Striatal $^\text{[123I]}\beta$-CIT SPECT and prefrontal cognitive functions in Parkinson’s disease

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Summary. Twenty non-demented patients with idiopathic Parkinson’s disease (PD) underwent single photon emission computed tomography (SPECT) with $^\text{[123I]}\beta$-CIT to further investigate the contribution of nigrostriatal dysfunction to cognitive and motor deficits. Compared to matched controls PD patients showed normal verbal intelligence, short-term memory and phasic alertness. There were significant ($p < 0.05$) deficits in tests of verbal working memory (digit ordering, reading span), strategic memory (story recall) and executive functions (card sorting), indicating a “prefrontal” cognitive deficit. Significant ($p < 0.05$) correlations were observed between dopamine transporter (DAT) density in the putamen and motor deficits as well as between DAT density in both striatal compartments (head of the caudate nucleus and putamen) and prefrontal functioning. Age was a major contributing factor to both cognitive status and nigrostriatal integrity as measured by $^\text{[123I]}\beta$-CIT SPECT. These results support the view that the striatum is part of a neuronal network that is mediating prefrontal cognitive functions.

Keywords: Parkinson’s disease, $^\text{[123I]}$beta-CIT, SPECT, working memory, cognition, prefrontal.

Introduction

Motor deficits (bradykinesia and rigidity) in Parkinson’s disease (PD) are mainly caused by degeneration of nigrostriatal dopamine neurones and resulting disturbances within basal ganglia pathways. The striatal deficit can be visualized by single-photon emission computed tomography (SPECT) using $^\text{[123I]}$-2β-carbomethoxy-3β-(4-iodophenyl)tropan ($^\text{[123I]}\beta$-CIT) as a marker for the presynaptic DAT. With refined equipment this method provides similar diagnostic information as positron emission tomography (PET) with
[18F]fluorodopa (Ishikawa et al., 1996) and allows to quantify the amount of nigrostriatal degeneration in PD and aging (Van Dyck et al., 1995; Tissingh et al., 1997). Severity (Seibyl et al., 1995), laterality (Marek et al., 1996), progression (Marek et al., 1998), and symptomatology of PD (Asenbaum et al., 1998) have been shown to correlate with [123I]β-CIT uptake in the putamen. This method has, however, not been used so far to investigate the relationship between striatal integrity and higher cognitive functions.

The neurobiological correlates of cognitive deficits in non-demented PD patients are less clear than those of patients with parkinsonism and concomitant Lewy-body dementia or Alzheimer’s disease (Braak and Braak, 1990; Jellinger, 1991; McKeith et al., 1998). Already in early stages of the disease many PD patients show deficits in tests of working memory, i.e. the short-term maintenance and manipulation of informations, strategic memory, i.e. the manipulation of information in long-term memory, and other executive functions. These neuropsychological findings are similar to those observed in patients with lesions of the dorsolateral prefrontal cortex (for review see Brown and Marsden, 1990; Saint-Cyr et al., 1995; Gabrieli et al., 1996). Another typical finding is impaired procedural learning of both motor sequences (Dominey and Jeannerod, 1997) and habits (Knowlton et al., 1996). Cognitive deficits in early PD have been attributed to disrupted connections between prefrontal cortex, basal ganglia and thalamus (Gabrieli et al., 1996; Owen et al., 1998) as well as to reduced dopamine levels at both striatal and cortical (prefrontal) dopamine receptors (Goldman-Rakic, 1987; Dubois and Pillon, 1995).

Only a few neuroimaging studies have addressed the relationship between striatal or cortical pathophysiology and cognitive deficits in PD. Marié et al. (1995a) found verbal working memory performance (Brown-Peterson task) to correlate positively with resting brain glucose metabolism ([18F]deoxyglucose PET) in the dorsolateral prefrontal cortex and negatively with thalamic metabolism. The same group has recently reported new data indicating a correlation between working memory functions (object alternation task) and striatal uptake of [11C]-S-nomifensine (Marié et al., 1999), a radioligand for the presynaptic dopamine and noradrenaline transporters (Marié et al., 1995b). Deficits in paired associate learning (Selective Reminding task) in a subgroup of moderately to severe PD patients have been shown to correlate with [18F]dopa binding in the caudate nucleus (Holthoff-Detto et al., 1997). These findings are in accordance with another preliminary study using [18F]dopa PET and a somatosensory discrimination task that requires working memory among other cognitive functions (Weder et al., 1998, 1999). So far, only one study correlated [123I]β-CIT ratios with perceptual functions (colour vision task) and did not find a relationship with nigrostriatal degeneration in PD (Müller et al., 1998). In patients with Huntington’s disease cognitive performance has been shown to correlate with striatal D2 (Lawrence et al., 1998), DAT and cortical D1 receptor densities (Bäckman et al., 1997) as measured with [11C]raclopride, [11C]β-CIT and [11C]SCH23390 respectively. There are, however, several methodological problems with those studies that are often based on small patient samples, suffer from a lack of variability of