Delay in P300 Latency in Patients with Organic Solvent Exposure

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- Event-related potentials were examined in 12 individuals with a history of organic solvent exposure and in 19 nonexposed controls. The latencies of the N250 and P300 components of the auditory event-related potential were significantly delayed in the solvent-exposed patients compared with those in normal controls. Amplitudes of the N100, P200, and N250 components were larger in the solvent-exposed group, but the P300 amplitude did not differentiate between groups. A comparison with data from clinically stable outpatient schizophrenics indicated that P300 latencies were longer in the solvent-exposed group. Within the exposed group, P300 latency was positively correlated with length of exposure. The delay in N250 and P300 provides evidence that solvent exposure slows central nervous system mechanisms that evaluate and/or process relevant stimuli. The assessment of event-related potentials may be an especially useful way to evaluate central nervous system integrity in persons who have had a neurotoxic exposure.

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Organic solvents have a special affinity for lipid-rich tissue (eg, brain tissue), and clinical disease states associated with solvent exposure have been documented for well over a century. Research during the past decade has provided a clearer understanding of the somatic, behavioral, and cognitive changes (eg, dizziness, memory complaints, and irritability) that result from solvent exposure, but there remain a number of questions about the cause of this disorder. Specifically, there is still controversy regarding the existence/extent of chronic central nervous system (CNS) damage and dysfunction following solvent exposure.

There is a history of association between organic brain dysfunction and increased latency of event-related potential (ERP) waveforms, especially the later components such as P300. Average P300 latencies for patients with dementia are reported to exceed 400 milliseconds (ms) in auditory tasks. This may be contrasted with decreased amplitudes that are typically observed in psychopathologic states, such as schizophrenia. Decreased amplitude has also been reported for affective disorder, though to a lesser extent, and has been reported to be sensitive to mood shifts in patients with renal disease. Relatively little work has been conducted utilizing ERP assessment of cognitive function in toxic exposure, although its potential has been recognized. One study reported that while overall amplitude and latencies were within normal ranges for 10 solvent-exposed workers, changes in both N100 and P300 amplitudes were significantly smaller in the solvent-exposed workers than they were in controls as subjects switched between attentive and nonattentive conditions. Increases in P300 latency have been reported for three workers exposed to hydrogen sulfide. Although actual latency values were not presented, the authors reported abnormally long P300 latency in all three workers. Over a 2-year period, normalization of the P300 was seen in one patient, whose symptoms also improved.

In cases of organic solvent exposure, diagnosis of "toxic encephalopathy" relies mainly on history, psychiatric findings, and cognitive changes. The assessment of ERPs may provide a useful marker of CNS dysfunction unconfounded by motivational factors that may be especially problematic in cases of occupational exposure, as such patients are often involved in litigation.

**PATIENTS AND METHODS**

Nine men and three women with CNS complaints (eg, headaches, dizziness, and fatigue) following organic solvent exposure were examined. No person had a history of psychiatric disorder, head injury, hearing loss, or consumption of alcohol exceeding one to two drinks per day. A detailed occupational and environmental chemical exposure questionnaire was administered to each person by an occupational health specialist. The mean duration of exposure was 3 years (range, 1 day to 30 years), and the average length of time from the last exposure to the present assessment was 2 years (range, 1 month to 10 years). All of the persons in the exposed group had been occupationally exposed to mixtures of organic solvents (eg, toluene and trichloroethylene) and met criteria for mild toxic encephalopathy, type 2A2B (personality and cognitive changes). In addition to a history of long-term exposure to solvents, one patient had an additional history of possible exposure to inorganic mercury.

Normal controls consisted of 19 healthy male volunteers carefully screened for medical and psychiatric disorders using semi-
structured interviews to assess Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) Axis I (psychiatric clinical syndromes) and Axis II (personality syndromes) disorders. Psychiatric control data were also available from a sample of 26 male psychiatric patients meeting DSM-III-R criteria for chronic schizophrenia,10 tested in the same laboratory, whose data have previously been reported.11 Mean ages were 47, 34, and 36 years for the exposed subjects, normal controls, and schizophrenic patients, respectively. Informed consent, after the nature of the procedures had been fully explained, was obtained for all subjects.

