

Selected (early) publications of Dubois, Lhermitte, & Pillon

- 1 de Smet, Y., Ruberg, M., Serdaru, M., Dubois, B., Lhermitte, F., & Agid, Y. (1982). Confusion, dementia and anticholinergics in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *45*, 1161-1164.
Notes: Among a population of 75 hospitalised Parkinsonian subjects, confusional states were observed in 46% of demented patients not receiving anticholinergic drugs and in 93% of demented patients under anticholinergic therapy. The sensitivity of demented Parkinsonians to anticholinergic drugs can be attributed to a cholinergic deficiency which has been detected in the cortex and hippocampus of Parkinsonian patients post-mortem. The observations suggest that anticholinergic medication should be avoided in Parkinsonians with intellectual impairment
- 2 Dubois, B., Ruberg, M., Javoy Agid, F., Ploska, A., & Agid, Y. (1983). A subcortico-cortical cholinergic system is affected in Parkinson's disease. *Brain Research*, *288*, 213-218.
Notes: CAT activity was decreased in the frontal cortex and the substantia innominata of parkinsonian subjects, post-mortem. The decrease was greater in the frontal cortex of parkinsonians with dementia. The density of muscarinic cholinergic receptors increased in the cortex. This increase was inversely correlated with tremor. The effects on these parameters of both neuronal degeneration and anticholinergic therapy are discussed
- 3 Laplane, D., Baulac, M., Widlocher, D., & Dubois, B. (1984). Pure psychic akinesia with bilateral lesions of basal ganglia. *Journal of Neurology, Neurosurgery and Psychiatry*, *47*, 377-385.
Notes: Three patients showed dramatic psychic akinesia after recovery from toxic encephalopathy. They had no or only mild motor disorders. The spontaneous psychic akinesia was reversible when the patient was stimulated, as if there was a loss of self psychic activation. Intellectual capacities were normal. Two patients had stereotyped behaviours resembling compulsions. In all patients CT scans showed bilateral lesions in the basal ganglia, mainly within the globus pallidus
- 4 Pillon, B., Dubois, B., Lhermitte, F., & Agid, Y. (1986). Heterogeneity of cognitive impairment in progressive supranuclear palsy, Parkinson's disease, and Alzheimer's disease. *Neurology*, *36*, 1179-1185.
Notes: Patterns of cognitive and behavioral impairment were analyzed in patients with progressive supranuclear palsy (PSP), Parkinson's disease (PD), and senile dementia of Alzheimer's type (SDAT), matched for age, sex, manual laterality, educational level, and degree of intellectual deterioration. The scores of the three groups of patients were significantly lower than those of controls and were comparable on tests of verbal and visuospatial functions as well as global memory. Patients with SDAT could be distinguished by the severity of verbal memory disorders; patients with PSP, and to a lesser degree those with PD, by impaired performances on tests sensitive to frontal lobe dysfunction
- 5 Agid, Y., Ruberg, M., Dubois, B., & Pillon, B. (1987). Anatomoclinical and biochemical concepts of subcortical dementia. In S.M.Stahl, S. D. Iversen, & E. C. Goodman (Eds.), *Cognitive neurochemistry* (pp. 248-271). Oxford: Oxford University Press.
Notes: (This discussion of the concept of subcortical dementia focuses on Parkinson's disease and progressive supranuclear palsy. The putative lesions that can be detected by biochemical assay of post-mortem brain tissue from patients with these diseases are presented along with histopathological data, and hypotheses concerning the contribution of the lesions to cognitive impairment is discussed)
- 6 Dubois, B., Danze, F., Pillon, B., Cusimano, G., Lhermitte, F., & Agid, Y. (1987). Cholinergic-dependent cognitive deficits in Parkinson's disease. *Annals of Neurology*, *22*, 26-30.
Notes: In a double-blind cross-over study, the effects of a subthreshold dose of scopolamine

