Auditory Sensory Dysfunction in Schizophrenia

Imprecision or Distractibility?

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Background: Schizophrenia is associated with large effect-size deficits in auditory sensory processing, as reflected in impaired delayed-tone matching performance. The deficit may reflect either impaired sensory precision, which would be indicative of neural dysfunction within auditory sensory (temporal) regions, or of increased distractibility, which would be indicative of impaired prefrontal function. The present study evaluates susceptibility of schizophrenic subjects to same-modality distraction to determine whether patients fit a “bitemporal” or “prefrontal” model of sensory dysfunction.

Methods: Tone-matching ability was evaluated in 15 first-episode patients, 18 outpatients with chronic illness, and 21 patients in long-term residential care, relative to 32 nonpsychiatric controls of a similar age. A staircase procedure determined individual thresholds for attaining criterion level correct performance.

Results: Tone-matching thresholds in the absence of distractors were significantly elevated in patients in long-term residential care relative to all other groups (P<.001). The effect size (d) of the difference relative to controls was extremely large (SD, 1.95). Schizophrenic patients, even those with elevated tone-matching thresholds, showed no increased susceptibility to auditory distraction (P=.42). Deficits in tone-matching performance in subjects with chronic illness could not be attributed to medication status or level of symptoms.

Conclusions: These findings suggest that sensory processing dysfunction in schizophrenia is particularly severe in a subgroup of patients who can be considered poor-outcome based on their need for long-term residential treatment. Furthermore, the absence of increased auditory distractibility argues against prefrontal dysfunction as an origin for auditory sensory imprecision in schizophrenia.

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Cognitive dysfunction is a significant and enduring feature of schizophrenia and a primary predictor of poor outcome and long-term disability.1-3 Information-processing deficits are most commonly investigated in schizophrenia using complex stimuli and tasks that activate wide regions of cortex and subcortical systems.4-7 However, recent studies have demonstrated that schizophrenic subjects are significantly impaired even in routine processing of simple stimuli. Such processing may occur preattentively and require involvement only of limited areas of cortex. Thus, for example, chronic schizophrenic subjects show significant impairment in the generation of mismatch negativity (MMN), an event-related potential component that is generated within primary auditory cortex.8 Relatively, patients are significantly impaired in the ability to perform the simple cognitive task of matching 2 similar tones separated by a brief delay.9-11 Similar deficits are present in other sensory modalities, indicating widespread dysfunction of sensory, along with cognitive, processing in schizophrenia.

See also pages 1131 and 1139

Critical structures regulating tone-matching ability reside within both auditory sensory and prefrontal cortical regions. Lesions to both these areas may disrupt tone-matching performance20-28 and lead to impaired MMN generation.29,30 However, the contribution of these structures to tone-matching performance differs considerably. Monkeys with bilateral lesions of superior temporal plane involving auditory cortex show increased discrimination thresholds (ie, require greater pitch difference between tones to perform an
SUBJECTS AND METHODS

SUBJECTS

This study included 54 individuals with schizophrenia or schizoaffective disorder diagnosed according to DSM-IV criteria and 32 nonpsychiatric comparison subjects of similar age and sex (Table 1). All subjects provided voluntary informed consent. All patients were receiving antipsychotic medications (typical, atypical, or combination) at the time of testing (Table 1). One quarter of patients were also receiving anticholinergics. Diagnoses were established by a board-certified attending research psychiatrist (D.C.J.) or a licensed research psychologist (E.F.R. and R.G.) using a semistructured clinical and/or Structured Clinical Interview for Axis I DSM-IV Disorders, medical record review, and discussion with mental health professionals familiar with the case. Subjects with a DSM-IV Axis I diagnosis other than schizophrenia or schizoaffective disorder, including psychotic mood disorder, alcoholism, or other substance abuse during the past year, were excluded from the study, as were patients with clinically apparent neurological abnormalities. Also excluded were any individuals with significant musical training or ability, as well as any controls who were receiving any psychiatric medications or who had a history of significant Axis I diagnosis. All subjects were comparably compensated at the completion of testing.

