

Cognitive Aspects of Parkinson Disease and Related Disorders

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Disclosures

- Salary support for movement disorders fellowship at Washington University via NIH training grant (completed 6/30/2007); Grant support for research from private donor via St. Louis chapter of the APDA
- Upcoming year at University of Rochester will be supported by APDA postdoctoral scholarship
- No stocks or other financial relationship with any pharmaceutical companies

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Knowledge is Power

- The spectrum of memory and thinking problems associated with PD (and related disorders)
- Things that can make cognitive problems worse, and things that you can do to help
- Understanding the cause(s), finding the cure(s)

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Parkinson Disease is not just a movement disorder

- As first described by James Parkinson in 1817, PD is characterized by movement problems, including tremor, rigidity, slowness of movement and difficulty with walking and balance
- The non-motor symptoms of PD have become increasingly recognized in the last 20-30 years.

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Non-motor symptoms associated with PD

- Memory and thinking problems
- Mood
 - Depression common in PD
 - Distinguish from *appearance* of depression due to motor manifestations of PD (masked face)
 - Sadness, worthlessness, hopelessness are most specific
- Apathy / reduced motivation
 - Can occur without depressed mood

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Non-motor symptoms associated with PD

- Sleep disturbance
 - Insomnia
 - Initial (difficulty falling asleep) and/or terminal (difficulty staying asleep)
 - Depression associated with insomnia (chicken vs. egg?)
 - Excessive sleep during the day, frequent urination at night, and/or wearing off of PD medications may contribute
 - REM sleep behavior disorder
 - Failure of normal mechanisms that suppress movement during dreams
 - Shouting, kicking, punching
 - Associated dreams often unusually vivid and/or disturbing

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The spectrum of memory and thinking problems in PD

- None
 - Subtle changes may nonetheless be evident on psychometric testing
- Some
 - Noticeable changes, but still functioning at normal level
- A lot
 - The changes are significant enough to interfere with usual activities Dementia

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Specific types of cognitive impairment in PD found by psychometric testing

- “Psychomotor slowing” or “bradyphrenia”
 - The mental equivalent of slow movements
- Memory problems
 - Difficulty retaining new information; older memories remain intact
 - Difficulty with learning information (attention) and with retrieval of learned information (can be helped with cues)
 - Forgetting is not faster
- “Executive functioning”
 - Problem-solving, processing complex information
 - Abstract thinking, shifting rules

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GREEN

YELLOW

BLUE

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Dementia in PD

- Progressive decline in cognitive function
- Significantly impacts quality of life, caregiver stress, need for nursing home placement
- Associated with older age; longer disease duration; loss of responsiveness to PD medications; “bradykinetic/rigid” > “tremor” type
- Overall risk of dementia is 4-6 times higher in individuals with PD compared to people the same age without PD

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Features of dementia in PD

- In individuals without PD, Alzheimer disease (AD) is most common cause of dementia
- Dementia in PD (PDD) differs from AD
 - clinically
 - neuropathologically

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Clinical differences between PDD and AD

- Types of cognitive deficits differ, especially early
 - Memory and language dysfunction more prominent in AD; executive dysfunction more prominent in PDD
 - Type of memory loss in AD different than memory loss in PDD
 - Retention vs. retrieval (latter is helped by cues; former is not)
 - Visuospatial problems more prominent in PDD
 - Psychometrics: Identifying an incomplete picture; reproducing a visual pattern
 - Everyday life: Driving; dressing; eating

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Clinical features of dementia in PD

- Fluctuations in cognition
 - May have marked variation in degree of confusion throughout the day
 - Often more prominent right after awakening
 - Does not necessarily relate to dosing of medications for PD
 - Well-recognized by caregivers, not necessarily by clinicians

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Clinical features of dementia in PD

- Hallucinations
 - Usually well-formed visual hallucinations (people, animals)
 - Visual illusions also
 - May be provoked by medications, even in the absence of dementia
 - May also have auditory hallucinations
- Delusions
 - Fixed ideas that are untrue; may have paranoid character

