Do supercharged brains give rise to autism?

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IMAGINE a world where every sound jars like a jackhammer, every light is a blinding strobe, clothes feel like sandpaper and even your own mother's face appears as a jumble of frightening and disconnected pieces. This, say neuroscientists Kamila and Henry Markram of the Swiss Federal Institute of Technology in Lausanne, is how it feels to be autistic.

According to their "intense world" hypothesis, all of autism's baffling and sometimes incongruous features - social problems, language impairment and obsessive behaviour, sometimes allied to dazzling savant abilities - can be explained by a single neurological defect: a hyperactive brain that makes ordinary, everyday sensory experiences utterly overwhelming.

If they're right - and the idea is generating a deal of interest among autism experts - the husband-and-wife team could be on course to add a significant new theory to autism research. "It is a very compelling idea," says neurobiologist Asaf Keller at the University of Maryland School of Medicine in Baltimore, who has arranged a symposium to discuss it at November's Society for Neuroscience meeting in Washington DC.

Recognition of sensory disturbance in autism goes back as far as the 1940s, and today it is widely seen as a fundamental aspect of the condition. "There is a lot of evidence for sensory hypersensitivity," says Simon Baron-Cohen, director of the Autism Research Centre at the University of Cambridge. He notes that hypersensitivity can affect the vision, hearing and touch of people with autistic spectrum disorders (ASD, see "Autism basics").

"If you talk to practitioners, invariably they will say, 'I've never seen a child with autism who doesn't have sensory problems'," adds Keller. "There's a strong correlation, maybe 100 per cent."

The Markrams, however, are the first to put sensory overload at the heart of the condition. "Our hypothesis is that autistic people perceive, feel and remember too much," says Kamila Markram. Faced with this blooming, buzzing confusion, autistic infants withdraw, with serious consequences for their social and linguistic development. Repetitive behaviours such as rocking and head-banging, meanwhile, can be seen as an attempt to bring order and predictability to a blaring world (*Frontiers in Neuroscience*, vol 1, p 77).

Most theories of autism assume the affected person has a neurological deficit of some kind - that some part of their brain isn't working properly (see "Five leading theories of autism"). According to the Markrams' theory, though, the brain isn't underperforming but overperforming.

System overload

Along with colleague Tania Rinaldi, they developed their hypothesis largely from work on an animal model of autism, plus human brain imaging, autopsy evidence and the subjective experiences of people with ASD, including Henry Markram's son who is borderline autistic. "That's the curse of having parents who are neuroscientists, they are constantly analysing you," says Kamila Markram. She has observed the boy's intense fears and anxieties and his struggles with oversensitivity.

For the animal work they used an autism model called the VPA rat. This model is based on dozens of case studies of children whose mothers took the anticonvulsant and mood-stabilising drug valproic acid (VPA) while pregnant. A frighteningly high proportion of these children ended up with some form of autism - around 10 per cent, compared with some 0.08 per cent of the general population.

In the mid-1990s, researchers working on the adverse effects of VPA tried exposing rat fetuses to the drug and found that giving it on the 12th day of gestation - equivalent to the early part of the first trimester in humans - caused major damage to the rats' developing brainstem. This has far-reaching effects on later brain development and results in socially withdrawn behaviour that looks eerily similar to humans with autism. The VPA rat is now an established animal model of autism.

When the Markrams examined the brains of VPA rats in minute detail, they found that they didn't just share behavioural traits with autistic humans. Their neuroanatomical changes were similar too.

One of the most replicated findings in autism neurology is abnormal brain growth. At birth the brains of autistic children are small or normal sized, but grow unusually quickly. By age 2 to 3 their brain volume is roughly 10 per cent larger than average. Human autopsy findings by Manuel Casanova of the University of Louisville in Kentucky suggest that part of this extra volume consists of structures called minicolumns in the brain's outer layer, the cerebral cortex.

You can think of minicolumns as the brain's microprocessors: clusters of around 80 to 120 neurons that crunch basic neural information, including perception, memory and so on, before it is somehow integrated into a whole. They are the smallest independent processing units in the cortex.

