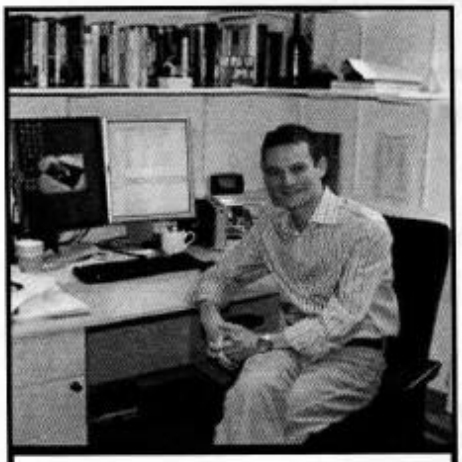
LINKING THE LABYRINTHS: *NEUROSCIENCE AND MEMORY*



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Interview: Shani McCoy

Can you give me a broad outline of your main areas of interests in terms of your research?

My research focuses on the brain areas involved in human memory. We take a convergent view and use a range of methods because no single method can tell you everything about how the brain works. Neuroimaging techniques like functional magnetic resonance imaging can show which brain regions may be activated during specific memory tasks but can't show whether those areas are' necessary' to the task or playing a key role. In order to assess this we might test people with lesions to areas of the brain we're interested in to see if these adversely affect completion of the task.

As I understand it, patterns of lesions are different for different people; does that make it more difficult?

Yes, it's very difficult generally. Lesions differ widely between people and tend not to be very specific to individual brain areas. For example, lesions may involve a large part of the right hemisphere, whereas we might be interested in a specific area of the right frontal lobe, or of the temporal lobes and you very rarely find patients who have lesions that specific.

Presumably you don't know what kind of function they had prior to the lesion either?

Yes that is an issue. You can give memory tasks to a lot of healthy people and get an idea of how most people will perform but when trying to assess things like general knowledge, where everyone is different, it can be more difficult. There are ways of getting around this, one technique Transcranial Magnetic Stimulation (TMS) is a very new method of creating what's termed a virtual temporary lesion in healthy people, so you can compare performance in the same individual both before and after the "lesion". It

uses a focused magnetic field to over stimulate a defined area of the brain so that information processing can't happen in the usual way for a very short period like a few seconds. Because the area doesn't operate functionally for that time you've created what seems to be a virtual lesion and this can be done quite specifically so you can look at a particular region. It's a technique we are just starting to employ. Other groups across the world have made some progress with it, but not many people are using it to understand memory and it's not really clear yet how effective it's going to be.

A few seconds is a very small time frame?

Yes that's a potential difficulty, although even in a few seconds you can determine whether somebody is temporarily finding it harder to retrieve certain memories compared to their ability before (or a minute or two after) the stimulation.

One main area of your research looks at interactions between the prefrontal cortex and other brain regions involved in strategic control; can you explain what you mean by strategic control?

Well the evidence suggests that memory isn't an automatic process. We don't just think 'I'm going to remember something' and boom it pops out just like that. What we seem to be doing is creating recall strategies, a kind of specification program allowing us to search through our stored memories in an efficient manner. If we just went through our memories one by one we'd be doing that for a very long time because of the sheer volume, so we tend to employ a more efficient process by creating some sort of goal specification describing the memory we're hoping to retrieve using strategic processes and its thought that the frontal lobes (or prefrontal cortex) are very important in that process.

Is that because these areas are involved in Executive Functions?

Exactly, one role of executive functions is to create strategic plans for doing any task and the frontal lobes are very involved in that. The idea is that memory recall is just another type of problem that needs to be solved in the same way as any other problem. So, you might come up with an efficient strategy for a memory search, perform a search using that strategy, hopefully retrieve the right kind of memory, then you might monitor that memory and evaluate it in terms of its match to the strategic criteria. If it matches then that's the right memory hopefully, if not, you modify the strategy by changing the

specification or rejecting it outright and coming up with something else, then go do another search.

Not like a random search?

No, random searches may be possible, but for most tasks it's much more efficient to use some kind of strategy to guide your retrieval search. People have thought for a long time that the frontal lobes are involved in strategy generally so we're looking at which specific regions may be recruited to support memory retrieval. The frontal lobes make up the whole frontal third of the brain, that's a huge amount of cortex so if this area is doing something as complicated as problem solving and executive functions then it's quite probable that there are multiple processes and regions within the frontal lobes that may be working together doing different tasks.

It's been suggested the dorso-lateral region may be involved as the working memory, workhorse part of that system so how does that relate to the anterior prefrontal cortex that you are looking at?

