

The restless brain

Christian Jarrett enters the strange and controversial world of the 'default mode network'

Functional brain imaging promised to lift the lid on the black box. Psychologists responded in earnest, prodding the brain and watching which areas light up and which stay dark. But what if the brain's most important functions are intrinsic, only occurring when we're 'at rest'? The recent discovery of an energy-guzzling default mode network (DMN) that ramps up several gears when we disengage from the outside world has rendered such a scenario plausible, perhaps probable. Physics had to come to terms with the fact that most of what the universe is

made of is as yet virtually unstudied and unknown. Perhaps resting brain activity, and the mind-wandering it gives rise to, is psychology's very own dark matter. The question looks set to divide the brain sciences. Neuroscientists are heralding the dawn of a paradigm shift while leading psychologists remain sceptical.

The network

The DMN describes a swathe of brain regions, including parts of the prefrontal cortex, the midline and the parietal and medial temporal cortices, which paradoxically are more active when we're at rest compared with when we're engaged in a taxing, externally focused task. The network was first named and documented formally in a 2001 paper by Marcus Raichle, at Washington University in St Louis, and colleagues. 'What began to trouble people like me,' says Raichle, 'was that even if you just had somebody lying in the scanner with their eyes open or closed and they weren't doing anything other than being awake and then you asked them to do something demanding, not only did the areas that you might expect light up, but areas went down – that was the opening for us.'

Evidence that the brain remains active when we disengage from the outside world can be traced back at least as far as the 1950s to a paper by Louis Sokoloff and Seymour Kety. The pair used a classic technique involving

nitrous oxide to show that, metabolically speaking, students' brains were just as active when at 'rest' as during a mental arithmetic task.

We now know that the brain uses 20 per cent of the body's energy consumption even though it only accounts for 2 per cent of the body's mass, and that this barely changes regardless of whether we're engaged in a demanding mental task or we're resting. 'When you're lying quietly and then we ask you to do something – move your hand, talk, read, whatever – and we measure the total cost of running your brain, we can't see much of a difference,' says Raichle. 'So what's emerging here is this notion that a large part of the functional activity of the brain – neurons talking to each other – is ongoing all of the time, and the input/output of the system is only a small addition to that.'

The further discovery that there might be a specific network, active at rest and suppressed when we're outwardly engaged, emerged more recently. Gordon Shulman – a former student of psychologist and attention pioneer Mike Posner – had the idea in the late 90s of combining imaging results from nine different studies, involving 134 people, in an attempt to find a system that was present whenever attention was engaged. 'It was the biggest collection of PET data put altogether that's ever been done,' says Raichle, a long-time colleague of Shulman's. 'To Posner's disappointment, that attention system didn't emerge out of these brain scans. But what did emerge was a very consistent set of areas, now known as the DMN, that became less active during any demanding task, such as reading or moving your hand.'

Raichle says the implication that there was this brain system that flickered to life when we disengage from external tasks met with immediate resistance from the psychological community. He believes this is in part because of the dominant view in the 80s and 90s, and to some extent today also, that to study brain function you present a stimulus or you ask subjects to

reading

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do something. 'There was this mindset that you're turning the brain on,' he says.

A common criticism was that the resting activity of what we now know as the default network, rather than being truly intrinsic, must instead reflect some uncontrolled activation. Raichle considered this and came up with a way that he thinks shows default brain activity is more than unconstrained activation. His argument is based on the levels of oxygen supply and demand in the brain, and specifically his observation that this supply and demand is in near total balance when we're 'at rest', disengaged from the outside world. It was these ideas that were published in his now classic 2001 paper. 'The paper basically said the DMN, in the conventional way of looking at things, is not "activated" in this resting state,' Raichle explains, 'therefore it must represent something about the intrinsic activity of the brain that it's organised in that state.'

The influence

The paper 'A default mode of brain function', published in the *Proceedings of the National Academy of Sciences*, dropped like a bomb and its reverberations have been felt ever since. A casual PubMed search with the term 'default mode network' reveals 31 studies have been published on the topic in the first three months of 2009 alone. Today the idea of a default system inspires new approaches to research on depression, Alzheimer's disease, mental time travel, autism, comparative research and many other topics (see 'Findings'). One area of psychology that's probably felt the influence more keenly than most is in the study of mind-wandering.