When the Markrams looked at minicolumns in VPA rats they saw some striking changes similar to the human autopsies. First and foremost the minicolumns were unusually abundant. They were also extraordinarily well connected. "Using a technique for recording directly from neurons, we found consistently, over many experiments, that these circuits are hyperconnected," says Kamila Markram. Each minicolumn neuron in a VPA rat has up to 50 per cent more connections than normal and this causes them to be hyper-reactive, firing more readily when stimulated by an external electrical current. The circuits are also "hyperplastic", meaning they form connections with other neurons more readily than normal.

Taken together, hyper-reactivity and hyperplasticity mean that minicolumns in VPA rats (and presumably in autistic humans too) have a higher than normal capacity for processing information. And this, say the Markrams, is autism's fundamental problem.

Take sensory disturbance, for example. Excessive information processing in the microcircuits that handle incoming data from the senses leads to exaggerated perception, producing extremely intense images, sounds, smells and touch, the Markrams claim. Hyperactive microcircuits, meanwhile, could prove difficult to integrate into a whole, so perception would be highly fragmented. This sensory overload causes autistic kids to withdraw from the world, or pay excessive attention to small fragments of it. "It's what anyone would do if they were embedded in a welter or cacophony of unpredictable events," says autism researcher Matthew Belmonte of Cornell University, Ithaca, New York.

The hypothesis also provides an explanation for the three core deficits of ASD. Social problems, for example, are a direct consequence of children withdrawing from the world during critical developmental windows. Because the developing human brain requires repeated exposure to relevant stimuli at the right time to develop properly, early avoidance of social stimuli can have a devastating effect on a child's social development. "They don't learn because they don't interact," says Kamila Markram.

Similarly, children whose exposure to language during infancy is inadequate will have impaired language skills all their lives. When almost every sensation is overwhelming it's hard to socialise at all, let alone speak.

Hyperplasticity, meanwhile, could account for repetitive behaviour and the compulsive desire for routine in people with ASD. Plasticity underlies learning and memory, so hyperplastic brains could be primed for what the Markrams call "hypermemory". "They build very strong memories," says Kamila Markram. "So strong that you establish a routine that you can't undo: you are stuck on a track."

At the same time, however, by locking them into specific narrow interests and compelling them to practise compulsively, hypermemory may be what drives some autistic people to develop savant skills. This appears to be how musical, artistic and mathematical savants develop their talents.

Unfortunately, if their focus is too narrow, savant-like skills can appear to be the exact opposite. "If your focus of attention becomes too local then you may become an expert on such a tiny system - the wheel of your toy car, say - that you end up with very little demonstrable knowledge about other, wider systems," says Baron-Cohen.

Wired for fear

Another crucial element of the new hypothesis is that VPA rats also have hyperconnectivity and hyperplasticity in the amygdala, the almond-shaped brain structure where memories of fear are made and stored, which looms large in many theories of autism. VPA rats learn to avoid frightening situations more quickly than other rats, readily fear non-threatening stimuli, and are quick to generalise fear from one situation to another. They also have a much harder time learning that a once-scary situation is now safe (*Neuropsychopharmacology*, vol 33, p 901).

Assuming humans also have these changes in their amygdala, this could further explain some of the symptoms of autism. As a result of an overactive amygdala, says Kamila Markram, autistic people find the world "not only intense, but also aversive". Ordinary situations can be terrifying and fear is easy to learn and hard to forget. This is another reason why autistic people prefer predictable, repetitive routines and can overreact, sometimes explosively, to change.

So far the intense world hypothesis is playing well with autism experts. "I really think it is spot on," says Belmonte. "For some years the autism literature has needed a greater focus on the idea of autistic behaviour as a normal response to an abnormal perceptual and cognitive world." Baron-Cohen too sees many positives. While he disagrees with some aspects of the idea, overall, he says: "The attraction of the research is to find basic differences between the autistic and typical brain, out of which higher cognitive differences such as in systemising may develop. In this view, the higher cognitive differences are secondary to these more basic sensory differences. This is a view I have a lot of sympathy with."