Well, there are three main regions talked about with regards to memory, the ventro-lateral, dorso-lateral and anterior regions. The ventro-lateral region is involved in short term maintenance functions, when you retrieve something and hold it online then it's thought to be the ventro-lateral prefrontal cortex that does that. The dorso lateral prefrontal cortex seems involved more in what we would think of as the real executive functions, the monitoring processes organising information and other kinds of problem solving operations. Finally, it's the anterior frontal cortex, which is the area right at the front of the brain, just behind your forehead, that seems to be key for coordinating those operations and specifically applying them to complex memory tasks. So when you're involved in complex recall, not simple memory tasks like "have you seen this before?" but "where and when did you see it?" then it's the anterior prefrontal cortex that seems to be involved.

So that's conscious, controlled recollection as opposed to unconscious recollection like intrusive memories?

Yes, intrusive memories seem to involve the middle of the frontal lobes, the medial frontal cortex. If you have a lesion in this area then you can have intrusive memories and disorders like confabulation, where people recall sometimes bizarre memories of an event and false memories. The anterior prefrontal cortex is involved in conscious recollection or discriminations like

'Was it here or there? Did I think it, hear it or imagine it?' Those sorts of very fine grained memory discriminations.

I've also read suggestions that communication between the prefrontal cortex and the medial temporal areas are important in encoding, is the anterior prefrontal cortex involved in that?

That's an interesting question, and not a lot of people have really looked at what role anterior prefrontal cortex might play during encoding. There's a whole body of research that broadly agrees that areas of the prefrontal cortex and interactions between the prefrontal cortex and the medial temporal lobe are key for encoding. Engaging the prefrontal cortex at encoding particularly helps in later recall. The ventro-lateral region appears to be involved during in-depth semantic processing while encoding. If you look at something briefly then processing is not very deep and you'd be less likely to remember it but if you think about it harder including the semantic detail, for example is it a natural or manmade thing, then you're processing it more deeply. There's an interaction between those processes. A brief glance may be enough to leave a medial temporal lobe trace because pretty much everything you look at leaves a trace there, but it may be difficult to access that trace again later. It's only when you have interactions with the prefrontal cortex to encode the memory deeply that you are likely to have very accurate recall. Whether anterior prefrontal cortex has a role at encoding is very much up for grabs, however.

Your research concerning the 'necessity' of specific regions like the parietal lobe in memory suggests that this area may pertain primarily to the subjective experience of recollection as opposed to accuracy. Can you elaborate on that?

We're still in the preliminary stages of understanding this, but while the parietal lobes have long been considered to be involved in visual attention and object manipulation (for example, visual neglect often results from parietal lesions), no one had made a connection with the memory debate because these patients did not appear to have any overt memory problems. Almost all memory studies using functional imaging have concentrated on activation observed in the frontal and medial temporal lobes, because these areas have been highlighted for years in studies of amnesia. What the neuroimagers haven't really talked about but can be seen from the research papers is often a whacking great activation in the parietal lobes, usually much bigger and more common than that of the

frontal and medial temporal lobes. So what we've been trying to do in the last couple of years is to understand what's going on there. Previously, researchers interested in patients with parietal lobe lesions have studied visual spatial attention or visually guided reaching and haven't considered giving memory tests so it's possible there may be subtle memory deficits that have been missed. We felt sensitive memory tests might uncover any deficits and potentially help these patients.. So we give people very specific recollection tasks that even healthy people may only correctly complete 60-70% of the time, asking them to recall specific contexts in which they saw something for example. Initially we found patients with huge parietal lesions and problems with visual spatial attention nevertheless complete these tasks as well as anyone else. However, we discovered recently that despite their memory being accurate they can be less confident about their recollections than a healthy person would be. When we talk to them outside the experimental situation, they say they don't remember things in a rich or vivid way. Unlike other people who can picture and relive to some extent events in a kind of mental time travel, patients with parietal lesions, report at least, that they don't experience recall that way.

So what you seem to be saying is they may not be getting all of the associations?

That's what we're looking at. For whatever reason they don't seem able to use visual imagery to recreate a memory or scenario in the normal way. It may be that while they can access specific details they're unable to link different memories together to form a coherent whole representation of the experience. That might be because of some problem with attending to all the different elements and we know they have a problem there, or it could be a binding problem. It could be a problem with subjective experience so they just don't experience retrieval in the same way because of something that the parietal lobes are doing. There are lots of hypotheses connected with this so it's ongoing.

I was interested to read your proposal that episodic memory involves multiple inputs from semantic and perceptual systems; can you tell a little more about your ideas there?