The patients were recruited from 3 sites (Table 1). First-episode (FE) patients (n=15) were recruited from the Hillside Hospital–Long Island Jewish study of first-episode schizophrenia. This group included 9 patients who were considered stabilized (namely, without active psychotic symptoms), and who were either working or in school, as well as 6 patients who were persistently symptomatic and in day treatment. Outpatients with chronic illness (n=18) were recruited from the Day Treatment Center of the Rockland County Robert Jeager Health facility, Pomona, NY. These patients lived either at home or in community residences, but were primarily responsible for their own daily living needs. Only 1 patient within this group had been hospitalized within a state hospital within the preceding 5 years (Table 1). The last patient group (n=21) consisted of 13 individuals residing in a residential aftercare facility located on the premises of Rockland Psychiatric Center, along with 8 inpatients at the Bronx Psychiatric Center, a New York State long-term care facility. Eighteen of the 21 patients had been hospitalized within a state institution during the preceding 5 years (mean time in hospital, 872 days). All patients were receiving active treatment at the time of testing (Table 1).

Comparison subjects included 32 individuals who were associated personnel of the institutions from which the patient samples were drawn. Controls were divided by age into 2 groups. Young comparison subjects (n=18) were 34 years or younger, corresponding to the age range of the FE patient group. Old comparison subjects (n=14) were older than 34 years, and were comparable with the residential care subjects in age. Intelligence quotient (IQ) was assessed for all subjects by the Ammons and Ammons Quick Test.

STIMULI

Tones were derived from 3 reference base frequencies (500, 1000, and 2000 Hz). Comparison tones were created that differed by a specified percentage change in frequency (Δf). Levels of Δf used for testing were 1%, 2%, 2.5%, 3%, 5%, 7.5%, 10%, 15%, 20%, 30%, 40%, 50%, 75%, and 100%. All tones were 100 milliseconds in duration and were presented at a nominal intensity level of 75 dB. Blocks of 24 tone pairs were presented for each level of Δf. Within each block, half of the tone pairs contained identical tones, and half contained pairs of tones that differed to a fixed degree. In half of the ‘different’ trials, the lower-pitched tone was presented first; in half, the higher-pitched tone.

In both no-distractor and distractor conditions, the interval between reference and test tones was 2 seconds. In the no-distractor condition, the interval was silent. In the distractor condition, a composite 1000-millisecond distractor stimulus was presented starting 500 milliseconds after the reference tone and terminating 500 milliseconds before the test tone. The distractor stimulus consisted of a

auditory discrimination) even when only simple tone pairs are presented. In contrast, monkeys with prefrontal lesions show elevated discrimination thresholds only when distractor stimuli are interposed into the tone sequence. A similar dissociation is seen after bilateral temporal vs prefrontal cortical damage in humans. Thus, the relative contribution to sensory vs prefrontal cortex to tone-matching deficits can be assessed by analyzing tone-matching dysfunction in schizophrenia in the absence vs presence of same-modality distractor stimuli.

This study evaluates the hypothesis that tone-matching deficits in schizophrenia are caused by or reflect sensory, rather than prefrontal level dysfunction, and reflect decreased precision of tonal representations within auditory sensory regions. Tone-matching performance was assessed in the absence and presence of same-modality distractors. In addition, for this study, patients were recruited from first-episode, outpatient, and state-hospital inpatient and/or residential care settings to also evaluate between-measure relationships across a broad range of subject functionality.

