4. Muroy, S. E., Long, K. L., Kaufer, D. & Kirby, E. D. *Neuropsychopharmacology* http://dx.doi.org/10.1038/npp.2016.16 (2016)
5. Krishnan, V. *et al. Cell* **131,** 391–404 (2007).