(0.25 mg) on memory were compared in 32 control subjects and 32 parkinsonian patients who were without any sign of intellectual and mnemonic impairment. Although the scores of the controls in the memory test battery showed no deterioration after the administration of scopolamine, the same dose resulted in significantly reduced memory performance in parkinsonian patients in two tests which involved the recognition of meaningless drawings. The selective vulnerability of parkinsonian subjects without cognitive impairment to a subthreshold dose of scopolamine suggests the existence of an underlying alteration of central cholinergic transmission. The neuropsychological findings in our study agree with postmortem biochemical data, which showed decreased cortical choline acetyltransferase activity in all parkinsonian patients, suggesting the existence of neuronal compensation in parkinsonian patients who are without cognitive impairment

- 7 Dubois, B., Pillon, B., Legault, F., Agid, Y., & Lhermitte, F. (1988). Slowing of cognitive processing in progressive supranuclear palsy. A comparison with Parkinson's disease. *Archives of Neurology*, 45, 1194-1199.
Notes: Clinique de Neurologie et Neuropsychologie, INSERM, Paris To investigate central processing time in patients with progressive supranuclear palsy and Parkinson's disease, reaction times were measured using tasks with different levels of cognitive complexity but with the same motor response. In patients with Parkinson's disease, the additional central processing time required for more complex situations was no different from that in control subjects, suggesting that cognitive aspects of the reaction time procedures tested were possibly too simple to reveal a slowing of thought processes in these patients. Conversely, the central processing time was increased in patients with progressive supranuclear palsy compared with both Parkinson's disease and control subjects. The increase was associated with impairment in frontal lobe test performance. These results confirm that a slowing of central processing is a prominent feature of the cognitive disturbances of progressive supranuclear palsy and, furthermore, suggest that this slowing may be related to striatofrontal dysfunction
- 8 Laplane, D., Levasseur, M., Pillon, B., Dubois, B., Baulac, M., Mazoyer, B. et al. (1989). Obsessive-compulsive and other behavioural changes with bilateral basal ganglia lesions. A neuropsychological, magnetic resonance imaging and positron tomography study. *Brain*, 112, 699-725.
Notes: Eight patients are reported who shared the combination of bilateral basal ganglia lesions and a frontal lobe-like syndrome. The main features were inertia and loss of drive, with preservation of intellectual function. Some patients showed stereotyped activities with compulsive and obsessive behaviour which were sometimes highly elaborate in pattern. Extrapyramidal clinical signs were absent or mild. Brain damage, related to anoxic or toxic encephalopathy, was demonstrated by CT scans and MRI. The lesions appeared to be confined to the lentiform nuclei, particularly affecting the pallidum, although there was generalized brain atrophy in 2 cases. Positron emission tomography (PET) in 7 patients revealed hypometabolism of the prefrontal cortex relative to other parts of the brain. The PET studies suggest dysfunction of the prefrontal cortex as a result of damage to the lentiform nuclei. These clinical, anatomical and functional observations emphasize the role of the circuits linking the prefrontal associative cortex and some specific areas of the neostriatum, including the pallidum. The existence of distinct nonoverlapping circuits in the motor field or in the associative field can explain the fact that basal ganglia lesions may give rise to a clinical picture that is either purely motor, purely behavioural (as in some of our patients), or both. Similarities existed between some symptoms found in our patients and certain features of major psychiatric illnesses such as severe depression, catatonic schizophrenia, and obsessive-compulsive disorder. This raises the hypothesis that some aspects of these psychiatric disorders could be related to structural and physiological disturbances in the systems linking the frontal associative cortex and the basal ganglia

