Stability and Course of Neuropsychological Deficits in Schizophrenia

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Background: Neuropsychological deficits in schizophrenia appear to predate clinical symptoms of the disease and become more pronounced at illness onset, but controversy exists about whether and when further neuropsychological progression may occur.

Objective: To identify and characterize any subset of patients who evidenced progressive neuropsychological impairment, we compared the longitudinal stability of neuropsychological functioning in schizophrenic outpatients and normal comparison subjects.

Methods: One hundred forty-two schizophrenic outpatients and 206 normal comparison subjects were given annually scheduled comprehensive neuropsychological evaluations during an average of 3 years (range, 6 months to 10 years). Clinically and demographically defined subgroups were compared, and test-retest norms were used to identify individual patients who showed unusual worsening over time.

Results: The schizophrenic group was neuropsychologically more impaired than the normal comparison subjects but showed comparable test-retest reliability and comparable neuropsychological stability over both short (mean, 1.6 years) and long (mean, 5 years) follow-up periods. No significant differences in neuropsychological change were found between schizophrenic subgroups defined by current age, age at onset of illness, baseline level of neuropsychological impairment, improvement or worsening of clinical symptoms, and occurrence of incident tardive dyskinesia. Norms for change also failed to show neuropsychological progression in individuals with schizophrenia.

Conclusions: Neuropsychological impairment in ambulatory persons with schizophrenia appears to remain stable, regardless of baseline characteristics and changes in clinical state. Our results may not be generalizable to the minority of institutionalized poor-outcome patients.

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There is a high prevalence of neuropsychological impairment in persons with schizophrenia, ranging from mild deficits to frank dementia.1-3 Consistent with a neurodevelopmental view, some such deficits appear to predate clinical symptoms and exacerbate with typical illness onset during late adolescence or early adulthood.6-8

There remains considerable controversy about whether there is further progression of neuropsychological deficits after the onset of the illness.9 With a few notable exceptions,10-12 cross-sectional studies generally have not found evidence of increased neuropsychological deficits in association with duration of illness or (relative to age-matched controls) in older than in younger patients with schizophrenia.13-17 Definitive answers to questions regarding possible progression of neuropsychological deficits in schizophrenia must come from longitudinal studies. The available studies, however, provide conflicting results and have a variety of methodologic limitations (eg, small or nonrepresentative samples, no controls, brief follow-ups, and/or limited neuropsychological testing).2,18-36

Both neurodevelopmental and neurodegenerative views of neuropsychological deficits in schizophrenia seemingly remain viable.10 While progression of deficit after illness onset clearly is not universal, or even typical of the disorder, a subset of persons with schizophrenia may evidence cognitive deterioration over time. The size and nature of that subgroup are unclear, but the existing studies suggest that potentially relevant issues include subject age, duration of illness, level of initial neuropsychological impairment, improvement or deteriora-
SUBJECTS AND METHODS

SUBJECTS

Subjects included 142 outpatients with schizophrenia and 206 NCs, who had completed at least 2 comprehensive neuropsychological evaluations. Each patient and NC was a participant in 1 of 3 university-based clinical research centers, and most have contributed baseline neuropsychological data to previously published reports. Subjects in both groups included the Structured Clinical Interview for the DSM-III-R or DSM-IV. Subjects were also screened by a physician using a physical examination and a structured medical history questionnaire; those with current or past medical conditions likely to affect central nervous system functioning (such as significant head injuries, seizure disorder, or acute medical conditions), as well as those meeting DSM-III-R or DSM-IV criteria for current alcohol or substance abuse or dependence, were excluded. All subjects provided written informed consent before participation in the research.

NEUropsychological EXAMINATIONS

The patients and NCs were assessed with an annually scheduled comprehensive neuropsychological test battery (in actuality, the mean test-retest interval between the first 2 of these evaluations was 16.6 months [SD, 8.6 months; range, 6-81 months]). Eighty-nine schizophrenic patients and 119 NCs completed at least 1 additional neuropsychological follow-up evaluation. The total number of evaluations ranged from 2 to 10 (mean, 3.38; SD, 1.57; median, 3.00). The interval between the first and last neuropsychological evaluations ranged from 6 to 125 months and was not significantly different for the schizophrenic patients vs NCs (mean and SD, 37.0 and 22.3 months vs 37.1 and 25.7 months, respectively; t = 0.5, P = .96).

