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Association of Tardive Dyskinesia with Increased Frequency of Eye Movement Disturbances in Chronic Schizophrenic Patients

A Clinical Note

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Summary. The study of eye movement dysfunction in chronic schizophrenics by electronystagmography revealed a significant increase of saccadic dysmetria as well as saccadic intrusions in smooth pursuit in schizophrenic patients with tardive dyskinesia (TD) compared with those without TD and with healthy controls. The pattern of eye movement dysfunction in schizophrenia allows clear discrimination from patients with similar movement disorders due to Huntington's disease. Of several possible explanation's of the schizophrenic eye movement dysfunction the authors favour the hypothesis of a common pathogenetic link between TD and eye movement disorders in schizophrenia, consisting in an underlying dysfunction of regions involved in the regulation of involuntary attention such as the parietal cortex and striatolimbic structures of the right hemisphere. Recent literature supports the assumption of right hemispheric dysfunction in schizophrenia.

Key words: Schizophrenia – Eye movement dysfunction – Right hemisphere dysfunction – Nystagmography

Introduction

In recent years, after many clinical and experimental studies, it has been generally accepted that tardive dyskinesia (TD), the characteristic extrapyramidal disorder often associated with chronic schizophrenia, is no more than an antidopaminergic side-effect of a neuroleptic treatment affecting nigrostriatal structures of the brain. The same conclusion could be drawn for the disturbed eye movements frequently found in chronic schizophrenic patients. This is underlined by the observation, for example, that the same pattern of eye tracking dysfunction described for schizophrenia can be found in patients with parkinsonism [28], a non-specific syndrome commonly produced by neuroleptics as a side-effect. On the other hand, the arguments that would deny eye movement and extrapyramidal disorders any primary diagnostic significance in schizophrenia are more problematic than they might seem. Long before the development of neuroleptic treatment for schizophrenia, it was known that eye movement disturbances and extrapyramidal movement disorders may be associated with the schizophrenic syndrome [3, 12]. Over the past two decades, Holzman and colleagues [7–9] have found that eye tracking disorders occur in 70% of schizophrenic patients and 45% of first-degree relatives, suggesting not only that these disorders are independent of neuroleptic medication, but that they may even be regarded as a genetic marker for disposition to schizophrenia. The evidence, however, contradicts the idea that specific patterns of eye movement disorders are genetically linked to schizophrenia: twin studies have revealed a discordant pattern of psychopathology in 80% of monozygotic twins concordant for eye tracking disorder [13].

Although contradictory conclusions have been drawn on the basic significance of eye tracking dysfunction in schizophrenia, there is no reason to sup-

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pose a priori that the various forms of data available are inherently imcompatible with one another. Consequently, our study aimed to test the hypothesis that some basic form of eye tracking dysfunction (and extrapyramidal motor disorder) is indeed a consequence of schizophrenia itself but that the degree, if not the actual qualitative pattern, of the dysfunctioning is susceptible to modulation by neuroleptics. We proposed that the discovery of similar proportions of eye movement dysfunction in schizophrenics both with and without TD would argue against the case for a primary causal link between neuroleptics and eye movement dysfunctioning in schizophrenia. On the other hand, the discovery of significant differences in the extent and pattern of eye movement disorders between the two groups would suggest a modulating influence of neuroleptics on the clinical expression of this symptom.

We would like to add that we are also hopeful that careful studies of the patterns of eye movements found in schizophrenia might also permit us ultimately to distinguish more effectively between cases of chronic schizophrenia accompanied by marked levels of involuntary movements (TD) and Huntington's chorea with psychiatric complications. As is well known, such cases, from a clinical point of view, are often virtually indistinguishable from each other [2].

Patients and Methods

Fifty patients with chronic schizophrenia (DSM-III: 295.32 and 295.62) were compared with 25 age- and sex-matched controls (neurological inpatients with spinal complaints, free of central nervous system pathology: 11 women, 14 men, age 50.9 ± 14.1 years). Three schizophrenic patients had to be eliminated later on after developing symptoms of a marked organic brain syndrome. From those remaining, 24 patients suffered from TD and 23 did not. All patients had received chronic neuroleptic medication for at least 5 years, without significant group differences. Neuroleptic and tranquilizer medication was not disrupted during examination for ethical reasons. The average unbroken duration of hospitalization of the schizophrenic patients was 17 years ± 11.7. The schizophrenics with TD (12 men, 12 women) had an average age of 53.2 years ± 12.7 (range 28–70 years); those without TD (2 women, 21 men) an average age of 44.4 years ± 14.4 (range 24–69 years). Abnormal involuntary movements were assessed by the abnormal involuntary movement scale (AIMS). Although most expressed in the orofacial region, these movements extended to the trunk and distal extremities to a sometimes remarkable degree in patients with TD.

