Diagnosing Parkinson's disease before the onset of motor symptoms

Therapeutic intervention that can halt or cure Parkinson's disease before motor impairments occur is a major unmet medical necessity. Although new treatments show promise for treating the condition, there is currently no procedure available that can diagnose Parkinson's prior to the onset of debilitating motor symptoms, at which stage most dopamine neurons have died or become damaged. **Dr Good** and **Dr Robertson** capitalised on two pre-clinical non-motor features of Parkinson's. If tested for in combination, these two attributes may hold the key to early stage diagnosis and therapeutic intervention of the world's most common debilitating movement disorder.

Dr Kimberley Good is an Associate Professor working in both the Department of Psychiatry and the Department of Psychology and Neuroscience at Dalhousie University, Nova Scotia, Canada. There she works with Dr Harold Robertson, Professor Emeritus in the Departments of Pharmacology and Psychiatry to investigate indicators of Parkinson's disease, with the aim of developing a method capable of detecting the neurological condition at an early stage.

It is estimated that in the UK and Canada about one person in every 500 is affected by Parkinson's disease, making it the most common movement disorder and the second most common neurodegenerative disorder. The majority of those diagnosed are over the age of 50, but the disease also affects many individuals at a younger age. Due to the steady global increase in life expectancy, the number of cases of Parkinson's disease will continue to rise.

A COMPLEX COMBINATION OF SYMPTOMS

Although the symptoms of the condition vary between each individual, the primary motor symptoms characteristic of the disease are ubiquitous in their presentation. Due to the loss of muscle control, patients experience rigidity, slowness of movement, loss of fine motor skills, impaired balance, and tremors. The disease is progressive and symptoms appear gradually, becoming increasingly severe over time, and lead to difficulties in completing simple tasks, walking, and talking. Many people die from complications resulting from the disease, although Parkinson's itself does not directly result in death. In addition to impairing movement, the disease is associated with a wide range of other non-motor symptoms. These include problems with the sense of smell, sleep difficulties, fatigue, depression, anxiety, and bladder and bowel problems.

THE DEATH OF DOPAMINE NEURONS

The classical symptoms of Parkinson's disease are caused by the progressive death of dopamine-producing cells in the part of the brain known as the substantia nigra. One of dopamine's key functions in the brain is to act as a neurotransmitter for the transmission of signals that co-ordinate movement and smooth muscle control. A dopamine deficit leads to a progressive decrease in the amount of effective signalling, and increasingly severe motor symptoms.

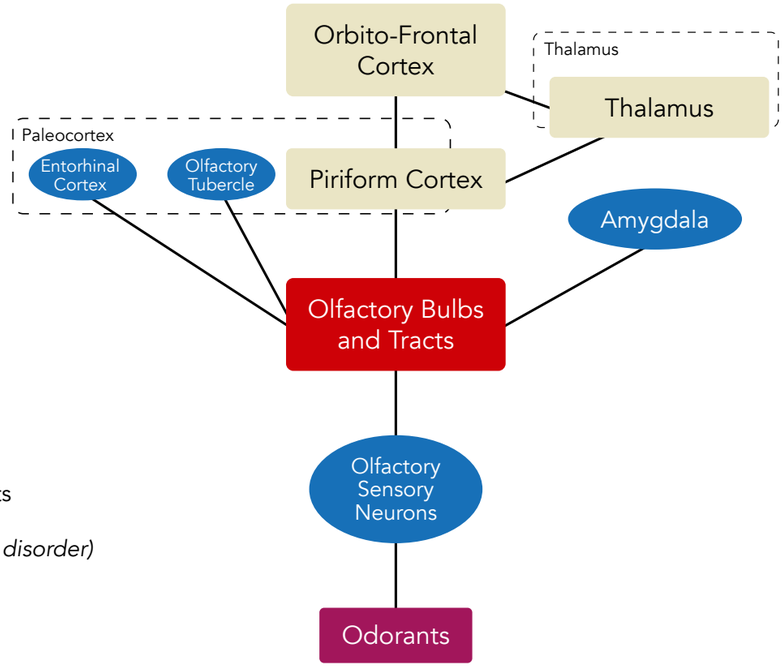
Changes in sleep and olfaction (the sense of smell) occur in the majority of patients in the earliest stages of Parkinson's, with subtle changes occurring up to a decade prior to clinical diagnosis

Study objectives

1. Is olfaction altered in asymptomatic at-risk population?
   (relative to healthy controls (HC) and early stage PD)
2. If so, is the olfactory bulb/tract changed in these at-risk populations?
3. Alternatively, is the substantia nigra also changed in these at-risk populations?

Asymptomatic at-risk populations:
- First degree relatives of PD patients
- Patients with REM-BD
  (Rapid eye movement behavioural disorder)

Key region of interest: Olfactory bulb/tract



Although it is well established that the death of the dopamine-producing cells is the cause of the motor symptoms of Parkinson's disease, why this deterioration occurs in some individuals in the first place remains a mystery. It is suspected that people develop Parkinson's due to a combination of genetic and environmental factors, and it has been shown that the disease involves the build-up of abnormal aggregates of proteins called Lewy bodies in the brain. Despite this knowledge, no specific causative factor has been isolated as the trigger for this devastating neurological disorder.