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Other features more prominent in PDD vs. AD

- Sleep disturbances
 - Excessive sleepiness during the day
 - Insomnia (initial, terminal, or both)
 - REM sleep behavior disorder
- Depression
- Apathy

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Strategies for coping with cognitive problems

Things to watch out for that can
make cognitive problems worse,
and things that you can do to help

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Strategies: Talk about it

- Make sure your doctor is aware of the cognitive symptoms
 - Evaluation of motor symptoms tends to predominate the clinic visit
 - We have better drugs to treat the motor symptoms
 - Testing motor function easier/faster than testing cognitive function
 - Clinicians are more familiar with Alzheimer disease
- Consider more in-depth evaluation

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Clinical assessment for dementia

- Take a good history
 - Family and caregivers are much more sensitive than tests for detecting early changes
 - Patients may be aware of changes, but not necessarily
- Mini Mental State Examination
 - Brief office screening tool assessing a wide range of cognitive functions (scored on a 30 point scale)
 - orientation, language, memory, attention, calculation, drawing
 - Sensitivity is relatively poor

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Clinical Dementia Rating

CLINICAL DEMENTIA RATING (CDR):	0	0.5	1	2	3
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	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests; poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

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Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors. © December 2000

Acute changes should be evaluated promptly

- Dementia progresses slowly
- An acute change in mental status = "Delirium"
 - Can have confusion, disorientation, fluctuating mental status, agitation, hallucinations, delusions, but onset is relatively sudden
 - Most common causes are new medication, infection (even a minor one), stress (e.g. surgery)
 - Review medication list
 - Thoroughly evaluate for source of infection (UTI, pneumonia, cellulitis)
 - Minimize perioperative use of sedatives and narcotics

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Strategies: Fix treatable causes

- Systemic disorders can cause cognitive impairment
 - B12 deficiency, hypothyroidism, chronic infections (HIV, syphilis)
- Depression can cause cognitive impairment (“pseudodementia”)
 - Medications not always successful the first time
 - KEEP TRYING!!
 - Avoid tricyclic antidepressants

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Strategies: Reduce polypharmacy

- Many medications have cognitive side effects
- Know what each medication is for, and the potential side effects
 - Are there other agents that can do the same thing without cognitive side effects?
- Reassess periodically
 - Is the medication working?
 - Are the side effects of the medication worse than the symptom being treated?
 - Is the problem still active? Does it still need to be treated? Will it recur if the medication is stopped?

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Medications most likely to adversely affect cognition

- Benzodiazepines
 - Used for anxiety and/or as sleeping pill
 - Most commonly used: alprazolam (Xanax); diazepam (Valium); lorazepam (Ativan); clonazepam (Klonopin)
 - Of these, clonazepam likely best tolerated due to longest half-life (less peak-trough fluctuation)
 - MANY superior alternatives for treating anxiety and insomnia
 - SSRI's for anxiety; antidepressants mirtazepine (Remeron) or trazodone (Desyrel) also good for sleep
 - Short-acting hypnotics like zolpidem (Ambien), zaleplon (Sonata), eszopiclone (Lunesta) are not benzodiazepines but can cause memory impairment

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Medications most likely to adversely affect cognition

- “Anticholinergic agents”
 - May be particularly problematic in PDD due to prominent loss of cholinergic neurons
 - Often overlooked because the purpose of the drug is not necessarily related to anticholinergic activity
 - Many different classes of prescription and over-the-counter drugs have anticholinergic side effects; unknowingly used for relatively “benign” symptoms

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Beware Anticholinergic Drugs

- Antihistamines
 - Diphenhydramine; -pheniramines (Benadryl; OTC cold and allergy medicines; OTC sleeping aids)
 - Hydroxyzine (Atarax, Vistaril); clemastine (Tavist); cyproheptadine (Periactin)
- Nausea and dizziness
 - Meclizine (Antivert); dimenhydrinate (Dramamine); scopolamine; cyclizine

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Beware Anticholinergic Drugs