Except where otherwise indicated, each of the neuropsychological measures was part of the expanded Halstead-Reitan battery, and details of administration and scoring were as described by Reitan and Wolfson and Heaton and colleagues. The individual measures were grouped into 7 ability areas based on the neuropsychological constructs that are putatively designed to measure. The verbal ability area included the Aphasia Screening Test, Boston Naming Test, and the Controlled Oral Word Association Test. Scores on the latter test were unavailable for a few subjects, so the Thurstone (written) Word Fluency task was substituted for 2 subjects at the baseline evaluation and 5 subjects at the first follow-up. The psychomotor ability area included the block design, object assembly, and digit symbol subtests from the Wechsler Adult Intelligence Scale–Revised (WAIS-R) and the Trail Making Test Part A (total time), Tactual Performance Test (total time), and Digit Vigilance Test (time). The abstraction and cognitive flexibility ability area included the Category Test (errors), Trail Making Test Part B (total time), and Wisconsin Card Sorting Test (perseverative responses). The attention ability area included the digit span and arithmetic subtests from the WAIS-R, the Rhythm Test, Speech Sounds Perception Test, and Digit Vigilance (errors). The learning and delayed recall ability areas included those scores from the Figure and Story Memory Tests, and the California Verbal Learning Test. The motor skills ability area included the right- and left-hand scores on Finger Tapping, Grooved Pegboard, and Hand Dynamometer.

We also had data from baseline and at least 1 retest evaluation with an even more comprehensive neuropsychological evaluation on a subsample of patients and NCs, permitting calculation of the WAIS-R Verbal, Performance, and Full-Scale IQs for 81 patients and 86 NCs, and the Halstead-Reitan battery Average Impairment Rating for 74 patients and 82 NCs.

Neuropsychological test raw scores were converted to standardized scaled scores (mean and SD, 10 and 3, respectively, in normal subjects), by means of published normative data. We then calculated the mean scaled scores and T-scores within each ability area, and a composite global scaled score and T-score.

PSYCHIATRIC AND MOTOR SYMPTOM RATINGS

Longitudinal ratings of psychiatric symptoms were also obtained for a subset (n = 116) of the schizophrenic patients, as well as a smaller subset of NCs (n = 86 to 88). Psychiatric symptom rating scales included the Brief Psychiatric Rating Scale and the Scales for the Assessment of Positive and Negative Symptoms (SAPs and SANS, respectively). Dystonic dyskinesia was assessed with the Abnormal Involuntary Movement Scale.

STATISTICAL METHODS AND ANALYSES

The test-retest reliability of neuropsychological measures and symptom rating scales was assessed in terms of

Continued on next page
McGraw and Wong’s\textsuperscript{58} intraclass correlation coefficients for degree of consistency between measurements at the baseline and 1-year follow-up evaluations. The magnitudes of the intraclass correlation coefficients for the neuropsychological and symptom rating scale scores of patients and NCs were compared by means of Fisher r-to-z transformations for intraclass correlation coefficients.\textsuperscript{58} The neuropsychological scaled scores, rather than T-scores, were used for these analyses, since the latter would underestimate the stability of neuropsychological performance by removing variance related to the stable traits of education and sex.

To examine the effects of length of follow-up on neuropsychological stability, patients and NCs were divided into diagnosis–by–length of follow-up groups, wherein “short” follow-up was defined as less than 36 months and “long” follow-up was defined as 36 months or longer. This yielded 121 NCs and 75 schizophrenic patients with short follow-up (mean, 19.5 months; SD, 6.8 months) and 85 NCs and 67 schizophrenic patients with long follow-up (mean, 59.7 months; SD, 19.6 months).

In addition to the primary subject groupings described above, we were interested in examining the possible influence of substantial differences in current age, age at onset of illness, duration of illness, and symptom changes on the stability of neuropsychological performance among the schizophrenic patients. Hence, we conducted a series of analyses in which we dichotomized the schizophrenic patients in terms of these characteristics. The definition of the symptom change groups and the resulting samples are described later. The other groupings included 22 elderly patients (age at study entry, $\geq 65$ years; mean, 69.2 years; SD, 3.3 years) vs 120 younger patients (age at study entry, $< 65$ years; mean, 43.7 years; SD, 13.7 years); 24 patients with late-onset schizophrenia (aged $\geq 45$ years at onset of prodromal symptoms; mean, 55.0 years; SD, 5.6 years) vs 118 with earlier onset (onset at age $< 45$ years; mean, 22.7 years; SD, 7.3 years); and 30 patients with a duration of illness less than 5 years (mean, 2.0 years; SD, 1.4 years) vs 105 subjects with a duration of illness of 5 years or more (mean, 23.6 years; SD, 12.5 years). We also dichotomized patients in terms of sex and initial level of neuropsychological functioning (low [global neuropsychological T-score, $\leq 39$] vs high [global neuropsychological T-score, $> 45$]) and anticholinergic use (receiving vs not receiving anticholinergic medication).

