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Cognitive dysfunction in chronic schizophrenia followed prospectively over 10 years and its longitudinal relationship to the emergence of tardive dyskinesia

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SYNOPSIS Basic cognitive function was assessed at initial and at 5- and 10-year follow-up assessments among 41 primarily middle-aged in-patients manifesting the severest form of schizophrenia; additionally, the presence and severity of tardive dyskinesia was evaluated on each occasion. Overall, there was a modest but significant deterioration in cognitive function over the decade, particularly among older men. Longitudinally, patients with persistent tardive (orofacial) dyskinesia continued to show poorer cognitive function than those consistently without such movement disorder, though within neither group did cognitive function change over the decade. Those patients demonstrating prospectively the emergence of orofacial dyskinesia showed a marked deterioration in their cognitive function over the same time-frame within which their movement disorder emerged, but this decline did not progress further thereafter. There appears to exist some modest, progressive deterioration in cognitive function even late in the chronic phase of severe schizophrenic illness which appears to derive primarily from patients showing *de novo* emergence of tardive orofacial dyskinesia.

INTRODUCTION

While it is well recognized that cognitive function is impaired in schizophrenia (Blanchard & Neale, 1994), the general extent to which such dysfunction does or does not deteriorate over the course of chronic illness is less clear. Cognitive deficits somewhat similar to those evident in patients with an established illness are apparent at the first psychotic episode (Bilder *et al.* 1992; Hoff *et al.* 1992; Saykin *et al.* 1994), but their longitudinal course thereafter remains to be specified. The issue is of some importance because of renewed interest in the concept of schizophrenia as a neurodevelopmental disorder (Waddington, 1993*a*) and the attendant question as to the existence of active disease long after the emergence of psychosis (Waddington, 1993*b*). On the basis of prospective studies of relatively short duration and inherently less powerful cross-sectional studies, it has been argued that in neuropsychological terms the disorder fails to show further deterioration beyond the period following the onset of psychosis and thus shows the characteristics of a 'static encephalopathy' (Heaton & Drexler, 1987; Goldberg *et al.* 1993). Conversely, on the basis of other cross-sectional studies, it has been argued that progressive neuropsychological deterioration ensues in the long-term (Buhrich *et al.* 1988; Bilder *et al.* 1992). Indeed, the often prominent intellectual deficits of some older, chronically ill patients with schizophrenia continue to attract considerable attention (Buhrich *et al.* 1988; Purohit *et al.* 1993). These cognitive deficits can sometimes be so severe as to seem incompatible with an origin solely at, or soon after, the onset of psychosis in the absence of subsequent deterioration; yet little is available in the way of prospective data to address the issue.

Clarification of the nature of cognitive dys-

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function in schizophrenia is of importance for a second reason: greater impairment therein seems to be one of the characteristics that more reliably (though not invariably) distinguishes patients with tardive dyskinesia from those without such movement disorder, particularly in relation to involuntary movements with an orofacial (buccal–lingual–masticatory) topography (Waddington, 1989, 1995). While several aspects of the association remain poorly understood, a fundamental issue is the nature of the temporal relationship between cognitive impairment and tardive dyskinesia: does the emergence of further cognitive dysfunction precede that of involuntary movements, in accordance with a classical 'organic vulnerability' hypothesis of predisposition to this movement disorder, or does further cognitive dysfunction emerge over the same time-frame in which involuntary movements become apparent, suggesting two related manifestations of a common pathophysiological process (Edwards, 1970; Waddington *et al.* 1993; Waddington, 1995)? Only long-term prospective studies can adequately address these questions.

