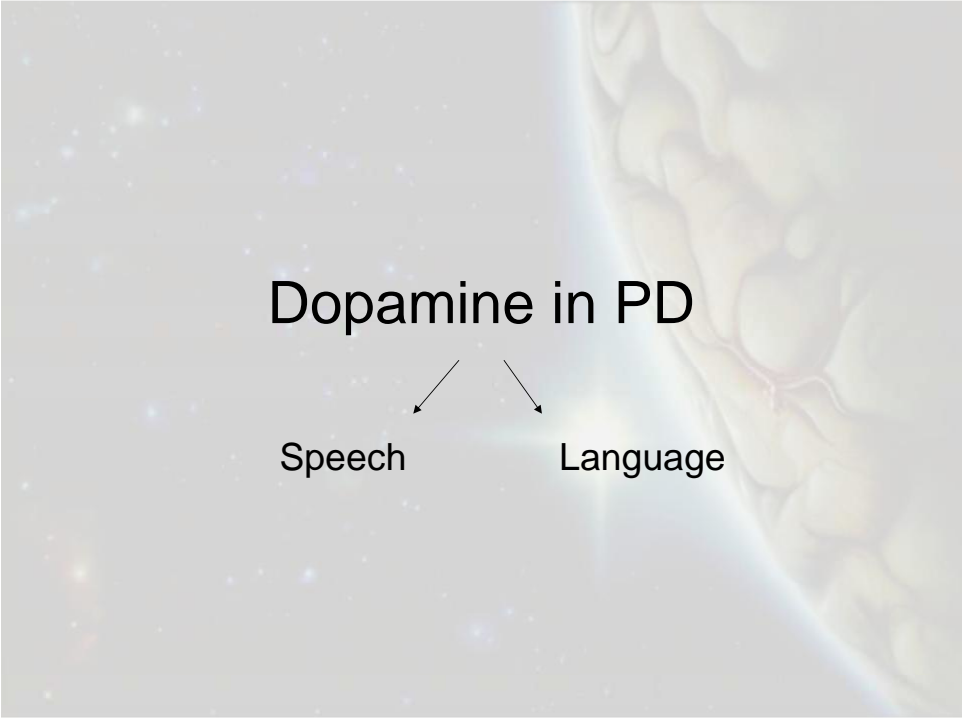




**Neurophysiological investigation of the effects of
levodopa administration on speech and language in
Parkinson's Disease**

Miet De Letter

2nd International Symposium
Basal Ganglia Speech Disorders & Deep Brain Stimulation



Dopamine in PD

Speech

Language

Dopamine studies ~ methodological variabilities

- On/Off-studies

- Protocol:

- PD or Parkinsonism?
 - De novo/Levodopa treated
 - Stage-dependency
 - Capsit-protocol/variation in the duration of the off-episode
 - Instrumental/perceptual research
 - Perceptual research: experience of the rater!

- Patient related variations

- Variations in drug effect from cycle to cycle
 - Dosis Levodopa
 - Emotional aspects, fatigue, depression, arousal

(Brown et al., 1984; Delis et al., 1982; Golham et al., 1988)

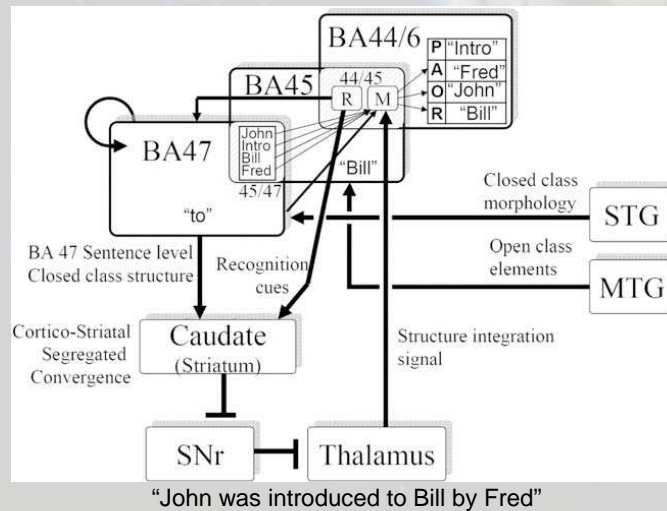


Message 1

Be careful in interpreting the results of
pharmacological studies in PD + individualize

Subcortical control of language

GRAMMATICA



Dominey, Inui and Hoen., 2009

Subcortical control of language

PHONOLOGY

- ❖ Phonological processing: involvement of the right nucleus caudatus (Adullaev et al, 1997)
- ❖ Phonological failure in PD (Darkins et al, 1988)
- ❖ Improvement of phonology after STN-stimulation in PD (Zanini et al, 2003)
- ❖ The level of accuracy in phonological processing significantly correlated with tracer binding potential in the left dorsal caudate nucleus (Tettamanti et al, 2005)
- ❖ The speed in phonological processing significantly correlated with tracer binding potential in the left dorsal putamen (Tettamanti et al, 2005)
- ❖ A more accurate and fast phonological processing was associated with a reduced dopamine requirement in the left striatum (Tettamanti et al, 2005)