- Tricyclic antidepressants
 - Amitriptyline (Elavil); Nortriptyline (Pamelor); Imipramine (Tofranil); Desipramine (Norpamin); Trimipramine (Surmontil); Amoxapine (Asendin); Doxepin (Sinequan); Clomipramine (Anafranil); Protriptyline (Vivactil)
- Certain PD medications
 - Trihexyphenidyl (Artane); benztropine (Cogentin)
- Muscle relaxants
 - Cyclobenzaprine (Flexeril)
- Antipsychotics

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Beware Anticholinergic Drugs

- Bladder (and GI) antispasmodic agents
 - Mechanism is known to be anticholinergic; however, urologists often ignore the brain
 - Bladder dysfunction is very common in PD
 - Avoid: oxybutinin (Ditropan; Oxytrol patch); hyoscyamine (Levsin); flavoxate (Urispas); solifenacin (Vesicare); dicyclomine (Bentyl)
 - tolterodine (Detrol) also reported to cause cognitive problems
 - May be OK: trospium (Sanctura); darifenacin (Enablex)
 - These agents are anticholinergic but less likely to enter the brain
 - More research is needed!

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Other drugs to carefully weigh risks vs. benefits

- Narcotic pain medications
- Dopamine agonists—e.g. pramipexole (Mirapex) and ropinarole (Requip)
 - Should be avoided in patients with dementia
 - Narrower therapeutic index (toxic dose: effective dose) than levodopa/carbidopa (Sinemet)
 - More likely than levodopa to cause hallucinations and daytime sedation
 - Side-by-side comparison of psychometrics on dopamine agonists vs. Sinemet would be informative

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Strategies: Keep busy

- “Use it or lose it”
 - Research has shown that remaining mentally and physically active can slow cognitive decline
 - Social interaction also beneficial
- Apathy may exacerbate the decline
 - Caregivers should encourage activity, but also recognize apathy as part of the disease

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Strategies: Drugs for dementia

- Cholinesterase inhibitors [donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne, formerly Reminyl)]
 - Marked loss of cholinergic neurons in PDD
 - Cholinesterase inhibitors increase acetylcholine in the brain
 - In clinical trials, benefits for cognitive fluctuations, apathy, and hallucinations have been shown
 - As in AD, may slow cognitive decline

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Strategies: Drugs for dementia

- NMDA receptor antagonists [memantine (Namenda)]
 - Memantine has some modestly benefit for AD
 - Reported data for PD are inconclusive
 - Randomized, blinded studies with large numbers of patients needed
 - Effect on motor fluctuations?
 - Amantadine (also an NMDA receptor antagonist)
 - In clinical practice, makes memory worse

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Strategies: Treatment of psychosis

- Management of acute or chronic psychosis (agitation, hallucinations, and delusions) in PD is complicated by the fact that most antipsychotics make the movement symptoms of PD worse
- For delirium, treatment of the underlying cause should be the #1 priority
- Never, ever let a doctor administer haloperidol (Haldol)
 - May precipitate neuroleptic malignant syndrome, which can be fatal
- Newer “atypical” antipsychotics (e.g. risperidone, olanzapine) are touted to be safer but studies have shown that even these worsen motor symptoms

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Strategies: Treatment of psychosis

- Clozapine (Clozaril) is the only medication proven in a clinical trial to improve psychosis without worsening movement symptoms
 - Requires weekly blood counts due to risk of agranulocytosis (loss of white blood cells)
- Quetiapine (Seroquel) does not adversely affect movement, but not clearly beneficial in clinical trials thus far
 - Usually tried first since blood count monitoring is not needed
- Cholinesterase inhibitors (e.g. Aricept) may be beneficial
 - More research is needed!!!

