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# Is There Cognitive Decline in Schizophrenia?
## A Cross-sectional Study

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The issue of progressive cognitive decline in patients with schizophrenia has been debated. We performed a cross-sectional study of patients with chronic schizophrenia, aged from 18 to 69 years, in order to address this issue. The patients included in this study passed a rigorous screen for any comorbid condition with an adverse impact on central nervous system function. We assessed intellectual deterioration with a battery of neuropsychological tests known to be sensitive to cognitive impairment in progressive dementia. No evidence of accelerated intellectual decline was found. No significant differences were found between the five age-derived cohorts (18–29, 30–39, 40–49, 50–59, and 60–69 years of age) on the Mini-Mental State Examination, Dementia Rating Scale, or other tests sensitive to dementia. While performance on the Boston Naming Test significantly declined with age, this was mainly due to age rather than duration of illness. However, it is important to note that mean performances on the majority of the tests were abnormal across all cohorts studied. These results suggest that intellectual function does not markedly decline during the adulthood of patients with schizophrenia. The course of schizophrenia is more consistent with a static encephalopathy than a dementing disorder.

A dementing disorder is properly defined as an illness which produces a gradual and progressive loss of cognitive function. When an acute or subacute process diminishes cognitive function, resulting in a relatively stable deficit state, the disorder is more properly classified as a static encephalopathy. Despite decades of study, controversy surrounds the issue of dementia in schizophrenia.

Over the past century, most research has indicated that patients with schizophrenia suffer from cognitive impairment. Kraepelin (1919) termed schizophrenia 'dementia praecox' because of its onset in early adulthood and the abrupt period of 'mental enfeeblement' which follows. Despite what is commonly attributed to him, Kraepelin noted that most cases of schizophrenia resolve into a stable deficit state. Bleuler (1978), in his seminal studies on the clinical course of schizophrenia, reported stabilisation and even amelioration of cognitive dysfunction, basing his findings on the long-term follow-up of chronic schizophrenic patients over 20 years or more. Bleuler however based his findings on clinical impressions and patient symptomatology rather than neuropsychological parameters. Ciompi (1981), in his longitudinal study of 289 schizophrenic patients followed for 37 years, suggested a favourable course in a high number of cases. This study suggested that advancing age has a stabilising effect on schizophrenic symptomatology, but it lacked parametric confirmation of cognitive performance.

Few studies have quantitatively examined the course of cognitive dysfunction in schizophrenia. Schwartzman & Douglas (1962) investigated the intellectual changes in chronic schizophrenic patients over a 17-year interval. In this longitudinal study of Canadian Army veterans, the investigators found an initial decrease in the level of intellectual performance, with the chronically hospitalised group showing a steady decline throughout the period, while the ambulatory cases exhibited improvement to a level that approached their premorbid scores. The psychological status of chronic schizophrenic patients has been studied longitudinally by two groups over an 8-year interval. IQ scores showed no evidence of decline in either cohort (Smith, 1964; Klonoff *et al*, 1970). Most recently, Goldstein & Zubin (1990) examined the neuropsychological differences between young and old patients with schizophrenia using the Halstead-Reitan Battery. In this study, schizophrenic patients without neurological comorbidity had the same rate of cognitive decline with advancing age as controls.

The modern standardised diagnostic criteria for schizophrenia were introduced in the mid-1970s, which limits the validity of earlier studies. These studies are also limited by the lack of modern screening techniques, such as computerised tomography or magnetic resonance imaging, for alternative causes of intellectual deterioration. Nevertheless, it is impressive that none of the older quantitative studies were able to demonstrate a progressive deterioration in cognitive function with increasing duration of illness, such as has been amply demonstrated in more classic forms of dementia, such as Alzheimer's disease.

