THE UTILITY OF PSYCHOPHYSIOLOGICAL MEASURES IN ASSESSING THE CORRELATES AND CONSEQUENCES OF ORGANIC SOLVENT EXPOSURE

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SOLVENT NEUROTOXICITY

By definition, organic solvents are chemical agents that have the ability to dissolve non-water-soluble substances. They are found most frequently in paint products, dyes, glues, and cleaning agents, and are prominent in the manufacture of plastics, textiles, and agricultural products. Estimates suggest that at least nine million people in the United States are routinely exposed to organic solvents in the workplace (National Institute for Occupational Safety and Health, 1987).

Reports of adverse behavioral effects associated with neurotoxic exposure have been prevalent in the occupational and medical literature for over a century. In this country, Francis Braceland was one of the first investigators to describe the neurobehavioral consequences of carbon disulfide exposure in workers employed in the viscose rayon industry (Braceland, 1942). The hallmark symptoms that he noted — headaches, fatigue, insomnia, confusion, amnesia, changes in personality, depression, irritability — describe the primary symptoms of solvent neurotoxicity. Because solvents are highly lipophilic, the neuropsychiatric symptoms have been attributed to a depression of central nervous system (CNS) activity. In fact, chemicals of this class are often used as anesthetics.

The somatic and neuropsychiatric consequences of exposure to chemicals at levels below threshold limit values (TLVs) have been the subject of several consensus workshops (Baker and Fine, 1986; Cramer and Goldberg, 1986). A typology describing the neurobehavioral symptoms associated with solvent neurotoxicity, which reflects both the severity and reversibility of symptoms, has been proposed. The mildest form, Type I, is characterized by

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symptoms including decreased concentration, fatigue, loss of initiative, and memory loss. There is no evidence of impairment on formal neurobehavioral measures, and symptoms are thought to be reversible if exposure is terminated. Type 2A/2B is characterized by more severe symptomatology that may or may not be reversible. Type 2A refers to a change in mood or personality, such as increased lability, irritability, depression, and poor impulse control, whereas impairments on neuropsychological evaluation constitute a marker for Type 2B. Typically, psychomotor slowing, memory impairment, decreased attention, and poor learning can be documented. Subtle neurological signs may also be present. The most serious impairment, Type 3, follows years of voluntary abuse of solvents (e.g., glue sniffing) or long-term chronic occupational exposure with repeated overexposures. There is a generalized decrease in intellectual function, neuroradiological evidence of structural brain damage, and little likelihood of reversibility.

It is unfortunate that this tripartite typology has not been widely embraced by researchers. Nevertheless, one could argue that most of these individuals would meet current criteria for Type 2A/2B solvent neurotoxicity. On formal neuropsychological evaluation, exposed workers typically perform more poorly than nonexposed control subjects on measures of reaction time, learning and memory, abstract reasoning, visuospatial ability, and perceptuo-motor speed (Gregersen et al., 1984; Ekberg et al., 1986; Ryan et al., 1988; Morrow et al., 1990b; Morrow et al., 1991; Morrow et al., 1992a; Morrow, 1994). In addition, self-report measures of psychological symptomatology reveal more somatic complaints: fatigue, tension, irritability, and mood changes (Hane et al., 1977; Lindstrom, 1980; Morrow et al., 1989; Morrow et al., 1993).

Although this symptomatology is consistent with solvent-induced central nervous system damage, there is still skepticism about the extent of actual solvent-induced cognitive and emotional dysfunction. Baker and Fine (1986), among others, have argued that a strong dose-response relationship is necessary to support the hypothesis that solvent exposure produces cognitive and behavioral impairment. Unfortunately, while many studies of exposed and nonexposed workers have found evidence of neuropsychological and psychological dysfunction, a dose-response relationship is often lacking (a situation not unique to solvents, but found with virtually any neurotoxic substance). That is, increased duration or dose of solvent exposure is not always associated with increased psychological and cognitive impairment. Because solvents have such a short half-life — 24 to 48 hours — it is rare that measurements are available in order to quantify solvent "body burden." If blood or urine samples are not available, and air sampling measures from the workplace have not been obtained, then estimates of duration, frequency, and amount (i.e., dose) of exposure must rely on the workers' recollection. Furthermore, accurate assessment of neurotoxicity may be confounded by other factors, such as job stress or previous alcohol use. Other organismic variables such as liver dysfunction (Tarter et al., 1988) or a history of multiple peak exposures (Morrow et al., 1991) may increase the risk of neuropsychological impairment. In addition, serious methodological limitations (e.g., failure to equate experimental and control groups on demographic variables) may restrict the generalizability of many earlier studies.
FUNCTIONAL IMAGING AND PSYCHOPHYSIOLOGICAL STUDIES