**Experimental Procedures**

Subjects performed modifications of an auditory "oddball" paradigm in both a counting or a choice reaction time (RT) paradigm. In the counting task, subjects silently counted the occurrence of infrequent high-pitched tones (target tone, 1500 Hz), but not frequent low-pitched tones (nontarget tone, 800 Hz), presented with an interstimulus interval of 3 seconds. Tones were presented for 40 ms at 65 dB, with 80 trials per block. In the choice RT task, subjects pressed a button following each high tone, and a different button following each low tone. There were two blocks of the counting task followed by two blocks of the choice RT task.

The two tasks have unique characteristics. The counting task places mild demands on memory and is free of any obligatory motor-related activity. However, it does not allow a measurement of accuracy to be observed for each trial. The choice RT task does not require memory updating but does allow evaluation of response accuracy on individual trials. Furthermore, attention is forced to every trial, since a response is required even after predictable events.

For both the counting and the choice RT tasks, subjects were informed that the target tone would occur less often and that it would never be followed by another target tone. There were therefore three conditional probabilities: when a target tone was presented, there was a 100% probability that the following tone would be a nontarget; when a nontarget was presented, the following tone could either be a target (P = .33) or a nontarget (P = .67).

Electrophysiological data were collected from scalp electrodes at midline frontal, central, parietal, and occipital and lateral parietal locations (F3, C3, P3, O1, Pz, P4) referred to linked ears, amplified ×20000 by amplifiers with a frequency band pass of 0.01 to 30 Hz (Grass Model A5). An eye movement artifact channel was also recorded. Data were digitized at 8-ms intervals for a 1200-ms epoch, beginning 200 ms prior to stimulus onset, by a computer system (PDP-11/73), and stored on magnetic media. From artifact-free single trials, averaged ERPs were calculated only for counting blocks in which the subject performed five or fewer target detection errors. Performance for all subjects on the counting task was accurate, with only two of the exposed subjects counting with more than one error/block: one subject had four and three errors on successive blocks, and another had zero and five errors. For the choice RT task, three exposed subjects had more than two but fewer than 10 errors on any block, while one subject had as many as 20 and 17 errors. All incorrect trials were excluded from the analysis.

Individual ERP components were identified with an interactive program to detect positive and negative peaks in predefined windows, using the electrode for which each component is normally found to be maximal for these types of tasks. For N100, P200, and N250 the vertex (Cz) electrode was used to identify the peak. The midline parietal (Pz) electrode was used to determine P300. After the peak was verified, the latency and peak amplitudes for all electrodes observed at that latency (after subtracting the median baseline for the 200-ms prestimulus epoch) were automatically stored on computer.

All data were analyzed with repeated-measures analysis of variance. Evaluation of peak amplitudes and latencies were compared for the solvent-exposed and the normal control groups across tasks (counting vs choice RT) and event probability (.33, .67, and 1.00). In the case of amplitude measurement, analyses were also carried out across electrode sites. Where appropriate, degrees of freedom were reduced by the epsilon correction factor.

**RESULTS**

The Table presents means and standard deviations of the ERP values for normal control and solvent-exposed patients, as well as P300 data for the schizophrenic sample.

**Normal Controls vs Solvent-Exposed Patients**

**ERP Amplitudes.**—For all ERP components, there were significant main effects across electrodes (P<.0001), and interactions of electrodes with either task or probability.
Fig. 1.—Grand mean event-related potentials across subjects for the control (n = 19) and solvent-exposed (n = 12) groups in the counting and choice reaction time tasks. The midline electrodes and electro-oculogram (EOG) artifact channel are presented (positivity down). Conditional probabilities of .33, .67, and 1.00 are represented by the solid, dashed, and dotted lines, respectively. Decreasing event probability is associated with increasing P300 amplitude (the large, downward deflection between 300 and 400 milliseconds [ms]).

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ences in amplitude but significantly delayed P300 latencies in the solvent-exposed group (F[1,14] = 6.50; P = .02). P300 latencies were 340 ms for the older controls and 383 ms for the solvent-exposed patients.