In the present study we have attempted to examine the clinical course of cognitive dysfunction in schizophrenia in order to answer a fundamental question: is schizophrenia a dementing disorder with progressive intellectual deterioration beyond the effects of normal ageing, or is it a static encephalopathy with minimal decline or progression after the initial onset of illness? This question has obvious implications for understanding the relationship between the underlying neurobiology and the clinical course (Weinberger, 1987). We assessed intellectual deterioration in patients with schizophrenia with a battery of neuropsychological tests sensitive to memory impairment and progressive dementia. These patients were diagnosed by DSM-III-R criteria and were carefully screened for substance abuse, other elemental neurological disorders, and systemic diseases with an adverse impact on the central nervous system, such as insulin-dependent diabetes mellitus or hypertension. Exclusion of such conditions is critical if the results are to be attributed to schizophrenia *per se*. A cross-sectional paradigm was used in order to assess cognitive performance in schizophrenia across a wide age range, namely from 18 to 70 years.

## Method

After an initial review of the records of 1500 in-patients at St Elizabeth's Hospital, Washington, DC, those with a diagnosis of schizophrenia by DSM-III-R criteria (American Psychiatric Association, 1987) were selected for additional screening. Exclusionary criteria included any psychiatric disorder other than schizophrenia (including mental retardation and other developmental disorders), head trauma with loss of consciousness, substance abuse including alcoholism, coexisting neurological disorders such as seizures or stroke, therapy with electroconvulsive therapy (ECT) or lobotomy, hypertension, insulin-dependent diabetes mellitus, incomplete or abnormal baseline laboratory studies including complete blood count, serum chemistries, thyroid function tests, hepatic and renal function tests, and syphilis serology, and patients in an acute psychotic exacerbation.

In addition to chart review, patients were interviewed about exclusionary conditions. Psychiatric diagnosis was established by chart review and patient interview, using the Structured Clinical Interview for DSM-III-R (SCID; Spitzer *et al*, 1990), to confirm the diagnosis of schizophrenia. We screened 522 patients to yield 74 (see Table 1) who met all criteria. All patients studied were receiving neuroleptic drugs and most were also receiving anticholinergic agents. Patients were assigned to five age-derived cohorts: 18–29 years, 30–39 years, 40–49 years, 50–59 years, and 60–69 years (see Table 1 for demographics). Educational and socio-economic background, as well as age of onset of schizophrenia, were also recorded. Informed consent was obtained from all participants.

The Mini-Mental State Examination was performed on each patient selected for the study, along with a battery of other neuropsychological tests sensitive to the cognitive decline typically associated with the early stages of well established dementing illnesses such as Alzheimer's disease (Folstein *et al*, 1975). These tests included List Learning (Knopman & Ryberg, 1989), Dementia Rating Scale (Salmon *et al*, 1990), Semantic Fluency (Butters *et al*, 1987), Boston Naming (Williams *et al*, 1989), and the Wisconsin Card Sort Test (LaFleche & Albert, 1991). Patients were also given the WRAT reading test as a measure of their premorbid intellectual ability (Dalby & Williams, 1986).

## Results

Statistical analysis first involved subjecting each dependent measure to an ANOVA. Age cohort served as the class variable. If a main effect or a trend for a main effect of cohort was observed, then age and duration of illness were entered into a stepwise regression equation in order to ascertain which made the greatest contribution to the score in question. WRAT reading, an index of premorbid IQ administered to ascertain the presence of cohort effects based on native ability and education, did not differ between cohorts ($F=0.98$, d.f. $=4,61$, $P=0.43$). Standard scores ranged from 94 to 102 for the groups. However, because WRAT reading significantly correlated with one of the cognitive measures (Boston Naming), it was used as a covariate in the analysis of this variable and this variable only.

No age cohort effects were found for the Dementia Rating Scale ($F=1.56$, d.f. $=4,61$, $P=0.20$), List Learning ($F=0.70$, d.f. $=4,61$, $P=0.59$), Semantic Fluency ($F=0.53$, d.f. $=4,61$, $P=0.71$) or perseverative errors on the Wisconsin Card Sort Test ($F=2.04$, d.f. $=4,37$, $P=0.11$). A trend for a significant cohort effect was found for the Mini-Mental State Examination ($F=2.03$, d.f. $=4,61$, $P=0.10$), and a significant cohort effect was found for the

