

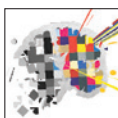


R. MANSI/GETTY

URBAN DECAY

SCIENTISTS ARE TESTING THE
IDEA THAT THE **STRESS OF
MODERN CITY LIFE IS A BREEDING
GROUND FOR PSYCHOSIS.**

BY ALISON ABBOTT



STRESS AND RESILIENCE

The links between adversity and
mental illness. nature.com/stress

In 1965, health authorities in Camberwell, a bustling quarter of London's southward sprawl, began an unusual tally. They started to keep case records for every person in the area who was diagnosed with schizophrenia, depression, bipolar disorder or any other psychiatric condition. Decades later, when psychiatrists looked back across the data, they saw a surprising trend: the incidence of schizophrenia had more or less doubled, from around 11 per 100,000 inhabitants per year in 1965 to 23 per 100,000 in 1997 — a period when there was no such rise in the general population (J. Boydell *et al. Br. J. Psychiatry* 182, 45–49; 2003). The result raised a question in many researchers' minds: could the stress of city life be increasing the risk of schizophrenia and other mental-health disorders?

The question is an urgent one. Back in 1950, less than one-third of the world's population lived in cities. Now, lured by the prospect of work and opportunity, more than half do. Mental illnesses already comprise the world's biggest disease burden after infectious diseases and, although global statistics do not yet show any major increase in incidence, the cost is rising. In Germany, the number of sick days taken for psychiatric ailments doubled between 2000 and 2010; in North America, up to 40% of disability claims for work absence are related to depression, according to some estimates. "It seems that cities may be making us sick," says Jane Boydell at the Institute of Psychiatry in London, who led the Camberwell study.

Anecdotally, the link between cities, stress and mental health makes sense. Psychiatrists know that stress can trigger mental disorders — and modern city life is widely perceived as stressful. City dwellers typically face more noise, more crime, more slums and more people jostling on the streets than do those outside urban areas. Those who have jobs complain of growing demands on them in the workplace, where they are expected to do much more in less time.

But the idea has not been widely tested. It is difficult to study whether

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something as complex as a 'city environment' has an impact on the brain. To complicate matters, many growing cities include immigrant populations, which already have an increased risk of psychiatric disease associated with social isolation.

Now, a few scientists are tackling the question head on, using functional brain imaging and digital monitoring to see how people living in cities and rural areas differ in the way that their brains process stressful situations. "Yes, city-stress is a big, messy concept, but I believed it should be possible to at least see if brains of city-dwellers looked somehow different," says Andreas Meyer-Lindenberg, director of the Central Institute for Mental Health in Mannheim, Germany. And if scientists can work out what aspects of the city are the most stressful, the findings might even help to improve the design of urban areas. "Everyone wants the city to be beautiful but no-one knows what that means," says Meyer-Lindenberg. Wider streets? Taller buildings? More trees? "Architects theorize a lot, but this type of project could deliver a scientific basis for a city code."

RELENTLESS STRESS

Considered from an evolutionary standpoint, the physiological stress response is definitely a good thing: it helps mammals to survive. Any threat, whether from a predator, dwindling food supplies or an aggressive enemy, triggers release of hormones such as cortisol and adrenaline. These hormones raise levels of sugar in the blood and redistribute blood flow to muscles and lungs, so that animals can respond to the threat by running, hunting or fighting.

Problems arise when the stress response doesn't switch off. Stress-hormone levels that stay too high for too long cause high blood pressure and suppress the immune system. And, although the mechanisms are unknown, scientists agree that severe or prolonged stress also raise the risk of psychiatric disease — most brutally in those who have a genetic predisposition, and when the stress occurs while the brain is still developing. In theory, then, the ceaseless challenges of the city could produce this kind of damaging stress. Some fear that they could end up driving an increase in mental illness around the world.

The only signs of an increase, however, come from relatively small, local studies. "It's frustrating — we feel it should be rising," says Ronald Kessler, a mental-health epidemiologist at Harvard Medical School in Boston, Massachusetts. "But globally we have not seen this, and there are also studies which indicate it isn't even rising in cities." However, reliable data on the prevalence of psychiatric disease are hard to find because diagnoses are often imprecise or incompletely recorded. The Camberwell study was influential because, unusually, it captured all those who were diagnosed with a mental disorder, even if they were not admitted to hospitals, and the researchers involved carefully reviewed every case.

Published in 2003, the Camberwell study deeply impressed Meyer-Lindenberg, who was then at the US National Institute for Mental Health in Bethesda, Maryland, researching how genetic risk factors for schizophrenia affect brain function. As a student in Manhattan some years earlier, Meyer-Lindenberg says, "I had been struck by the number of homeless mentally ill people on the streets, and the problems of the city somehow resonated with me". He wondered if city living was somehow making the brain more susceptible to mental-health conditions. When he returned to his native Germany in 2007, he decided to tackle the question directly. But at the time, Meyer-Lindenberg says, "people said the effect would be too subtle to make sense of".

