circumstances [which led to those events]. You need to look in the right place, and looking at the brain is not always the right place."

If every behaviour results from purely physical events ... every misdeed would have to be treated as an involuntary act

Looking in the right place has also proven difficult in the past. Scientific results and ideas about the morphological correlates of behavioural traits were repeatedly over-interpreted, but conclusions with considerable impact on society were drawn nonetheless. At the beginning of the nineteenth century, the German-French anatomist Franz Joseph Gall developed the field of phrenology—deducing personality traits from studying the shape of the skull—and claimed that this information should be taken into account when sentencing criminals. Some time later, the Italian anthropologist Cesare Lombroso argued that the 'born criminal' could be identified through physiognomic features, such as a large jaw, handle-shaped ears or fleshy lips. The German physician Oskar Vogt, best known for investigating Lenin's brain, also searched for personality traits in brain morphology. At the end of the Second World War, he unsuccessfully requested permission to examine the brains of Nazi criminals who were executed after the Nuremberg trials. Vogt hoped to find an explanation for the atrocities committed during the Nazi's reign of terror (Hagner, 2004), but probably would not have been very successful.

Today's scientific methods go far beyond measuring and weighing brains. Still, conclusions of socioeconomic relevance should be drawn with care. Popular media frequently produce articles that convey the impression that societal problems can be explained simply by neurology. Colourful magnetic resonance images from brains and other intriguing pictures add to peoples' beliefs in the limitless explanatory power of the neurosciences. One example of a story that could send the wrong message or confuse the public was an article in UK newspaper *The Guardian*, which described how neuronal reactions to black and white faces "may reveal brain's hidden centres of prejudice" (Adam, 2003). "The press is very good at interpreting things at that degree of crudity. This also applies to press releases put out by the university departments or by *Nature* or

Science when they want publicity for a particularly juicy paper," said Rose.

Despite the enormous advances that neuroscience has made over the past few decades, the field is still far from being able to understand the complex processes taking place in the human brain. Caution is therefore recommended when drawing conclusions of social relevance from such limited scientific knowledge, particularly when it comes to such central themes as the concept of guilt. This is not to say that neuroscientists should be prevented from commenting on social topics or the legal system. On the contrary, an interdisciplinary discourse can be very valuable. But they should exhibit a certain modesty when speaking about subjects, like the legal system, of which they know very little. "I think that, quite recently, there has been a tendency for some neuroscientists to speak outside their field of competence. I think most of us should shut up about consciousness and concentrate on the scientific questions that are amenable to our research," said Rose.

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Think small

Lab-on-a-chip technology shrinks the biological laboratory to the micro scale and expands the potential for future applications

Small is beautiful. Just ask an engineer from the computer industry. Although the first computers in the 1940s and 1950s filled entire buildings, a contemporary Mac mini—barely larger than a stack of compact discs—performs the same tasks in a fraction of the time. The driving force behind this enormous increase in computing power and decrease in size was the invention of the microchip and its subsequent miniaturization, with even more transistors being packed onto even smaller chips.

The same process is about to affect biological and chemical research. The idea that all the components needed for an experiment could be miniaturized and packed on a single carrier system, which is smaller than a penny and able to handle the tiniest samples, is prompting efforts to create chips for the analysis of biological material. These 'lab-on-a-chip' analytical devices operate on the micro- and nanometre scale. In essence, it means that all the beakers, pipettes and other lab tools are shrunk to fit on a single chip about the

size of a pea, said Andrea Chow, Vice President of microfluidics research and development at Caliper Life Sciences, a commercial chipmaker (Hopkinton, MA, USA). Because such chips work with small volumes of fluids—picolitres in many cases—they are able to perform complex analyses quicker and more economically than is possible with standard lab equipment, according to Chang-Jin Kim, head of the Micromanufacturing Laboratory in the School of Engineering and Applied Science at the University of California, Los Angeles (CA, USA).

Chips are usually made from silicon or glass wafers that are etched with channels about the width of a hair. The etching is done by photolithography, the same method used to fabricate computer chips. Tiny streams of fluid, which can be manipulated for analysis, travel through these channels. “Those channels are analogous to test tubes, but of course a lot smaller,” said Chow. “We deal with a much smaller format than macroscopic analysis, but the procedure is the same.”

The chips typically connect to a power source, reservoirs, pumps and valves that dispense the fluids, analytical instruments and data processing systems. Today, the technology is mainly used for microfluidics, the branch of nanotechnology that deals with the complexities of manipulating minute quantities of liquids. “Most of the applications we’re addressing with microfluidics are in the life sciences, [such as the] analysis of RNA, DNA, protein and cells,” said Tony Owen, product manager at Agilent Technologies (Palo Alto, CA, USA), a company that develops and produces analytical chips (Fig 1).