In 1983, we initiated a prospective study of cognitive dysfunction and tardive dyskinesia in a large population of older, chronically ill in-patients with a long-standing schizophrenic illness. At entry to the study those patients with orofacial dyskinesia showed, on a cross-sectional basis, greater cognitive deficits than did their otherwise similar counterparts without such movement disorder (Waddington & Youssef, 1986; Waddington *et al.* 1987). Five years later, in 1988, reassessment indicated that there had been no general deterioration in cognitive function over this period. Furthermore, not only absolute levels of cognitive function but also differences therein were essentially unaltered on comparing patients with *versus* those without orofacial dyskinesia on each occasion; the only group of patients to demonstrate significant deterioration in cognitive function over this interval was those who by 1988 now showed *de novo* emergence of orofacial (as opposed to limb–trunkal) dyskinesia (Waddington *et al.* 1990). The present report describes additional aspects of a 10-year follow-up study of this patient population (Waddington *et al.* 1995*a*). In relation to the present issues, it had two objectives: to ascertain longitudinally whether cognitive function shows any general deterioration over a time scale considerably longer than studied previously, and to determine prospectively whether cognitive deterioration associated specifically with *de novo* emergence of orofacial dyskinesia is a progressive or non-progressive phenomenon thereafter.

METHOD

Patients

The subjects of this study derive from an original population (Waddington *et al.* 1987) of 101 chronically ill, long-term in-patients residing in St Davnet's Hospital, Monaghan, who satisfied the Washington University criteria of Feighner and colleagues (1972) for a diagnosis of schizophrenia; their multiple and profound deficits constituted schizophrenia in its most severe form.

Initial assessment

In 1983 each of these 101 patients consented to evaluation using the Abnormal Involuntary Movement Scale (AIMS; National Institute of Mental Health, 1976) by a single rater who was unaware of each patients' clinical and treatment histories. In accordance with our previous finding that the relationship between cognitive dysfunction and tardive dyskinesia was confined to involuntary orofacial but not limb–trunkal movements, both cross-sectionally (Waddington *et al.* 1987) and longitudinally (Waddington *et al.* 1990), the presence of typical buccal–lingual–masticatory dyskinesia was defined by the presence of at least one score of 2 (mild) on one or more of the first four orofacial items of the AIMS with, or without, additional involvement of the limbs or trunk. After AIMS examination, 74 of these patients were assessed neuropsychologically using an abbreviated 10-question mental test (name, age, marital status, work history, orientation for time and place, recall of an address following three questions on general awareness as interpolated material: naming the Queen of England and two relating to major world events (see Waddington & Youssef, 1986)) that has proved effective in evaluating the basic cognitive functions of orientation, immediate memory and awareness in populations whose severe and often extreme debilities render them inaccessible to more detailed examination (Waddington *et al.* 1987,

1990); it was not possible to conduct neuropsychological assessment on the remaining 27 patients: 22 were mute and 5 declined to cooperate in such assessment.

Patient records were subsequently reviewed to determine *inter alia* the following demographic variables: age; duration of illness, defined from first presentation to a psychiatric service; duration of treatment with neuroleptics; mean daily dose of neuroleptics over that duration, expressed as mg of chlorpromazine equivalents (Davis, 1976); current dose of neuroleptic(s) on the day of these initial assessments, expressed similarly; duration of treatment with anticholinergics; presence or absence of anticholinergic treatment on the day of these initial assessments.

Follow-up assessments

In 1988 and again in 1993 the same investigators sought, without reference to their previous findings and in the absence of information on clinical and treatment histories over the intervening periods, to re-assess each patient in an identical manner; AIMS ratings and neuropsychological assessment were repeated, and thereafter any changes in neuroleptic and/or anticholinergic medication over each quinquennium were recorded.

Data analysis

Complete data on the above variables were available at each evaluation for a total of 41 patients, subject to one woman admitted in 1970 who had burned her case-notes in 1976 and for whom only current medication status at each evaluation could be recorded; by 1993, 46 of the original 101 patients had died, 8 patients had not completed all neuropsychological assessments due to muteness, 4 patients declined to cooperate at one or more assessments, and 2 patients could not be located at 1988 follow-up. It is to this group of 41 patients that all further discussion relates; their demographic characteristics and medication history at study entry in 1983 are shown in Table 1. Data are expressed as means ±S.D. or percentage prevalences; comparisons of non-categorical variables were effected within groups using the paired Student's *t* test and between groups using the unpaired Student's *t* test, while comparisons of categorical variables were effected using Fisher's exact probability test. Changes in cognitive function were hypothesised to be in the direction of deterioration and were evaluated using 1-tailed tests; all other tests were 2-tailed.

