New insights into causes of loss of orientation in dementia

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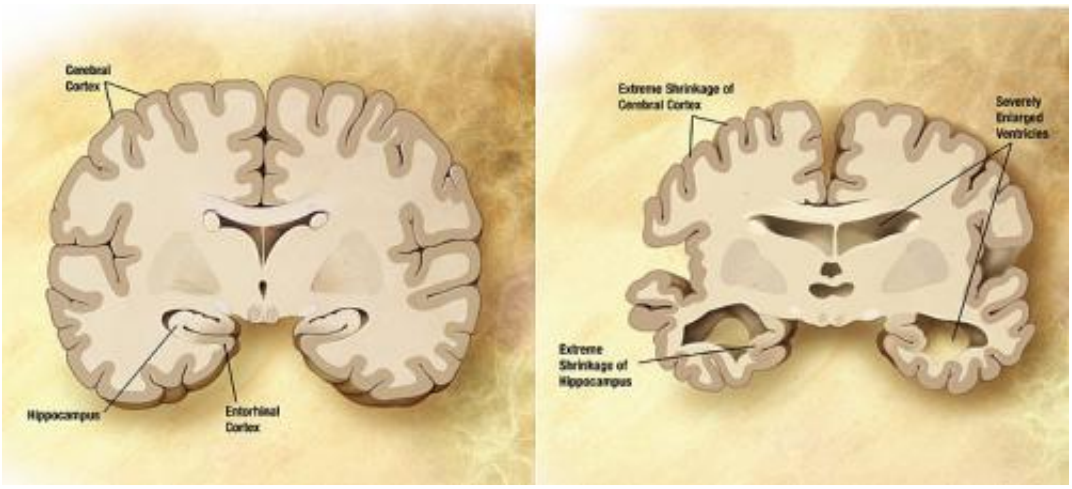

Diagram of the brain of a person with Alzheimer's Disease. Credit: Wikipedia/public domain.

New research has revealed how disease-associated changes in two interlinked networks within the brain may play a key role in the development of the symptoms of dementia.

The University of Exeter Medical School led two studies, each of which moves us a step closer to understanding the onset of dementia, and potentially to paving the way for future therapies. Both studies, part-funded by Alzheimer's Research UK, are published in the *Journal of Neuroscience* and involved collaboration with the University of Bristol.

Both studies shed light on how two parts of the brain's 'GPS' navigation system malfunctions in dementia, and point to likely underpinning causes for loss of orientation that is commonly experienced by people living with the condition.

In the first study, the team studied a part of the brain called the entorhinal cortex. Located near the base of the brain, this region is associated with functions including memory formation and navigation, and contains so-called "grid cells". These nerve cells fire electrical discharges in a grid-like pattern, much like the grid on an Ordnance Survey map. Paralleling the different scales employed by different maps, the grid firing patterns in the entorhinal cortex also have different scales, with cells at the top of the cortex having a more tightly packed grid pattern than those at the bottom. Scientists believe that this top-to-bottom gradient of different grid scales contributes pivotally to our sense of spatial location.

The team compared the activity in the entorhinal cortex of healthy mice and mice with dementia. They found that top-to-bottom gradients in electrical activity in the entorhinal cortex are not present in mice with dementia. Their findings suggest that the fine navigational detail, such as you would find on a large-scale map, is not correctly represented in patients with dementia.

Dr Jon Brown at the University of Exeter Medical School led the studies, as part of his Alzheimer's Research UK Senior Fellowship. He said: "This is an exciting discovery because it is the first time grid cell activity has been linked to the onset of disease. We now need further research to better establish how these findings translate to dementia in humans."

In the second study, researchers examined "place cells" located in the hippocampus, a brain structure known to be critical in processing learning and memory, both affected by dementia. Place cells help us to

identify where we are within a certain space.

The team found that the hippocampus of mice with dementia was associated with specific disturbances in synaptic, cellular, and network-level function, meaning that spatial information was wrongly encoded and spatial memory was impaired.

Dr Brown said: "Dementia is one of the greatest health challenges of our time, and we still have so much to learn about its causes, as well as about how our brains work. This research makes progress in both areas, and is another small step along the road to earlier diagnoses and finding new treatments and therapies."

Professor Andrew Randall, who co-supervised much of the work, said: "This has been a fascinating experimental journey for our research teams, and much of the pivotal work was carried out by talented PhD students. We look forward to producing much more work of this nature as members of Exeter's growing dementia research community."

Dr Laura Phipps from Alzheimer's Research UK, said: "There are 850,000 people in the UK with dementia and a tenth of those are living in the South West. It is vital that researchers explore the complexities of the brain, to understand more about the causes of the condition and how we can tackle it. Dementia is not just a synonym for forgetfulness - these findings in mice highlight the impact that diseases like Alzheimer's can have on spatial orientation. It will now be important to build on this research, to understand whether this chain of events can be targeted in the hunt for new treatments."

The University of Exeter forms part of the Alzheimer's Research UK South West Research Network - a community of dementia researchers in Exeter and Plymouth, working collaboratively to accelerate progress in dementia research.