Table 1
Demographic characteristics of the study population

| Cohort size | Mean (s.d.) age: years | Sex (F/M) | Mean (s.d.) duration of illness: years | Diagnostic subtype[1] | Anticholinergic therapy |
|---|---|---|---|---|---|
| 12 | 23.8 (3.2) | 4/8 | 4.7 (2.6) | 6/6/0 | 3/12 |
| 13 | 36.2 (2.9) | 4/9 | 15.2 (4.9) | 4/8/1 | 3/13 |
| 15 | 44.5 (3.4) | 4/11 | 19.5 (7.1) | 10/5/0 | 8/15 |
| 15 | 53.1 (3.0) | 9/6 | 30.5 (9.0) | 9/4/2 | 7/15 |
| 11 | 65.4 (2.8) | 8/3 | 36.1 (8.0) | 7/4/0 | 5/11 |

1. Undifferentiated/paranoid/disorganised.

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Boston Naming test ($F = 3.58$, d.f. = 4,60, $P = 0.01$). In the latter analysis, WRAT reading served as the covariate. Neither age nor duration of illness was a significant predictor of Mini-Mental State Examination score by stepwise regression equation ($F = 3.51$, d.f. = 1,58, $P = 0.07$, $r = 0.05$). For Boston Naming, only age entered the stepwise regression, accounting for 0.07 of the variance ($F = 4.33$, d.f. = 1,58, $P = 0.04$). Duration of illness did not enter. The mean performance for each cohort on each test is illustrated in Fig. 1.

With a preponderance of men in the younger cohorts and a preponderance of women in the older cohorts, we attempted to ascertain if a sex by cohort interaction were present. Using a $5 \times 2$ ANOVA for each of the cognitive measures, we found no significant interactions ($F < 1.26$, $P > 0.30$).