Table 1. *Characteristics of schizophrenic patients* (22 *men and* 19 *women*) *on entry to the study in* 1983

Variable	Mean ±S.D.
Age (years)	54·1 ± 12·5
Duration of illness (years)	27·9 ± 9·9
Duration of neuroleptic treatment (years)*	15·5 ± 7·0
Mean dose (mg/day of chlorpromazine equivalents)*	389 ± 256
Current dose (mg/day of chlorpromazine equivalents)*†	970 ± 1508
Duration of anticholinergic treatment (years)*‡	6·2 ± 5·0

* Not known for one patient, hence $N = 40$.

† Current dose in 1988, 1010 ± 1248 mg/day; current dose in 1993, 1257 ± 1416 mg/day.

‡ In 1983 21 (51%) of the patients were currently receiving anticholinergics; 28 (68%) of the patients were currently receiving anticholinergics in 1988; 28 (68%) of the patients were currently receiving anticholinergics in 1993.

RESULTS

Overall changes in cognitive function

On comparing cognitive function scores on initial assessment (6·5 ± 2·0) with those at 10-year follow-up (5·9 ± 1·9) among all 41 patients, significant overall deterioration was evident ($t = 2·08$, df = 40, $P = 0·02$) though the effect was rather variable between individuals; there were no significant changes in either neuroleptic

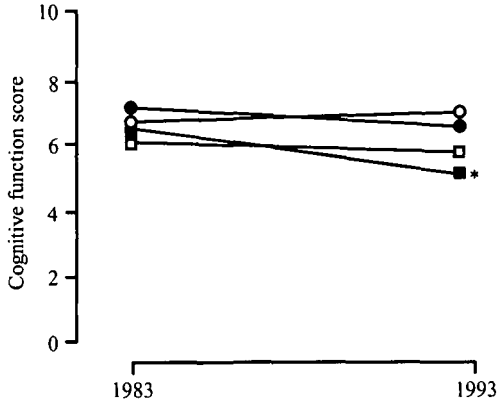

FIG. 1. Mean cognitive function scores at initial (1983) and 10-year (1993) follow-up assessments for schizophrenic patients subdivided by age and gender: 10 men age < 55 (●); 12 men age ⩾ 55 (■); 12 women age < 55 (○); 7 women age ⩾ 55 (□). * Significant difference between initial and 10-year follow-up assessments for men age ⩾ 55, $P = 0·03$).

or anticholinergic medication over this same period (Table 1). As this patient population encompassed similar numbers of men and women having a mean age in the mid-fifties but ranging in age from 25 to 78 years at study entry, such analyses were performed separately for men and women, each dichotomized into those age < 55 years and $\geqslant 55$ years at initial assessment. Men age < 55 years ($N = 10$, mean age $44{\cdot}6 \pm 7{\cdot}7$ years) showed slight deterioration, while men age $\geqslant 55$ years ($N = 12$, mean age $65{\cdot}7 \pm 5{\cdot}2$ years) showed significant deterioration in cognitive function over the 10-year period ($t = 2{\cdot}04$, df $= 11$, $P = 0{\cdot}03$) in the absence of any significant changes in neuroleptic or anticholinergic medication; little change in cognitive function was evident over the 10-year period among either women age < 55 years ($N = 12$, mean age $44{\cdot}3 \pm 7{\cdot}3$ years) or women age $\geqslant 55$ years ($N = 7$, mean age $65{\cdot}0 \pm 6{\cdot}2$ years) (Fig. 1). When compared between groups, cognitive function tended to be generally more impaired in patients age $\geqslant 55$ years at study entry relative to their counterparts age < 55 years, among both men and women, but only greater cognitive dysfunction in older relative to younger men at 10-year follow-up attained statistical significance ($t = 2{\cdot}12$, df $= 20$, $P = 0{\cdot}02$).