For N100 and P200, latency differences between conditions, though small, were significant. N100 latency was approximately 3 ms longer for high- as opposed to low-pitched tones (F[1,48] = 6.1; P = .006). P200 for predictable low-pitched tones was 4.5 ms longer than for the infrequent high tones (F[2,58] = 3.4; P = .003). Given these small averaged differences by condition (less than our sampling rate for individual data points), little importance is attached to these findings.

**RT Scores and P300 Latency**

For the choice RT task, the mean RT for each event-probability condition was computed from all correct trials (including those trials with physiological artifacts that were not included in computation of the ERP averages). Across conditions, control subjects had a shorter mean RT than did solvent-exposed patients (mean, 748.4 and 1053.4, respectively; F(1,29) = 7.02; P = .012). Given that P300 latency precedes the RT response, it might be assumed that prolongation of the P300 influences RT. Covarying P300 latency only served to strengthen the finding (F[1,28] = 15.8; P = .0004).

**Correlation with Exposure-Related Variables**

Rank-order correlations were performed between P300 amplitude and latency, at P3, for both counting and choice RT tasks with length of exposure and with interval from the last exposure to test. Significant correlations were found between P300 latency—counting and choice RT—and length of exposure (ρ = .80 and .64, respectively; P < .05).

**Psychiatric Controls vs Solvent-Exposed Patients**

Because symptoms following neurotoxic exposure are reported to be similar to psychiatric disorders, comparisons were made between the solvent-exposed patients and a group of schizophrenic patients. These data revealed a somewhat different pattern of results. The schizophrenic patients have previously been reported to show decreased P300 amplitudes compared with normal controls (though significantly smaller only in the counting task), while latency in these patients did not differ from that in the control group.14 Schizophrenics and solvent-exposed persons were compared using only data from P3 for the .33 probability condition in both tasks. There were no differences between the groups in amplitude. However, P300 latencies were significantly longer in the exposed group than those observed for the schizophrenic patients (F[1,36] = 15.1; P = .0004) (Table).

**COMMENT**

Results from this study suggest that persons with a history of organic solvent exposure who meet criteria for mild toxic encephalopathy (type 2A/2B) have significant delays in the N250 and P300 components of the ERP. As these delays were present for both counting and choice RT tasks, it suggests that the latency prolongation in the solvent group is not dependent on the unique aspects of either task, but reflects a more generalized dysfunction. Solvent-exposed patients, when compared with normal controls, also showed increases in the amplitudes of the
early waveforms (N100 and P200), components that have been related to stimulus reception. There were no differences between the groups in scalp topography, and both groups showed increased P300 amplitudes and longer latencies with decreasing event probability.

Regarding the morphological appearance of the ERPs in the solvent-exposed group, it was noted that several subjects had irregular waveforms of the late positive complex (N250-P300), as opposed to the smooth waveforms characteristic of normal subjects. Similar irregularities in P300 waveforms have been reported in patients with temporal lobe epilepsy, with greater amplitude reduction in patients with purported left temporal foci. P300 is generated in response to stimuli that have significant psychological value, such as infrequent or unpredictable events. Increased latency of the P300 has typically been associated with a variety of organic disorders, eg, Alzheimer’s disease,8 multiple sclerosis,25 and head injury. On the other hand, psychiatric disorders such as schizophrenia and affective state are reported more often to result in a reduction of P300 amplitude. All of the solvent-exposed patients had completed the Beck Depression Inventory.26 To determine if depressive state was related to changes in P300, we looked at the relationship between scores on the Beck Depression Inventory and ERP values for the exposed group. There were no significant correlations between the Beck Depression Inventory scores and the P300 amplitude or latency measures. Our findings of increased P300 latencies in the solvent-exposed group in comparison with the psychiatric control group, coupled with a lack of correlation between mood state and P300 values, suggest that the neurophysiological changes in the exposed group are not solely a consequence of an affective or psychiatric disorder.

The increase in both P500 latency and manual RT for solvent-exposed patients suggests slowing of several processing components. The delay in P500 latency, however, did not account for the greatly increased RTs in exposed patients. This suggests a deficit at some later stage of processing for these patients when they are carrying out the behavioral response task. The deficit may either involve the selection of the correct response following stimulus identification, or the initiation and execution of the response after the stimulus has been identified. More specific quantification of the critical stage cannot be determined with the present data.