Yet the results of his study, published last year in *Nature* (F. Lederbogen *et al. Nature* 474, 498–501; 2011), clearly showed that people who grow up in cities process negative emotions such as stress differently from those who move to the city as adults. His team scanned the brains of 55 healthy volunteers as they carried out arithmetic tasks under a constant bombardment of negative social feedback. "We'd always let them know through headphones that we thought they were failing, or at least not doing as well as other subjects we'd had in the scanner," says Meyer-Lindenberg. "In one set of experiments we let them see our impatient faces on computer screens."



Rush hour: phone apps are helping researchers to survey stress over the day.

This social stress activated two brain areas — but the pattern depended on the volunteers' histories of urban living. The amygdala, which processes emotion, showed much greater activity in people who were currently living in a city. And the cingulate cortex, which helps to regulate the amygdala and processes negative emotion, responded more strongly in those brought up in large cities than in those brought up in the countryside, irrespective of where they lived now. Meyer-Lindenberg thinks that this over-responsiveness to stress could make city-dwellers more prone to psychiatric conditions such as schizophrenia — and his results chime with the idea that stress in childhood or adolescence can have a lasting effect on the brain's development and increase susceptibility to psychiatric disease.

Other scientists are following Meyer-Lindenberg's lead. Daniel Weinberger, director of the Lieber Institute for Brain Development in Baltimore, Maryland (and a self-confessed addict "to the cultural stimulation of the city"), is planning a huge, long-term project to study environmental and genetic risk factors for schizophrenia in China, where urbanization is happening at lightning speed. The proportion of people living in cities there has doubled in the past two decades, to more than half. Together with colleagues at Peking University in Beijing,

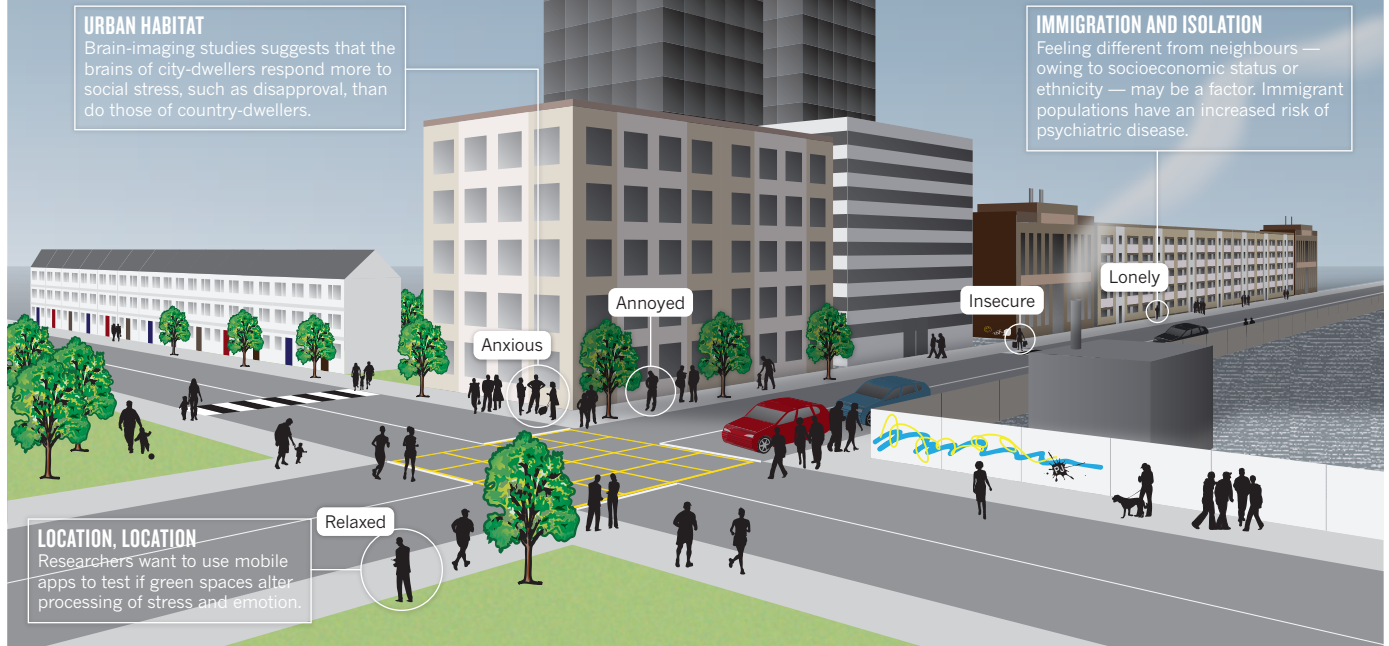
"THIS TYPE OF PROJECT COULD DELIVER A SCIENTIFIC BASIS FOR A CITY CODE."