Repeated-measures analysis of variance (ANOVA) was used to examine effects of diagnosis (schizophrenic patients vs NCs) and length of follow-up (as noted above, short vs long) on changes in neuropsychological performance. These analyses were conducted on T-scores (to correct for changes attributable to the effects of normal aging during long-term follow-up) for the entire neuropsychological battery (global neuropsychological T-score) as well as for each of the specific neuropsychological ability areas. We also used repeated-measures ANOVA to examine the various pairs of schizophrenic subgroups on changes in global neuropsychological performance and the 7 ability domains.

To assess the relationship between clinical change and neuropsychological functioning, patients were categorized into 3 groups based on change in clinical symptom scores from baseline to follow-up. Patients whose clinical symptom score (either SAPS or SANS total score) fell in the lower 25% of the distribution were considered to have a “low” level of symptoms, those in the middle 50% were labeled “middle,” and those in the upper 25% of the distribution were categorized as “high.” To meet criteria for a clinically significant change in symptoms, a subject had to move at least 1 category from baseline to follow-up, and by at least 3 points. Separate analyses were conducted for the SAPS- and SANS-defined change groups.

We also examined significant decreases in global neuropsychological T-scores of individual subjects, by means of the reliable change index method with adjustments for practice effect.\textsuperscript{59,60} This approach involves constructing prediction intervals around each subject’s expected follow-up score. The predicted follow-up score is the subject’s baseline score, adjusted for practice effects among cognitively stable individuals (as determined from the mean change observed among the NCs). The boundary values of the prediction interval around the predicted follow-up score are determined by the normal variability of baseline to follow-up changes (SE of the difference) determined from the NC group. Specifically, 90% prediction intervals were built around these predicted follow-up scores by multiplying the SD of the difference among NCs by 1.64. Subjects whose observed follow-up scores were below the lower limits of the 90% prediction interval (ie, the bottom 5% of normal controls) were considered to have shown significant declines in neuropsychological functioning. These procedures were conducted twice: once to evaluate changes from baseline to first retest among all patients and NCs, and then again in terms of changes from the first to last neuropsychological assessment among subjects with long follow-ups.

Two-tailed tests were used for all analyses. To help avoid type I errors associated with multiple comparisons, significance was defined as $P < .01$. 

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TEST-RETEST RELIABILITY

The test-retest reliability coefficients (intraclass correlation coefficients) of neuropsychological and psychiatric rating scale scores for NCs and patients were highly significant within each group (Table 2). With the exception of Performance IQ (where the test-retest reliability was higher in the schizophrenic group), the magnitudes of the test-retest correlations for the patients were not significantly different from those observed among the NCs.

ADDITIONAL SCHIZOPHRENIC SUBGROUP COMPARISONS

To further examine the change in cognitive functioning over time, we compared longitudinal global neuropsychological performance changes in subgroups of schizophrenic subjects defined on the bases of demographic and clinical variables (as listed and defined above). These ANOVAs disclosed no significant group effects. As shown in Table 4, with 1 exception there also were no significant group \times time interactions, indicating that the characteristics defining the various groups were not related.
to changes in neuropsychological performance over time. The significant interaction reflected the fact that the schizophrenic subgroup with short duration of illness (mean, 2 years at baseline) had a slightly larger neuropsychological improvement than the subgroup with long duration (mean, 24 years at baseline). The smaller “improvement” (practice effect) shown by the long-duration group was the same as that of the NCs (both means, 1.3 T-score points).

Using the SAPS to categorize clinical change status resulted in 11 patients being classified as worse, 27 as better, and 78 as stable. With the use of repeated-measures ANOVAs, no significant group\times time interactions were found for the neuropsychological global score or for scores on any of the 7 ability areas (Table 4). Categorization of schizophrenic patients on the basis of SANS scores yielded 19 subjects identified as significantly worse, 80 subjects as stable, and 17 subjects as better. The results of repeated-measures ANOVAs for the neuropsychological global score were similar to those with the SAPS change groups, ie, no significant group\times time interactions.

We also compared patients with initial high vs low global neuropsychological performance (global neuropsychological T-score ≥45 vs ≤39, respectively), and those with vs without tardive dyskinesia as defined by the Schooler and Kane criteria63 and those used by Wad-
Again, the groups did not differ significantly with respect to the change in the global neuropsychological score or the 7 neuropsychological ability domain scores (Table 4).