Subcortical control of language

SEMANTICS

- Functioning of the dopamine dependent frontal–striatal–thalamic system influences the speed of semantic activation (Grossman et al., 2002)
- Dopamine exerts a neuromodulatory influence on the speed of semantic activation (Angwin et al., 2004)
- The nature of altered semantic activation in PD may depend on the magnitude of dopamine depletion.
- Changes to the speed of activation may also contribute to PD patients' poor performance on other tests of semantic processing such as verbal fluency
- Delayed semantic activation may only be evident in a subset of PD patients (Angwin et al., 2005; Grossman et al., 2002) + interindividual differences (Angwin et al., 2007)
- The profile of cognitive dysfunction in PD may be a function of a complex relationship between the side of disease onset and the initial motor symptoms (Katzen et al., 2006)

doi:10.1093/brain/awn112

Brain (2008), 131, 2094–2105

Parkinson's disease and dopaminergic therapy—differential effects on movement, reward and cognition

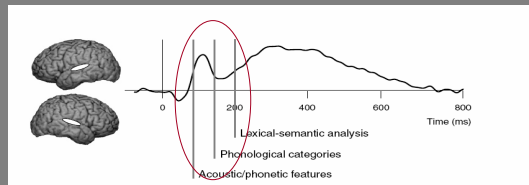
J. B. Rowe,^{1,2,3} L. Hughes,^{1,2} B. C. P. Ghosh,¹ D. Eckstein,^{1,2} C. H. Williams-Gray,^{1,4} S. Fallon,² R. A. Barker^{1,4} and A. M. Owen^{2,3}

- Levodopa medication can enhance or restore striatal function
- Levodopa can impair frontal functions by overdosing mesocortical dopamine (Gotham et al., 1988; Cools et al., 2001, 2003)



Neurophysiology of language in PD

- Normal Early left anterior negativity (ELAN) in PD (Dominey et al, 2009)



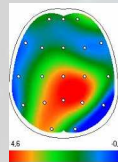
- Absence of P600 in PD (Friederici et al, 2003; Frisch et al, 2003; Kotz et al, 2003)

Influence of Levodopa on auditory lexical decision?

	Normal subject	PD OFF	PD ON
Mean time Fz (msec)	1) P177 2) P162	P 164	P 162
topography	1) Fz, Cz, F3 2) Fz, Cz, Fpz	Cz, Pz, P3, P4, C3, C4	Fz, Cz, Fpz

“more widely distributed brain activity” in OFF

- fMRI (Farid et al, 2009)



Pilot study

Aim

- To investigate the influence of dopamine on language function (off/on-study)
- To verify the lateralization hypothesis (Katzen et al., 2006)

Methodology

Subjects

- PD-patients (Hoehn & Yahr OFF-stage: 2-4)
- N=7 (male/female)
- Age: 45-74 y (mean 62)
- Right-handed, native speakers, normal vision, no comorbid neurological problems than PD, normal mental state

Pilot study



Stimuli

- Silent reading task
- 60 Dutch verbs: 30 hand manipulation verbs (eg to sew, to point, ...) and 30 nonmanipulative verbs (to leave, to develop, ...)
- The word groups were matched with respect to mean word length, word form frequency, and imageability
- Stimuli presented for 1 second, in pseudo-random order

Procedure

- CAPSIT-protocol
- Subjects were instructed to reduce eye-blinks and movements as far as possible
- After the session : 5 minutes rest
- Retest

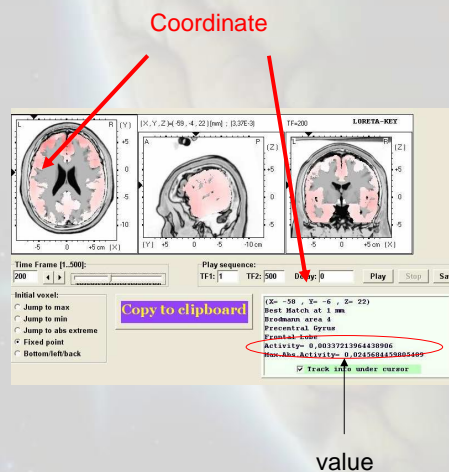
Data recording

- Electrophysiology (Neurosoft-system), electrically and acoustically shielded chamber
- Universal EEG Cap (Haube-S2)
- 24-channel EEG, electrodes 10/20 system

Pilot study

Data analysis

- EP – difference between manipulable and nonmanipulable – 5µ
- Loreta analysis on 4 different area's:
 - Left precentral gyrus (BA 4) (x=-58.4, y=-6, z=22)
 - Right precentral gyrus (BA 4) (x=63, y=-4, z= 22)
 - Left temporal gyrus (BA 22) (x=-61, y=-39, z= 22)
 - Right temporal gyrus (BA 22) (x=61, y=-40, z=22)