Jonathan Smallwood, a Scottish psychologist currently working at the University of California, has been studying mind-wandering for most of his academic career. In particular, he and his colleagues have been interested in the idea that attention flips back and forth between an internal and external focus

(see 'Watching the mind wander', overleaf). 'What I've noticed in the last five to six years', Smallwood says, 'is that when I used to talk about this model people would say it's interesting but essentially an epiphenomenon. The concept of the DMN has changed that. It's brought to everybody's attention that an awful lot of what the brain is doing is to do with imaginative processing that we can't necessarily observe, and there are some aspects which you can't study without accepting that they occur spontaneously.'

Raichle himself has proposed that one of the key functions subserved by the default mode network may well be mind-wandering, and especially thinking about the future. He refers to a case study, first documented by Antonio Damasio, in which a stroke patient, with damage to a part of the DMN, recovered and described her experience as being unable to have any thoughts – almost as if her ability to mind-wander had been lost.

The possibility that the DMN may support mind-wandering was tested explicitly in 2007. Malia Mason and colleagues first asked participants to report how often their minds wandered during either highly practised or novel tasks. As you might expect, mind-wandering was more prevalent during

Findings

Many psychologists and neuroscientists now routinely scan the brain at rest. Here's a sample of recent default-mode-related findings from disparate fields.

Autism: In 2006 Daniel Kennedy (University of California) and colleagues reported that children with autism failed to show 'deactivation' in the DMN when engaged in a Stroop-like task compared with rest, whereas the deactivation was seen as usual in control participants. The researchers said the result was likely to be due to the children with autism having reduced DMN activity at rest – an anomaly they argued might play a causal role in the children's social impairment.

Depression: Could resting-state brain activity help identify patients with depression who are unlikely to respond to treatment? A brain-imaging study by Michael Greicius (Stanford University) and colleagues revealed abnormal patterns within the DMN of patients with major depression – exaggerated connectivity between a region called the subgenual cingulate, known to be involved in emotion processing, and the rest of the DMN. This was especially the case among those patients who'd been depressed for longer.

Alzheimer's disease: In another study, Greicius and colleagues found reduced resting-state activity in the hippocampus and posterior cingulate of Alzheimer's patients compared with controls. They argued that scanning resting-state brain activity could prove to be a sensitive way of detecting the disease.

Comparative studies: Chimpanzees show greater activity in the DMN during rest compared with during externally focused cognitive tasks, in a similar way to humans. James Rilling and colleagues made the observation in a 2007 study after comparing the resting brain activity of eight humans and five chimps. Species differences were also apparent. For example, the chimps showed less left-side activity, probably because they lack language.

more practised tasks. Next Mason's team scanned the same participants under similar conditions, as they performed either novel or practised tasks. They found that the DMN was more active during the highly practised tasks and that this was particularly the case among those participants who claimed to mind-wander more.

'Since Raichle made his claims in 2001, people had been floating around the idea that off-task thoughts and day-dreams are subserved by the DMN,' says Smallwood. 'But the Mason paper, and to some extent a 2003 study by Kristen McKiernan (which showed increased DMN activity during easier tasks) made a leap, in the sense they made this the focus of their investigation; before then it was just speculation.'

All of sudden, it seems, mind-wandering, day-dreaming, mental time

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travel, prospective thinking, call it what you will, have become the focus of heated research in psychology. 'There's a whole new field opening up,' says Smallwood. 'There's all these different buzz words, different approaches, but what's underlying all of them is the understanding that we're beginning to get the tools and concepts to look at imaginative and introspective thought that's really been ignored for various reasons.'

In Marcus Raichle's view, the discovery of the DMN has indeed led to something of a paradigm shift as psychology wakes up to the fact that, far from being a passive input/output device, the brain is constantly anticipating the future and bringing a rich context to its interactions with the world. 'Only eight per cent of the terminals in the visual cortex come from the outside world,' he observes. 'This should make people pause for a moment – how come everything is so clear? It's because of what the brain brings to the table.'

The sceptics

In a simple world, the story could end here: Brain network that's more active at

rest is discovered; psychologists respond by showing renewed interest in intrinsic mental activity. But the reality is a little more complicated. When Malia Mason's 2007 paper linking the DMN with mind-wandering was published, it was accompanied by a critical commentary by psychologist Sam Gilbert at UCL and his colleagues, including cognitive neuroscience luminary Chris Frith.

Gilbert and his colleagues argued that what Mason's group had inferred was mind-wandering activity could just as plausibly be

construed as enhanced watchfulness – in other words, an exaggerated focus on the outside world. Supporting this alternative view, Gilbert's team pointed

to research they'd conducted showing that in a simple reaction-time task, medial prefrontal cortex activity (a key part of the DMN) was actually higher when performance was better, consistent with the idea that this brain activity reflected increased watchfulness.