Because such chips work with small volumes of fluids...they are able to perform complex analyses quicker and more economically than is possible with standard lab equipment...

Although most commercially available chips are used by the pharmaceutical industry in drug discovery, researchers see many future applications, such as blood-based diagnostics, pathogen detection or water-safety monitoring. The main advantage to using chips in these situations

Fig 1 | The ‘core’ of an Agilent lab-on-a-chip cartridge showing the microfluidic channels. This technology is rapidly replacing slab gel electrophoresis in nucleic acid and protein analysis applications, generating more precise data, improving reproducibility, shortening analysis times, using smaller quantities of precious samples and facilitating automated workflows. Other applications includes pharmaceutical quality-control and environmental analysis. Image courtesy of Agilent Technologies, Inc.

would be to save on labour and reagent costs: a traditional microplate assay, for instance, requires up to 100 mg of an enzyme, whereas a lab-on-a-chip assay would need only 1 mg, according to Chow. In addition, chips perform analyses much faster than traditional laboratory methods, according to Art Pontau, co-manager of microfluidics at Sandia National Laboratories (Livermore, CA, USA).

Although the chip may be tiny, its operation still depends on supporting machinery—the chip itself is only one part of a larger instrument. “Some systems are the size of multiple desks and include dozens of mechanical pumps and valves connected to the chip, as well as

electronic instruments,” Kim said. “Others are of tabletop size, and include electronic instruments that are difficult to scale down to one board.” For example, two commercially available chip-based instruments for gel electrophoresis—the 2100 Bioanalyzer from Agilent and Experion from Bio-Rad (Hercules, CA, USA)—are both about the size of a large toaster. High-throughput systems for drug discovery, in which the instrument analyses up to tens of thousands of samples per day, are about the size of a refrigerator, Chow said, but she expects these instruments to become smaller in the future.

For now, it is the pharmaceutical companies that benefit most from miniaturization, Chow said, as it allows them to cut

drug discovery times when screening their compound libraries against target molecules. Although this is already largely automated, chip technology allows researchers to further standardize and automate the process, while saving reagent and labour costs. "It's like a conveyor belt; every compound is treated exactly the same," Chow said. "It's a little like during the industrial revolution, where the line work was fashioned into stations where people did just one thing. So the results were reproducible."

Shrinking the size of the reaction core also provides other benefits because environmental factors, such as ambient temperature or humidity, can be controlled better. Indeed, drug discovery researchers often find that chips produce a much smaller margin of error than is possible with standard laboratory equipment. "In the macroscopic environment, the temperature may be different across a three to five inch plate, or reagents may be dispersed using differently sized pipettes," Chow explained. In the regular laboratory, chemists may therefore find only those compounds that slow down enzyme activity by 50%. However, "with microfluidics, they can find compounds that inhibit activity by a smaller amount, say 10 or 20 percent," said Chow. "Sometimes those lower-potency compounds are actually more specific. They may target just that one enzyme and not affect others, which would cause side effects."

However, when shrinking reaction volumes to the micro- or nanometre scale, researchers encounter a new set of problems. Usually, fluids are more viscous when flowing in a small space, Kim explained. "It may become an issue when high-throughput becomes important or one needs to miniaturize further down from the typical channel size of today," he added. Also, aqueous solutions do not usually create turbulence when flowing through microchannels, so mixing happens by diffusion, Chow said. Highly viscous liquids diffuse slower, so chip researchers need to take viscosity into account when they develop chips for specific applications.

Another problem is surface contamination; when the same chip is used for a series of different samples, residues from one sample may remain inside the channels and interact with a new experiment.

Illustration: Simon Walter

According to Kim, the surface-to-volume ratio is generally high in lab-on-a-chip devices, which makes it difficult to avoid fluid absorption through the walls of the channel. To that end, the researchers at Caliper are working on buffer additives and coatings to prevent samples from sticking to the channels. Other systems use cleaning techniques such as flushing to remove residues, whereas other chips are disposable to avoid cross-contamination. The chip can also become clogged if the sample contains larger particles. For example, in cell-based assays, cells up to 15 μm flow through the channels for hours. However, as mass production further drives down manufacturing costs and thus makes disposable chips more economically feasible, Chow expects that the problems of contamination and clogging will eventually be eliminated.

Beyond high-throughput screening and standard laboratory experimentation, scientists see a huge range of potential applications for lab-on-a-chip technology in medical practice and public health. Kim expects that physicians and patients stand to benefit most once chip researchers nudge the microfluidics technology further to produce diagnostic systems for physicians. These could eliminate the nerve-racking wait for results when blood is tested for a specific disease or infection. "What if the doctor can run the blood tests right there in his office?" Kim asked. "If the doctor has a tabletop machine in his office, he doesn't need to send samples back and forth. And the pos-

sibility of mixing them up is eliminated...With lab-on-a-chip, this is completely feasible in a scientific sense, but unfortunately it's not there in a business sense yet."