THE IMPORTANCE OF OLFACTION

Over 100 scientific papers have described the loss of the sense of smell in patients with PD. Changes in olfaction occur in 80–90% of patients in the earliest stages of Parkinson's, with subtle changes occurring up to a decade prior to clinical diagnosis. However, olfactory dysfunction is not specific to Parkinson's but is also noted in other neurodegenerative disorders (e.g., Alzheimer's disease). So although olfactory testing may identify those who are at risk, this process may also identify those who are at risk for other disorders.

As there are currently no testing procedures available to diagnose PD before a patient exhibits motor symptoms, Dr Good and Dr Robertson have embarked on a project to develop a method that will enable earlier identification. They have employed a combination of smell testing and a sensitive MRI technique known as diffusion tensor imaging (DTI), to investigate non-motor features that appear in the very early stages of the disease. The association between Parkinson's disease and olfactory deficits is so strong that olfaction has been included in the most recent criteria for PD by the International Parkinson's and Movement Disorder Society. Although in isolation these changes are not sufficient to identify that a person is developing the disease, Dr Good and Dr Robertson have discovered that the testing methods they are using may be able to accurately detect the condition years before it can be diagnosed clinically.

SMELL TESTING AND BRAIN IMAGING

Initially, they confirmed that a group of patients exhibited a distinctly impaired sense of smell. Using a well validated test of the sense of smell along with imaging of the olfactory bulb region using DTI, differences were observed between Parkinson's patients and control subjects. Brain imaging techniques can provide insights into the physiological changes that have occurred and may be associated with the olfactory deficits.

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Q&A

What led to you researching whether this particular combination of testing methods might be a viable approach for diagnosing Parkinson's disease at such an early stage?

Olfactory deficits have been reported in Parkinson's for many decades. However, the lack of specificity hampers our prognostic ability. Others have used expensive and invasive imaging techniques to do similar studies. We wished to provide a simple (smell testing) and available (DTI MRI) method to be able to identify those who may be at risk of developing Parkinson's.

What are the next steps you plan to take in your research towards establishing the technique as a method for diagnosing early stage Parkinson's disease?

We need to test this paradigm on patients with other neurodegenerative disorders (e.g., Alzheimer's) to determine the specificity of our findings.

What have been the most challenging aspects of undertaking this study?

Recruitment of first-degree relatives. Our projected number of first-degree relatives is ambitious and our numbers are low compared to what we had anticipated.

> **Olfactory deficits have been reported in Parkinson's for many decades**

How do you think early treatment will be approached in patients who are highly likely to develop the disease but it is in the pre-clinical stages?

At-risk individuals are in a difficult bind: they may or may not develop the disorder. So, taking a medication that might prevent a disorder but that has side effects, might not help those who are not going to be affected. In fact, unnecessary medication may be detrimental instead of helpful. So, we need to find true 'biomarkers' that identify with great certainty those who are on the path towards developing Parkinson's.

Are there any other related studies you are working on or are planning to undertake in future?

We will be including Alzheimer's disease and Mild Cognitive Impairment patients in our protocol.

The DTI technique they are using for this research – a specialised type of MRI scan designed to measure the fluid diffusion characteristics within brain regions – has revealed that in the olfactory bulb of Parkinson's disease patients there is a change in the amount of water diffusion in the area, suggesting structural abnormalities in this brain region. They have also found microstructural changes in the substantia nigra of these patients. These differences in diffusion imaging parameters likely reflect pathological changes that have occurred in the brain as a result of early stage Parkinson's disease.

PAVING THE WAY FOR PRE-CLINICAL PARKINSON'S DISEASE DIAGNOSIS

The next phase of the project has an ambitious goal: to demonstrate the utility of using these methods for detecting Parkinson's disease at a far earlier stage than has ever been possible before. To do this, they are administering the smell identification test to a large sample of over 1000 neurologically healthy test subjects, who are first-degree relatives of Parkinson's disease patients. They identify those participants whose smell test scores fall into the highest and lowest 10%. These subjects are scanned using DTI and the data is compared with Parkinson's patients and healthy control subjects. If the protocol developed by Dr Good and Dr Robertson is successful in identifying at-risk individuals, this novel approach will provide an unprecedented window of time for therapeutic intervention. If the disease can be diagnosed and its progression halted before permanent damage occurs, we will finally have found a way of effectively curing Parkinson's disease.

Detail

RESEARCH OBJECTIVES

Drs Robertson and Good's research focuses on the neurobiology of neurodegenerative disorders such as Parkinson's disease. They are particularly interested in the olfactory system as a predictor of outcome in these disorders and in finding ways to assist in early diagnosis.

FUNDING

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COLLABORATORS

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BIO

Dr Kimberley Good completed her MSc and PhD in Neuroscience at the University of British Columbia. She is currently an Associate Professor in the Department of Psychiatry at Dalhousie University and is cross-appointed in the Department of Psychology and Neuroscience. Dr Good is a scientific member of the Nova Scotia Early Psychosis Program and the co-director of the Nova Scotia Psychosis Research Unit. She is also a faculty member associated with the Brain Repair Centre in Halifax NS, Canada.

Dr Harold Robertson is a Professor Emeritus of Pharmacology at Dalhousie University and is a Fellow of Royal Society of Canada. Dr Robertson is the former Scientific Director of the Brain Repair Centre in Halifax, NS, Canada.

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