Abnormal psychophysical visual perception in Parkinson's disease patients

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Abstract

Several visual dysfunctions in Parkinson's disease (PD) are described. Most of them are subtle or only demonstrated by stimulus-specific electrophysiologic or psychophysical testing. However, these minor deficits are thought to be of clinical relevance as they are related to direct or indirect complaints. Special emphasis is laid on visual hallucinations. These are most likely of multifactorial origin. The relation between hallucinations in PD and in dementia with Lewy bodies has to be elaborated further.

Visual loss, as a possible and reversible cause of visual hallucinations should be actively sought and corrected as far as possible. An underlying role of dopaminergic retinal cells in visual dysfunction of PD patients is widely recognised. However, whether the basic abnormality resides also in the visual cortex remains to be elucidated. Other neurotransmitters may also be involved. It has not been answered whether visual dysfunction might distinguish PD from other forms of parkinsonism.

Key words : Vision ; perception ; psychophysics ; hallucinations ; neuropsychology ; Parkinson's disease.

Introduction

Studies on Parkinson's disease (PD) mainly focus on the nigrostriatal dopaminergic decline and the impact on motor behaviour. However, non-motor complaints are often very disabling. Cognitive and psychological abnormalities have also gained interest. Degeneration of the visual system is less well known but can further limit the quality of live of PD patients.

Visual dysfunction in patients with PD is common, although seldom as a primary complaint. It seems not surprising that patients in the mean age group of PD have visual blurring, impaired near vision or light sensitivity. However, as the deficient neurotransmitter in PD, dopamine is widely present in several anatomical structures subserving visual function, a relationship between visual dysfunction and PD could been expected.

The neurobiology of retinal amacrine dopamine cells is well known (for review see Djamgoz *et al.*, 1997). Both dopamine D1 and D2 receptor types have been found on neurons of the inner and outer retina in many vertebrates. Dopaminergic neurons mediate centre-surround functions that are important to receptive field organisation. Other visual structures including the lateral geniculate and the visual cortex are also dopaminergic innervated.

We will discuss negative and positive visual dysfunction. Negative perceptions represent decreased function, positive perceptions e.g. hallucinations represent increased function.

Negative visual perceptions

Group comparison between PD patients and controls reveals a difference in visual acuity. Possibly the reduction of retinal dopamine results in an increase of receptive field size and a decrease of vision (Repka *et al.*, 1996). Although the severity of visual loss in PD seems related to advanced disease state, it is not reversible by treatment (Jones *et al.*, 1992). It is to be remembered that other factors than visual acuity *per se* interfere with "good vision", e.g. convergence insufficiency and lowered visual contrast sensitivity. Furthermore, the anti-parkinsonian anticholinergics typically cause impaired accommodation and blurred vision.

Convergence insufficiency is quite common in PD (Repka, 1996) and may functionally impair near vision. Prisms or monocular occlusion for reading can correct this dysfunction. A unique PD patient with convergence insufficiency responsive to levodopa has been described (Racette *et al.*, 1999).

In a recent retrospective study, it was suggested that patients with PD or Alzheimer's disease may have an increased occurrence rate of glaucoma (Bayer *et al.*, 2002). An association of glaucoma with neurodegenerative diseases with apoptotic cell death has been proposed. However, this has to be confirmed in larger, prospective cohort studies.

Intact contrast sensitivity is important for depth perception and depth discrimination. It is also important in a striped environment. Contrast sensitivity is reduced in PD, most at intermediate spatial frequencies (Bulens *et al.*, 1988). It is still not answered whether the underlying abnormality is localised in the retina or the visual cortex.

Abnormal colour vision in PD patients has repeatedly been described. The defect is characterised in the blue-yellow (tritan colour) axis and is reversible after levodopa treatment. Chromatic and visual contrast processing deficits progressively worsen in PD (Diederich *et al.*, 2002) and distorted colour discrimination has been found related to PD severity (Müller *et al.*, 1997). In a recent pilot study, also a relation with rated activities of daily living appeared (Müller *et al.*, 2002). The accumulated evidence is that visual impairment in PD correlates with motor severity, progresses with motor disability and fluctuates in parallel with motor fluctuations (Bodis-Wollner, 2002). It remains unclear whether the chromatic alteration reflects striatal dopamine deficiency, changes of retinal dopaminergic pathways (Ingster-Moati *et al.*, 1996) or both.

It is to be noted that several visual dysfunctions in PD are relatively subtle or can only be demonstrated by electrophysiologic or psychophysical testing. Moreover, it appears important to specify the precise stimulus conditions, as results reveal to be stimulus-dependent e.g. visual evoked potentials (VEP) and pattern electroretinogram (PERG) elicited by reversing grating patterns at midspatial frequency and low contrast (Bodis-Wollner and Yahr, 1978 ; Peppe *et al.*, 1995). In PD, these VEP and PERG are abnormal and both can be improved by levodopa, especially the latter (Peppe *et al.*, 1995).

