Imaging Reveals Cognitive Deficits in Parkinson's

BY DAMIAN McNAMARA

MIAMI BEACH — Changes in brain volume and networks could someday predict which patients with Parkinson's disease are at highest risk to develop dementia, according to recent studies.

It has been known for some time that hippocampal atrophy, for example, is a common feature of Parkinson's disease with dementia. However, a recent study is the first to show that the decrease in hippocampal volume could predict which patients are at a higher risk for development of dementia, Irena Rektorová, Ph.D., said at the World Federation of Neurology World Congress on Parkinson's Disease and Related Disorders.

"What is important from a practical point of view is that atrophy of the hippocampus probably predicts a switch to dementia," said Dr. Rektorová, who is on the neurology faculty at Masaryk University in Brno, Czech Republic.

A Swiss research team calculated that the risk for dementia increases almost 25% with every 0.1 mL decrease in hippocampal volume, based on a study of 70 patients who had subthalamic deep brain stimulation (Parkinsonism Relat. Disord. 2009;15:521-4). The 14 patients in this cohort who later developed dementia had significantly smaller preoperative hippocampal volumes than did those who did not develop dementia.

Dr. Rektorová provided some additional perspective on the extent of volume changes. "Hippocampal atrophy is definitely present in those with Parkinson's disease, and especially those with Parkinson's disease dementia, but it is lower than atrophy with Alzheimer's disease."

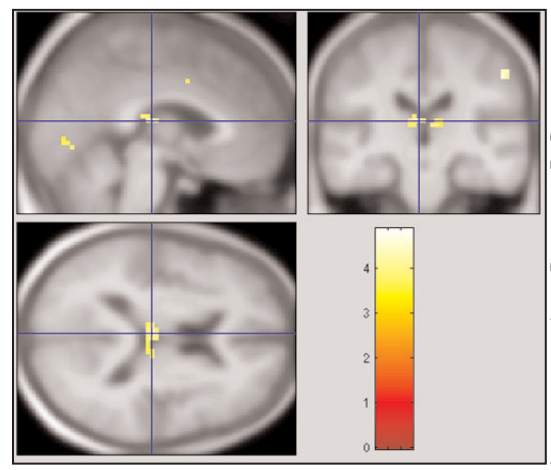
Using voxel-based morphometry, other researchers have reported grey matter loss in the frontal areas of the brain in patients with Parkinson's disease that extends to the temporal, occipital, and subcortical areas with comorbid dementia (Brain 2004;127:791-800). Occipital atrophy, in particular, may be an important distinction between Parkinson's patients with and without dementia.

Mild cognitive impairment (MCI) is common among people affected by Parkinson's disease. A goal for researchers is to identify "the malignant form" of MCI that will progress to dementia, said Dr. Rektorová, who had no relevant disclosures.

"Would brain imaging of mild cognitive impairment or dementia in Parkinson's disease be of any help?" Dr. Rektorová asked. It is possible, she said, based on the promising results of multiple studies using ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography or functional MRI.

"These studies show posterior rather than anterior cortical involvement in Parkinson's disease dementia versus Parkinson's disease alone," Dr. Rektorová said.

A study using ^{18}F-FDG PET, for example, revealed metabolic network changes consistent with a Parkinson's disease-related cognitive pattern (NeuroImage 2007;34:714-23). These researchers found hyperactivation in the cerebellar vermis and dentate nuclei and reduced activation in the medial frontal and parietal regions. This cognitive pattern was not altered by routine Parkinson's disease treatment (for example, levodopa).



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In the Stroop test, brain activity in some areas decreased in medicated PD patients without cognitive dysfunction (above), relative to healthy controls, despite similar performances.

In a study currently in preparation, Dr. Rektorová and her colleagues found decreased activity in certain brain areas of patients with Parkinson's disease, compared with controls, while performing the Stroop test (see image above). During this measure of executive function, decreases were seen in the cuneus, middle temporal gyrus, inferior parietal lobule, insula, and medial dorsal nucleus of thalamus. "It is worth mentioning that these Parkinson's disease patients were medicated and they had no cognitive impairment in this task," Dr. Rektorová said. "They actually performed as well as healthy controls."

It also could be that what is not turned off during executive functioning in Parkinson's disease plays a role in cognitive impairment, Dr. Rektorová said. During executive task performance in healthy volunteers, fMRI shows deactivation of the medial prefrontal cortex, posterior cingulate cortex, precuneus, and medial temporal cortices. However, this imaging also shows that people with Parkinson's disease may fail to shut off this resting brain activity, called the "default mode network." Dr. Rektorová said the full function of the default mode network is not yet known.