Horizontal and vertical eye movements were recorded by routine methods of DC-electro-oculography using skin surface electrodes (Ag/AgCl) [10, 18, 29]. The occurrence of spontaneous nystagmus, velocity of saccadic eye movements ranging from 10° to 40° in horizontal and vertical direction (measured in the dark by fixation of alternating light spots), horizontal pursuit following a sinusoidal stimulus (frequency 0.3, 0.4, 0.5 Hz, amplitude 60°), optokinetic nystagmus horizontally and vertically (30°, 60°, 90° stripe velocity in both directions) as well as gaze directional nystagmus (40° excentricity) were recorded, and vestibular rotational and caloric stimulation effects were studied. Statistical elaboration was performed using the one-sided comparison of mean values from independent measurements [14, 29].

Results

The frequency of a dysmetria of saccades was significantly elevated in schizophrenics with TD compared with controls ($P < 0.05$ for 20° and $P < 0.01$ for 40° saccades). The average percentage of hypometric saccades (two or more hypometric saccades) was 13% in healthy controls, 35% in schizophrenics without TD and 42% in schizophrenics with TD (Fig. 1).

There was no difference between the average saccadic velocity in horizontal and vertical saccades between groups, nor was there any group difference in mean velocity of slow and fast components in either optokinetic or vestibular reflexive eye movements.

Number of saccades per period of sinusoidal pursuit stimulus was about 3 times as high in schizophren-

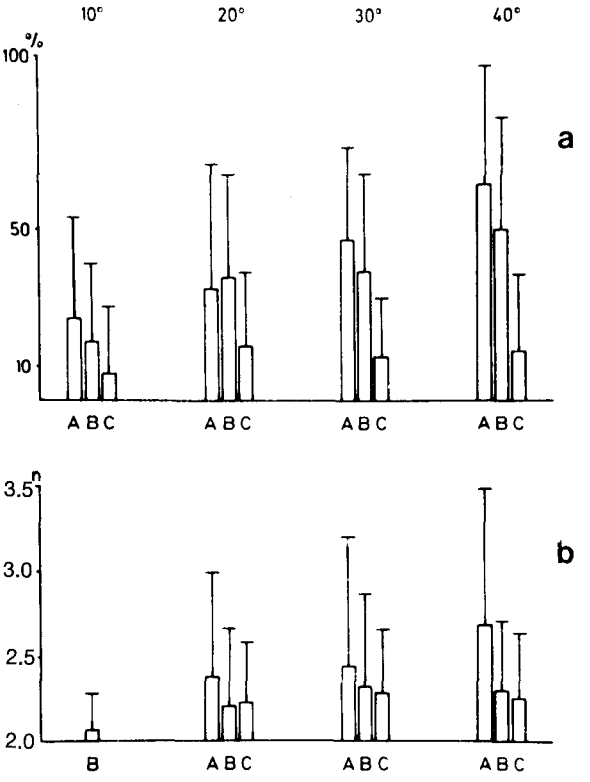

Fig. 1a, b. Dysmetria of horizontal saccades. **a** Percentage of fixational saccades with one or more hypometric saccades ($x \pm SD$). Significant differences (Lord test): A/C: 10°, $P < 0.05$; 20, 30, 40°, $P < 0.01$. B/C: 20°, 30°, $P < 0.01$; 40°, $P < 0.05$. **b** Number *(n)* of saccades in fixational changes with two or more hypometric saccades ($x \pm SD$). *A*, Schizophrenic patients with tardive dyskinesia (TD); *B*, schizophrenic patients without TD; *C*, controls

