"Dopaminergic modulation of memory and affective processing in Parkinson depression"

Lee X. Blonder, John T.Slevin, Richard J. Kryscio, Catherine A. Martin, Anders H.Andersen, Charles D. Smith and Frederick A.Schmitt

Presented by Zoloo Enkhbayar and Adam Katz
BIONB 4410 Spring 2014

Overview

- Journal and Researchers
- Purpose of paper
- General Background Information
  - Parkinson Disease (PD)
  - Depression within PD patients
- Methods
  - Testing Conditions
- Results
- Discussion
- Further Research

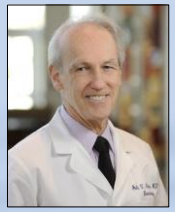
The Journal

- Psychiatry Research Journal published by Elsevier
- Impact Factor of 2.456 according to Thomson Reuters Journal Citation Reports 2013.
- Reports on basic psychiatric studies, clinical studies on human behavior, clinical laboratory techniques, and advances in research methodology.
- Monthly Publication
- 1961- Present

Lee X. Blonder

- UPenn, 1986
- Professor at Department of Behavioral Science and Neurology and Sanders-Brown Center on Aging at University of Kentucky
- Research on neural substrates of mental and emotional processing in humans.
  - effects of strokes in right hemisphere and associated "flat affect" on social and marital behavior.
- PI in "Neural Substrates of Facial and Lexical Emotion Using fMRI" 1997-2000
- "Brain and emotion relations in culturally diverse populations." (1999)

John T. Slevin

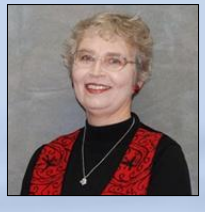


- MD at West Virginia University (1975)
- Professor of Neurology, Molecular and Biomedical Pharmacology at University of Kentucky
- Research Associate at Morris K. Udall Parkinson's Disease Research Center of Excellence
- Interested in movement disorders, Parkinson's disease, and deep brain stimulation

Richard J. Kryscio

- Professor at Sanders- Brown Center on Aging
- Chair in Department of Statistics and Biostatistics at University of Kentucky
- Research and lab focus on providing expert advice on data analysis to investigators in Center on Aging
  - Longitudinal analysis of Markov transition states, prevention in Alzheimer's disease, screening for early detection of ovarian cancer.
- Recent Publication: "Modeling the association between 43 different clinical and pathological variables and the severity of cognitive impairment in a large autopsy cohort of elderly persons. (2010)

Catherine A. Martin



- MD from University of Kentucky (1976)
- Department of Psychiatry at the University of Kentucky.
- Research focus on child psychiatry.
- Research Publication: "Measurement of the Subjective Effects of Methylphenidate in 11- to 15-Year-Old Children with ADHD" (2007)

Anders H. Andersen

- Purdue University (1983)
- Assistant Professor of Anatomy and Neurobiology
- Research focus on functional neuroimaging at Magnetic Resonance Imaging & Spectroscopy Center
  - Overall detectability issues, mathematical modeling, data- pre and post processing, etc.
- Publications: "Functional fMRI of apomorphine activation of the basal ganglia in rhesus monkeys." (2000)

Charles D. Smith

- Robert P. and Mildred Moore's Professor in Alzheimer's Research in Dept. of Neurology at University of Kentucky.
- Research Focus: Application of fMRI techniques in predicting, quantifying, and diagnosing patients with Alzheimer's disease other related dementias.
- Research Publications:
  - "Age and gender effects on human brain anatomy: voxel-based morphometric study in healthy elderly." (2007)

Frederick A. Schmitt

- Professor at Sanders- Brown Center on Aging and Dept. of Neurology at the University of Kentucky
- Research Focus: Brain behaviors associations in neurological diseases
  - Early detection of dementia
  - Results of therapeutic interventions in Alzheimer's disease
  - PI in clinical trials in Alzheimer's disease and Mild Cognitive Impairment
- Research Publications:
  - "Comprehensive cognitive neurological assessment in stroke" (2009)