It also rings true with autistic people. "When I was younger, the school bell was like a dentist's drill hitting a nerve," says Temple Grandin, an animal scientist at Colorado State University in Fort Collins well known for being autistic. "I think it's difficult for people to imagine a reality where sounds hurt your ears and a fluorescent light is like a discotheque," she says. The Markrams have also received a positive response from families affected by ASD. "It gives them comfort," Kamila Markram says, "there are actually reasons why these children aren't responding well."

Some experts, however, are not convinced. The strongest critique comes from those who think the hypothesis extrapolates too much from the VPA rat. "[The Markrams are] extremely good on the neurophysiology... but we don't yet know how to translate what the neurons are doing to what's happening psychologically," says neuropsychologist Chris Frith at University College London. "I think they made a leap too far."

Keller, however, defends the use of animal models, noting that VPA causes the same anatomical and behavioural abnormalities in humans, monkeys and mice. "I see it not as a model, but as a recapitulation of the disease in other species," he says.

These arguments aside, the intense world theory also has implications for the debate over the ultimate causes of autism. Although autism is highly heritable, genes alone are not enough to explain it; in pairs of identical twins where one twin has autism, the other is affected only 60 per cent of the time at most.

The VPA rat's striking similarities to autism suggest that the condition might arise early in pregnancy when an as-yet unknown environmental insult combines with genetic vulnerability to damage the brainstem at a vital time. "What this study emphasises is not genetics but environment," says Casanova. "It also emphasises the idea of a window of vulnerability. The timing of the insult is of great importance."

This could also explain the wide range of the autistic spectrum, from severe impairment requiring 24-hour care to the near-normality of high-functioning Asperger's. The later in the window exposure occurs, the less wide-ranging the attack on the fetal brainstem would be, reducing the subsequent damage as more regions would already have had time to develop unharmed.

Testing times

So how can the intense world idea be tested further? One way is to look for a correlation between sensory problems and the severity of ASD. If people with the worst oversensitivity - as measured by reactions to light, sound and touch - have the most incapacitating autism, that would offer support. And if intervening early in sensory problems mitigated the symptoms of autism this would also be evidence in favour.

Keller is collaborating on just such a study with researchers at Johns Hopkins University in Baltimore, Maryland, who have pioneered early detection in children as young as 6 months. Together they are looking at autistic children at the earliest possible stage to see whether reducing their sensory overload can help. Strategies include noise-reducing headphones and other ways of producing calmer, less stimulating environments.

These same measures already work for children who have endured severe early trauma and neglect, such as being raised in an understaffed or abusive orphanage. These children often have overactive amygdalas, heightened fear memories, are withdrawn and exhibit repetitive behaviours indistinguishable from autism.

The results of early intervention to help autistic children will be watched with interest, not least because one of the most striking features of the intense world hypothesis is that it casts almost everybody on the autistic spectrum as highly gifted. "Basically, our theory really says that most autistic people or people with Asperger's are savants," says Kamila Markram. "But this is buried under social withdrawal and fear of new environments. Their resistance to interaction and fear may obscure the hypercapability that they have. It may well turn out that successful treatments could expose truly capable and highly gifted individuals."

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Autism basics

The autistic spectrum disorder (ASD) includes classical autism (now known as autistic disorder), Asperger's syndrome (also known as high-functioning autism) and a constellation of similar but somewhat ill-defined conditions including Rett's syndrome, disintegrative disorder and pervasive developmental disorder-not otherwise specified (PDD-NOS).

Five leading theories of autism

Weak central coherence

Sees autism as a failure to integrate sensory information in a holistic or "gestalt" manner.

Executive function

Impairment of the brain's frontal lobes causes loss of the top-down "executive" controls which build the big picture at the expense of minutiae.

Mind-blindness

An underactive amygdala - a brain structure central to the processing of emotional information, especially fear - leads to severe problems with empathy and theory of mind.

Extreme male brain

An excess of testosterone during early development magnifies typical male cognitive traits, such as systemising, at the expense of empathy, sociability and other more typically "female" thinking styles.

Intense world

The new kid on the block. Proposes that the root cause of autism is a supercharged brain (see main story).