RESULTS

TONE-MATCHING PERFORMANCE UNDER BASELINE (NO-DISTRACTOR) CONDITIONS

Tone-matching in the absence of distractor stimuli (Figure, open bars) varied significantly across groups (F(2, 81)=11.6, \(P<.001\)) with residential care patients showing substantially worse performance than subjects in other groups (least significant difference, \(P<.001\)). Patients in long-term residential care needed a 20% difference in pitch between reference and test tones to detect a between-tone pitch difference, whereas other groups required only a 3% to 5% difference. The effect size (\(d\)) of the difference between subjects in long-term residential care and
controls was extremely large (SD, 1.95). Only 6% (2 of 32) of controls needed more than a 10% difference in tones to obtain criterion level performance, as compared with 71% (15 of 21) of patients in long-term residential care ($\chi^2 = 26.6$, $P < .001$).

First-episode and patients with chronic illness did not show significant threshold elevations, and effect sizes relative to controls were small to moderate (0.38 and 0.53, respectively). However, 33% of FE patients (5 of 15) required more than a 10% difference in tones to obtain criterion level performance ($\chi^2 = 3.8$, $P = .02$ vs control), indicating a greater number of outliers in this group.

Tone-matching performance was evaluated at individually determined $\Delta f$ threshold at both the beginning and end of the test sessions (Table 2). Only patients in long-term residential care showed a significant change in performance from test to retest (paired $t = 3.0$, $P = .007$), indicating that initial testing may, in fact, have underestimated their degree of impairment on this measure.

**ACROSS-GROUP SUSCEPTIBILITY TO DISTRACTION**

Susceptibility to distraction was assessed first by evaluating the degree to which the introduction of distractors degraded tone-matching performance assessed at no-distractor threshold (Table 2), and, second, by evaluating the degree to which between-tone pitch separation had to be increased for subjects to regain threshold (Figure). Similar results were obtained from the 2 analyses. All groups showed a significant degradation in performance with the introduction of distractors, indicating effectiveness of the distraction manipulation ($F_{1, 80} = 176.3$, $P < .0001$ across groups). For all groups, the correct performance rate in the presence of distractors was approximately 20 percentage points lower than in...
the absence of distractors (Table 2). Schizophrenia subjects showed no more degradation in performance than did controls with the introduction of distractor stimuli (Table 2) \( (F_{4,83} = 0.98, P = .42) \). Power for rejecting a between-group difference was greater than 0.75. All groups continued to perform significantly above chance (50% correct) even in the distractor condition.

Once distractors were introduced, more than 75% of subjects required a greater level of \( \Delta f \) to attain threshold level performance than they had under baseline conditions. This included 8 subjects in long-term residential care who were unable to regain threshold even at the highest levels of \( \Delta f \) tested and were therefore considered to have increased thresholds. Patients who were unable to regain threshold in the presence of distractors had higher baseline thresholds than those who were able to regain threshold (mean \( \Delta f = 43\% \) vs 22\%). This finding may indicate that beyond a certain level, increasing between-tone pitch separation does not increase discriminability, as has previously been observed in the case of MMN.

The percentage of subjects whose thresholds increased with distraction did not differ across groups \( (\chi^2 = 4.8, P = .31) \). The degree to which \( \Delta f \) levels needed to be increased in subjects for whom distractor thresholds could be obtained was also similar across groups (Figure, difference between open and solid bars). Tone-matching thresholds in the presence of distractors were significantly greater for inpatient subjects than for controls or other patient groups \( (F_{3,73} = 8.8, P < .001) \). However, this difference was accounted for by the elevated tone-matching thresholds in this group obtained in the absence of distraction. No significant difference was observed between groups after covariation for no-distractor thresholds \( (F_{3,71} = 1.0, P = .41) \).

**CORRELATIONAL ANALYSES**

Patient groups differed significantly in terms of Clinical Global Impression scores and duration of illness (Table
1). However, when these factors were entered as covariates into an analysis of covariance of tone-matching threshold vs patient group, the between-group differences in tone-matching performance remained significant ($F_{1, 39} = 5.44, P = .004$). Furthermore, in this analysis, neither Clinical Global Impression score nor duration of illness was independently predictive of impaired tone-matching performance. When age, Clinical Global Impression score, Positive and Negative Syndrome Scale symptom ratings, hospitalization length, and medication status were entered into a logistic regression equation that reflects dysfunction at the level of sensory cortex.