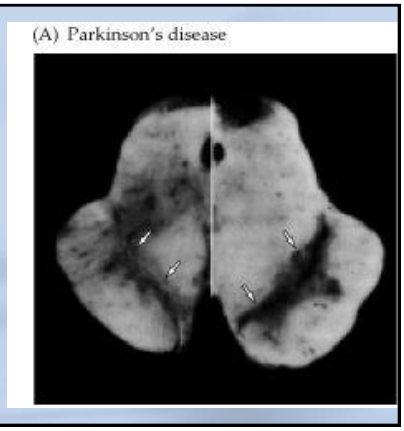
Research Locations

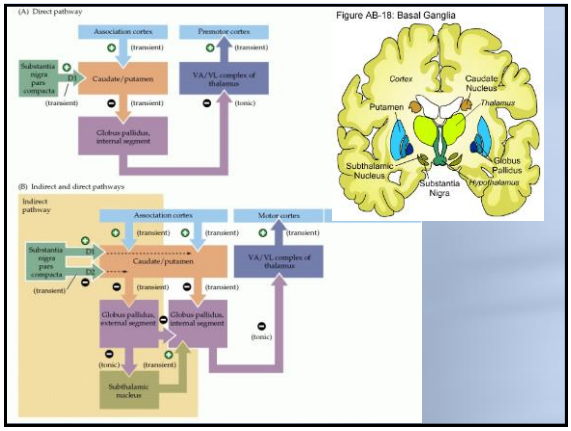
University of Kentucky Dept of Neurology specializing in treating neuromuscular and neurological diseases (Parkinson's and stroke) through collaboration with:

- Kentucky Neuroscience Institute, Lexington, KY, USA
- Sanders Brown Center on Aging, Lexington, KY, USA
- Veterans Administration Medical Center, Lexington, KY USA

General Information

Parkinson's disease: a disorder of the brain that leads to shaking (tremors) and difficulty with walking, movement, and coordination.





Common symptoms include:

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- Decrease in facial expressions
- Difficulty starting and controlling movement
- Loss or weakness of movement (paralysis)
- Soft voice
- Stiffness of the trunk, arms, or legs
- Tremor

- **T.R.A.P.:** Acronym for four primary PD symptoms:

Tremor: Shaking of limb (usually hand) while at rest

Rigidity: Muscle stiffness and resistance to movement

Akinesia/bradykinesia:

i) Inability to move spontaneously

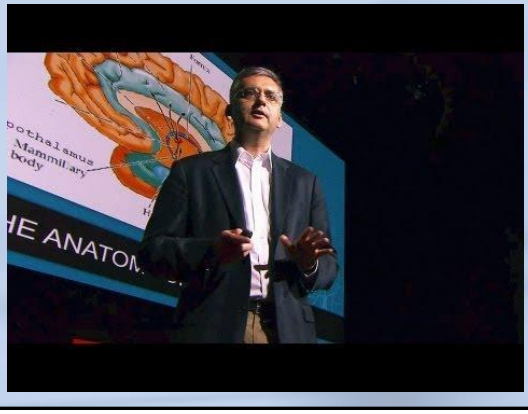
ii) Slowed movement

Postural instability: Impaired balance & coordination

Secondary parkinsonism may be caused by health problems, including:

-
- AIDS
- Encephalitis
- Meningitis
- Stroke
- Diffuse Lewy body disease
- Multiple system atrophy
- Progressive supranuclear palsy

-
- **carbidopa/levodopa:** Medication to relieve PD symptoms
- **dopamine:** Acts as one of the brain's messengers to signal movement and maintain balance and coordination
- **dyskinesia**: Abnormal involuntary movements
- **PD:** Parkinson's disease
- **PWP:** Person (or people) with Parkinson's disease



Veterans who develop Parkinson's disease and were exposed to Agent Orange or other herbicides during military service do not have to prove a connection between their disease and service to be eligible to receive VA health care and disability compensation.

Hypothesis

Purpose of this experiment:

"..was to examine dopaminergic modulation of cognitive and affective task performance in depressed Parkinson's Disease patients."

Hypothesis:

"..Withdrawal of dopaminergic medications is associated with increased depressive mood as well as impairment in cognitive and affective task performance.

Based on previous studies that point to dopaminergic pathways playing a role in supporting

- working memory
- affective (i.e. emotional) processing
- dopamine agonist as an agent of alleviating depression in PD patients?

