Out of sync

Memory research has largely neglected the question of how the brain uses memories. **Professor Armin Schnider** steps in to bring understanding of a rare reality confusion condition, leading to the discovery of a specific reality-filtering function

What is the focus of your research and what attracted you to this field?

Amazingly, the question at the heart of our research has never attracted much attention from memory researchers: how is it possible that we can freely think about the past, present, and future, think about our duties or roam in fantasies and still maintain our behaviour in phase with reality? How does the brain distinguish between thoughts that pertain to current reality and thoughts that do not?

I was attracted to this field while, as a neurologist, I was caring for patients who failed in that capacity: they confabulate about recent events that are invented and act according to imagined duties that do not relate to reality. Imagine, for example, a 58 year-old woman – amnesic after bleeding to the brain – who desperately searches for her baby she has to feed, while in reality her baby is over 30 years old! In the course of our studies, I realised that this disorder, which I called behaviourally spontaneous confabulation, is actually a human lesion model for the ability to keep thinking in phase with reality.

How common are conditions involving memory and reality confusion?

Impaired memory is a very frequent consequence of brain damage because the correct storage and retrieval of information depends on diverse, delicate processes. In comparison, confusion of reality with inappropriate acts, as we observe in our patients, is extremely rare. Even among patients who have the typical lesion for the disorder, only a small minority – around 5 per cent – will actually confuse reality over a prolonged period.

What is extinction capacity and how does it relate to reality filtering?

Extinction capacity describes the ability to learn that a previously valid anticipation no longer applies. It was described a century ago in conditioned animals and depends on the orbitofrontal cortex. Our patients act according to plans that were appropriate in the past but which have no relation with present reality. Thus, we hypothesised that they fail to extinguish previously valid anticipations. A recent study supported this hypothesis: we asked patients to perform a task in which they learned to associate an outcome with a cue. The failure to later abandon this association when it was no longer valid was very strongly associated with the degree of reality confusion. We concluded that rather than developing a new high-level monitoring process, the human brain recurs to an old biological faculty (extinction) to keep thought and behaviour in phase with reality.

Can false memories occur in healthy humans? Under what circumstances could this occur?

Oh yes! Every time we think about an event, we lay down a new memory trace of it, which is influenced by current circumstances. False elements are likely to be included in the trace if they are plausible and the original memory is not very strong. These falsifications of memory mainly happen during encoding and re-encoding of information and are, therefore, completely different from reality confusion of patients with orbitofrontal damage. Healthy subjects do not confuse reality as it happens in pathological states.

How has collaboration with other researchers played a part in your investigations?

It has been crucial. Our research is translational: it uses multiple methods including neuropsychological exploration of patients, imaging of brain activity, recording of electrical brain activity with electroencephalography in healthy subjects or even depth-electrodes that some patients have for clinical reasons. We are interested in a specific question, namely, how the brain adapts thought and behaviour to ongoing reality. We use any available technology that allows us to respond to that question. We therefore critically depend on collaboration with research laboratories with expertise in the different technologies.

What do you see as the opportunities and main obstacles to your research?

The area of false memory, as it occurs in brain pathologies, is still dominated by hypothetical models devoid of experimental support. For many, these models still prevail over experimental data even if the data clearly contradict the models. I hope that in the future more memory researchers will become interested in the field. I also hope that fundamental researchers will join in. Basic science will be necessary to better understand the precise cellular mechanisms underlying reality filtering and its interaction with the storage of memories. Such research might eventually lead to better treatments for disorders of reality confusion.

Encoding and filtering memories

Leading neurological research at the University Hospitals of Geneva observes patients with damage to the orbitofrontal cortex to find clues into how the brain screens thoughts to keep actions in line with reality

HUMANKIND'S ABILITY TO recall the past and store information and experiences is known as memory. More and more studies reveal evidence that infants as young as six months old are able to retain and retrieve information. Most agree that an individual's mental abilities peak in his or her 20s and 30s and begin to decline thereafter. In the later years of life, memory capacity decreases and elderly adults often experience difficulty recalling names or recent events. In contrast to the normal ageing processes that decrease memory capacity, a number of disorders dramatically impair memory capacity, such as Alzheimer's disease.