Because quantifiable changes to the central nervous system (CNS), as measured by neurological examination, computerized tomography, or magnetic resonance imaging, are often absent following exposure, researchers have begun to utilize functional imaging and psychophysiological measures to document the extent to which the central nervous system may be altered following solvent exposure.

Several recent reports have found evidence of decreased neurofunctional capacity in both cortical and subcortical areas following solvent exposure. Blood flow measurements in solvent-exposed workers show the lowest flow to the frontotemporal areas (Hagstadius et al., 1989). Studies utilizing single photon emission computerized tomography (SPECT) imaging procedures in persons with neurotoxic exposure demonstrated significantly lower perfusion in frontal and temporal cortex and in the basal ganglia and thalamus (Callender et al., 1993). Positron emission tomography (PET) demonstrated reduced glucose uptake to frontal and medial temporal cortex, as well as in the basal ganglia, hippocampus, amygdala, putamen, and thalamus, in a worker with a single peak solvent exposure (Morrow et al., 1990a). In this latter study, there was an association between deficits seen on neuropsychological tests and reduced glucose uptake in certain brain areas. This underscores the notion that even relatively brief exposures can eventuate in significant neurological and neuropsychological decrements.

The use of psychophysiological measures [e.g., event-related potentials (ERPs), cardiac and pupil reactivity] to assess persons with toxic exposure has been limited, but recent findings suggest these procedures may be particularly sensitive to chemical exposure. It has been argued that the assessment of ERPs may be more sensitive to CNS dysfunction than cognitive measures (Newton et al., 1989). That is, a higher level of impairment may be required before deficits are detected on the cognitive tests, but subclinical impairments may be ascertained with ERPs. In one of the first studies measuring ERPs in solvent-exposed persons, amplitude and latency values were within normal ranges, but changes in the amplitudes of the N100 and P300 components during attentional switching tasks were significantly smaller than those of controls (El Massiou et al., 1986). The latency of the P300 was delayed in a small group of persons tested after exposure to hydrogen sulfide (Wasch et al., 1989).

Work in our lab assessing ERP waveforms and information processing changes has demonstrated evidence for disruptions of both neurophysiological function and cognitive processing in individuals with a history of organic solvent exposure (Morrow et al., 1992b). Data on ERP measures were compared for solvent-exposed subjects, nonexposed controls, and psychiatric controls. Measures of visual sensitivity were determined with a Continuous Performance Test (CPT) and discrimination of a target presented with distractors provided a probe of iconic memory [Span of Apprehension (SOA)]. Two "oddball" paradigms — Counting and Choice Reaction-Time (RT) — were employed to assess ERPs (Steinhauer and Zubin, 1982). In the Counting task, subjects silently counted the occurrence of infrequent high-pitched tones, but not low-pitched tones. In the Choice RT task, subjects pressed a
button following each high tone, and a different button following each low tone. For all subjects, the same order of tasks is purposely employed: Counting first, Choice RT second. This is done because it is emphasized that only target tones are overtly task relevant for the initial Counting task, while all tones become relevant for the Choice RT task.