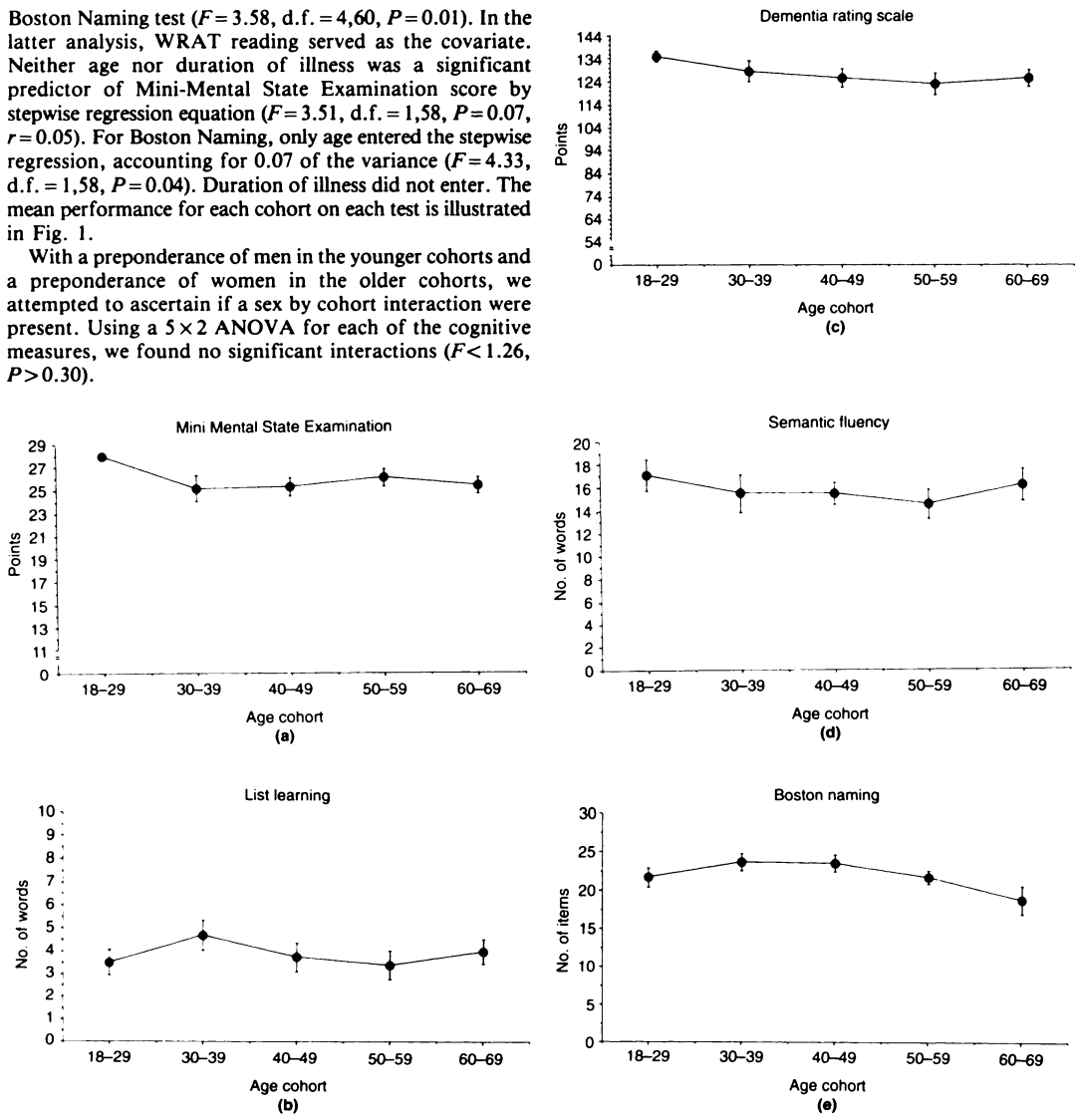


Fig. 1 Performance of age cohorts of schizophrenic patients on cognitive tests sensitive to progressive dementing disorders. (Bars represent the standard error of the mean.)

## Discussion

The essential finding of this study is that after the first few years of illness cognitive function in patients with schizophrenia does not appear to decline beyond the effects of normal ageing. There were no significant differences between age cohorts on the Mini-Mental State Examination, Dementia Rating Scale, or other tests sensitive to dementia. The absence of age-related changes suggests that intellectual function does not markedly decline during the adulthood of patients with schizophrenia. Only performance on the Boston Naming Test significantly declined with age in our patients. Age itself rather than duration of illness was the key factor in explaining this decline. It should be noted that stability of performance did not correspond to normality of performance. Indeed, the performance

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of our patients in such tests as List Memory, Wisconsin Card Sort, and the age-adjusted Mini-Mental State Examination (Bleecker *et al*, 1988) was well into the impaired range.

The findings from our study are in agreement with those of most previous studies of progression in schizophrenia. Several studies have been unable to demonstrate significant progression of cognitive impairment with advancing age in schizophrenia as compared to control populations, although they used different measures of neuropsychological performance, some of which have an unknown sensitivity to dementia (Foulds & Dixon, 1962; Klonoff *et al*, 1970; Goldstein & Zubin, 1990). In a study of monozygotic twin pairs discordant for schizophrenia, Goldberg and colleagues found no correlations between duration of illness and intrapair differences in cognition between affected and unaffected co-twins (Goldberg *et al*, 1994). This twin paradigm is unique because the difference between endowment (in the unaffected twin) and disease-specific level of functioning (in the affected twin) is known. Our finding also is in agreement with the view of Heaton & Drexler (1987). In their review of the progression of neuropsychological deficits in schizophrenia, which summarised both cross-sectional and longitudinal studies, they concluded that there is no accelerated rate of cognitive decline in schizophrenia.

The results from this study may be placed in a broader context regarding the course of schizophrenia. Prior to clinical diagnosis, patients may have subtle deficits in information processing tasks or on neuropsychological tests, but IQ, reading level, and many other abilities are well within the normal range (Cornblatt & Erlenmeyer-Kimling, 1985; Nuechterlein, 1985; Goldberg *et al*, 1991; Pogue-Geile *et al*, 1991). At the clinical onset of the disorder, deterioration in intellect (Goldberg *et al*, 1988) and in neuropsychological function has been noted (Bilder *et al*, 1991; Hoff *et al*, 1991). As suggested by the present study, there is little further deterioration above and beyond that occurring in the normal ageing process in patients who have been ill for up to 50 years. This is not to say that some individual patients might not show deterioration due to neurological or other forms of comorbidity, or that other patients might not show improvement due to treatment. Neither should the obvious be overlooked: changes in an individual's score also might be due to simple measurement error.