At the University Hospitals of Geneva, Switzerland, Professor Armin Schnider has been researching memory for more than 15 years. His work is unique from other approaches to memory research because instead of focusing only on how memories are stored within the brain, he is looking at how the brain makes use of memories: how it is able to make the distinction between thoughts associated with reality and those that represent fantasy. A key component of memory is that it allows organisms to apply their knowledge and ideas from the past to their present actions. To do this correctly, a mechanism is needed allowing organisms to determine whether memories and thoughts relate to current reality – and therefore deserve to be acted upon – or not.

REALITY VS FANTASY

His work has focused largely on a memory disorder he dubs 'behaviourally spontaneous confabulation'. When the brain is unable to distinguish between reality and fantasy, it may be experiencing spontaneous confabulation and disorientation. This manifests as a false sense of reality. In one case, a female lawyer was admitted to hospital for severe amnesia after suffering from encephalitis. She believed for several weeks that she was at work and constantly searched around the hospital unit for collegues and files to prepare for court appearances. This type of reality confusion can result from a lesion of the region of the brain just above the eyes – known as the posterior medial orbitofrontal cortex – or to the structures directly connected to it. Bleeding, inflammation, tumours, malnutrition due to alcohol abuse or hypoxic brain damage can all cause harm to this area of the brain.

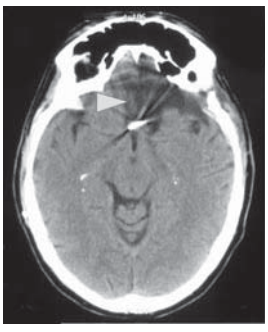


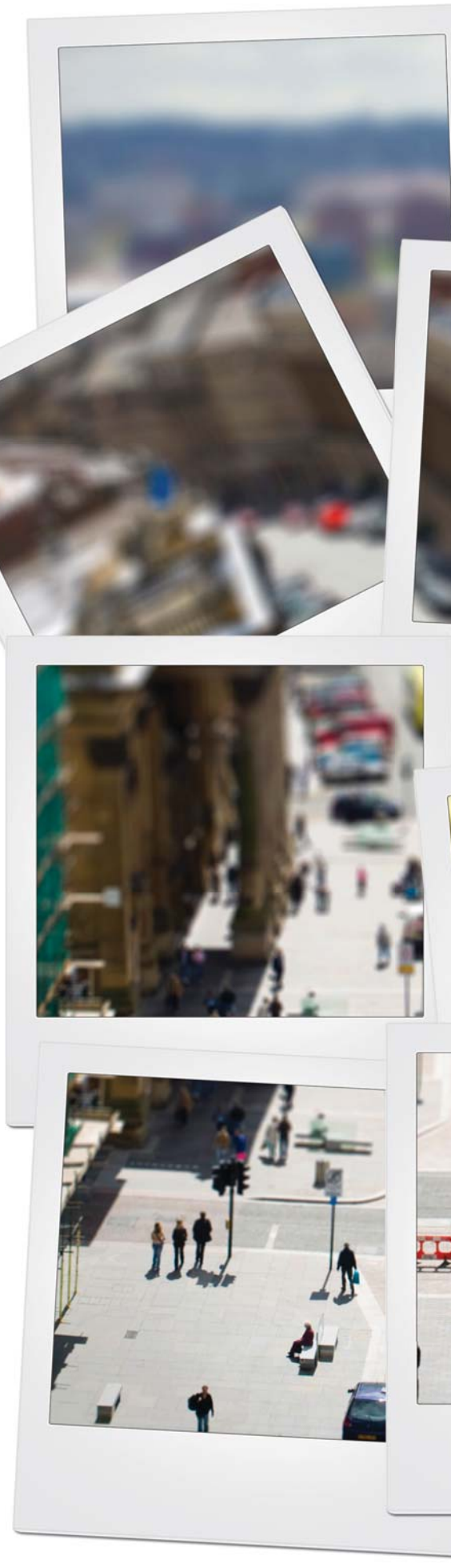
FIGURE 1. CT SCAN OF A PATIENT WHO CONFUSED REALITY AFTER SUFFERING BLEEDING AND SUBSEQUENT DESTRUCTION OF HIS ORBITOFRONTAL CORTEX. THE ARROW SHOWS THE AREA OF DESTRUCTION IN BLACK

Researchers determined that the orbitofrontal cortex plays a critical function in maintaining thought and behaviour in phase with reality because patients exhibiting confabulation experienced lesions to this exact area, whereas those diagnosed with amnesia but still able to grasp reality had damage to a more posterior brain region, the hippocampal area. Schnider also uncovered corroborating evidence for this conclusion by measuring brain activity in healthy subjects using functional imaging. "When these subjects successfully performed a task on which the reality confusing patients had failed, they activated the orbitofrontal cortex, precisely the area that is typically damaged in the patients," he asserts.