Pilot study

Data analysis

- Measurement in Loreta on the 4 neuroanatomic localizations, in OFF and ON, every 5msec between 150msec and 260msec.
- Mean group on the 8 conditions
- Off versus ON (Wilcoxon Signed Ranks Test)
- Fluctuations over time
- Intrasubject variability

Previous study

Neurophysiological distinction of action words in the fronto-central cortex (Hauk et al., 2004)

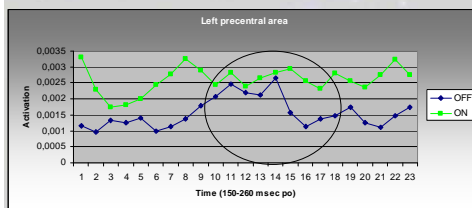
- 12 Normal subjects
- ERP silent reading arm (hand)-related words
- Analysis 35 electrodes between 210-230 msec

Results

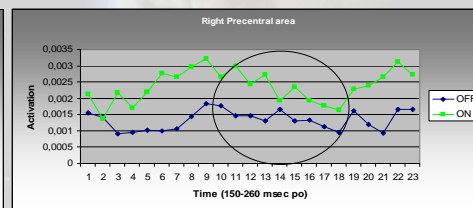
Arm (hand)-related words specifically activation right-frontal area's between 210-230 msec

Results

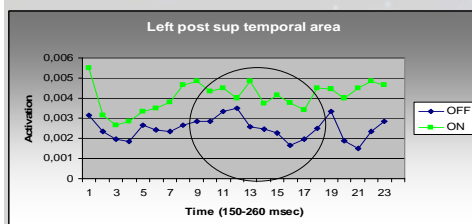
OFF versus ON (n=7) (Wilcoxon Signed Ranks Test)



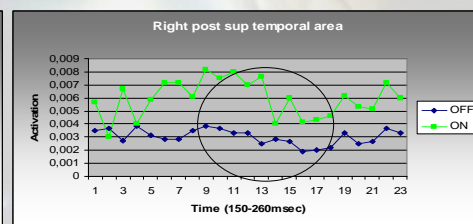
P < 0.01



P < 0.01

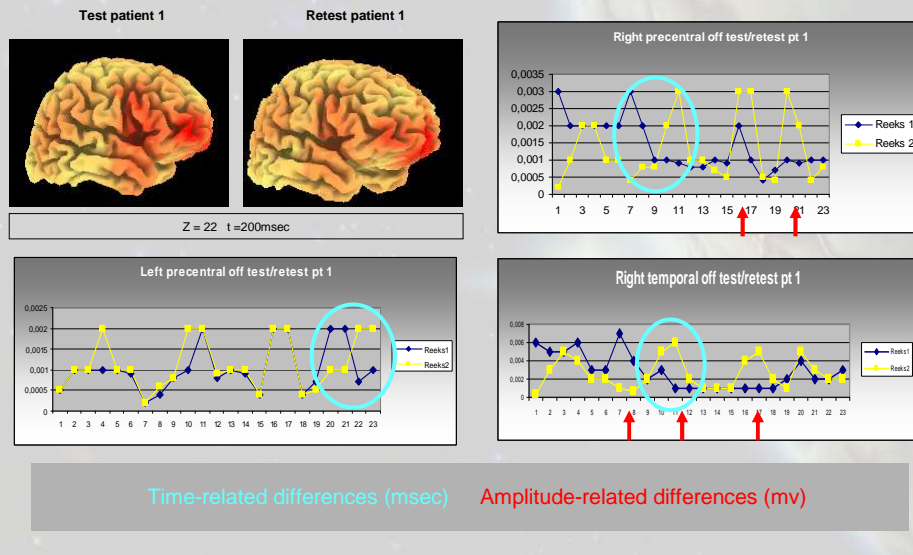


P < 0.01



P < 0.01

Intrasubject reliability



Lateralization

- Unilateral symptoms are caused by reduced dopaminergic activity in the basal ganglia opposite to the side of symptoms (Agid, 1980; Schapira, 1999)
- No neurophysiological studies that took the lateralization of the cognitive functions in PD systematically into account



Message 3

- Intrasubject reliability: amplitude and time-related differences
- Levodopa changes the processing of differentiating between manipulative and nonmanipulative verbs
- Lateralization effects



Conclusion

- A lot of variables influencing the results and interpretation of clinical and neurophysiological levodopa studies
- Levodopa changes the processing of differentiating between manipulative and nonmanipulative verbs
- Language function is dopamine dependent
- Lateralization effects !
- Overdosis dopamine can impair cortical functions

Further research required



With thanks to our research group

P. Santens (PhD)
J. Van Borsel (PhD)
M. De Letter (PhD)



S. Vanhoutte (MSc)
K. Batens (MSc)
A. Aerts (MSc)