For the first time, other researchers have used fMRI to assess the potential contribution of the default mode network in patients with Parkinson's disease (Arch. Neurol. 2009;66:877-83). They demonstrated a decrease in ventral medial prefrontal cortex activity similar to controls during executive functioning. However, participants with Parkinson's disease featured increased precuneus and posterior cingulate cortex activity whereas controls showed deactivation in these regions. ■

Optimal Screening Strategy for Early PD Remains Elusive

BY DAMIAN McNAMARA

MIAMI BEACH — Widespread screening for early Parkinson's disease with olfactory testing followed by neurologic imaging holds promise but is not yet practical, based on studies that have revealed the limitations of each method.

Olfactory impairment is common enough in premotor Parkinson's disease that some researchers propose using it as an early predictor of risk (Ann. Neurol. 2008;63:167-73).

However, olfactory testing has not garnered widespread adoption because it lacks sufficient specificity for population-based screening, Dr. Henk W. Berendse said at the World Federation of Neurology World Congress on Parkinson's Disease and Related Disorders.

He and others have proposed coupling olfactory testing with highly specific brain imaging, such as dopamine transporter single photon emission computed tomography (DAT SPECT).

There is a catch, though. The imaging would have to be done in a large number of individuals, many of whom would not develop Parkinson's disease, said Dr. Berendse, head of the movement disorders service at the VU University Medical Centre in Amsterdam.

In a subsequent presentation at the meeting, Dr. Andrew D. Siderowf of the department of neurology at Pennsylvania Hospital in Philadelphia called population screening for Parkinson's disease a "numbers game." The incidence of Parkinson's disease is low, so the number of potentially identifiable cases in a population at any given time also is low, he said.

'The numbers start to look really good' when two-stage screening is considered for first-degree relatives of people with Parkinson's disease, particularly those with multiple risk factors.

In 2005, the worldwide prevalence of the disease was estimated to be between 4.1 million and 4.6 million (Neurology 2007;68:384-6).

Dr. Berendse calculated that "If you expect to detect 125 patients in the premotor phase [of Parkinson's disease], somewhere between 1,000 and 7,000 individuals would have to undergo SPECT scans. Assuming a 10% prevalence of hyposmia, we would need to screen 70,000 individuals." He based the 10% prevalence of hyposmia on the results of a study he coauthored that screened 361 asymptomatic, 50- to 75-year-old relatives of patients who had idiopathic Parkinson's disease. All of the relatives underwent olfactory testing, and the 40 who tested positive also underwent serial ^{123}I-beta-CIT SPECT scanning. Hyposmia in first-degree relatives was associated with at least a 10% risk of developing Parkinson's disease within 2 years (Ann. Neurol. 2004;56:173-81).

He and his colleagues recently published the 5-year data for this cohort (J. Neurol. Neurosurg. Psychiatry 2009 Dec. 3 [doi:10.1136/jnnp.2009.183715]) and were surprised to find that, compared with the 2-year data, "there was only one more individual who met clinical criteria for Parkinson's disease."

Those two studies support use of two-step olfactory and SPECT scanning in first-degree relatives because all of the five hyposmic individuals who developed Parkinson's disease had an abnormal baseline SPECT scan.

Dr. Siderowf said he remained optimistic about screening first-degree relatives of people with Parkinson's disease as a higher-risk group even though widespread screening would be cost-prohibitive. "The numbers start to look really good" when two-stage screening is considered for first-degree relatives, particularly those with multiple risk factors, he said.

However, he noted that access to DAT SPECT is restricted. It is costly and not commercially available in the United States.

In addition to DAT SPECT, researchers have proposed other imaging modalities to follow olfactory testing. For example, German researchers assessed transcranial sonography and assessed patients at 4 years (Mov. Disord. 2007;22:839-42).

"So far, transcranial sonography does not seem to be the way to go," Dr. Berendse said. "Two patients who progressed to Parkinson's disease did not have initial transcranial abnormalities, for example, but more studies are on the way."

Dr. Siderowf said the optimal screening strategy remains unknown. "Not only do these tests need to be used, but they have to be used repeatedly. What is the optimal screening frequency? The time at which imaging becomes abnormal varies—some say 5 years."

Dr. Berendse said that ideally, he would like to find a noninvasive marker of early Parkinson's disease risk with a higher specificity than olfactory dysfunction and a less costly second screening step.

Neither Dr. Berendse nor Dr. Siderowf had relevant financial disclosures. ■