Our theory was built from traditional ideas about episodic and other aspects of memory. The model proposed by Tulving and others since the 70's says that episodic and semantic memory are separate processes with episodic memory dependent on semantic memory. This

came from years of research evidence from amnesia studies where people unable to remember were still able to semantically process information. The pattern of deficit was intact semantic memory but impaired episodic memory and you would never see the opposite pattern. What we did a number of years ago, during my PhD, was to test patients with semantic dementia. That's an extremely rare form of frontal temporal dementia where patients have very early, very specific atrophy of the lateral temporal lobes and impaired semantic memory. It's a progressive disorder so as the atrophy spreads semantic memory declines and we were interested in any subsequent effects on episodic memory. So we ran different memory tests in these patients. The problem with testing these patients is because they have damage to the left temporal lobe they also have language impairments because that area is very important for language so a recall task involving words isn't possible. Instead we showed them a series of pictures of everyday objects and gave them a semantic memory task like. 'What is this object?' 'What's it used for'. They would invariably fail those tasks as that is the standard finding for semantic dementia. Then later we would go back and show them the pictures again but adding a surprise episodic memory test, so we might show 2 cups and ask which one they'd seen before or we might vary the room during the study phase and then ask later which room they previously saw the item in. What we found was that mostly, these patients were relatively intact in terms of their episodic memory.

So that undermined the idea that episodic memory was completely reliant on semantic memory because if their semantic memory was compromised then episodic memory should also have been adversely affected?

Exactly, Tulving would have predicted a high correlation between semantic and episodic memory impairment but we were able to show this wasn't a sufficient explanation. In fact patients with amnesia and patients with semantic dementia could be thought of as representing two sides of a double dissociation which of course is considered the gold standard for separating functions. So that led us to consider that semantic memory can't be, as Tulving's model predicts, the only route into episodic memory. We hypothesised that as pictures are a perceptually rich and detailed stimulus that maybe there's a route from perception directly into episodic memory, perhaps bypassing semantic memory. We then conducted tests manipulating the perceptual image between study and test, so for example we'd give participants one cup in the study phase and a different one in the test phase. It was still a cup but it was

perceptually different to the one they'd seen before. An ordinary person would say "Yes I've seen a cup before " whereas our patients would fail. We knew they couldn't process the information semantically and the perceptual information was no help because we'd taken that away effectively so they'd fail the episodic recall task. This showed that perception was the previous source of their episodic memory. That in turn implied multiple routes into episodic memory, not just semantic but also perception. It's possible that different modalities of perception may be implicated here alongside visual like auditory, touch and smell etc. Smells for example are a very strong and powerful retrieval cue so it's highly likely there's a route from the olfactory system into episodic memory as well.

What about people with psychiatric/ psychological disorders? Are there functional memory differences in those kinds of disorders?

Certainly memory can be affected in psychiatric disorders and there tends to be a difference in terms of the neuroimaging activations you see, although it can be difficult to characterise. Generally people with psychiatric conditions experience memory differently, but there's so much variability between people that it can be difficult to arrive at a consistent picture for any one condition. Depression tends to be associated with memory reduction although with all that's going on in that disorder it's difficult to pinpoint specific types of memory impairment. However, typically someone with depression will struggle with recollection tasks.

Cognition is generally lowered across the board in depression so that must make it harder to isolate memory issues?

Exactly, it's very difficult because there's so much variability and they can have a blunted affect with motivation reductions which makes memory problems difficult to isolate from other cognitive reductions. In schizophrenia we can say a little bit more but again it's very difficult to look at because of that variability as well as issues like medication and hospitalization which themselves affect general cognition. Some studies have tried, not always perfectly, to control for those factors and they seem to converge on the idea that there are some specific memory deficits occurring in schizophrenia. For example patients often do well in simple recall tasks, like have you seen a cup before and contextual recollection like asking where or when they saw it. Their specific deficit seems to relate to the whether the source of their memory was internal or external to themselves, for instance whether

they or someone else did something or whether they imagined or actually saw something. For example if I showed you a cup and asked "Earlier on when I talked about a cup of coffee did you see this cup or did you just imagine it?" we are generally quite good at saying "No you didn't show me a cup I imagined it" whereas someone with schizophrenia would, at least sometimes, have difficulty discerning between that internal and external information. We usually know we dreamt something or saw it in a film rather than experienced it in reality. We can imagine a particular thing but then we generally don't believe it actually happened so we're good at knowing the difference between things we internally generate and things we see in the outside world but it seems patients with schizophrenia are not so good at this. What's been hypothesised, not only by us but previously by others like Chris Frith who has been very prominent in this field, is that this discrimination deficit between internally generated and externally derived information may be a potential cognitive explanation for phenomena in schizophrenia like delusions or hallucinations. These patients see or hear something that isn't really there but are unable to discriminate that it was internally generated. They therefore think it's coming from the outside world and it feels real to them. That brings the clinical schizophrenia field and the cognitive memory field together to say 'Well can we find evidence to support this cognitive hypothesis? Does this account for the clinical symptoms?'

One theory seems to indicate incorrect encoding of information coupled with a high level of confidence in hallucinations and delusions. Confidence in memory pertains to the kinds of brain regions you're talking about, would that implicate those regions in this disorder?