The Experiment

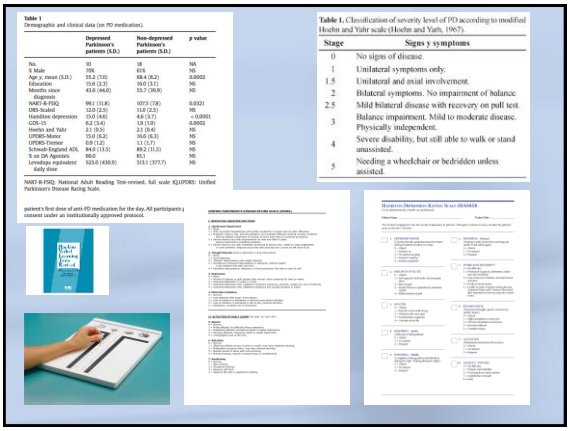
Table 1
Demographic and clinical data (on PD medication).

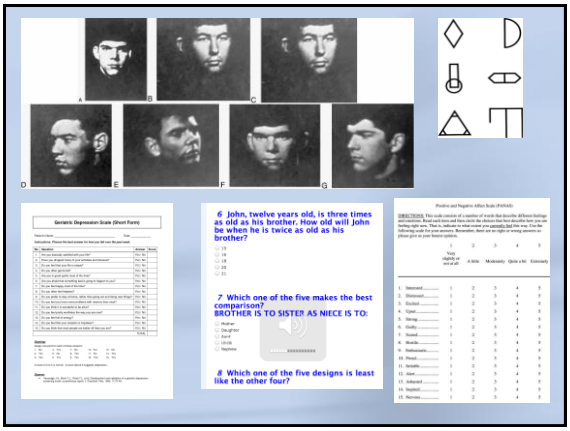
	Depressed Parkinson's patients (S.D.)	Non-depressed Parkinson's patients (S.D.)	*p* value
No.	10	18	NA
% Male	70%	61%	NS
Age *y*, mean (S.D.)	55.2 (7.0)	68.4 (8.2)	0.0002
Education	15.6 (2.3)	16.0 (3.1)	NS
Months since diagnosis	43.6 (44.0)	55.7 (39.9)	NS
NART-R-FSIQ	99.1 (11.8)	107.5 (7.8)	0.0321
DRS-Scaled	12.0 (2.5)	11.0 (2.5)	NS
Hamilton depression	15.0 (4.6)	4.6 (3.7)	< 0.0001
GDS-15	6.2 (3.4)	1.9 (1.9)	0.0002
Hoehn and Yahr	2.1 (0.5)	2.1 (0.4)	NS
UPDRS-Motor	15.0 (6.2)	16.6 (6.3)	NS
UPDRS-Tremor	0.9 (1.2)	1.1 (1.7)	NS
Schwab-England ADL	84.0 (13.5)	89.2 (11.5)	NS
% on DA Agonists	60.0	61.1	NS
Levodopa equivalent daily dose	525.0 (430.9)	513.1 (377.7)	NS

NART-R-FSIQ: National Adult Reading Test-revised, full scale IQ.UPDRS: Unified Parkinson's Disease Rating Scale.

patient's first dose of anti-PD medication for the day. All participants gave informed consent under an institutionally approved protocol.

- DSM-IV diagnostic criteria
  7 major
  3 minor
  DSM - V (2013)
- Hoehn and Yahr scale
  1-5 scale
  patients with idiopathic
  PD eligible (<3)
- All treated with levodopa carbidopa either alone or combined with dopamine agonist





The Experiment

- 3 visits to University of Kentucky Medical Center
- 1st Visit - consisted of cognitive tests and screenings
  - DSM IV, Hamilton Depression Scale- 21 item version, Hoehn and Yahr Scale, neurological examination, and the Unified Parkinson's Disease Rating Scale (UPDRS)
- Prior to visit 2 or 3, patients stopped taking anti-PD medication after last dose of previous evening (before midnight), allowing test to commence at minimum 9 hrs after last dose
- On the other visit, patients took normal prescribed PD medication morning of the session.
- Neuropsychological tests during visits 2 and 3
  - Hopkins Verbal Learning Test- Revised
  - Purdue Pegboard
  - Benton Test of Facial Recognition
  - Brief Visuospatial Memory Test - Revised
  - Wechsler Adult Intelligence Scale - Revised
  - Positive and Negative Affect Scale
  - A facial affect naming task consisting of photos with varied emotions.
  - National Adult Reading test