An association between duration of exposure and outcome, especially on cognitive and behavioral measures, is often equivocal.37 However, most occupational health specialists maintain that a dose-response relationship is necessary to make a clear diagnosis of neurotoxic disease.38 Our results support a pattern of increasing P300 latency associated with increasing duration of exposure. In the Wasch et al study reporting increased P300 latency following hydrogen sulfide exposure, the most “severely exposed” person also showed the longest P300 latency. In our sample, 64% of the variance of the P300 component (counting task) was accounted for by length of exposure. This is not to say that other variables, such as peak exposure or frequency of exposure, do not have an impact on these electrophysiological measures. However, because of our relatively small sample size, we are unable to conduct a detailed multivariate analysis.

A significant correlation between P300 latency and interval from exposure to test was not obtained, although correlations between P300 latency and interval were in the expected direction (−26, and −30, respectively, for counting and choice RT). This suggests a trend, in the direction of normalizing P300 latency values with increasing time away from the last exposure. The findings of longitudinal follow-up studies of exposed workers have not always supported the belief that removal from the exposure source results in a reduction in somatic symptoms and cognitive function.9−12 Recovery rates vary between 25 and 50%. A history of peak exposure, higher levels of psychological distress, increasing age, and longer durations of exposure have been reported to contribute to poor functional outcome.6,13 Measurements of cerebral blood flow have documented decreased metabolism in both subcortical and cortical structures in workers occupationally exposed to solvents. It is interesting to note that in one solvent-exposed case a positron emission tomographic scan reported decreased glucose uptake in the hippocampus and amygdala, areas that have been implicated in generation of the P300 component.35 Neurobehavioral studies have also speculated that medial temporal structures may be particularly vulnerable to the effects of organic solvents.6 Overall, our findings offer additional support for the hypothesis that organic solvent exposure (type 2A/2B) results in a disruption of neural function.

As mentioned earlier, very little work has been conducted on the use of electrophysiological measurements in adults with toxic exposure. This is the first study, to our knowledge, comparing ERP measurements of solvent-exposed adults with both normal and psychiatric control groups. Our data indicate that solvent-exposed patients are particularly responsive to the sensory effects of stimuli (ie, increase in P200 amplitude), but they require additional time to process relevant stimuli (delay in N250 and P300). A number of studies have documented neuropsychiatric impairments following solvent exposure.1 The determination of pathogenesis, however—psychogenic vs organic—with mechanisms, is hampered by the fact that solvent exposure typically results in impairment on a wide range of cognitive measures (eg, motor speed, learning and memory, and attention) and changes in personality (eg, irritability and depression).3 Changes in the ERP, especially increased latency of the P300, may serve as an empirical marker for CNS impairment following neurotoxic exposure. It is interesting to note that in our sample of 12 solvent-exposed patients, six persons had P300 latencies that exceeded the control mean by more than 2 SD, with four of the six exceeding 2.5 SD. This underscores the possible usefulness of the P300 as a clinical assessment tool. It has also been suggested that ERPs may be more sensitive to CNS dysfunction than cognitive measures.25 That is, a higher level of impairment may be required before deficits are detected on the cognitive tests, but subclinical impairment may be ascertained with ERPs.

Estimates of occupational exposure to organic solvents exceed 9 million annually: approximately 8% of the US population. The attribution of CNS impairment following solvent exposure is complicated by several factors. First, quantifying solvent “dose-burden” is difficult because of the short half-life of these substances. Second, many of these patients are involved in some type of litigation, increasing the possibility of symptom exaggeration. Finally, many health professionals maintain that the effects of solvents are reversible; when they persist they are often
regarded as psychogenic. The need for an objective marker of neurotoxic encephalopathy, minimally con-

founded by motivational or affective state, is imperative. Assessment of P300, a noninvasive objective measure, may provide just such an indicator.

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References

13. Pfefferbaum A, Ford JM, White PM, Roth T. P3 in schizophrenia is affected by stimulus modality, response requirements, medication status and negative symptoms. Arch Gen Psychiatry. 1989;46:1035-1044.