Psychological, Neuropsychological, and Electroecortical Effects of Mixed Mold Exposure

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ABSTRACT. The authors assessed the psychological, neuropsychological, and electroecortical effects of human exposure to mixed colonies of toxigenic molds. Patients (N = 182) with confirmed mold-exposure history completed clinical interviews, a symptom checklist (SCL-90-R), limited neuropsychological testing, quantitative electroencephalogram (QEEG) with neurometric analysis, and measures of mold exposure. Patients reported high levels of physical, cognitive, and emotional symptoms. Ratings on the SCL-90-R were "moderate" to "severe," with a factor reflecting situational depression accounting for most of the variance. Most of the patients were found to suffer from acute stress, adjustment disorder, or post-traumatic stress. Differential diagnosis confirmed an etiology of a combination of external stressors, along with organic metabolically based dysregulation of emotions and decreased cognitive functioning as a result of toxic or metabolic encephalopathy. Measures of toxic mold exposure predicted QEEG measures and neuropsychological test performance. QEEG results included narrowed frequency bands and increased power in the alpha and theta bands in the frontal areas of the cortex. These findings indicated a hypoactivation of the frontal cortex, possibly due to brainstem involvement and insufficient excitatory input from the reticular activating system. Neuropsychological testing revealed impairments similar to mild traumatic brain injury. In comparison with premorbid estimates of intelligence, findings of impaired functioning on multiple cognitive tasks predominated. A dose-response relationship between measures of mold exposure and abnormal neuropsychological test results and QEEG measures suggested that toxic mold causes significant problems in exposed individuals. Study limitations included lack of a comparison group, patient selection bias, and incomplete data sets that did not allow for comparisons among variables.

<Key words: dose-response relationship, neuropsychological testing, Symptom Checklist-90-R, quantitative electroencephalograph, toxic encephalopathy, toxic mold>

NEUROTOXICITY can cause irreversible nervous system damage related to cell death or permanent alterations of cell structure and receptor sensitivity. Clinical signs are classified as organic mental impairments, seizures, movement disorders, involvement of cranial nerves or spinal peripheral nerves, and neuromuscular dysfunction. Neurotoxic exposure and injury are assessed by careful neurological and neuropsychological evaluation, complemented with functional imaging of the brain. Occupants of mold-infested structures develop multiorgan symptoms that involve the upper and lower respiratory systems, central and peripheral nervous systems, skin, gastrointestinal tract, connective tissue, immune system, and musculoskeletal system. Complaints of neurocognitive dysfunction are prevalent among the symptoms reported. A large body of literature exists on the effects of various neurotoxins on neuropsychological functioning, including cognitive...
impairment.23 However, only 4 studies have reported measurements of neurobehavioral changes related to mold and mycotoxin exposure.18,20,22 The changes described include impairments in balance, reaction time, cognition, verbal learning, recall, visual spatial learning, memory, attention/concentration, and set shifting.

Only a few complementary neuroimaging studies have been published in regard to assessment of the effects of mixed mold exposure on the central nervous system. Adolescents with suspected acoustic mycotic neuroma resulting from environmental exposure to toxic molds had abnormal brainstem evoked potentials.7 In another study, abnormal electroencephalogram (EEG) examinations in 7 of 10 patients exposed to toxic mold were reported. All 10 patients had frontal-temporal theta wave activity, which indicated diffuse changes characteristic of metabolic encephalopathy. Abnormal brainstem auditory evoked potentials were demonstrated in 9 of these patients, and 4 of the 10 patients showed clear abnormalities.3

All of the patients in the current study reported wide-ranging symptoms, including headache, dizziness, visual changes, cognitive impairment, and emotional dysregulation. Their illness has been defined as “mixed mold mycotoxicosis.”19

It is likely that studies of mold-induced neurotoxicity will yield findings similar to other studies of neurotoxicity from other causes. Single photon emission computed tomography (SPECT) has been used to complement and define the effects of toxic exposure on the central nervous system. A review of the literature on the use of SPECT scans following neurotoxic exposure confirmed that abnormalities can exist from months to years after exposure has ceased, and can involve asymmetrical abnormalities with hypoperfusion in the frontal, parietal, and temporal lobes.24 Moreover, in 33 workers with encephalopathy following toxic exposure, 94% had abnormal SPECT scans. The most frequent areas of abnormality were the frontal lobes (67.7%), frontal lobes (61.3%), basal ganglia (45.2%), thalamus (29.0%), parietal lobes (12.9%), and motor strip (9.7%).25

In recognition of the complexity of health problems associated with mixed mold exposure, a multicenter investigation of patients with chronic health complaints from mold exposure was undertaken. We used generally accepted, standardized, detailed health and environmental history questionnaires, environmental monitoring data, physical examination, accepted pulmonary function testing protocols, routine clinical chemistry, standardized measures of specific immune markers (T, B, and natural killer [NK] cells), measures of antibodies to molds, neuropsychological testing, and 19-channel quantitative EEG (QEEG). The results of this project are being reported in a series of papers. The study presented herein was conducted to assess the psychological, neuropsychological, and electrocortical effects of mixed toxic mold exposure.