In a nicely designed event-related potential study, Arakawa *et al.* (1999) suggest that PD patients may have impaired higher processing of the magnocellular pathway with preserved parvocellular function.

A recent study has confirmed a limitation of visuospatial perception in PD (Barret *et al.*, 2001). Patients 'see trees but not the forest'. Thus PD may feature a restricted visual attentional 'floodlight' (the widely distributed attention) which can be very inconvenient e.g. when driving at high speed whereby diffuse attention is demanded.

Visuo-cognitive deficits further contribute to visual dysfunction. In PD patients with bilateral and left-sided symptoms, 'subcortical' visuospatial neglect has been demonstrated on a cancellation test (Villardita *et al.*, 1983). Neglect in PD is usually mild or can only be demonstrated by specific tests such as a specially designed line bisection task (Lee *et al.*, 2001) or by side preferences in spontaneous visual exploration illustrating a subtle manifestation of left-sided hemineglect (Ebersbach *et al.*, 1996). This is in line with a recent observation of hemispatial neglect bridging the magnocellular and parvocellular visual streams with neglect of the visual information that was not attentionally processed (Crevits *et al.*, 2003). Visual neglect in PD may be reversed by extracranial magnetic fields in the picoTesla range (Sandyk and Iacono, 1993).

Akinetopsia and prosopagnosia have not been reported in PD.

Positive visual perceptions

A hallucination is defined as "a sensory perception without external stimulation of the relevant sensory organ". It is distinguished from an illusion, in which an external stimulus is perceived but misinterpreted (DSM-IV, 1994). Although there are reports of visual hallucinations in PD already before the dopamine era (Rabins, 1982), the phenomenon has only been noted as a frequent complication of the disorder since levodopa treatment was introduced. The visual hallucinations typically begin some 10 years after levodopa therapy is initiated.

Clinical experience suggests that hallucinations are common among patients with PD, especially at an advanced stage of the disease when the patient already has substantial motor dysfunction, cognitive impairment and depression. In a prospective study of 98 consecutive PD patients without psychosis, 26.5% had visual hallucinations. Although epidemiologic studies confirm that hallucinations are frequent in PD, the occurence seems not markedly higher in PD than in non-neurological patients with visual loss. To compare, complex visual hallucinations have been reported in 21% of 104 consecutive patients with visual pathway lesions causing trivial to severe visual loss (Lepore, 1990). Visual hallucinations in PD are significantly associated with worse visual acuity, suggesting that abnormality of the visual system may be related to visual hallucinations, as has been found in other disorders with visual hallucinations (Holroyd, 2001). Moreover, it has been shown that patients with eye disease experience the same pathologies of visual perception as patients with cerebral lesions (ffytche and Howard, 1999). Clearly, we advocate that even mild visual loss should be sought as a cause of visual hallucinations in PD.

Theories of the aetiology of hallucinations in general include (1) stimulation, e.g. neurochemical, electrical, seizure or ephaptic, and (2) inhibition, e.g. destruction of normally inhibitory functions resulting in disinhibition as in the visually impaired (the Charles Bonnet syndrome). Hallucinations may be a non-specific response to a range of circumstances in conditions which predispose to their occurrence. Imaging studies have revealed decreased metabolic activity in the primary visual cortex in PD (Bohnen *et al.*, 1999 ; Wang *et al.*, 2000).This could be an argument for a release mechanism of visual hallucinations in PD. Otherwise, hallucinations in PD were hypothesized to be narcolepsy-like phenomena resulting from partial activation of rapid eye movement mechanisms (Arnulf *et al.*, 2000).

A recent review disclosed common factors associated with visual hallucinations in PD including greater age and duration of illness, cognitive impairment, depression and sleep disturbances

(Barnes, 2001). Regarding medication, the situation of individual PD patients developing hallucinations after increasing dopaminergic medication or adding an anticholinergic is familiar to clinicians. However, it seems that more complex mechanisms than simply drug levels are involved. In a prospective study, no association was found between the use, dosage and duration of all antiparkinsonian drugs including levodopa (Holroyd *et al.* 2001). Thus, apart from dopamine, serotonin or other neurotransmitters may be involved (Korczyn, 2001) as has been suggested for antisaccade behaviour in PD (Crevits and De Ridder, 1997 ; Crevits *et al.*, 2000). The presence of persistent visual hallucinations in persons with PD has a prognostic value as it predicts rapid deterioration, dementia, permanent nursing home placement and death (Brasic, 1998), although increased mortality has been refuted in a prospective longitudinal assessment of hallucinations in PD (Goetz *et al.*, 2001).