The Experiment

- Clinical evaluations based on the scores of the Unified Parkinson's Disease Rating Scale; on and off-scores and motor UPDRS on and off scores.
- Tests conducted during visit 2 or 3 were performed in an operationally defined "off" condition
  - Anti-PD medication withheld for two times the lifespan of the half life of each drug.
  - Testing done prior to patient's first regular dose of medication on the day of testing.
- Tests performed in an operationally "on" condition
  - Tests conducted within 1-2 hours after PD patient's first dose of medication of the day

Results

- No statistical difference between dPD and non-dPD patients on
  - gender (chi square test) ,
  - education, Dementia Rating Scale scores (t-test)
  - Hoehn/Yahr stage of PD
  - Unified PD Rating Scale Motor/Tremor subscales
  - activities of daily living abilities
  - % PD patients taking DA and levodopa daily dose
- Significant differences btwn dPD and non-dPD patients
  - dPD patients younger and scored lower in National Adult Reading Test- Revised, measure of pre-morbid intelligence
  - dPD patients sig. more depressed on Hamilton depression and GDS.
    - Higher levels of depression in dPD patients while on dopaminergic medications
    - No statistical difference among non-dPD patients while on versus off medication

Results

There was a significant difference between depression and medication status for

- facial affect naming test (p=0.016)
- Hopkins Verbal Learning Revised Total Recall (p=0.011), delayed recall, and recognition subscores.

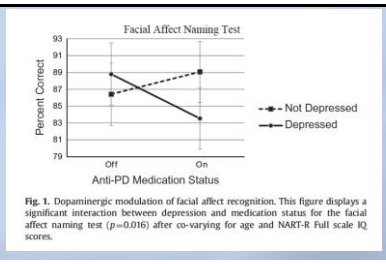


Fig. 1. Dopaminergic modulation of facial affect recognition. This figure displays a significant interaction between depression and medication status for the facial affect naming test ($p=0.016$) after co-varying for age and NART-R Full scale IQ scores.

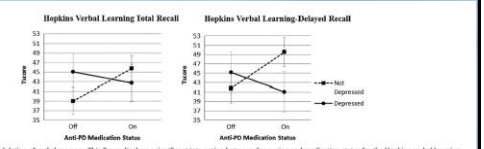


Fig. 2. Dopaminergic modulation of verbal memory. This figure displays a significant interaction between depression and medication status for the Hopkins verbal learning-revised total recall ($p=0.019$) and delayed recall ($p=0.010$) after co-varying for age and NART-R Full scale IQ scores.

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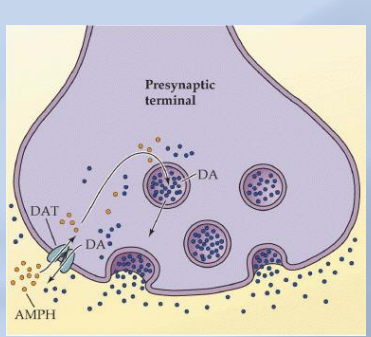

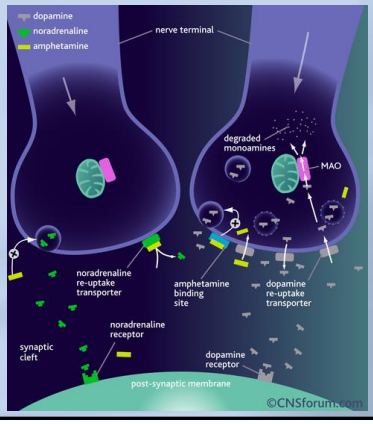

Questions

1. What kinds of responsibilities do doctors have in regards to administering future Parkinson's patients with particular medical regimens?

1. What kinds of responsibilities do pharmaceutical companies have in making new Parkinson's medication available to the public before all possible side effects are tested for and analyzed? For instance, should pharmaceutical companies hold off on releasing a potentially effective drug if they are not sure about how or for whom it will work best or should they release such drugs with a disclosure regarding potential effects on patients with depression?