Materials and Method

Patients. Adult patients (N = 182) with a history of exposure to mixed colonies of molds and their associated mycotoxins (confirmed with environmental and serologic testing) as a result of structural water intrusion in residential, workplace, or school-based settings,19 were included in this multicenter study of data gathered from chart review. All patients had been referred for evaluation of health problems related to toxic mold exposure. Because of the prominence of neurological symptoms and complaints of cognitive dissonance, patient assessments included the following neuropsychological and neurophysiological evaluations: a structured psychometric symptom checklist, neuropsychological testing, and QEEGs. The patients (age 42.7 ± 16 yr [mean ± standard deviation]) were evaluated from September 1999 through June 2003. The group comprised 126 females (age 39.3 ± 18.1 yr) and 36 males (age 36.6 ± 21.1 yr). All of the patients were evaluated for this study. Test results were compared against a national normative database in all cases. Inasmuch as our study was based on data from chart reviews, the numbers of subjects for each measure varied slightly.

Measures of psychological distress. Each patient was evaluated with a standard clinical interview and a psychometric self-report symptom inventory—the Symptom Checklist 90-R (SCL-90-R).26 Patients rated each item on a 5-point scale of distress, ranging from not at all distressed (0) to extremely distressed (5). Their ratings were computer-scored and produced normalized t scores for 9 symptom dimensions (i.e., Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism) and 3 global indices (i.e., Global Severity Index, Positive Symptom Distress Index, and Positive Symptom Total). For comparison, we used an adult nonpsychiatric patient normative database because it best represented the individuals examined in this study.

Neuropsychological testing. We selected neuropsychological tests on the basis of specific patient complaints, clinical efficiency, and time constraints. All tests chosen had appropriate and comparable norms for adults and children. To obtain estimates of premorbid and general intellectual functioning for all patients, we administered the Vocabulary subtest from the Wechsler Adult Intelligence Scale, 3rd ed. (WAIS-III) and/or from the Wechsler Abbreviated Scale of Intelligence (WASI).27 Three subtests from the WAIS-III were administered. The Digit Span subtest measures attention and working
memory capacity. The Digit Symbol Coding subtest measures visual motor learning and psychomotor speed. The Symbol Search subtest is an indicator of visual scanning and concentration.

Two subtests from the Delis-Kaplan Executive Function System (D-KEFS) were selected to measure executive or higher-level cognitive functions.28 The D-KEFS Color-Word Test produces baseline measures of color naming and word reading to compare with executive measures of inhibition and inhibition switching. The D-KEFS Trail Making Test provides baseline measures of visual scanning, number sequencing, letter sequencing, and motor speed, as well as an executive measure of number-letter switching.

The Integrated Visual and Auditory Continuous Performance Test (IVA-CPT) is a computerized test designed to evaluate auditory and visual attention over time.29 The IVA-CPT produces global composite scores consisting of a Response Control Quotient (a positive way to describe the problem of response inhibition) and an Attention Quotient (a positive way to describe problems of inattention, loss of focus, and slow processing speed). Resulting measures are normed with a mean of 100 and a standard deviation of 15.

**QEEG.** Brain electrical activity was recorded from 19 cortical positions in accordance with the International 10/20 electrode-placement system, using a Lexicor Neurosearch Digital EEG acquisition system (Lexicor Research Center [Boulder, Colorado]). Electrodes were positioned on the scalp using appropriately sized electrolytes. We used impedance measurements for each cortical site to ensure accurate data collection. The raw data were edited for artifacts and then subjected to quantitative and neurometric analyses of amplitude, power, and mean frequency, using the NxLink database.30-32 (The NxLink database has received a 510(k) clearance from the FDA [July 1998, #K974748], indicating that construction of the database was scrutinized for good manufacturing practices, and signifying the legitimacy of marketing claims made concerning the database.)

The NxLink database uses the following grouped band frequencies: delta (1.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), and beta (12.5-25.0 Hz). Absolute power magnitude is the amount of electrical activity at each frequency band. Relative power is a proportion of the total absolute power across the different frequency bands. Measures of power reflect different levels of cortical electrical activity and offer insight into cortical regional differences in activation, functional differentiation and integration, and corticothalamic regulation. Decreases in mean frequency are commonly referred to as "slowing," indicating that the average speed of oscillation is decreased relative to the population normal values for that frequency band. The reverse is true of higher-than-expected average frequency, which would be considered "accelerated."

For each QEEG variable, the 5 cortical sites or positions with the most deviant scores were chosen to create a distinct QEEG summary variable. The effects of toxic mold exposure on cortical functioning were related primarily to prefrontal and frontal dysfunctions, with some involvement of other cortical regions. We used these summary variables as predictor variables in forward stepwise regression analyses to determine the amount of variance accounted for by these symptom sets for each neuropsychological testing finding, SCL-90-R factor, and exposure measure.