This study has significant methodological limitations. As its design was cross-sectional rather than longitudinal, comparisons were made between groups, rather than within subjects. The increased variability associated with a cross-sectional study could lead to a type II statistical error. Moreover, each age cohort contained only a moderate number of patients, a necessary result of a careful screening process. However, cross-sectional studies have a major advantage over longitudinal studies because they allow comparisons over an extremely wide range of duration of illness, thereby surmounting problems of attrition. Regardless of the limitations of the cross-sectional approach, it is difficult to imagine how it would obscure our finding a progressive deterioration if it were obvious, especially in the light of the excellent matching of the cohorts in likely premorbid ability (i.e. WRAT reading). The fact that we could not show any significant differences between schizophrenic patients in their 20s as opposed to those in their 60s suggests that any decline, if present, cannot be terribly dramatic.

There are other significant issues concerning the design of this study. One might argue that those patients with a 'progressive' form of schizophrenia are more prone to substance abuse or serious head injury, which would have excluded them from this study. But inclusion of such patients would have confounded the results, making it impossible to differentiate between the effects of schizophrenia and the effects of comorbid conditions. The inclusion of patients with other known neurological diseases would also obscure the interpretation of the findings of this study. For example, impaired testing performance in a schizophrenic patient with a seizure disorder could be secondary to cumulative brain injury from untreated or inadequately treated seizures or reflect the side-effects of the anticonvulsant just as much as it might reflect the pathological course of schizophrenia (Simon, 1985; Trimble, 1987). The same reasoning holds true for other processes, including systemic illnesses such as hypertension, and insulin-dependent diabetes mellitus. While schizophrenia itself may place an individual at risk for a large number of neurological disorders, these disorders and their attendant brain dysfunction are not neurobiologically linked to schizophrenia. In other words, we believe that the care exercised in the selection of this study population is a critical factor in the interpretation of the results.

The lack of normal cohorts tested under the same conditions is also a potential deficiency in defining 'decline', although normal control data have been published on most of the tests in this study. Our approach, in which we use stepwise regression analysis to examine the relative contribution of age and duration of illness to cognitive scores, was necessitated by multicolinearity (i.e. correlations between the regressors). It is the analysis of choice

in such situations (Cohen & Cohen, 1983). Since there was no *a priori* reason why age rather than duration of illness entered in the Boston Naming analysis, and moreover, the proportion of variance explained by the age and/or duration of illness in both the Boston Naming and Mini-Mental State analyses was small ($r^2 < 0.10$) in absolute terms, we believe these results are consistent with a lack of marked progression of cognitive decline in schizophrenia. Additionally, the lack of social integration and environmental demand in a chronically institutionalised sample may account for some of the fall-off in performance on linguistic tests such as the Boston Naming. Perhaps most important of all psychometrically was the use of the WRAT reading score. It ensured that the groups were relatively equivalent in premorbid intellectual competency, thereby minimising the chance that the findings were spurious and due to *a priori* group differences.

Psychotropic medications can have an adverse impact on cognitive function as assessed by neuropsychological testing. All patients in this study were on neuroleptic therapy at the time of testing. However, some were also receiving anticholinergic therapy in varying proportions (see Table 1). Moreover, the proportion of patients on anticholinergic drugs tended to increase in the older cohorts. The adverse effects of anticholinergics on cognitive performance may explain a part of the decline seen on a few tests in the older cohorts. This further strengthens our contention that the minor changes in cognitive performance in the older cohorts reflects factors extrinsic to schizophrenia.

The notion that cognitive deficits in schizophrenia are relatively stable and not progressive has received considerable reinforcement from neuro-imaging studies. Weinberger *et al* (1979) pointed out that ventricular size did not correlate with the duration of illness over the first 30 years of illness, a finding that has been confirmed by most cross-sectional ventricular size reports (Golden *et al*, 1980; Nybäck *et al*, 1982; Nasrallah *et al*, 1983; Shelton *et al*, 1988). In a prospective longitudinal study of patients with chronic schizophrenia, Illowsky *et al* (1988) failed to show any progression in ventricular enlargement in a cohort whose computerised tomography scans were compared across an 8-year interval. This stability in ventricular size is consistent with a static lesion in schizophrenia and argues against a degenerative process. This finding has been confirmed by several other groups (Vita *et al*, 1988; Abi-Dargham *et al*, 1991; DeLisi *et al*, 1991; Losonczy *et al*, 1991; Sponheim *et al*, 1991).