MEDICATION EFFECTS

Correlational analyses were also performed to evaluate potential effects of medication. Antipsychotic dose varied significantly across groups (Table 1). However, there was no significant correlation between dose and performance either within or across groups ($F_{1, 31} = 1.9, P = .20$). Moreover, between-group differences in performance remained significant after covariation for antipsychotic dose ($F_{1, 31} = 5.2, P = .01$). Patients receiving anticholinergic medications performed similarly to those using typical agents ($F_{1, 31} = 0.45, P = .50$).

Patients receiving anticholinergic medications performed significantly worse than those not receiving anticholinergics ($F_{1, 39} = 5.44, P = .02$). However, similar percentages of subjects were receiving anticholinergic medications in all patient groups and no significant group x anticholinergic treatment interaction was observed ($F_{1, 39} = 1.42, P = .30$). Neither antidepressant medications nor benzodiazepines were significantly associated with performance.

The present study investigated the degree to which auditory sensory deficits, as manifest by impaired delayed tone-matching performance, correspond to a sensory-level vs prefrontal pattern of dysfunction. There are 2 major findings from the present study. First, this study confirms previous observations of elevated tone-matching thresholds in chronic schizophrenic inpatients relative to controls. As in prior studies of tone matching, the effect size of the deficit is large, and at least comparable in magnitude to deficits observed in more complex tasks. Second, this study demonstrates that despite increases in tone-matching threshold, schizophrenic subjects are no more sensitive to the effects of same modality distractors than are controls. This latter finding contrasts with the pattern of deficit observed in patients with prefrontal damage, and strongly supports the concept that tone-matching deficits in schizophrenia are caused by or reflect dysfunction at the level of sensory cortex.

A second goal of this study was to evaluate the relationship between deficits in tone-matching performance in schizophrenia and clinical and demographic characteristics. We have previously observed deficits in tone-matching performance in several separate cohorts of chronic schizophrenic subjects recruited predominately from a state-hospital inpatient setting. In these previous studies, effect sizes were large, and more than 80% of subjects could be correctly classified based on tone-matching performance alone. In contrast, a recent study in which patients were drawn primarily from an outpatient setting reported significant deficits in tone matching, but the percentage of patients with deficits, 34% (13 of 38), was relatively smaller than we had previously observed. Results of the present study clarify the apparent discrepancy between prior studies, and demonstrate that patients drawn from an inpatient and/or residential care setting are significantly more impaired in performance than those drawn from outpatient settings. The validity

**Table 2. Baseline and Distractor-Condition Performance for All Groups**

<table>
<thead>
<tr>
<th>Performance</th>
<th>Controls</th>
<th>Controls</th>
<th>First-Episode</th>
<th>Long-term</th>
<th>Long-term</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>34 Years Old</td>
<td>&gt; 34 Years Old</td>
<td>First-Episode</td>
<td>Long-term</td>
<td>Long-term</td>
<td>Residual Care</td>
<td>F (df)</td>
</tr>
<tr>
<td>Mean baseline no-distractor threshold, %</td>
<td>3.2</td>
<td>3.5</td>
<td>5.4</td>
<td>5.4</td>
<td>19.1</td>
<td>11.6 (4, 81)</td>
</tr>
<tr>
<td>Percentage correct, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-distractor condition, initial (repeat) testing</td>
<td>92.8 ± 5.1</td>
<td>92.5 ± 5.0</td>
<td>93.2 ± 5.3</td>
<td>93.0 ± 5.9</td>
<td>91.1 ± 4.4</td>
<td>0.48 (4, 81)</td>
</tr>
<tr>
<td>Distractor condition</td>
<td>73.4 ± 10.5</td>
<td>72.3 ± 14.0</td>
<td>78.3 ± 11.9</td>
<td>72.5 ± 13.2</td>
<td>67.3 ± 13.0</td>
<td>1.60 (4, 80)</td>
</tr>
<tr>
<td>Change: no-distractor - distractor</td>
<td>19.4 ± 10.0</td>
<td>20.2 ± 15.8</td>
<td>14.9 ± 13.4</td>
<td>20.6 ± 13.6</td>
<td>23.8 ± 13.2</td>
<td>0.98 (4, 80)</td>
</tr>
</tbody>
</table>