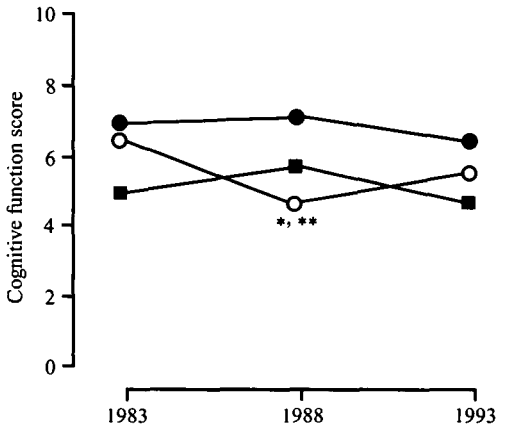

FIG. 2. Mean cognitive function scores at initial (1983), 5-year (1988) and 10-year (1993) follow-up assessments for schizophrenic patients subdivided by tardive orofacial dyskinesia status: 16 patients without orofacial dyskinesia at each occasion (●); seven patients with orofacial dyskinesia at each occasion (■); six patients without orofacial dyskinesia at initial assessment but showing emergence of orofacial dyskinesia at 5-year and 10-year follow-up assessments (○). * Significant difference between initial and 5-year follow-up for patients showing the emergence of orofacial dyskinesia, $P = 0{\cdot}04$; ** significant difference at 5-year follow-up assessment between patients showing the emergence of orofacial dyskinesia and patients without orofacial dyskinesia at each occasion, $P = 0{\cdot}01$.

Cognitive function in relation to tardive dyskinesia

Among the 41 patients followed prospectively over 10 years, outcomes were as follows: 16 patients (39%: 10 mean, six women; mean age $48{\cdot}8 \pm 6{\cdot}6$ years) were consistently without orofacial dyskinesia at each of initial, 5-year and 10-year assessments; seven patients (17%: three men, four women; mean age $63{\cdot}0 \pm 11{\cdot}5$ years) manifested orofacial dyskinesia continuously at each of these assessments (total orofacial AIMS scores: initial assessment $5{\cdot}1 \pm 1{\cdot}5$; 5-year assessment $7{\cdot}0 \pm 1{\cdot}4$, $t = 7{\cdot}12$, df $= 6$, $P < 0{\cdot}001$ *v.* initial assessment; 10-year assessment $7{\cdot}7 \pm 1{\cdot}7$, NS *v.* 5-year assessment); for six patients (15%: 3 men, 3 women; mean age $56{\cdot}3 \pm 15{\cdot}5$ years) orofacial dyskinesia was not evident at initial assessment but had emerged by the 5-year assessment and persisted at 10 years (total orofacial AIMS scores: initial assessment $0{\cdot}8 \pm 0{\cdot}8$; 5-year assessment $6{\cdot}3 \pm 1{\cdot}9$; 10-year assessment $6{\cdot}8 \pm 2{\cdot}0$, NS *v.* 5-year assessment). There were 12 patients (29%: six men, six women; mean age $54{\cdot}8 \pm 15{\cdot}1$ years) who manifested orofacial dyskinesia only at any one of the three assessments, or at initial and 10-year assessments but not at the 5-year assessment; these were considered to be instances of transient dyskinesia and, in view of their uncertain status and small group sizes, they were not analysed in detail. No patient manifested orofacial dyskinesia at initial and 5-year assessments but not at the 10-year assessment.

Patients consistently without orofacial dyskinesia failed to show deterioration in their cognitive function over the 10-year period; those who manifested orofacial dyskinesia continuously were significantly older ($t = 3{\cdot}77$, df $= 21$, $P < 0{\cdot}001$) and evidenced significantly poorer cognitive function (at initial assessment: $t = 2{\cdot}63$, df $= 21$, $P = 0{\cdot}01$; at 10-year assessment: $t = 2{\cdot}37$, df $= 21$, $P = 0{\cdot}01$) than their counterparts without such movement disorder, but also failed to show any deterioration in their cognitive function over the 10-year period (Fig. 2). Similarly, patients manifesting transient dyskinesia did not show any change in cognitive function over the decade (mean cognitive function scores: initial assessment $6{\cdot}8 \pm 2{\cdot}3$; 5-year assessment $6{\cdot}1 \pm 2{\cdot}2$; 10-year assessment