Weinberger hopes to study thousands of people who moved to Beijing from the countryside before they were 12 years old, after they turned 18 and between the two ages. He will use brain imaging and genetic analyses to try to understand how urban upbringing and genes alter cognition and reasoning, functions that are often disrupted in schizophrenia.

Researchers suspect that the stress of city living leads to psychiatric disease mainly in people who are already at risk because of other environmental stresses or because they carry risk genes. One candidate gene, the details of which have not yet been published, has emerged from a large brain-imaging study being conducted by Meyer-Lindenberg in Iceland. He chose more than 500 people who had been identified by the Reykjavik-based company deCODE Genetics as carrying rare mutations that confer a high risk of schizophrenia, and subjected them to functional magnetic resonance imaging tests similar to the ones he used in his city study. "We've already found that people carrying that one particular gene variant activate the cingulate cortex when they process social stress, just like those who were brought up in cities,"

STRESS AND THE CITY

RESEARCHERS ARE TRYING TO IDENTIFY WHICH PARTS OF CITY LIFE ARE THE MOST STRESSFUL, AND HOW THIS MIGHT CONTRIBUTE TO MENTAL-HEALTH DISORDERS.



he says. He expects to find many more gene candidates through the project, which will run for several more years.

Identifying which parts of a busy city life are the most stressful is another massive challenge (see ‘Stress and the city’). The common urban experience of feeling different from your neighbours because of socioeconomic status or ethnicity could be one factor, Meyer-Lindenberg thinks. If so, immigrant groups, who often experience isolation, may be processing stress in a similar way to city-dwellers. He is now testing this hypothesis in the children of immigrants to Germany. (First-generation immigrants are not suitable because the stress of social isolation could be confounded by the stress of moving country.)

Jim van Os, a psychiatrist and epidemiologist at Maastricht University in the Netherlands, is planning a detailed look at city living to identify sources of stress. “It had been slowly dawning on me that as

“NOTHING IN MENTAL HEALTH WILL BECOME CLEAR UNLESS WE CAN LOOK AT THE ENVIRONMENT.”

we know that the brain interacts with the environment, nothing about mental health will become clear unless we can look at the environment,” he says. Van Os has developed a smart-phone app that allows participants to record their moods, thoughts, location and activities as they go about their daily lives. “This is important because mood and affect change dynamically in the brain, just as blood pressure does,” he says.

In a €2-million (US\$2.6-million) field study, van Os intends to use the app to collect regular information on these factors from 264 people who have started to show psychological disturbance. He will combine these data with brain imaging to test his hypothesis that risk of progressing from disturbance to full-blown psychosis is connected to a distorted ability to learn which aspects of a new environment are rewarding and which are threatening. “For example,” he says, “if you

move to a new district, you’ll need to quickly learn which neighbours you like enough to develop a relationship with, and how to interpret social signals that could be harmful.”

Meyer-Lindenberg is planning an even more technologically ambitious project with geoscientists at the nearby University of Heidelberg, who have generated a high-resolution map of their city, and physicists at the Karlsruhe Institute of Technology in Germany, who have developed a mobile device that allows people to be tracked and tested for a week as they walk and work around Heidelberg. The device can recognize when participants reach a specific location — such as a green space or a particularly noisy intersection — and instantly question them about their state of mind or send them a cognitive test to be completed on the spot. The scientists will then ask the participants to come into the lab for brain-imaging studies that examine how they process stress and emotion. By correlating the imaging data with their states of mind at different locations, the team hopes to trace how different aspects of city life affect the brain — whether, for example, strolling through a park really does have a calming influence on the amygdala and cingulate cortex.

It is a high-risk project that has yet to tempt funders. But Meyer-Lindenberg sees the future of the city in it. So too does Annette Rudolph-Cleff, an architect and city planner at the Technical University of Darmstadt in Germany, who contacted Meyer-Lindenberg after reading his *Nature* paper last year and is now advising him on the project. “We know far too little about the city at the moment and we need these new technologies and approaches to help us make decisions about how the city should best be developed,” she says.

As well as helping in the design of future cities, such work might also pinpoint the most stressful parts of an existing metropolis — and help to make a case for urban regeneration. Cities are already great economic and cultural incubators; Rudolph-Cleff hopes that the new science of urban stress could also allow them to be turned into cradles of mental health. ■ [SEE EDITORIAL P. 143](#)

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