Data preparation included examination of medication effects. Anxiolytic and narcotic medications were found to have significant effects on some QEEG variables; therefore, our analysis and interpretation excluded such cases.

**Measures of exposure and dose-response relationship.** Our analyses also took into account the degree of exposure to toxic molds for each individual in the sample. For each patient, we used the following predictor variables: average hours per day present in the building, days of exposure, maximum exposure (calculated as: hr/day x days of exposure), average number of colony forming units (CFUs) per m^2 from all available air samples in a given building, average CFUs x maximum exposure, and whether *Stachybotrys* was present (yes = 1, no = 0). Scores for each of these measures were then used as predictor variables in a forward stepwise regression analysis to determine the amount of variance accounted for by each of these measures of exposure on the SCL-90-R factors, the neuropsychological test measures, and the QEEG results.

**Statistical analysis.** Repeated measures analyses of variance (ANOVA's) were used to examine the relationships between the QEEG measures, neuropsychological testing results, SCL-90-R factors, and measures of exposure.31

**Results**

**Psychological disturbance (SCL-90-R).** The descriptive statistics summarizing the group means for 106 of the toxic-mold-exposed population revealed that most of the patients reported a wide range of somatic, affective, and cognitive symptoms, as well as a very high level of general distress. Figure 1 shows that all SCL-90-R scores were significantly elevated. The Global Severity Index had a mean average t score of 67—and almost 2 standard deviations above the norm. The 4 highest scores on subtests occurred on the Obsessive-Compulsive, Somatization, Depression, and Anxiety subscales.

Examination of the items that made up each of the SCL-90-R scaled scores revealed considerable overlap in symptoms across the categories of cognitive, affective, and somatic symptoms. A factor analysis of all items defined 6 factors. After examination of the indi-
Fig. 1. Average T scores on the Symptom Checklist 90-R (SCL-90-R), demonstrating the significantly high level of psychological distress experienced by the study group as a whole. Notes: SOM = Somatic, O-C = Obsessive-Compulsive, I-S = Interpersonal Sensitivity, DEP = Depression, ANX = Anxiety, HOS = Hostility, PHOB = Phobia, PAR = Paranoia, PSY = Psychoticism, GSI = Global Symptom Index, PSDI = Positive Symptom Distress Index, and PST = Positive Symptom Total.

At the time of our analysis, item-by-item data were available for only 52 of the 106 patients who had taken the SCL-90-R. We used scores for each of the 6 factors as predictor variables in forward stepwise regression analyses to determine the amount of variance that these symptom sets accounted for in each neuropsychological testing finding and QEEG finding.

Neuropsychological testing vs. normative data. Patients’ levels of completed education (if they were born after World War II) and a measure of vocabulary (from the WAIS-III subtest scaled score) are widely accepted methods for estimating premorbid levels of intellectual functioning. The average level of education for the 109 adults in this sample was 14.57 yr, indicating a slightly higher than average level of premorbid functioning. This finding agreed with the average WAIS-III
vocabulary scores for this sample, which was almost 1 standard deviation above normal.

We found statistically significant differences between the high average range scaled score for the group's estimate of premorbid intelligence (the Vocabulary subtest from the WAIS-III) and the group's scaled scores for performance on the D-KEFS Color-Word subtests of Color Naming, Word Reading, Inhibition, Inhibition-Switching (p < 0.0000), and the group's scaled scores on the D-KEFS Trail Making Test subtests of Visual Scanning, Number Sequencing, Number-Letter Switching, and Motor Speed (p < 0.0005) (Fig. 2). Statistically significant differences (p < 0.05) were also found between the scaled score for the Vocabulary subtest from the WAIS-III and the group's scaled scores for performance on other WAIS-III subtest measures of "fluid" intelligence (e.g., attention, working memory, visual motor learning, speed, and visual scanning).

The IVA-CPT, which tests response inhibition and the ability to maintain attention over time, has a normative population mean of 100 and a standard deviation of 15. Figure 3 summarizes the results of the normative scores on the IVA-CPT. All scores were below expectations, given the group's estimated level of intelligence on the WAIS-III Vocabulary subtest and the average level of education. Attention scores were especially depressed. We also found dissociation between response control and attention across both auditory and visual domains of the IVA-CPT. Attentional functioning in this group was significantly impaired (p < 0.0126) compared with response inhibition capacities.

**QEEG measures vs. normative data.** Without regard to any categorical predictors, the group as a whole exhibited a definite pattern of slowing in the faster beta frequency (F(18, 2,574) = 2.8707; p = 0.00005) and acceleration of the slower delta (F(18, 2,592) = 2.9554, p = 0.00003) and theta (F(18, 2,592) = 3.1680; p = 0.00001) frequencies. The QEEG summary variables for these measures identified frontal cortical positions as the most significantly deviant (mean frequency delta: Fp1 Fp2 F3 F4 F8; mean frequency theta: Fp1 Fp2 F3 F4 C4; mean frequency beta: Fp1 Fp2 F7 F8 T3).