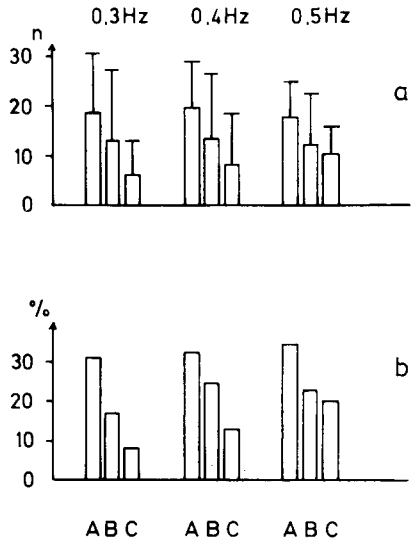

Fig. 2a, b. Smooth pursuit to a pendular sinusoidal stimulus. **a** Number of saccades per 10 half-sinusoidal pendular stimuli ($x \pm$ SD). *A*, Schizophrenics with TD; *B*, schizophrenic patients without TD; *C*, controls. Significant group differences (Lord test): A/C: 0.3, h.s.; 0.4, n.s.; 0.5 Hz, $P < 0.01$. A/B: 0.3, n.s.; 0.4 Hz, $P < 0.05$; 0.5 Hz, $P < 0.01$. B/C: 0.3 Hz, $P < 0.01$; 0.4 Hz, $P < 0.05$. **b** Percentage of saccadic pursuit of pendular sinusoidal stimulation, defined as the average number x amplitudes of saccades per ½ product of period related to total amplitude of pursuit movement

ics with TD and twice as high in schizophrenics without TD as it was in controls ($P < 0.01$). These saccades occurred irregularly (not only in the direction of gaze). As there was no difference in gain between the schizophrenic patients and controls, the observed saccades are regarded as saccadic intrusions. The percentage of saccadic pursuit was significantly more frequent during the sinusoidal stimulation in schizophrenics with TD compared with schizophrenics without TD, especially at 0.5 Hz ($P < 0.01$) (Fig. 2).

Instability of fixation was seen in all groups without significant differences. However, the resolution of the method applied did not allow exact measurement of saccades smaller than 2°–3°.

Discussion

Our results revealed a clear correlation between the occurrence of TD in schizophrenic patients and increased eye movement dysfunctioning that followed a pattern usually considered typcial for schizophrenia [7–9]. We are thus in a position to support the work of Spohn et al. [25], who reported an increased tendency towards disturbed eye pursuit in schizophrenics with (especially orofacial) TD compared with patients with less expressed TD. However, stepwise regression analysis showed a correlation between TD and eye movement disorders that was independent of the amount of medication, age or sex. This points therefore to an individual sensitivity to neuroleptics and to the development of extrapyramidal side-effects, which is not simply a function of the neuroleptic dose applied, as is clinically well-known. That means that factors of individual predisposition (such as underlying brain damage) have to be considered as well as possible neurophysiological interactions between extrapyramidal motor and eye movement disturbances, or even methodological issues. The matter is still controversial, as shown by a recent publication of Spohn et al. [26] reporting strong evidence that neuroleptics do not produce eye tracking dysfunction, and that most substantial differences between patients with and without TD were in the frequency of cycles with large and non-tracking saccades, and that cognitive focusing greatly attenuated these differences. This is contradicted by a methodologically more sophisticated study by Hock et al. [6], who used electronystagmography and an infrared-reflection technique as well and reported data which clearly showed a neuroleptic influence on eye movement disorders of a regular "saw-teeth" pattern in schizophrenic patients, interpreted as an oculomotor type of TD. However, the finding of a greater amount of eye tracking dysfunction in schizophrenic patients with TD compared with those without seems well substantiated.

One often-discussed explanation for this correlation between TD and eye movement disorders blames it on methodological imprecision [25]. Since the prevailing TD is orofacial, the argument is that it could be that patients with more TD produce more involuntary grimaces, which in turn produce movement artefacts that are then misinterpreted as disturbances of smooth pursuit. Regardless of the same pattern of eye movement dysfunction with the infrared-reflexion technique [6], we tried to rule out this source of error by carefully analysing each electronystagmogram and rejecting all doubtful recordings in our study. The conclusion of Hock et al. [6], however, that eye tracking dysfunction in schizophrenic patients is in any case due to neuroleptic treatment and is a kind of "tardive dyskinesia of the eye movements" can be simply ruled out by the sophisticated photometric analysis of Diefendorf and Dodge [3] performed long before the neuroleptic era.

There is some reason to believe that, in the generation of smooth, ramp-like eye movements, occipitoparietal structures interact with several subcortical structures, including the corpus striatum. However, the similarity between the pattern of eye movement dysfunction in schizophrenic patients and that in parkinsonian patients [28] further suggests a possible

striatal subcortical link between eye movement disorder and extrapyramidal symptoms like TD in schizophrenia.

Interestingly, a wholly different pattern of eye movement disorders is found in patients with Huntington's chorea – another disorder associated with striatal dysfunctioning, clinically opposite to parkinsonism, but sometimes (when psychotic symptoms are present) clinically indistinguishable from chronic schizophrenia with TD [2]. In this disorder, patients' eye movement pursuit is disrupted by irregular jerks of unpredictable size and frequency [18]. Schizophrenics (and parkinsonian patients), on the other hand, display a more regular pattern of saccadic intrusions, with smooth pursuit following a "saw–teeth" pattern [3, 7–9, 13]. In addition, we have consistently failed to find in our schizophrenic patients anything similar to the slowed saccadic velocity typical of Huntington's disease patients [18]; in the literature also there is no report of any such discovery [3, 7–9, 13, 23–26, 29].