...chip technology allows researchers to further standardize and automate the process, while saving reagent and labour costs

Bio-Rad, Agilent and Caliper's systems to replace classical gel electrophoresis are already the first steps towards this goal; lab-on-a-chip technology separates DNA, RNA and proteins within minutes, according to Owen. In addition to gel electrophoresis, chips for enzymatic and cell-based assays are already available. Caliper is working on chip-based polymerase chain reaction applications with plans to commercialize the technology soon, Chow added.

Another important area in the development of chips is the effort to replace liquid or gas chromatography. Such systems could be integrated with a mass spectrometer to analyse biological markers in the blood, thus speeding up medical diagnosis. "That's the Holy Grail," Chow said. "To take a patient's blood and drop it on one end of the chip, then the chip processes it and shoots it into the mass spectrometer to see if you have an elevated protein in your blood that would show you have the symptom of a disease." Kim is quite confident that further research and miniaturization will make such a system possible. "I won't be sur-

prised to see a bulky system for a general blood analyser within a year," he said, and he expects a handheld blood analyser to become available in about five years.

...scientists see a huge range of potential applications for lab-on-a-chip technology in medical practice and public health

Like Caliper, Sandia is also working on chips to detect biochemical indicators of human disease, partly funded by a grant from the National Institutes of Health (Bethesda, MD, USA). One of their projects investigates the use of chips to detect early indicators of periodontal disease in saliva. "We've shown we can detect biomarkers in the blood as well as the saliva," Pontau explained. "One can imagine a broad range of diseases, from heart attacks to cancer, for which early indicators can be found in blood and saliva."

This may also become vital in the case of a terrorist attack that uses biological or chemical weapons. Emergency responders could immediately analyse victims' blood and saliva to determine the agent that has been used. "In that case, we'd be looking not for the virus or the bacteria, but to the body's response to the attack," Pontau said. In a similar approach, Sandia researchers are also working on wall-mounted or handheld units to detect biological or chemical warfare agents. Although these units are being developed for national security personnel and first responders, potential applications exist for other uses in monitoring air and water quality, in medical diagnostics, and in biotechnology and industrial process control, Pontau said.

Sandia's MicroChemLab system is already capable of verifying several chemical, bio-toxin and pathogen signatures in the environment. Tests showed that the unit detects seven forms of ricin, a highly toxic compound derived from castor beans. According to Pontau, ricin was chosen because it is particularly easy to obtain and thus presents a possible threat to national security. Sandia is also cooperating with two companies, Tenix (Sydney, Australia), a defence and technology contractor, and CH2M HILL (Englewood, CO, USA), an engineering services provider, to develop chemical detection units that will continuously monitor water systems for chemical and biological agents. Once available, the system would analyse water every half hour for a range of biological agents and could operate for weeks between maintenance cycles.

...potential applications exist for other uses in monitoring air and water quality, in medical diagnostics, and in biotechnology and industrial process control...

"There's a little probe inserted directly into water lines, a small amount of water is brought into the system and processed by concentrating species of concern and throwing away everything else," Pontau said. "We're basically analysing microliquids." The compounds of interest are extracted and concentrated through solid-phase extraction and other techniques. Samples must be condensed because the compounds only appear in concentrations of a few molecules per litre and the unit analyses a microlitre of fluid. "We want to make sure the microlitre

Lab-on-a-chip technology may therefore spark a revolution...

contains the agent we're looking for," Pontau said. Sandia is now testing a field unit and expects to produce the first autonomous water-testing devices in about a year.

Another of Sandia's handheld chip-based units is the size of a telephone handset, runs on batteries and can carry out hundreds of analyses over the course of a day. Pontau envisions first responders taking these units with them on emergency calls. "They could analyse a white powder on the spot to see if there's anthrax in it," he said. With funding from the US Department of Defense, the laboratory is now working on a similar wall-mounted unit that could be attached in a subway station or public area. The unit would work throughout the day collecting and analysing air samples for biological and chemical contamination. Units that test for chemical contaminants are now under development, but Pontau said that future units will check for both types of agent.

This is just the beginning of what lab-on-a-chip technology can do. As the technology matures, many other, increasingly complex uses will become available, not only to help researchers in the laboratory to conduct their standard experiments faster and more efficiently, but also to create enormous potential in medical and public health settings. Lab-on-a-chip technology may therefore spark a revolution similar to the changes in the computer industry in the early 1980s, when the technology had progressed to the point at which personal computers became cheap and powerful enough to penetrate nearly every aspect of public life.

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