Results showed significant decrements on the CPT and poorer iconic memory for both solvent-exposed subjects and psychiatric patients, compared to normal controls. While the exposed subjects did not show evidence of significantly reduced P300 amplitudes, there was evidence of greatly increased N250 and P300 latencies across tasks and conditions when compared to both controls and schizophrenic patients. The average P300 latency for the exposed group was over 400 msec, while the normal and psychiatric groups had latency values of 344 msec and 350 msec, respectively. The morphology of the waveforms that we have observed in the solvent-exposed subjects was similar to that seen in patients who have evidence of CNS disease, epilepsy, and Alzheimer's disease (Goodin et al., 1979; Nelson et al., 1991). Solvent-exposed subjects did show larger amplitudes of the early waveforms (N100, P200), suggesting a heightened sensitivity to the sensory effects of stimuli. In addition, when we compared the two oddball paradigms — Counting and Choice RT — there was a tendency for the exposed subjects, like normal subjects, to have longer P300 latencies for the Choice RT task — a more cognitively challenging task. We also found a rank order correlation between length of exposure and P300 latency (rho = 0.50). These data indicate that ERPs may be sensitive to subclinical impairment. Of the patients we have assessed on the ERPs, four had cognitive test results that were within normal limits but showed substantial increases in P300 latency (over 400 msec). All of these patients reported irritability and mood changes which have been hypothesized to precede evidence of clinically significant cognitive changes (Parkinson et al., 1990).

In addition to the ERP measures, data are also available for autonomic nervous system function. Both cardiac and pupillary reactivity were measured in exposed subjects and nonexposed controls (Morrow and Steinhauer, 1994). Autonomic functions such as heart rate and pupil size provide objective measures of mental activity and are sensitive to changes in information processing. Both are highly correlated with the ability to initiate and maintain attention. For this study we looked at cardiac and pupil reactivity during the Counting and Choice RT conditions in the oddball paradigm and found atypical responding in the solvent-exposed subjects. While control subjects show a decline in heart rate going from the Counting to the Choice RT task — the normal habituation response, exposed persons show an increase in heart rate. Likewise, initial pupil diameter was similar for both groups, but only the control subjects exhibited habituation across the two tasks. This increase in heart rate and pupil diameter demonstrated for exposed subjects suggests an increase in sympathetic arousal. We have suggested that this failure to habituate may be a response to a cognitively challenging event. That is, the Choice RT condition requires more demands on cognitive processing since the subject must attend to each stimulus, make a decision about each stimulus, and select the appropriate response. The Counting task only requires attention to the rare tones and no attention is demanded when the frequent tones are presented. Indeed, many of our subjects
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tonomic nervous system in exposed subjects and actions such as heart rate re sensitive to changes in y to initiate and maintain during the Counting and responding in the solvent going from the Counting persons show an increase oups, but only the control in heart rate and pupil sympathetic arousal. We cognitively challenging cognitive processing since m stimulus, and select the o the rare tones and no d; many of our subjects spontaneously report that the Choice RT condition is more difficult, and in looking at error rates, the average error rate is higher for the Choice RT condition.

To determine the extent to which these measures change over time, we reevaluated eight of the exposed persons on both ERP and autonomic functions. None of these persons worked with solvents in the interim. For the ERP measures, there was evidence of mild improvement in one subject: P300 latency improved from 440 msec to 384 msec on the Counting task and 416 msec to 392 msec on the Choice RT task. It should be noted that the latencies at the follow-up testing are still more than two standard deviations slower than controls. The other seven subjects showed virtually no change, or an increase, in P300 latency.

Surprising findings were noted for the autonomic measures. Six of the eight subjects demonstrated a more severe alteration of autonomic reactivity at follow-up. For example, one person initially showed a normal cardiac habituation response — an average heart rate of 77 beats per minute (bpm) on the Counting task and 76 bpm on the Choice RT task — but no habituation of pupil response (7.09 cm to 7.16 cm). This initial testing was completed two weeks after a peak exposure to aromatic solvents. After 33 months, a second evaluation was done. Both pupil and heart rate failed to show habituation: the average heart rate increased from the Counting to the Choice RT — 83 and 86 bpm, respectively. Pupil diameter also showed a dramatic increase across tasks — 7.10 cm on the Counting task to 7.65 cm on the Choice RT task. The P300 latency of this subject of 384 msec and 384 msec for Counting and Choice RT at first testing was virtually unchanged at the second testing — 400 msec and 384, respectively. This same atypical response pattern — increasing sympathetic arousal when comparing the initial and follow-up testings — was noted in five other exposed subjects, the majority having a history of peak exposure. Only two of the eight subjects had a normal habituation response at both test sessions 1 and 2.