'This idea that if you put people in the scanner and give them nothing to do,

they'll only be engaged in internal processes just doesn't accord with my subjective experience when I've been in a scanner,' says Gilbert. 'If you're given nothing to do, especially if it's your first time, you're suddenly a bit anxious, you're wondering what's going on, there are also these beeps and strange noises, and you may be waiting for something to come up on the screen. So it's just as plausible that you're actually in a state where you're really looking out for something in the environment.'

What the discussions about Mason and colleagues' paper betray is a growing unease among large quarters of the psychological community that it can ever be a good thing to

focus on scanning people's brains when they are at rest. After all, if there's room for multiple and contrasting interpretations about the mental processes involved during a practised task (as in the Mason study) then the scope for disagreement about the possible mental activities involved 'at rest' must surely be even greater.

'The growth in the DMN literature has provoked good questions and good experiments,' says Gilbert, 'but I don't think that studying rest itself is a particularly useful thing to do. If you're interested in self-initiated behaviour, then you can study that experimentally – you just have to come up with good tasks for how to do it in a careful and controlled way. The DMN literature reflects, in a way, a decognitivation of cognitive neuroscience.'

These methodological concerns were expressed most explicitly and forcefully in a 2007 paper 'Does the brain have a baseline? Why we should be resisting a rest' by Alexa Morcom, now at the University of Edinburgh, and Paul Fletcher at the University of Cambridge. Morcom, a psychologist, investigates memory decline and ageing, and the DMN first came to her attention when other researchers started talking about the DMN changing with ageing. 'It sounded like some kind of theory about brain ageing but when I looked closely I realised that it wasn't really telling me anything,' Morcom says. 'The DMN theory is very unpsychological. I didn't feel I'd learned anything about what these regions are doing and how they might actually be underpinning memory decline.'

Morcom and Fletcher's paper acknowledged the potential diagnostic utility of scanning the brain at rest. But

"what the mind is doing when it is turned in on itself is a vitally important topic for investigation"

Watching the mind wander

Instruct a participant to mind-wander: if they obey, then paradoxically, they're not really mind-wandering. What's more, give a participant a boring task and ask them to indicate when they're mind-wandering and by definition the moment you get a signal means they're not mind-wandering any longer. So just how do psychologists study such an intractable form of mental behaviour? 'We've looked at this issue with the view that attention isn't static but can ebb and flow,' says Jonathan Smallwood. 'So we've attempted to come up with tools to find out how and when people switch to an offline mode.'

One such tool used by Smallwood is called the SART (sustained attention to response task), originally developed by Ian Robertson at Trinity College Dublin and Tom Manly at the University of Cambridge as a way to study cognitive deficits arising from head injuries. 'One of the clever things about the SART', Smallwood says, 'is that it turns the attentional process backwards so people have to withhold a response to a target, and this allows us to identify those moments when a person has failed to attend.'

A typical SART task will require participants to respond to the numbers 0 to 9, but excluding the number 3. An inappropriate response to 3 acts as a marker for an attentional lapse and the period preceding an error is a strong candidate for a mind-wandering episode.

Another approach is to use thought probes, which involves unexpectedly asking a participant to report what they were just thinking about – whether they were 'on task' or if their minds had wandered. An obvious disadvantage with this approach is that participants will soon cotton on to the purpose of the research, which is likely to have an effect on their tendency to mind-wander.

Earlier this year, Smallwood and colleagues combined brain imaging with use of thought probes and measures of attentional lapses to show that default mode network regions are activated during mind-wandering episodes. In other studies they've looked at the links between mind-wandering and creativity and comprehension. Together with Jonathan Schooler, Smallwood is currently developing a model to explain why we sometimes catch ourselves in the act of mind-wandering and sometimes don't. 'One idea is that the brain needs to periodically take stock of what it's doing,' he says.

beyond that, the pair argued in detail that studying the resting brain has no use to cognitive neuroscience whatsoever. In their view there is nothing inherently special or mysterious about the 'resting state' of the brain. They also rejected Raichle's claims that the DMN being 'active', but not 'activated', in the resting state means that it therefore reflects a baseline, intrinsic mode of operation.