6·2 ± 2·3, NS *v.* initial assessment). While patients without orofacial dyskinesia at initial assessment but in whom such movement disorder had emerged by the 5-year assessment did not differ in age from any of the above groups, their cognitive function at initial assessment was indistinguishable from that of those consistently without such movement disorder and was greater than that of those who continuously manifested such movement disorder ($t = 1{\cdot}72$, df = 11, $P = 0{\cdot}06$); however, among these patients, in whom orofacial dyskinesia had emerged between initial and 5-year assessments, cognitive function showed significant deterioration over this same interval ($t = 2{\cdot}10$, df = 5, $P = 0{\cdot}04$) such that, at the 5-year assessment, their cognitive function was now significantly poorer than that of patients consistently without orofacial dyskinesia ($t = 2{\cdot}41$, df = 20, $P = 0{\cdot}01$) and indistinguishable from that of patients who continuously manifested orofacial dyskinesia. In these new cases of orofacial dyskinesia, deterioration in cognitive function between the initial and 5-year assessments over which such movement disorder emerged did not increase further between the 5- and 10-year assessments over which such movement disorder persisted. Rather, at the 10-year assessment their cognitive function scores (5·5 ± 1·2) evidenced the least variability between individuals that we encountered, were indistinguishable from that at the 5-year assessment and remained less than that at their initial assessment ($t = 1{\cdot}73$, df = 5, $P = 0{\cdot}07$); however, their cognitive function at the 10-year assessment was intermediate between, and did not differ from patients either without orofacial dyskinesia at any assessment or continually manifesting such movement disorder (Fig. 2). There were no significant gender differences in the above pattern of cognitive change; neither were there any significant changes among subgroups in neuroleptic or anticholinergic medication between the assessments over which these changes in cognitive function were recorded.

DISCUSSION

At initial assessment, patients already showed marked cognitive debility that appeared generally static at 5-year follow-up (Waddington *et al.* 1990) but which had declined over the decade. Losses in such fundamental cognitive domains are extremely rare among persons traversing the decade between their mid-50s to mid-60s. Furthermore, while there were no prominent differences in overall cognitive function between male and female patients, cognitive decline within individual patients appear to be primarily a phenomenon of males, particularly those age ⩾ 55 years; using the similar Mini-Mental State Examination, such basic cognitive functions have been reported not to differ between males and females among the normal elderly, even in their eighth decade, and to be more impaired in women than in men among persons with Alzheimer's disease (Buckwalter *et al.* 1993).

Whether cognitive function in schizophrenia deteriorates further in the long-term, subsequent to those deficits already present at the first psychotic episode or emerging over the first few years immediately thereafter, continues to be debated widely (Heaton & Drexler, 1987; Bilder *et al.* 1992; Goldberg *et al.* 1993). In particular, two recent cross-sectional studies comparing groups of 'purified' patients over a wide age range have suggested that no such between-subject differences in cognitive function are apparent and that schizophrenia therefore demonstrates the characteristics of a non-progressive encephalopathy (Heaton *et al.* 1994; Hyde *et al.* 1994). However, the present study takes advantage of the considerably greater statistical power of a within-subject, prospective design using the same team of investigators who were able to proceed in an identical manner over a particularly long period, and finds some evidence for a progressive process. It must be emphasized that our subjects were very severely ill in-patients with multiple pre-existing deficits that rendered them inaccessible to more detailed neuropsychological examination, and this limits the extent to which these findings can be generalized to other patient populations and cognitive domains. However, they constitute a perhaps more 'naturalistic' population; indeed, that the cognitive decline encountered was particularly a phenomenon of older male patients would be consistent with the classical and still enduring (Kraepelin, 1919; Goldstein, 1988; Shtasel *et al.* 1992) notion in schizophrenia of generally poorer outcome among males.