There were significant increases in absolute (F(18, 2,538) = 12.007; p = 0.0000) and relative (F(18, 2,520) = 9.5775; p = 0.0000) power alpha, and in absolute (F(18, 2,538) = 6.5807; p = 0.0000) and relative (F(18, 2,520) = 3.4143; p = 0.00000) power theta. Again, the QEEG summary variables identified the frontal cortical

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**Neuropsychological test**

Fig. 2. Results of neuropsychological testing, compared with normative data. Premorbid intelligence, estimated with the Wechsler Adult Intelligence Scale, 3rd ed. (WAIS III) Vocabulary subtest, was compared with results for WAIS III subtests (Digit Span, Digit Symbol Coding, and Symbol Search); Delis-Kaplan Executive Function System (D-KEFS) Trail Making subtests (Visual Scanning, Number Sequencing, Number-Letter Switching, and Motor Speed); and D-KEFS Color Word subtests (Word Reading, Inhibition, and Inhibition Switching).
areas as being the most deviant (absolute alpha: Fp1 Fp2 F4 F8 Fz; relative alpha: Fp1 Fp2 F4 F7 Fz; absolute theta: F3 F4 F7 F8 Fz; relative theta = Fp1 Fp2 F7 F8 F4).

The absolute power Z scores in the delta frequency band across the scalp were significantly decreased relative to the normative values ($F(18, 2,538) = 2.4576; \ p = 0.00058$). Specifically, the decreases were most notable in the prefrontal, parietal, and occipital areas (i.e., Fp1, Fp2, Cz, P3, P4, Pz, O1, and O2).

**Exposure measures vs. SCL-90-R, QEEG, and cognitive measures.** Measures of exposure were highly predictive of neuropsychological test performance, moderately predictive of QEEG measures, and only slightly predictive of measures of subjective stress on the SCL-90-R.

There were predictive, nonsignificant trends for performance on the D-KEFS Trail Making Test and the Color-Naming subtest (in which maximum exposure, average CFUs, and whether *Stachybotrys* was present in the environment yielded an adjusted multiple $R^2 = .240, p < 0.070$); the D-KEFS Word Reading subtest (in which maximum exposure and whether *Stachybotrys* was present in the environment yielded an adjusted multiple $R^2 = .220, p < 0.053$); and the D-KEFS Color-Word Inhibition (classic Stroop) subtest (in which maximum exposure, average CFUs, and whether *Stachybotrys* was present in the environment yielded an adjusted multiple $R^2 = .235, p < 0.073$).

Table 1 shows the significant predictive power ($p < 0.05$) observed for the D-KEFS Trail Making subtests of visual scanning, letter sequencing, number-letter sequencing, and motor speed; the D-KEFS Color-Word Inhibition/ Switching subtest; the WAIS-III Digit Symbol Coding and Symbol Search subtests; and the IVA-CPT full-scale attention quotient and the visual and auditory attention quotients.

It should be kept in mind in reviewing these findings that the sample sizes are smaller than those for other analyses reported herein, which can affect the degrees of freedom and the variability accounted for by these scores. Although some of the values reported in Table 1 are quite high (e.g., WAIS-III Symbol Search subtest adjusted multiple $R^2 = .787$), it is still safe to conclude that measures of exposure account for a significant amount of the variance in neuropsychological test performance on the basis of these findings.

Table 2 shows that 6 of the 8 QEEG summary variables were related significantly to measures of mold exposure. Four of the 6 variables were measures of power in the theta and alpha frequencies. Significant predictive power was found for estimates of degree of exposure and for the QEEG variables of mean frequency delta, relative power theta, relative power alpha, absolute power delta, absolute power theta, and absolute power alpha.