Postmortem studies of brains from patients with schizophrenia show that they lack the characteristic neuropathological changes (including inclusion bodies, inflammatory cells, and/or marked neuronal loss and grey matter atrophy) often associated with progressive neurological disorders of adulthood. Although there is at least one report of excessive gliosis (another neuropathological sign of progressive neurological disease) in the brains of patients with schizophrenia, this study lacked adequate controls (Stevens, 1982). Other studies have failed to find excessive gliosis that could not be attributed to other processes (Roberts *et al*, 1986, 1987; Bruton *et al*, 1990). If schizophrenia produced a progressive cognitive decline secondary to an active neuropathological process, it should be associated with the characteristic postmortem findings of such disorders.

The absence of neuropathological findings consistent with an active degenerative process does not imply that there are no neuropathological changes in the brains of patients with schizophrenia. The most consistent structural abnormalities include ventriculomegaly and cytoarchitectural abnormalities in the mesial temporal lobe (Bogerts *et al*, 1985; Brown *et al*, 1986; Jakob & Beckmann, 1986; Shelton & Weinberger, 1986; Arnold *et al*, 1989; Jeste & Lohr, 1989; Altshuler *et al*, 1990; Suddath *et al*, 1990). However, these changes are more characteristic of a developmental lesion than of an acquired progressive disorder of adulthood (Jakob & Beckmann, 1986).

Irrespective of the obvious shortcomings of cross-sectional designs, shortcomings which preclude consideration of the findings of such a study as definitive, it might be expected that tests sensitive to dementia in a chronically ill and often chronically institutionalised sample would be sufficiently sensitive to ascertain any marked and progressive declines associated with the course of the illness. In order to increase the power of our study, our selection process was biased towards those patients who might suffer from dementia, in that we chose them from the chronic in-patient wards of a public institution for mental patients. Given the legal and financial pressures on long-term institutionalisation, patients who can function to any degree in the community are placed out of the hospital. The remainder do not respond to treatment and require too much care for placement in the community. In fact, we studied these patients specifically because it is in this population that dementia is most likely to be found. Therefore it is exceedingly unlikely that our failure to find progressive changes was due to a loss of more demented patients from the elderly cohorts. The patients in this study population, like most chronically institutionalised patients, impressed us with their inertia, lack of self-care skills, coarsened and blunted affect, and overall dilapidation. This obvious

dilapidation, however, appears to be dissociable from a progressive decline in cognitive function, implying that different biological and/or psychological systems are involved.

Tests of the semantic system, visual and verbal memory, and the orientation praxic, language, and gnostic functions included in dementia screening tests reliably reveal impairments in patients with Alzheimer's disease and most other dementing disorders as the duration of illness lengthens. In particular, patients with Alzheimer's disease decline by approximately 2 points yearly on the Mini-Mental State Examinaton and at least 10 points yearly on the Dementia Rating Scale (Salmon *et al*, 1990), so that, after 10–15 years of illness, such patients perform in the profoundly demented range. In contrast to the findings in a well established dementing disorder such as Alzheimer's disease, very few in our sample of schizophrenic patients, most of whom had been ill longer than 10 years, were functioning at the profoundly impaired level. The small cohort differences we noted on these key tests were in no way consistent with the Alzheimer's disease model of progressive dementia. While this does not mean that a patient with schizophrenia would not decline precipitously, the fact that we did not find such declines makes it considerably less likely that they are an obligate feature of schizophrenia. In addition, the relatively longer duration of illness in schizophrenia as compared with Alzheimer's disease is consistent with a considerably less dramatic, or non-existent, decline in cognition.

To summarise, there does not appear to be a progressive decline in cognitive function in chronic schizophrenia greater than would be expected from the normal effects of ageing, in spite of the multiple cognitive abnormalities associated with this disorder. Our findings are consistent both with the classification of schizophrenia as a static encephalopathy rather than a progressive dementia, and with the prescient observation of Kraepelin (1919) who over 50 years ago wrote: "As a rule, if no essential improvement intervenes in at most two or three years after the appearance of the more striking morbid phenomena, a state of weak-mindedness will be developed, which usually changes only slowly and insignificantly".

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