The clinical features of the hallucinations in PD are quite distinctive. The typical visual hallucination is a complex visual image experienced while PD patients are alert and have their eyes open. The image appears without any known trigger or voluntary effort, is in colour, somewhat blurred and commonly moves. It stays present for a period of "seconds" or "minutes". The content can be variable within and between hallucinators and includes such entities as people, animals, buildings or scenery. These features resemble those highlighted in hallucinations in the visually impaired (Charles Bonnet's syndrome). Hallucinations in PD lack the déjà-vu phenomenon of temporal lobe disease. Unlike schizophrenic hallucinations, they usually fluctuate and initially they last only a short time. The lack of multimodality hallucinations and of secondary paranoia as well as the clear sensorium are helpful features in distinguishing 'benign' hallucinations in PD from toxic psychosis. Drug-induced hallucinations in PD range from benign hallucinosis to florid psychosis and paranoid delusions.

At first, PD patients are aware of the non-reality of their experiences. An ominous evolution is reflected in the hallucinations becoming paranoid and delusional, finally leading to a permanent confusional state. Auditory hallucinations (in a non-imperative way) in PD are less common and, when present, are generally experienced by patients with visual hallucinations.

Reference to dementia with Lewy bodies (DLB), a type of dementia with parkinsonian features and prominent visual hallucinations seems mandatory. Although visual hallucinations have become a core feature in the consensus guidelines for DLB, little more is known about their phenomenology than that they are typically well-formed and detailed (McKeith *et al.*, 1996). No data comparing hallucinations in DLB and PD are available. Mori *et al.* (2000) reported visual perception to be defective in

DLB. The defective visual perception even should play a role in the development of visual hallucinations, delusional misidentifications, visual agnosias, and visuoconstructive disability characteristic of DLB. A PET study suggests that hypometabolism in the primary visual cortex is associated with the occurrence of visual hallucinations in DLB (Imamura *et al.*, 1999).

Treatment of hallucinations in PD should start with the general measurements taken in any patient becoming delirious ; attention to the general condition (including infection, electrolyte disturbances), taking of non-essential drugs and curtailing doses of antiparkinsonian drugs. Low doses of the atypical neuroleptics clozapine and quetiapine have been found very helpful without worsening the parkinsonism (Rabey *et al.*, 1995, Fernandez *et al.*, 1999). Rivastigmine is likely to be beneficial in the way it is for the hallucinations in DLB (Korczyn, 2001), another analogy of visual hallucinations in PD and in DLB.

There are undoubtedly multiple factors in the genesis of hallucinations in PD. However, as visual loss is well-documented and may be related to visual hallucinations in PD (Holroyd *et al.*, 2001) as a potentially reversible cause, ophthalmologic therapy for the hallucinating PD patient is advised first. However, this recommendation is to be evaluated in future studies.

Conclusions

Visual dysfunction in PD is common. It manifests as negative or as positive phenomena. Visual defects are usually subtle or only demonstrated by special tasks. However, it seems of clinical relevance to realise that these visual deficits, though minor, may be related to vague visual complaints, blurred vision, impaired contour perception, distress in a striped surrounding and visual hallucinations. Visuo-cognitive defects also are mild and can be overlooked by conventional neuropsychological testing.

Errors in processing of the visual input may raise the potential for misinterpretation and even visual hallucinations, and cause or contribute to various clinical signs, such as misperception of depth, frequent falls and enhanced motor impairment. For these reasons, it is strongly recommended to correct all visual deficits as far as possible.

The question about the anatomical location responsible for visual dysfunction in PD is not fully answered. Is it in the retina, the (visual) cortex or both ? Does it include the lateral geniculate or the basal ganglia ? In the monkey model of PD, the retina shows dopaminergic deficiency owing to loss of (a subset of) amacrine cells in the retina (Bodis-Wollner, 1990). Animal experiments (Albrecht *et al.*, 1996) show that contrast gain is modulated by dopaminergic agents in the lateral

geniculate. Recent imaging studies (Bohnen *et al.*, 1999 ; Wang *et al.*, 2000) have revealed decreased metabolic activity in the primary visual cortex in PD. At this point it is not settled whether a specific postretinal site of the lesion is responsible for the visual cortical involvement in PD or whether it is the consequence of impaired retinal input.

However, the question to find a single anatomical locus responsible for visual dysfunction in PD may be futile in light of actual concepts of distributed parallel processing. Dopamine has been shown to be a functional modulator at different levels of the visual system. However, other neurotransmitters could also be involved in different psychophysical visual disturbances of PD patients.

Whether abnormalities of visual psychophysics might distinguish between PD and other forms of parkinsonism remains to be demonstrated.

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