FILTERING THOUGHTS

The further question remained of why a lesion of this particular region of the brain caused a person to be unable to distinguish between memories that pertain to reality and memories that do not, that is, fantasies. The answer came from a simple experimental task in which patients with orbitofrontal cortex injuries were shown a series of images and were asked to signal whenever a picture was repeated. The process was conducted again an hour later, with the order of images rearranged. Schnider noticed that patients with a distorted sense of reality recorded a much higher number of false positives in the second round, meaning they thought they saw images in the present task when, indeed, they had seen them an hour before. This was not the case with amnesic patients without reality confusion. Thus, the researchers concluded that the orbitofrontal cortex is responsible for signalling when a thought is not related to the present situation, and therefore constitutes a fantasy. Recent studies showed that the patients also failed to abandon previously learned anticipations when they were no longer valid: they had a specific deficit of extinction capacity.

Schnider notes that results like these are some of his most crucial findings to date: "The most important, truly decisive step, was the development of experimental tasks in which



reality-confusing patients, in comparison with other populations, specifically failed". This allowed specific exploration of the brain mechanisms that shape humans' perception of reality. "The most fascinating insights have been that our human sense of ongoing reality depends on a specific orbitofrontal memory filtering function, that it occurs before we recognise the content of our thoughts, and that such a high-level mental capacity depends on a phylogenetically old capacity – extinction – which was already present in primitive creatures like aplysia or the fruit fly," Schnider enthuses. Knowing this, researchers now understand that reality filtering is likely to have developed in parallel with memory storage capacity.

Schnider's conclusion that reality filtering occurs early and pre-consciously before the content of memories is consciously recognised resulted from a series of studies into the electrical brain activity of healthy subjects using high-resolution electroencephalography. The subjects were asked to perform a memory task which reality-confusion patients failed. This method revealed that the content of retrieved information is recognised at 400-600 milliseconds whereas reality filtering – the distinction between currently relevant and currently irrelevant memories – occurs at 200-300 milliseconds. "This means that, before we even know what to think, the brain has already determined whether an upcoming thought refers to reality or not," Schnider elucidates.

TREATMENT AND FUTURE

Despite an enhanced understanding of the causes behind reality confusion, treatment options for the condition are an area for future development. Since patients are absorbed by their distorted reality and believe it to be true, it can often be very difficult to care for them.

Schnider describes a common treatment option in use at his clinic: "We accept the patients' false reality as long as they do not put themselves into danger. Medication may be useful: we have discovered that reality filtering is modulated by a specific transmitter – dopamine. Some patients indeed improve under neuroleptics, which are dopamine antagonists". Over time, virtually all patients recover from reality distortion, although most remain amnesic.

Seeking to further understand reality filtering, Schnider's team recently began working with a company called Genomera in Palo Alto, California to explore the idea that the human sense of reality may be controlled by genes. The study will be performed by analysing the genotype of healthy volunteers who then perform a reality-filtering task. This will allow comparisons between subjects' performance and the composition of specific genes. Schnider looks to the future of his research: "We hope to learn more about the cellular mechanisms of reality filtering from this study. We also have to better understand the criteria the brain uses to establish reality in thinking". Responses to such questions may help to devise more specific treatments for disorders marked by reality confusion.

INTELLIGENCE

REALITY FILTERING – SORTING OUT RELEVANT MEMORIES

OBJECTIVES

How can the human brain accumulate memories and ideas and still know which ones refer to present reality? Starting with observations in brain damaged patients, the project has led to the discovery of a mechanism that filters our thoughts according to their relation with reality. Ongoing studies will determine the genetic and precise functional basis of this fundamental capacity.

KEY COLLABORATORS

Postdocs and doctoral students

Functional Brain Mapping Lab of Professor Christoph Michel, Geneva

Centre d'Imagerie Biomédical (CIBM) a partnership between **Ecole Polytechnique Fédérale de Lausanne** (EPFL), **Université de Lausanne** (UNIL), **l'Université de Genève** (UNIGE)

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