Exposure measures predicted scores on only 2 of the SCL-90-R factors. The only statistically significant relationship was found between CFU x maximum exposure and a combination of SCL-90-R Factor 3 (Cognitive Distortion) and Factor 6 (Cognitive Complaints), which together yielded an adjusted multiple $R^2$ of 0.291, $p <$
Table 1.—Relationships between Measures of Exposure and Performance on Neuropsychological Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>n</th>
<th>Variables in model</th>
<th>Significant β weights*</th>
<th>Adjusted multiple R²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-KEFS Trail Making Test: Visual Scanning</td>
<td>19</td>
<td>Hours of exposure, days of exposure, maximum exposure, average CFU, Stachybotrys present</td>
<td>Hours of exposure = 0.836</td>
<td>.350</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days of exposure = 3.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-KEFS Trail Making Test: Letter Sequencing</td>
<td>19</td>
<td>Hours of exposure, days of exposure, maximum exposure, CFU x maximum exposure</td>
<td>Days of exposure = 4.99</td>
<td>.326</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maximum exposure = -4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-KEFS Trail Making Test: Number-Letter Switching</td>
<td>19</td>
<td>Hours of exposure, days of exposure, maximum exposure, Stachybotrys present</td>
<td>Hours of exposure = 0.997</td>
<td>.399</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days of exposure = 5.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maximum exposure = -4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-KEFS Trail Making Test: Motor Speed</td>
<td>19</td>
<td>Hours of exposure, days of exposure, maximum exposure, average CFU, CFU x maximum exposure, Stachybotrys present</td>
<td>Stachybotrys present = 0.963</td>
<td>.705</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days of exposure = 5.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maximum exposure = -4.7</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CFU x maximum exposure = 0.626</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hours of exposure = 0.642</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-KEFS Color-Word Inhibition: Switching</td>
<td>18</td>
<td>Stachybotrys present, maximum exposure</td>
<td>Stachybotrys present = 0.623</td>
<td>.298</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maximum exposure = 0.546</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS-III: Digit Symbol Coding</td>
<td>36</td>
<td>Hours of exposure, days of exposure</td>
<td>Hours of exposure = -0.47</td>
<td>.259</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days of exposure = 0.325</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS-III: Symbol Search</td>
<td>15</td>
<td>Hours of exposure, maximum exposure, average CFU, CFU x maximum exposure</td>
<td>Hours of exposure = -0.64</td>
<td>.787</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days of exposure = 0.325</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maximum exposure = 0.598</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Average CFU = 0.804</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CFU x maximum exposure = -0.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVA-CPT: Full-Scale Attention Quotient</td>
<td>30</td>
<td>Maximum exposure, average CFU, CFU x maximum exposure</td>
<td>Maximum exposure = 0.399</td>
<td>.300</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Average CFU = -0.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVA-CPT: Visual Attention Quotient</td>
<td>15</td>
<td>Maximum exposure, average CFU, CFU x maximum exposure</td>
<td>Average CFU = -0.41</td>
<td>.276</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stachybotrys present = 0.255</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVA-CPT: Auditory Attention Quotient</td>
<td>15</td>
<td>Maximum exposure, average CFU</td>
<td>Maximum exposure = 0.469</td>
<td>.278</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stachybotrys present = 0.270</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: The fluctuating sample sizes reflect the fact that the statistics program selected only cases from the chart review for which all data in the model were present. CFU = colony-forming unit.

*p < 0.05.

Table 2.—Predictive Power for Estimates of Degree of Exposure and Quantitative Electroencephalogram (QEEG) Variables

<table>
<thead>
<tr>
<th>QEEG variable</th>
<th>n</th>
<th>Variables in model</th>
<th>Significant β weights*</th>
<th>Adjusted multiple R²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean frequency delta</td>
<td>62</td>
<td>Average CFU</td>
<td>Average CFU = -0.29</td>
<td>.069</td>
<td>0.022</td>
</tr>
<tr>
<td>Relative theta</td>
<td>62</td>
<td>CFU x maximum exposure, Stachybotrys present, days of exposure, average CFU</td>
<td>None</td>
<td>.096</td>
<td>0.043</td>
</tr>
<tr>
<td>Relative alpha</td>
<td>62</td>
<td>CFU x maximum exposure, Stachybotrys present, hours/day of exposure, maximum exposure</td>
<td>CFU x maximum exposure = 0.344</td>
<td>.124</td>
<td>0.020</td>
</tr>
<tr>
<td>Absolute delta</td>
<td>62</td>
<td>Stachybotrys present</td>
<td>Stachybotrys present = 0.270</td>
<td>.057</td>
<td>0.034</td>
</tr>
<tr>
<td>Absolute theta</td>
<td>62</td>
<td>Stachybotrys present</td>
<td>Stachybotrys present = 0.255</td>
<td>.049</td>
<td>0.046</td>
</tr>
<tr>
<td>Absolute alpha</td>
<td>62</td>
<td>Average CFU, CFU x maximum exposure</td>
<td>None</td>
<td>.086</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Note: CFU = colony-forming unit.

*p < 0.05.
That is, 29.1% of the cognitive distortion and cognitive complaints were predicted by the variance observed in CPU x maximum exposure. A nonsignificant trend was found between hours of exposure and Factor 3 (Cognitive Distortion), which yielded an adjusted $R^2$ of 0.064, $p < 0.096$.

**QEEG and neuropsychological test performance.** We observed several statistically significant relationships between the QEEG summary variables and performance on neuropsychological tests. The data in Table 3 demonstrate that significant QEEG predictors of test performance were found for measures of number and letter sequencing, number-letter switching, motor speed, response inhibition, and visual attention. The specific tests were the D-KEFS Trail Making Number Sequencing, Letter Sequencing, Number-Letter Switching, and Motor Speed subtests; the D-KEFS Color-Word Inhibition subtest; and the IVA-CPT Visual Attention Quotient. QEEG variables showing the greatest predictive power were those that involved the theta or alpha frequency bands and, most often, the mean frequency theta or relative power theta summary variables.