- 9 Pillon, B., Dubois, B., Bonnet, A. M., Esteguy, M., Guimaraes, J., Vigouret, J. M. et al. (1989). Cognitive slowing in Parkinson's disease fails to respond to levodopa treatment: the 15-objects test. *Neurology*, 39, 762-768.
Notes: Clinique de Neurologie et Neuropsychologie, Hopital de la Salpetriere, Paris, France To evaluate clinically the slowing of cognitive processing in Parkinson's disease, we used a visual discrimination task consisting of 15 superimposed images of objects. The time needed to identify 12 objects increased by 58% in 70 patients withdrawn from levodopa treatment compared with 20 controls matched for age and education. Perceptual, motor, and psycholinguistic factors, as well as mood, only partially accounted for the slowness of performance. The 15-objects test scores of the parkinsonian patients correlated significantly with both their intellectual impairment and the severity of their parkinsonian disability, but not with the duration of the disease. The scores did not correlate with depression. Levodopa had no effect on the score, although the parkinsonian motor disability score was improved by 54%. The results indicate a cognitive slowing in Parkinson's disease which is probably related to abnormalities of nondopaminergic neuronal systems in the brain
- 10 Dubois, B., Pillon, B., Sternic, N., Lhermitte, F., & Agid, Y. (1990). Age-induced cognitive disturbances in Parkinson's disease. *Neurology*, 40, 38-41.
Notes: Clinique de Neurologie et Neuropsychologie, Paris, France We investigated the influence of age on the occurrence of cognitive disturbances in Parkinson's disease (PD), by evaluating neuropsychological performances in early- and late-onset groups of patients (less than 45 and greater than 65 years, respectively), individually paired for all the variables of parkinsonism and compared with age-matched controls. Cognitive disorders were limited in the early-onset PD group compared with their age-matched controls. Conversely, we found global cognitive changes, including marked frontal lobe dysfunction, in the late- onset group. This specific cognitive impairment in older patients related to a significant interaction between the aging and disease processes. Late onset seemed to compound the subtle cognitive changes associated with the disease for which the early- onset group compensated. This compounding effect of aging may explain, at least partially, the high frequency of dementia in older PD patients
- 11 Dubois, B., Pilon, B., Lhermitte, F., & Agid, Y. (1990). Cholinergic deficiency and frontal dysfunction in Parkinson's disease. *Annals of Neurology*, 28, 117-121.
Notes: Inserm U 289 et Clinique de Neurologie et Neuropsychologie, Hopital de la Salpetriere, Paris, France To investigate the influence of central cholinergic deficit on cognitive function in Parkinson's disease (PD), we compared the neuropsychological performance of a group of 20 patients who were treated with anticholinergic drugs (mean daily dose, 10.2 mg) with that of a group of 20 patients who received no anticholinergics. The two groups were matched for all the variables of parkinsonism and levodopa therapy. At the dose used, there was no significant difference between the two groups of patients for intellectual, visuospatial, instrumental, and memory function. In contrast, in the group that received anticholinergics severe impairment was observed on tests believed to assess frontal lobe function. These results suggest that the lesion of the ascending cholinergic neurons, which has been demonstrated post mortem in PD, may play a role in the subcortical behavioral impairment of this disease
- 12 Dubois, B., Boller, F., Pillon, B., & Agid, Y. (1991). Cognitive deficits in Parkinson's disease. In F.Boller & J. Grafman (Eds.), *Handbook of neuropsychology*, Vol.5 (1 ed., pp. 195-240). Amsterdam: Elsevier.
- 13 Dubois, B. & Pillon, B. (1992). Biochemical correlates of cognitive changes and dementia in Parkinson's disease. In S.J.Huber & J. L. Cummings (Eds.), *Parkinson's disease: Neurobehavioral aspects* (pp. 178-198). New York: Oxford University Press.

- 14 Dubois, B., Verin, M., Teixeira-Ferreira, C., Sirigu, A., & Pillon, B. (1994). How to study frontal lobe functions in humans. In A.-M.Thierry, J. Glowinski, P. S. Goldman-Rakic, & Y. Christen (Eds.), *Motor and cognitive functions of the prefrontal cortex* (pp. 1-16). Berlin: Springer.
Notes: (Review of neuropsychological tests used to study frontal lobe deficits, and a study of 10 patients with focal lesions (7 left, 3 right hemisphere) compared with 10 patients with posterior lesions and 24 normal controls. The task was a computer delayed response task with 3 phases: delayed response, delayed alternation, and delayed non-alternation with reversals. Rules changed automatically upon criterion of the previous phase being met, and had to be discovered by deductive reasoning. Frontal lobe patients made errors on delayed response, alternated (surprisingly) spontaneously, and were highly deficient in delayed non-alternation)

- 15 Dubois, B., Defontaines, B., Deweer, B., Malapani, C., & Pillon, B. (1995). Cognitive and behavioral changes in patients with focal lesions of the basal ganglia. *Advances in Neurology*, 65, 29-41.
Notes: AD: Service de Neurologie et Neuropsychologie et de l'INSERM U 289, Hopital de la Salpetriere, Paris, France