**SUBJECTS WITH UNUSUAL DECREASES IN GLOBAL NEUROPSYCHOLOGICAL T-SCORES**

The modified Reliable Change Index method, described above, was used to identify and compare the percentages of individual NCs and schizophrenic patients who evidenced unusual neuropsychological worsening from baseline to first retest. With the use of the 90% prediction interval, 10 NCs were so identified (about 5% of the total sample); the latter proportion did not differ significantly from the 5.6% of patients with schizophrenia who evidenced unusual worsening ($\chi^2_{1,N=548}=0.10; P = .75$).

The above procedures were also used to evaluate baseline to final follow-up scores of the 85 individual NCs and 67 patients with schizophrenia with follow-up intervals of 36 months or longer (mean, 59.7 months; SD, 68 months). Again, the proportion of patients below the 90% prediction interval was not significantly different from that of the NCs (7.5% vs 4.7%, respectively; $\chi^2_{1,N=152}=0.51; P = .48$).

To our knowledge, this is the first longitudinal study to compare comprehensive neuropsychological test results of large samples of NCs and patients with schizophrenia during a multiyear follow-up period. After comparing the two groups with respect to test-retest reliabilities, we attempted to determine whether the schizophrenic patients, or even a subset of that group, evidenced progressive neuropsychological decline.

Consistent with previous reports, presence of psychosis did not appear to affect the reliability of neuropsychological test performance. Across the entire neuropsychological battery, reliability estimates were quite high, and were at least as high for the schizophrenic group as for the NCs. This was true even though clinical symptoms were relatively variable over time (Table 2), and even though the test-retest intervals were longer than those in most previous reliability studies with NCs. These stability results support the view that neuropsychological deficits in schizophrenia are stable traitlike dimensions of the disorder, rather than reflecting state-related features.

Acceptable test-retest reliability does not rule out the possibility that neuropsychological deficits may be progressive in at least some patients with schizophrenia. Our results, however, provided no evidence of a deteriorating neuropsychological course in the total schizophrenic group, or in subgroups defined on the basis of age, sex, early versus late or recent versus remote onset of illness, baseline level of neuropsychological impairment, or length of follow-up. In each analysis, the schizophrenic groups showed slight improvements that were comparable with those evidenced by the NCs, and these likely represented practice effects. Even rather extreme clinical changes did not appear to influence the subjects’ neuropsychological performance.

Longitudinal research in institutional settings has shown evidence of neuropsychological decline in some low-functioning, chronically hospitalized patients with schizophrenia. Even in those studies, however, such worsening was observed only in small subsets of the groups being followed up. In the absence of longitudinal data from a neurologically stable comparison group, it is unclear whether these observed neuropsychological changes represent true neuropsychological decline, as in a neurodegenerative disorder, or whether they represent the tail of the distribution of test-retest fluctuations in neurologically stable (albeit very low-functioning) persons. It might be argued that the types of change observed in these patients (eg, change in the rated level of dementia) are too gross to be considered “normal fluctuation” and are pathognomonic of a progressive disorder. During approximately a 4-year follow-up interval, however, Ivnik and colleagues found remarkable test-retest differences in neuropsychological performances of some elderly subjects who did not have any neuromedical disorder likely to affect cognition, eg, on neuropsychological factor scores with IQ-type scaling, test-retest differences of 20 or more points were not unusual. Therefore, the outer range of possible fluctuation in performance of neurologically stable persons cannot be assumed and should be established by means of an appropriate comparison group.

The mean global neuropsychological score for our patient group was 1.62 SDs below that of NCs (Table 1), consistent with the range of effect sizes in a recent meta-analytic review of studies comparing controls and schizophrenic patients. Although severely demented patients were not represented in our sample, our “low-functioning” subgroup (n = 45; Table 4) was very significantly impaired (ie, more than 3 SDs below NCs on the global neuropsychological T-score).

Limitations of this study include absence of chronically institutionalized patients, and therefore its results may not be generalizable to that minority of patients (but...
most contemporary schizophrenic patients are not institutionalized.\(^{66,67}\) Also, there was limited representation of elderly subjects, and subjects who evidenced substantial clinical change or incident tardive dyskinesias during follow-up (Table 4). Although relatively few of our patients were tested initially very early in the course of their illness, 2 recent studies of first-break schizophrenia showed no significant cognitive decline during the first several years of illness.\(^{35,36}\) Moreover, despite the limited power associated with some of the subgroup analyses in the current study, the data summarized in Table 4 show that these various subject characteristics were associated with clinically trivial effect sizes for changes in cognitive performance.