Minimal QEEG predictors of test performance or nonsignificant trends ($p < 0.10$ through $p < 0.051$) were found for measures of visual scanning, color naming, attention, and response inhibition (WAIS-III Symbol Search subtest, D-KEFS Color-Word Color Naming subtest, IVA-CPT Attention Quotient, IVA-CPT Response Control Quotient, and IVA-CPT Auditory Response Control Quotient).

**SCL-90-R and cognitive performance.** We could address only partially the mitigating influence of psychological factors on cognitive test performance in this study. However, sufficient cases were available to compare the results of the SCL-90-R with Digit Symbol Coding and the results of the IVA-CPT scales.

The SCL-90-R scales and factors did not predict performance on Digit Symbol Coding (adjusted $R^2 = .002$). The SCL-90-R scales of depression and anxiety were found to have the opposite effect on the IVA-CPT Attention Quotient, even though these SCL-90-R scales correlate in this data set at $R = .81$.

We observed a significant relationship for Factor 1 (Melancholic Depression) and Factor 5 (Anxious Depression) with the IVA-CPT full-scale Attention Quotient (adjusted $R^2 = .241$, $p < 0.04$), Auditory Attention Quotient (adjusted $R^2 = .200$, $p < 0.06$), and Visual Attention Quotient (adjusted $R^2 = .305$, $p < 0.02$). In all of these cases, Factor 1 had a significant negative beta weight, whereas Factor 5 had a significant positive beta weight. Increases in Factor 1 were correlated with decreases in the attention quotient scores, whereas increases in Fac-

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### Table 3. — Quantitative Electroencephalogram (QEEG) Predictors of Neuropsychological Test Performance

<table>
<thead>
<tr>
<th>Test</th>
<th>n</th>
<th>QEEG variables in model</th>
<th>Significant $\beta$ weights*</th>
<th>Adjusted multiple $R^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-KEFS Trail Making Test: Number Sequencing</td>
<td>65</td>
<td>Mean frequency theta, absolute alpha, mean frequency beta</td>
<td>Mean frequency theta = 0.571</td>
<td>.220</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absolute alpha = -0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-KEFS Trail Making Test: Letter Sequencing</td>
<td>65</td>
<td>Mean frequency theta, absolute alpha, mean frequency beta</td>
<td>Mean frequency theta = 0.503</td>
<td>.169</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absolute alpha = -0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-KEFS Trail Making Test: Number-Letter Switching</td>
<td>65</td>
<td>Absolute delta, mean frequency theta, mean frequency beta, absolute alpha, absolute alpha, relative theta</td>
<td>Mean frequency theta = 0.502</td>
<td>.193</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absolute theta = -1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absolute alpha = 1.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relative theta = 0.886</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-KEFS Trail Making Test: Motor Speed</td>
<td>65</td>
<td>Absolute delta, relative theta, mean frequency delta</td>
<td>Absolute delta = -0.31</td>
<td>.110</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relative theta = 0.271</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-KEFS Color-Word Inhibition</td>
<td>65</td>
<td>Mean frequency theta, absolute theta, relative delta, a absolute alpha, relative alpha</td>
<td>Mean frequency theta = 0.560</td>
<td>.348</td>
<td>0.00002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absolute theta = -3.2</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Relative theta = 1.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absolute delta = 0.471</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Absolute alpha = 2.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relative alpha = -1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVA-CPT Visual Attention Quotient</td>
<td>98</td>
<td>Absolute alpha, relative alpha, absolute theta, relative theta, mean frequency delta, absolute delta</td>
<td>Mean frequency theta = 0.419</td>
<td>.137</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absolute theta = -2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relative theta = 0.904</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absolute alpha = 1.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relative alpha = -0.82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05.
tor 5 were correlated with increases in the attention score. The sample size available for each analysis (n = 19) made these findings tentative at best.

SCL-90-R and QEEG. We also explored the effect of stress on cortical electrical activity. A significant relationship was found between only 2 of the 12 QEEG summary variables and SCL-90-R factors that accounted for small amounts of the variance on item analysis. A positive beta weight was observed between relative power theta and Factor 5 (Anxious Depression); whereas a negative beta weight was seen between relative power theta and Factor 5 (Anxious Depression); adjusted multiple \( R^2 = .107, p < 0.025 \). That is, patients' reports of concern regarding cognitive abilities (Factor 6) were related positively to increasing relative power theta—often an indication of decreased cognitive arousal or efficiency. This can be interpreted as consistent with the negative relationship observed for Factor 5, in which symptoms of increased arousal, tension, and anxiety can indicate increased cortical arousal and vigilance and, therefore, decreased relative power theta.