*ANOVA indicates analysis of variance; Δt, change in tone frequency, reference vs test tone.
†P < .001 vs control.
‡P < .01, for significant difference between initial vs repeat performance.
§P < .001 vs no-distractor across groups.
||Power to exclude significant between-group difference > .70.
of subdividing patients according to recruitment site is supported by our observation that only 1 of the 18 subjects in the outpatient group had required long-term (state hospital) hospitalization during the 5 years before recruitment, as compared with 18 of the 21 subjects in long-term residential care.

It is unclear the degree to which sensory processing dysfunction, as reflected in impaired tone-matching performance (but presumably affecting other aspects of sensory processing as well), contributes to the need for persistent hospitalization vs the degree to which it indexes a form of schizophrenia associated with poorer functional outcome. In the present study, patients in long-term residential care showed significantly greater levels of negative symptoms than the outpatients with chronic illness but did not differ significantly in either global symptom ratings or in severity of positive symptoms. Tone-matching deficits, therefore, cannot be attributed simply to greater “severity” of illness, although such deficits may index a form of schizophrenia particularly associated with negative symptoms. The observation that roughly 33% of first-episode subjects showed elevated tone-matching thresholds may indicate etiological heterogeneity at first episode on the basis of either neurochemical or neuroanatomical differentiation. Whether tone-matching deficits at illness onset are predictive of poor outcome, however, requires longitudinal follow-up.

Even patients with significant elevation of tone-matching thresholds were no more affected by distractors than controls. The fact that resistance to distraction was preserved, even in subjects with elevated tone-matching thresholds, argues against this finding as being a manifestation of impaired attention, motivation, or cooperation. To the extent that the ability to maintain a tone representation in the presence of distraction represents a prefrontal function, patients with chronic illness were no more impaired in this aspect of prefrontal function than were other patient groups or controls. This finding does not imply that all aspects of prefrontal functioning are normal in schizophrenia. Rather, it indicates, first, that any study of higher-order processing in schizophrenia must be corrected for potential sensory level disturbance, and, second, that some elements of prefrontal function are preserved.

The present data suggest that information-processing deficits in schizophrenia may depend more on the types of processes that are involved than on the specific regions of cortex that are engaged. In support, it has recently been demonstrated that schizophrenialike deficits in both MMN generation (a sensory level process) and AX-type Continuous Performance Test performance (a prefrontal-type task) are induced by administration of the N-methyl-D-aspartate receptor antagonist ketamine. In both cases, the overall level of performance was diminished. However, rates of decay in performance as a function of interstimulus interval in the AX-type Continuous Performance Test were unaffected, as has previously been observed in schizophrenia. Thus, patients may have increased difficulty “constructing a representation of an object,” but it is a sensory or cognitive construct, but be relatively unimpaired in retaining it if interfering stimuli are presented.

The present study is limited by the fact that all subjects were receiving medication. However, the mean dose of medication was highly similar for outpatients with chronic illness and long-term residential care subjects. Nevertheless, the 2 groups differed significantly in tone-matching threshold. Thus, the sensory processing deficits in the residential care group cannot be attributed to antipsychotic effect. Across groups, there was a significant deleterious effect of anticholinergic medication on performance. This finding is consistent with considerable research demonstrating anticholinergic-induced impairments in cognitive performance. However, the percentage of patients receiving anticholinergic medication was not significantly different across patient groups, indicating that anticholinergic effects were not responsible for the between-group differences in performance.

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