at the brink

Ten million. In 2041, just 36 years

from now, that's how many Canadians will be aged 65 and over. With this aging explosion will come a surge in the number of people living with Alzheimer's disease (AD) and other dementias, and the cognitive aftershocks of stroke.

Related economic costs are as-yet incalculable. The human impact is easier to imagine, because it'll be much as it is now – but hugely magnified – as individuals and families struggle to cope with the frustration and upheaval that come with stroke and AD.

Powerful motivation, that. The kind that pushes neurosciences researchers Drs. Sandra Black and Simon Graham to test relentlessly the edge of possibility in their work.

Black doesn't have a lot of "free" time for interviews. Between caring for patients, running studies and writing up results for publication, finding a block of time to chat is a Herculean task. But Black, a clinician-scientist at S&W since 1985, manages to find time even for that.

There is much to talk about. Over the last two years, she has published many papers in her areas of expertise: stroke, AD and other dementias, like vascular dementia. Much of her work focuses on the interaction between AD and stroke, including the small, silent strokes, so-called because people aren't aware of having them. Cerebrovascular disease, the death of blood cells in the brain, can lead to a stroke, silent or otherwise, and is linked to vascular dementia.

"We've developed a sophisticated way to look at not just the strokes that are clinically obvious, but the silent strokes and the hardening of the arteries which look to be critical in the expression of dementia in older people," says Black. "You can die with Alzheimer's pathology and not be demented. You can die from strokes and not be demented, but if you have both, you're much more likely to be demented. They keep very bad company."

Her group has been working to understand the overlap between AD and stroke for 10 years. They've developed ways to analyze the brain using structural imaging to account for the probability of both diseases. "We don't have a direct way of knowing that a person has Alzheimer's, but there are patterns of shrinkage that suggest it, and if you can also look at the amount of 'silent' cerebrovascular disease, you get a much better reading of what's actually going on in the person and what their cognitive function is likely to be," she explains.

Understanding how these conditions interact is also important to developing targeted treatments. Black was the lead author reporting the results of a multinational clinical trial to test the effects of the drug donepezil on the cognitive functioning of more than 600 people with vascular dementia arising from cerebrovascular disease. Researchers knew donepezil, which acts on the cholinergic system, was effective for people with AD, but they didn't know if it would work for people with vascular dementia. The study, published in *Stroke* in 2003, showed that it was indeed therapeutic for these people.

More and longer-term study is needed, says Black, but the evidence is growing that the cholinergic system, involved in AD, also figures in vascular dementia. In addition to the treatment implications, results like these have immediate applications, she notes. "All of those healthy lifestyle and diet decisions, and taking medications if needed to keep your blood pressure and cholesterol under control, aren't just protecting you from heart disease and stroke; they're also protecting you from Alzheimer's."

In other research, she and Graham, an imaging scientist, are doing studies with functional magnetic resonance imaging, or fMRI, to track brain activity during a behaviour like navigation. They've been using fMRI to study which regions of the brain are involved in problems with finding one's way around, which can be an early sign of

"We're making some good strides, but there's lots more to undertake," says Graham. "A lot of people out there are living with the consequences of these types of injuries and not at their full potential."

AD. Sunnybrook & Women's Research Institute has a 3T-magnet for experiments, made possible by a grant from the Canada Foundation for Innovation. This magnet is double the strength of a hospital-grade MRI machine, and getting it ready for research use is no easy feat. "There's a bit of an art to it," says Graham. "And there's a lot of engineering," he adds, laughing.

The aim is to go beyond the standard paper-and-pencil maze tests used to measure navigation. "That's not a good representation of how people navigate in the real world. We're looking for a better, more real-world assessment," says Graham, who is also a medical physicist.

Enter the pairing of fMRI with virtual reality, or "pretend" environments. This is where the brain activity of people is measured as they do tasks in simulated environments while lying in an MRI machine wearing magnet-compatible gear, like gloves and goggles.

Graham and Black looked at how people first learn and then remember how to get around the virtual "Sunnybrook City." Participants learned a path while in the magnet and then were tested on their ability to retrace that path 20 minutes later – all virtually, of course. Because both tasks took place in the magnet, the brain activity of each was visible. "That's important," says Graham, "because if you have impaired memory, you want to know if it's a failure to store the information or to retrieve it." The findings suggest that many parts of the brain are implicated.

They're also using neuroimaging to study where the silent strokes are happening, how the location of a stroke affects cognition, and how the brain reorganizes after a stroke so that targeted treatments can be developed. Collaboration is essential to their success, they agree. Both belong to the Heart and Stroke Foundation of Ontario's Centre for Stroke Recovery, a partnership between S&W, the Baycrest Centre for Geriatric Care and the Ottawa Health Research Institute.

"We're making some good strides, but there's lots more to undertake," says Graham. "A lot of people out there are living with the consequences of these types of injuries and not at their full potential."

Although rehabilitation strategies and treatments to halt the downward cognitive spiral of stroke, AD and other dementias are still being developed, the notable progress of neuroimaging in the last decade offers hope for an aging population. With each new insight, researchers like Black and Graham move closer to the brink of a breakthrough, which, after all, is just a series of incremental achievements.

Achievements, Black emphasizes, that wouldn't be possible without her patients, who remain her priority. "My focus is to try to take good care of my patients and to learn from them and help them learn from me. They're the experts in their experience of the disease, and I'm an expert in what's known about the disease. It's very much a partnership." SR

The Alzheimer's Association (U.S.), the Alzheimer Society of Canada, the Canadian Institutes of Health Research, Eisai Inc. and Pfizer Inc. funded Black's research. The Ontario Research Development Challenge Fund, Heart and Stroke Foundation of Ontario and the Canada Foundation for Innovation funded Graham's work.