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Underlying causes of Parkinsonism and Dementia

- The “alphabet soup” of parkinsonian disorders
 - Idiopathic PD is the most common cause of parkinsonian motor manifestations (i.e. rigidity, bradykinesia, tremor, imbalance)
 - Other diseases can cause similar manifestations
 - PSP, CBGD, DLB, MSA (including Shy-Drager, SND, and OPCA)
 - Cognitive deficits are prominent in all but MSA
 - Clinical features can be helpful, but autopsy examination of the brain is the only way to be sure

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Clues that the cause is something other than idiopathic PD

- Lack of response to PD medications
- Lack of asymmetry
- Early onset of dementia
- Early onset of balance problems/falls
- Early onset of hallucinations or psychosis (prior to or with low doses of PD medications)

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Unique features of specific parkinson-plus disorders

- PSP—progressive supranuclear palsy
 - Eye movement abnormalities are prominent
 - Dementia is
 - Neuropathologic hallmark: abnormal tau protein
- CBGD—corticobasal ganglionic degeneration
 - “Strange” movement problems
 - Severe unilateral dystonia; Apraxia; Alien-limb phenomenon
 - Dementia very common
 - Neuropathologic hallmark: abnormal tau protein

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Unique features of specific parkinson-plus disorders

- MSA—Multiple systems atrophy
 - Subtypes are Shy-Drager syndrome (prominent, early autonomic symptoms like low blood pressure and severe bladder problems), Striatonigral degeneration (SND; early falls and signs of upper motor neuron loss on exam), and olivopontocerebellar degeneration (OPCA; ataxia in addition to parkinsonism); may have various mixtures of these features
 - Dementia and hallucinations may occur, but less than in other disorders
 - Protein neuropathology: synuclein inclusions in glial cells

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Unique features of specific parkinson-plus disorders

- DLB—Dementia with Lewy Bodies
 - Dementia symptoms start within 1 year of onset of movement symptoms
 - Hallucinations, fluctuations, and sleep disturbance are common

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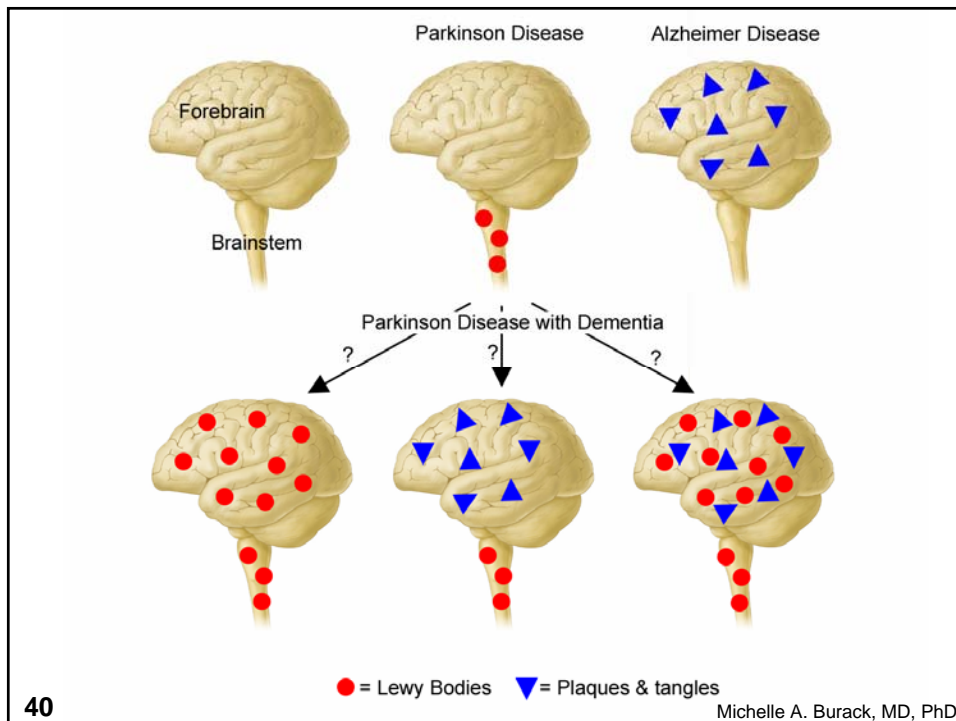
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DLB and PDD—the same disease?