Significant correlation (adjusted multiple \( R^2 = .112, p < 0.052 \)) was also found between the mean frequency beta summary score—a marker associated with cognitive efficiency (faster = greater efficiency; slower = lesser efficiency)—and SCL-90-R Factor 4 (Affective Loss of Control) and Factor 5 (Anxious Depression). Factor 3 (Cognitive Distortion) and Factor 6 (Cognitive Complaints) showed negative relationships with this cortical indicator.

Our results suggested that, to a limited extent, increased frontal cortical arousal (as indicated by decreased relative power theta and increased mean frequency beta) was associated with increased anxiety and less complaints of cognitive deficits. Furthermore, decreased frontal cortical arousal, as indicated by increased relative power theta and decreased mean frequency beta, was associated with increased cognitive complaints and decreased anxiety.

Discussion

Psychological distress. Patients—including multiple family members—exposed to toxic molds reported moderate to severe levels of psychological distress related to the development of a wide range of physical, cognitive, and emotional symptoms. Problems included the frustration of trying to find knowledgeable and appropriate medical care, interference with social and work life, temporary or permanent abandonment of homes and possessions, financial stress, and anxiety and helplessness as a result of continuing poor health.

Most of these patients, in absence of any significant premorbid psychiatric problems, could be diagnosed as suffering from acute stress, adjustment disorder, or post-traumatic stress. Only 3.8% of our sample population reported significant premorbid psychiatric or neuropsychiatric problems (e.g., history of major depression, post-traumatic stress disorder, seizure disorder, closed head injury). Individuals with significant historical problems were eliminated from the data analysis in order to minimize the effect of such problems in this patient population.

The patients in this study showed a significant level of psychological stress, with depression being the only factor to account for a substantial amount of variance in the reported symptoms. There were limited significant relationships between some of the SCL-90-R factors and QEEG findings. Although a strong relationship was found between the average number of CFUs present in the environment and the subjectively reported cognitive difficulties on 2 of the SCL-90-R factors, it must be remembered that these 2 factors accounted for only 8.9% of the total variance on the item analysis. The process of differential diagnosis supports the conclusion that the individuals in this study suffered severe psychological distress resulting from a combination of overwhelming personal stress and poor health, with the mitigating influence of organically based central nervous system deregulation of emotions as a result of toxic or metabolic encephalopathy.

At this point, it is difficult to say what the cost of these deficits might be in terms of productivity or personal relationships, although it would clearly be significant, to a reasonable medical and scientific certainty, if the distress experienced by the patients in this sample is any indicator.

One limitation in our study was that patient reports could not be validated independently. We considered the reports to be credible, however, given that the patients were interviewed individually and completed a questionnaire; there was little motive to deceive in this clinical situation. Another measure of credibility is the fact that patients who were involved in litigation did not report more symptoms than nonlitigants.

Neuropsychological testing. The results of the neuropsychological testing produced positive findings for impaired cognitive functioning on a wide variety of tasks, when compared with premorbid estimates of intelligence. The pattern and severity of results are similar to, and corroborate, the results obtained by other researchers who have conducted preliminary studies of cognitive functioning in toxic-mold-exposed individuals. This pattern is also similar to that for individuals diagnosed with mild traumatic brain injury.

Prior researchers have reported that symptoms of depression can impair neuropsychological test performance. Baldo assessed cognitive functioning and depression in a small group of 10 mold-exposed patients and found a significant relationship between cognitive impairment and depression. In the current study, in agreement with previous research, both anxiety and
depression were indicative of stress, but only depression had a detrimental effect on attention. One interpretation may be that symptoms of anxiety are associated with higher levels of vigilance, whereas symptoms of melancholic depression are associated with lower arousal and mental sluggishness. However, this preliminary and limited analysis does not offer conclusive evidence regarding the effects of psychological distress on neuropsychological test performance in this sample. The limitation of incomplete data sets for all of the neuropsychological tests prevents a clear interpretation at this time.

We acknowledge the complex relationships among toxic mold exposure, impaired cognition, psychosocial stressors, poor physical health, and emotional factors. Our overall findings, however, lend support to the hypothesis that patients’ cognitive deficits are frequently related to underlying organic deficits caused by toxic mold exposure. Most critical for this study was the significant and consistent effect of mold-exposure measures on the results of cognitive testing. Also, abnormalities in cortical electrical activity—primarily in the frontal and prefrontal lobes—were significantly and consistently related to deficits in cognitive functioning and mold-exposure measures. An additional factor that suggests that the observed cognitive deficits were of organic origin is the lack of variability of deficits between tests usually most influenced by psychological factors (e.g., measures of attention or working memory) and tests not usually influenced by psychological factors (e.g., color naming or word reading). Corroboration was also found in a study that examined the influence of personality traits on neuropsychological test performance in toxic encephalopathy cases vs. healthy referent cases. Persson et al., concluded that the neuropsychological performance decrements in toxic encephalopathy cases were not related to elevated mental stress, but were dominated by the effects of organic brain impairment.