The frontal lobes are among the regions which seem dysfunctional in schizophrenia but again with huge variability. The debate over these areas is still unresolved although we do think that some of the regions implicated contribute to making confidence judgements like the dorso - lateral prefrontal cortex or the anterior prefrontal cortex. These are involved in monitoring and evaluating information and it seems in schizophrenia when patients are mistaken in a memory they can be very confident about it. They may be very keen to say definitively that a voice is coming from outside and they didn't imagine it, so it's possibly a dysfunctional evaluative process. You know when you talk to these patients sometimes it's difficult to understand how they can believe something which is so obviously not true and yet they are so confident they think it strange that you doubt them and often have a rationale for

why they think these things. It's a very interesting phenomenon but very difficult to study.

There seems to be a perception that in terms of brain function, that these conditions are innate is that right?

Well, we don't know why people develop these conditions, there may well be a genetic basis but an unresolved question if it's innate is why doesn't it come on in childhood, why adolescence particularly, that's something we don't really understand yet.

What kind of progressive memory degenerations occur in conditions like Alzheimer's and how does that differ from the normal ageing process?

In Alzheimer's disease there's atrophy, shrinkage of the tissue, that early on is reasonably specific to areas like the hippocampus. We were talking earlier about semantic dementia being associated with shrinkage primarily in the lateral temporal lobe, the idea in Alzheimer's is that it's mainly in the medial temporal lobe in the early stages, specifically the hippocampus and the cortex surrounding it. It's also a progressive disorder, atrophy spreads gradually in a fairly bi- lateral way in both left and right sides but it also spreads to include areas outside the hippocampus until eventually a large part of the brain experiences atrophy and then there's generalised dementia. The interesting thing is if you can diagnose these patients early enough, you can differentiate between those with Alzheimer's disease and semantic dementia on the basis of the specific areas of damage but gradually atrophy in all these patients develops and eventually they all look like someone who has a globalised dementia.

So depending upon where the atrophy is impacts on the type of memory deficits they have?

Yes, that seems generally the case, if you have medial temporal lobe atrophy then you'll typically have major deficits in episodic memory, lateral temporal lobe atrophy usually causes major deficits in semantic memory. Frontal lobe atrophy is less clear but seems to implicate the strategic memory processes.

Are those patterns of atrophy different from the atrophy that occurs in the normal ageing process?

In normal ageing there is subtle atrophy which is fairly widespread perhaps with predominance in the frontal lobes. Older people do exhibit subtle memory deficits although some may not ever show any signs of dementia. However, if you give an

older person a really hard memory recollection task it's likely they'll have some difficulties relative to younger participants. However, usually a patient with Alzheimer's disease will have a considerably more profound memory impairment compared with a healthy person of the same age. So it seems like dementia and normal ageing are very different things.

If it's a different process of degeneration then, do we know the cause of Alzheimer's?

Not really, there seem to be plaques or tangles between the fibres in the brain which make the neurons dysfunctional, and these signs may be specific to Alzheimer's disease, but I don't think it's been nailed down yet as to whether these are the cause of the dementia, or just a consequence of the disease. I'm not an expert on these matters, but I think the neuropathological evidence favours the conclusion that dementia isn't just an accelerated ageing process. There's something different going on, a disease or other pathological process but we don't really understand that yet.

What specific areas are you going to be looking at next in terms of your research?

This parietal lobe and memory issue is the real hot potato for us at the moment and there are lots of hypotheses out there. It's nice because it's a relatively unexplored area considering the parietal lobe is such a large part of the brain and has been explored so much in many other areas of psychology. Quite what role it plays in memory is really up for grabs at the moment.

Presumably whatever comes from that research will also inform our understanding of other brain processes?

Yes they're all linked. Neuro-imaging has shown that the concept of specific brain areas handling distinct processes in isolation is hopelessly over-simplistic. It seems that the many areas of the brain operate together in a network to achieve any kind of cognitive function. Neuro-imaging during cognitive tasks shows the entire brain operating, not small areas of specificity. In fact we have to do very complex statistics to be able to distinguish at all which areas might be recruited slightly more during one task than another. So trying to understand how these areas all fit together and whether there are specific interactions between them in memory really is the goal over the next twenty years or so. Imaging techniques and ways of analysing data are getting more sophisticated and we're now starting to be able to ask questions like 'Are these regions working together or just activated at

the same time? Are the connections weighted differently for different tasks? Are there causal directions in the links between regions that indicate that this region is controlling or monitoring another region?' That's the kind of thing we are starting to look at now.

That's been really interesting, thank you very much Jon.

Dr Jon Simons is a university lecturer and researcher at Cambridge University's neuroscience department. He is a fellow in experimental psychology at Emmanuel College and External Director of Studies at Christ's Church College.. His research investigates the role of brain regions such as the frontal, medial temporal, and parietal lobes in human memory.