While a static encephalopathy is readily

compatible with contemporary perspectives of schizophrenia as a neurodevelopmental disorder (Waddington, 1993*a*), it must be emphasized that a progressive element to schizophrenia would not in itself contradict such a perspective; neurodevelopmental origin(s) and adult disease progression are not mutually exclusive, and may be sequential phases of one longitudinal process or separate dimensions of the same pathology (Waddington, 1993*b*; Waddington *et al.* 1995*a*). The overall rate of decline in cognitive function encountered in the present patient population, while both greater and more fundamental than would be otherwise expected, is considerably less than is found for major neurodegenerative processes such as Alzheimer's disease (Stern *et al.* 1994); this would complement neuropathological and post mortem neurochemical evidence that the marked cognitive deficits found in many older patients with schizophrenia do not occur in association with degenerative changes such as those found in dementia of Alzheimer or other type (Casanova *et al.* 1992; Purohit *et al.* 1993; Haroutunian *et al.* 1994). The variability in this effect appeared to derive from deterioration in older male patients and, particularly, in those patients demonstrating the emergence of tardive dyskinesia; thus, an alternative perspective may throw light on the process(es) potentially involved.

We found that, on a longitudinal basis, schizophrenic patients with persistent tardive (orofacial) dyskinesia were more cognitively impaired than those consistently without such movement disorder, in elaboration of the majority of cross-sectional studies (Waddington *et al.* 1993; Waddington, 1995). While patients with orofacial dyskinesia were older than those without, as expected (Waddington, 1989; Barnes, 1990), their greater cognitive deficits did not appear to reflect simply their greater age; neither those persistently with, nor those consistently without, orofacial dyskinesia showed any change in cognitive function over the decade. More importantly, we found also that patients demonstrating *de novo* orofacial dyskinesia evidenced a marked deterioration in their cognitive function over the same time-frame during which their movement disorder emerged; this deterioration was from a level similar to that of patients consistently without orofacial dyskinesia to a level even lower than that of those with persistent movement disorder. However, this cognitive deterioration did not appear to be the beginning of a progressive process; once *de novo* orofacial dyskinesia had become established, its persistence was not associated with further cognitive decline but, rather, with an arrest in that decline.

It seems that cognitive correlates of orofacial dyskinesia in schizophrenia may not simply precede the emergence of this movement disorder in the manner of a pre-existing organic vulnerability factor. Rather, these cognitive correlates appear to be in some part intrinsic to (or epiphenomena of) whatever pathophysiological process might underly the emergence of such dyskinesia, and two alternative schemes suggest themselves (Waddington *et al.* 1993; Waddington, 1995). Long-term treatment with neuroleptic drugs could exert subtle cumulative effects that result in two independent but perhaps temporally congruent sequelae: a further deterioration in cognitive function to an extent below that already associated with the illness itself, and the emergence of orofacial dyskinesia; vulnerability to orofacial dyskinesia would then involve individual cellular sensitivity to such drug effects. Alternatively, long-term treatment could disturb a unitary cerebral system that is already dysfunctional as an integral part of the pathophysiology of the illness itself: the result could also be the emergence of greater cognitive dysfunction and of orofacial dyskinesia, but with primacy attached to an interaction between neuroleptics and a specific substrate of the illness; vulnerability to orofacial dyskinesia would then depend more upon individual illness-related factors (see also Owens *et al.* 1982; Rogers, 1985; Waddington, 1989; Fenton *et al.* 1994; Waddington *et al.* 1995*b*). Multiple lines of evidence point to dysfunction in cortico–striato–pallido–thalamic systems in schizophrenia (Waddington, 1993*b*), and such a network would be a possible candidate for a substrate to the alternative schema considered above; long-term treatment with neuroleptic drugs might slowly induce further dysfunction in this and possibly related systems, the various striato–pallidal components of which might subserve differentially the emergence of involuntary orofacial *v.* limb–trunkal movements.

Irrespective of these considerations, one parsimonious interpretation of the present findings

would be that there exists prospectively some modest, progressive deterioration in cognitive function even late in the chronic phase of severe schizophrenic illness, with this further decline appearing to derive primarily in association with the emergence of orofacial dyskinesia; however, in the absence of vulnerability to involuntary movement disorder or following the expression of such vulnerability in the form of persistent movement disorder, cognitive dysfunction appears to be a phenomenon that shows little progression. The neuronal basis to these findings remains to be determined.

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