- In PDD, movement symptoms are present >1 year before onset of cognitive symptoms; otherwise the clinical manifestations are very similar
 - 1 year cutoff viewed by many as arbitrary
- Neuropathology: Diffuse Lewy bodies (synuclein) +/- Alzheimer disease pathology
 - A recent study showed that Alzheimer pathology is *more* common in DLB than PDD with late dementia
 - Cholinergic neuron loss more prominent in PDD with late dementia

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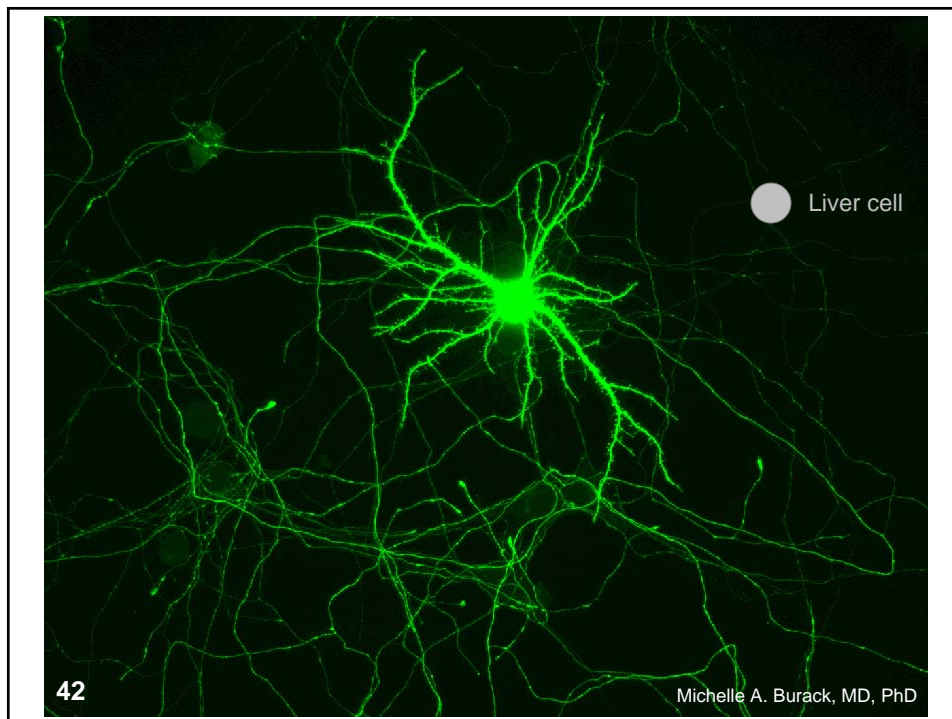
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Can we cure this?

- Better, cleaner drugs for the symptoms of the disease
- Save the neurons!!!
 - Better understanding of why they are dying
 - Likely different reasons in different diseases

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Use of PIB PET imaging to evaluate dementia subtypes in patients with Parkinson Disease

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Who is eligible?

People with idiopathic Parkinson disease (iPD)*, age 55 or older, with or without changes in memory and thinking function.

*Individuals with drug-induced, atypical, or familial parkinsonism are not eligible

OR

People age 55 or older without Parkinson disease or memory loss ("normal controls").

What does the study involve?

4. A detailed assessment of memory and thinking function and a physical examination (2.5-3 hours total)
 - 3 series of "games" that measure different aspects of memory and thinking function (~90 minutes)
 - interview of a family member or friend who can provide information about memory and thinking function in everyday life (~45 minutes)
 - assessment of Parkinson disease symptoms
5. A brief MRI scan (~15 minutes) and a PET scan (~1.5 hours)
6. Consent for brain donation after death

What are the benefits?

3. A free evaluation of memory and thinking.
4. Reimbursement for your time and travel

What are the costs? None. All procedures are for research purposes only and there is no charge to you or to the insurance company.

How can I get more information?

Contact our research nurse coordinator, Johanna Hartlein, MSN/APN
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