While it is somewhat premature to speculate about the mechanisms responsible for the deficits observed in exposed patients, several hypotheses have been developed. Jennings (1992) has postulated a midbrain inhibitory circuit, consisting of limbic structures that regulate autonomic requirements (e.g., slowing of heart rate). Recently, Bell and her colleagues have hypothesized that changes in neurophysiology, cognition, and affect following chemical exposure may result from kindling of limbic structures (Bell et al., 1992). Kindling refers to the sensitization of limbic neurons (including amygdala, olfactory bulb, piriform cortex, and hippocampus) to repeated intermittent stressors. Kindling develops from repeated intermittent exposures, either mild or marked, that initially do not elicit neuronal excitability. Over time, however, excitability of the neurons is altered so that subsequent low-level stressors may serve as triggers. It is this mechanism that "serves as an amplifier for reactivity to low level chemical exposures and as an initial common pathway for a range of clinical phenomenology, including cognitive and affective dysfunctions" (Bell et al., 1992, p. 221). Pathways regulated by the limbic system would thus be altered. Thresholds are lowered such that subsequent stressors, which were initially benign, result in neuronal excitability. Autonomic pathways regulated by limbic structures would also be modified. If this inhibitory
system were altered via limbic kindling, there would be a state of decreased attention, and disruptions of arousal. Exposure to organic solvents via the olfactory pathways (which are the primary access route to the CNS and particularly susceptible to kindling) may affect limbic nuclei such that subsequent stressors (e.g., low-level chemical or psychological stressors) occurring intermittently over time, could modify neuronal sensitization. This would lead to an increasing susceptibility to a cognitively challenging event, as well as an alteration of arousal and attention. Consistent with our model are our own pilot data showing, in a small sample of exposed patients, a failure to habituate that seems to worsen over time. Future studies to test the kindling model should focus on a challenge paradigm (e.g., exposing subjects to low-level chemicals) to determine psychophysiological alterations as a direct response to the stressor.

SOLVENTS AND MULTIPLE CHEMICAL SENSITIVITIES

Our work to date demonstrates the value of psychophysiological measures in studying individuals with significant solvent exposures. We are convinced that this approach may also be quite useful in studying individuals with multiple chemical sensitivities (MCS). If, as has been suggested by several investigators, some type of limbic system dysfunction underlies the development of neuropsychiatric symptoms in both groups of subjects, then psychophysiological evaluations of the sort outlined above might be particularly useful in identifying brain dysfunction in individuals suspected of having MCS. Unfortunately, before this endeavor can proceed further, investigators will have to establish working diagnostic definition(s) of MCS. Our own work in solvent neurotoxicity has used the typology developed at several consensus conferences to aid in the diagnosis and classification of individuals with a history of solvent exposure. A similar typology, perhaps established in the same way — at a consensus conference — could certainly facilitate the identification of subtypes of MCS individuals. It is our expectation that those individuals who meet criteria for even moderate MCS (equivalent to Type 2A/2B solvent neurotoxicity) will manifest atypical anomalies that are similar to those found in solvent-exposed adults.

CONTINUED APPLICATION OF PSYCHOPHYSIOLOGICAL TECHNIQUES

As may be evident from the foregoing discussion, the study of psychophysiological parameters during cognitive activation provides a variety of tools for the study of chemically exposed individuals. Moreover, these noninvasive techniques can be repeated over short time periods. Beyond the ability to identify group differences, these measures have a unique ability to supplement individual data on neuropsychological function. For example, P300 latency provides a clear indication of central nervous system integrity. P300 amplitude, the extent of pupillary dilation, and changes in phasic cardiac processes provide direct assessment of information utilization. Tonic autonomic measures, such as overall pupillary diameter and heart rate, provide an assessment of generalized autonomic arousal and maintenance of attention, and appear to be increased in subjects having difficulty attending to demands of specific tasks. Thus, not only are they useful in the research domain, but they are applicable to
decreased attention, and pathways (which are the edging) may affect limbic psychological stressors on. This would lead to an alteration of arousal, in a small sample of the clinical evaluation of patients in whom there are suspected changes in cognitive function following neurotoxic exposure.

REFERENCES