Considered together, the results of available longitudinal studies strongly suggest that the large majority of people with schizophrenia do not experience progressive neuropsychological decline after the initial onset of their illness. We found no evidence of such decline, even in our ambulatory patients with long follow-up, who were observed for an average of 5 years. It remains possible that a subset of patients with very poor outcome (not represented in our study) do experience progressive neuropsychological decline. Future research with this population should attempt to document such decline by ruling out nonsignificant fluctuations in performance as evidence of progressive impairment. This might be done by using neuropsychological norms for change developed with a similarly impaired but neurologically stable comparison group, and determining whether any unusual neuropsychological worsening in the schizophrenic patients remains stable or progresses further during a subsequent follow-up period. If future research should conclusively establish progressive neuropsychological decline in a subset of schizophrenic patients, questions arise as to why only a minority are so affected. Is this another example of the heterogeneous manifestations of a common disease,\(^ {71-74}\) or are other factors involved, such as treatment history\(^ {75}\) or comorbid neuromedical conditions (eg, age-related neurodegenerative changes, possibly in combination with schizophrenia-related low “cognitive reserve”?\(^ {76}\) There is a need for larger, collaborative studies using the same methods with patients in different treatment settings.

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Preliminary versions of this work were presented in part at the Mt Sinai Conference on the Role of Cognitive Dysfunc-

Table 4. Repeated-Measures Analyses of Variance of Schizophrenia Subgroups on Global Neuropsychological Functioning

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean (SD)</th>
<th>df</th>
<th>Group × Time F</th>
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<tbody>
<tr>
<td></td>
<td>Baseline Global</td>
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<tr>
<td></td>
<td>Neuropsychological</td>
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<tr>
<td></td>
<td>T-Score</td>
<td></td>
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<tr>
<td></td>
<td>Follow-up Global</td>
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<tr>
<td></td>
<td>Neuropsychological</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T-Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>41.9 (6.6)</td>
<td>1,140</td>
<td>3.28</td>
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<tr>
<td>&lt;65 (n = 120)</td>
<td>43.8 (7.1)</td>
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<tr>
<td>≥65 (n = 22)</td>
<td>42.1 (5.5)</td>
<td></td>
<td></td>
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<tr>
<td>Sex</td>
<td>42.2 (6.4)</td>
<td>1,140</td>
<td>2.17</td>
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<tr>
<td>Male (n = 99)</td>
<td>43.6 (6.5)</td>
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<tr>
<td>Female (n = 43)</td>
<td>43.4 (7.7)</td>
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<tr>
<td>Age at onset of schizophrenia, y</td>
<td>41.5 (6.5)</td>
<td>1,140</td>
<td>1.30</td>
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<tr>
<td>&lt;45 (n = 118)</td>
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<td>≥45 (n = 24)</td>
<td>44.4 (7.0)</td>
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<tr>
<td>Duration of illness, y</td>
<td>43.6 (6.5)</td>
<td>1,133</td>
<td>6.75*</td>
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<tr>
<td>&lt;5 (n = 30)</td>
<td>46.6 (7.0)</td>
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<tr>
<td>≥5 (n = 105)</td>
<td>42.7 (6.7)</td>
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<tr>
<td>Initial global neuropsychological T-score†</td>
<td>34.2 (3.4)</td>
<td>1,94</td>
<td>3.88</td>
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<tr>
<td>Low (&lt;=39) (n = 45)</td>
<td>36.7 (5.2)</td>
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<tr>
<td>High (&gt;45) (n = 51)</td>
<td>49.9 (3.6)</td>
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<tr>
<td>Change in positive symptoms</td>
<td>42.7 (6.8)</td>
<td>1,36</td>
<td>0.03</td>
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<tr>
<td>Better (n = 27)</td>
<td>44.0 (7.5)</td>
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<tr>
<td>Worse (n = 11)</td>
<td>46.6 (6.6)</td>
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<tr>
<td>Change in negative symptoms</td>
<td>41.7 (6.9)</td>
<td>1,34</td>
<td>0.29</td>
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<tr>
<td>Better (n = 17)</td>
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<td>Worse (n = 19)</td>
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<td>Schooler and Kane tardive dyskinesia criteria</td>
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<td>1.03</td>
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<td>No tardive dyskinesia (n = 41)</td>
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<tr>
<td>Incident tardive dyskinesia (n = 13)</td>
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<tr>
<td>Waddington oro facial tardive dyskinesia criteria</td>
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<td>1,31</td>
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<td>Incident tardive dyskinesia (n = 13)</td>
<td>39.1 (6.8)</td>
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</table>

\(^*\)P = .01.

†Because the single score distributions did not meet the repeated-measures analysis of variance requirements for normality and equal variances, the dependent variable in this analysis was the global score Δ.

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