'When Raichle says these [DMN] regions are not "activated" at rest, although they are active, he's making a technical point about the balance between the oxygen supply and demand in these areas and indeed the whole brain,' Morcom explains. 'But while there's this balance, the level of neural activity varies widely in the DMN and across the brain. So although the blood flow balance may be special at rest, there's no reason to think that the same is true of the neural function.' If Morcom and Fletcher are right, this would suggest that there isn't anything special about the brain activity observed at 'rest' – it doesn't deserve to be placed in a category all of its own. In fact, by this account, the most important distinguishing feature of neural activity at rest is that no one really knows what participants are doing with their minds during this time.

What about the 'tip of the iceberg' observation – the idea that the majority of brain metabolism fuels intrinsic activity, and that externally focused tasks make little difference? Morcom agrees that we need to find out more about the bulk of the iceberg, but she points out that that bulk is present during evoked or extrinsic tasks too. 'To my knowledge we've got nothing to say that this meaningful metabolic activity that is substantial is special to rest,' she says, 'It follows logically that the bulk of this iceberg is present across many different cognitive states, of which rest is only one, and therefore I don't see why they link it specifically to rest. I think the question of what all this activity represents is extremely interesting and there needs to be more research into neural activity that might not be the result of the substrate of information processing, but might somehow support it.'

The state of play

Technical issues aside, what everyone appears to agree on is that what the mind is doing when it's turned in on itself is a vitally important topic for investigation. If the discovery of a postulated DMN has

raised the profile of these so-called intrinsic processes, then that can only be a good thing. The points of contention, the state of play, revolves around whether scanning people at rest is the way to study these intrinsic processes, and whether the DMN, as it was originally conceived, really exists at all.

'I think there are lots of important mental functions that we perform every day that haven't been studied enough,' Morcom says. 'But I don't think the idea of the default mode or the idea of doing research using a resting state follows from these functions being really interesting.'

Sam Gilbert agrees: 'It would be great to figure out what's going on in these



Alexia Morcom says the DMN theory is 'very unpsychological'

DMN brain regions. But I'm not sure that it is constructive to do study after study where we just ask people to rest. At the moment it's very poorly understood what cognitive processes contribute to what aspects of DMN activity. In all likelihood, when we're at rest we're engaged in both internally oriented and externally oriented processes. The way to understand these processes is to have better experimental controls.'

Gilbert's own approach has been to use carefully controlled tasks to carve up the DMN into its functional subregions. He's focused on a medial prefrontal region that's associated with theory of mind – that is, thinking about other people's mental states. He and his colleagues had participants manipulate information that was either visible on a screen or held purely in their heads, and they were further led to believe that they were either working alone or collaborating with another. Gilbert found that the brain area activated when looking at a screen versus processing your own thoughts was as little as five millimetres away from the area that was activated when thinking about other people's thoughts. The

regions were almost on top of each other but it was still possible to separate them out according to their functionality. 'So when you dig into this network you can start seeing amazing functional specialisations,' Gilbert says, 'and I think we should be spending more time carving up this network rather than considering it as a homogeneous whole.'

However, Marcus Raichle and other DMN advocates, remain undeterred. They continue to believe that studying the brain at rest holds the key to many secrets. In fact, there is an entirely new field now in which investigators look for correlations in resting state activity between brain regions so as to create a functional map of the brain. Raichle points me to a noteworthy paper published last year in *PLoS Biology*, which is just the latest to take this approach.

Patric Hagmann and colleagues used diffusion tensor imaging (DSI) to create beautifully intricate maps of the dense cortical pathways within the cerebral cortex of five participants, and crucially, they then used fMRI to scan the same participants at rest. 'We found a close correspondence between the strengths of structural connections derived from DSI and functional connections derived from resting state fMRI in the same participants,' Hagmann's team concluded. In other words, neuroscientists like Hagmann are using the resting state as a functional template with which to inform their structural findings – exactly what psychologists like Morcom and Gilbert say they shouldn't be doing.

The onward march of the DMN doesn't end there. A further development has been to look at the resting state correlations between brain regions over longer periods than are usually studied in conventional brain-imaging tasks. These studies are revealing coordinated resting activity pulsing between disparate brain regions about once every 10 seconds. 'The sense I have about this is that there is a paradigm shift going on here,' says Raichle. 'We're beginning to recognise that there are actually slow cortical potentials which have been largely ignored. There's this coherent activity in the brain which has begun to define in an elegant way not only the relationships within systems like the DMN or the visual system, but the relationships between these systems. It's like the groundswell of the ocean.'

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