It is important to address the fact that most of the patients in this study subjectively reported moderate to severe ratings of cognitive impairment, rather than mild to moderate as measured by the testing. The pattern of deficits commonly seen in mild traumatic brain injury is very similar to that found in mold-exposed individuals. This phenomenon—clinically referred to as “brain fog”—is also common in individuals who suffer from multiple chemical sensitivity. Patients reported a loss of their sense of self, of their usual ways of doing things, and even of their personality. They were painfully aware of their deficits and were constantly frustrated by their loss of cognitive efficiency and frequent mistakes. This can be understood as a disturbance or dysfunction of the frontal cortical areas, as implicated in the QEEG findings and the relationship of exposure data to test performance in this study. In humans, the sense of self is organized in the frontal brain areas. For these reasons, we recommend that studies or clinical evaluations of cognitive functioning in mold-exposed patients employ functional imaging techniques to assess organic dysfunction.

QEEG. The results of the QEEG data recorded from mold-exposed patients indicate a restriction in the range of functioning (narrowed frequency bands) of the frontal lobes, that is, increased (accelerated) mean frequency of the slower frequencies (delta and theta) and decreased (slowed) higher frequencies (beta). These changes indicate a collapse toward the middle of the frequency spectrum. Such findings, coupled with the increased levels of absolute and relative power theta and alpha in the frontal sites, indicate a hypoactivation of the frontal cortex. The latter may result from brainstem involvement and may indicate insufficient excitatory input from the reticular activating system anatomically seated in the midbrain. Deviant QEEG findings of this magnitude should not have been observed in frontal lobe functioning without some insult to the functioning of the neural systems that depend on integrative coordination from the frontal lobes. These findings are consistent with other functional imaging studies mentioned earlier.

Measures of toxic mold exposure were related significantly to QEEG findings, and both measures of exposure and QEEG measures were related significantly to cognitive test performance. Psychological factors appeared to have only a limited relationship to QEEG results, reflecting the arousal level of the frontal lobes. This finding supports the conclusion that exposure to toxic mold results in central nervous system dysfunction, as measured by QEEG.

The use of QEEG and neurometrics in research and clinical practice has been the subject of some controversy, although recent opinions and evidence describe more strengths than weaknesses. Our decision to use QEEG and neurometrics included the facts that they are noninvasive, relatively inexpensive, free from cultural and ethnic factors, have good reliability and validity, and are highly sensitive for detecting dementias and encephalopathy.

The most significant limitation of the NxLink database is its exclusive reliance on banded EEG. Findings restricted to narrow frequencies are obscured with the use of relatively wide bands normed in the database. Plans for future investigations include examination of other indices of QEEG activity, such as coherence and phase lag relationships, and examination of the data using other databases that allow single-frequency analysis.

Summary and Conclusions

Patients exposed to toxic molds reported high levels of physical, cognitive, and emotional symptoms. Rad-
ings on the SCL-90-R were moderate to severe, with a factor reflecting depression accounting for most of the variance. Most patients could be diagnosed as suffering from problems of acute stress, adjustment disorder, or post-traumatic stress. Impaired cognitive functioning was observed on multiple cognitive tasks, compared with premorbid estimates of intelligence, in a pattern of impairment similar to that for mild traumatic brain injury. The QEEG findings indicated a hypoactivation of the frontal cortex, suggesting brainstem involvement and insufficient excitatory input from the reticular activating system. QEEG measures were correlated with neuropsychological test results.

Findings of a dose-response relationship between measures of exposure and the outcome of neuropsychological tests and QEEG measures suggest that evaluation of neuropsychological and neurobehavioral deficits in mold-exposed patients should consider degree of exposure, organic-based central nervous system dysfunction, and psychological variables. Differential diagnosis supported an etiology of organic-based dysregulation of emotions and cognitive functioning as a result of toxic or metabolic encephalopathy, with some degree of mitigation by psychological variables, especially depression.

Additional work is needed to examine the effect of the length of time since last exposure to toxic mold on outcome measures. Patients have reported some reduction in symptoms when they have been removed from continued exposure. How much of a reduction, under what circumstances, and for which patients have not been fully determined.

Limitations of this study included lack of a comparison group that underwent the same testing as the mold patients, and small sample size. The lack of a comparison group was mitigated by the fact that the measures used in this study were all compared with the published normative databases developed for each of the tests. With respect to sample size, the fact that the analyses were performed on data gathered from chart review resulted in inconsistent sample sizes and the variable sample sizes reported in some of the stepwise regression analyses and descriptive statistics. For this reason, the relative contribution to the variance accounted for by any given variable can be compared only with the relative contributions of variables for which a similar number of cases were available.

Future research will include expanded use of neuropsychological testing. QEEG measures, exposure measures, correlations with immune parameters, an increase in sample size, and more complete data analysis. The use of causal modeling and path analysis may improve the interpretability of the results, allowing the multidirectional relationships that exist within this complex topic to be modeled in several different ways.

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