This means that, as hoped, we are indeed in a position to discriminate more accurately between psychopathologically similar patients with choreatic movement disorders due either to Huntington's chorea or to TD: slow saccadic velocity combined with an irregular pattern of disturbed smooth pursuit eye movements points to Huntington's disease, while normal saccadic velocities combined with a more regular pattern of saccadic intrusions in smooth pursuit argue for a diagnosis of schizophrenia.

Mialet and Pichot [16] have suggested that TD itself disinhibits the occurrence of saccadic eye movements. However, if that were true, then a separate mechanism would have to exist for the origin of disturbed eye movements in schizophrenics without TD, which seems rather improbable. It is more likely that, in schizophrenics both with and without TD, the same subclinical brain structures are involved in the linked dysfunctioning of extraphyramidal systems and eye movements, but this dysfunctioning is both intensified and possibly modulated in schizophrenics with TD. These underlying dysfunctional brain structures can be regarded as those postulated to predominate in schizophrenics with TD in the form of an increased number of subclinical brain lesions [27]. Their site is probably above the brain stem, since brain-stem lesions should have led to a pathological pattern in the vestibular and optokinetic tests as well as to the occurrence of gaze directional nystagmus, none of which was found in our schizophrenic patients or previous studies [7–9, 13, 25, 26]. The critical and asymmetrical involvement of subcortical-striatal structures in schizophrenia has recently been highlighted by the discovery through PET scaning of significant alterations in the right hemispheric striatum in the course of neuroleptic therapy [1], and of significant neurometabolic changes in right hemispheric striato-limbic regions during mescaline-induced schizophreniform psychosis [21].

The observation that disturbed eye movement patterns in schizophrenic patients can be markedly improved by methods that increase the short-term attention of the patients [11, 23, 26] points to a likely major interaction of higher cortical centres with subcortical-striatal ones in the genesis of this patholo gy. There are indeed several hints in the literature, gleaned from a variety of methodological approaches, that suggest a parietal site of dysfunctioning in schizophrenia, especially in the right hemisphere ([1, 4, 15, 17, 19–21]; J. Gruzelier, personal communication); It is widely agreed that the parietal lobe, in a loop linked to subcortical (striato-limbic) temporal and frontal basal structures, is concerned with multimodal attentional processing [5]. Yet it would seem that involuntary attentional processes are predominantly right hemisphere based, while voluntary, detail-oriented attentional processes rely more on left hemispheric systems [5]. The evidence for a disturbance of involuntary attention in schizophrenia [9, 13] thus points once again to a possible basic right hemispheric dysfunctioning in schizophrenia ([1, 4, 15, 17, 19–21]; J. Gruzelier, personal communication).

The above argument for a right hemispheric proximate role in schizophrenic eye pursuit not only stresses the interaction of cortical and subcortical structures in this disorder, but offers further support for the case for a primary link between the schizophrenic syndrome itself (as it exists independent of neuroleptic treatment) and the disturbed eye movements. Recent studies point to a dominant role of the right hemisphere in the planning of eye movements [22]. We also recently reported finding a special impairment of left hand visual motor tracking in acute schizophrenic patients, which then improved during neuroleptic therapy [4]. We thus postulate a basic dysfunction in the right hemispheric parieto-cortico-temporo-subcortical (striato-limbic) loop as a causal mechanism in a least some aspects of eye movement disorder in schizophrenia. Our laterality model of cortical-subcortical mechanisms in schizophrenic eye tracking dysfunction takes a first step towards integrating this motor disorder with the basic psychopathology of the schizophrenic syndrome by seeking the source of both in the same asymmetrically disordered brain system. We thus find ourselves in a position to account for a reported correlation between schizophrenic thought disorder with disturbed eye movements, on the one hand [24], and schizophrenic thought disorder with neuropsychologically assessed right hemispheric dysfunction, on the other [21]. We

also conclude that neuroleptic medication is at least potentially able to interfere with or intensify this dysfunctional process. This is underlined by the asymmetrical impact of neuroleptic treatment on right hemisphere processing [17, 19]. To decide on this issue, further studies are needed to evaluate whether the nature or degree of postulated right hemispheric dysfunction is greater in chronic schizophrenic patients with neuroleptically induced TD than in those without.

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