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Part I: the effect of long-term exposure to organic solvents on memory: a cross sectional study

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Abstract

This study focuses on a wide range of different aspects of memory functions trying to ascertain a possible profile of memory changes, which take place following long-term exposure to organic solvents. The research design was cross-sectional. Study population included 31 industrial painters who were exposed at work to organic solvents and 31 unexposed workers. Workers after long-term exposure to organic solvents showed significant decline in memory as indicated in all three standard memory tests (i.e. Wechsler Memory Scale — Revised, Benton Revised Visual Retention Test, and Rey Auditory Verbal Learning Test). The results of Rey Auditory Verbal Learning Test showed a negative correlation with exposure index indicating that the more intensive and longer the time of exposure was, the more impaired is the verbal memory. It was also found that the affect of age on memory was stronger among workers after long-term exposure to organic solvents compared to the unexposed workers.

Keywords: Organic solvents; Exposure; Memory

1. Introduction

A solvent is defined as an organic chemical that is a volatile liquid at room temperature and is strongly lipophilic. It is this latter property which gives these chemicals their ability to produce neurotoxic effects on the central and peripheral nervous system (Cranmer and Goldberg, 1986). Industrial painters are among the occupational groups usually exposed to organic solvent mixtures. There is a concern that sustained low-level exposure to organic solvents may cause permanent brain damage with intellectual impairment. In the Scandinavian countries the 'solvent syn-

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drome' has been recognized as an occupational disease for approximately twenty years and it is accepted that it manifests itself in two distinct ways: (a) as an organic affective syndrome consisting mainly of diffuse psychological syndrome; and (b) as a chronic toxic encephalopathy. After long-term exposure the symptoms and signs develop in some, but not in all, workers (Seedorff and Olsen, 1990). Among the most common symptoms observed in examining workers after a long-term exposure to organic solvents are cognitive decline and memory disorders (Hanninen et al., 1976; Hane et al., 1977; Knave et al., 1978; Arlien-Soborg et al., 1979; Mikkelson, 1980; Orbaek et al., 1985; Gregersen et al., 1987; Baker et al., 1988; Bleecker et al., 1991; Hanninen et al., 1991; Spurgeon et al., 1992; Altmann et al., 1995; White et al., 1995). This research served as a basis for differentiating three different levels of psychological impairment produced by chronic neurotoxic over exposure to organic solvents. The mildest level of impairment, termed 'organic affective syndrome', was defined as one which includes subjective complaints of fatigue, mild memory and concentration difficulties. The term used to describe the second level of impairment was 'mild chronic toxic encephalopathy'; it includes both subjective neurotoxic symptoms and sustained changes in personality or mood, as well as deficits in performance on formal neuropsychological testing. Finally, the third level of solvent-induced toxic encelopathy refers to a severe neuropsychiatric condition characterized by global deterioration of intellectual and emotional functioning (National Institute for Occupational Safety and Health, 1987; Kuling, 1990).

Since decrease in memory had been one of the main complaints and had been one of the earlier symptoms to be detected in the different levels of psychological impairment, we decided to focus on a wide range of different aspects of memory functions trying to ascertain a possible profile of memory changes which take place following long-term exposure to organic solvents.

The literature on the cognitive effects of the central nervous system after long-term exposure to organic solvents mentions memory primarily as part of wider cognitive battery, usually evaluated with only partial measures which do not give an overall view of all memory aspects (Ratzon and Vakil, 1994). In the current study, we attempted to assess memory with standard memory tests that cover a large range of memory aspects and enable us to compare verbal vs. visual memory, learning rate vs. retention over time and efficiency of retrieval of both recently learned and long-stored information. Thus, we chose the following three tests: Wechsler Memory Scale — Revised (WMS-R) (1981), Benton Visual Retention Test (BVRT) (1938), and Rey Auditory Verbal Learning Test (RAVLT) (1964). The usage of a combination of this battery of three memory tests (WMS-R, BVRT and RAVLT) aimed to give a better perspective on memory features of long-term exposed workers.

2. Methods

2.1. Subjects

The group of subjects consisted of 31 industrial painters mate males who were exposed at work to organic solvents in a systematic and repetitive way, during the course of at least five years (mean years of employment 18.06). All members of the painting department were participants in the research (except for those who were excluded according to exclusion criteria). The department included workers who were spraying in closed indoor areas, spraying near a fume hood, rolling and brushing. The control group included 31 male workers not exposed to the organic solvents or other neurotoxic agents.

The control group was closely matched for age, education and country of origin. The mean age of exposed workers was 45.03 (S.D. = 8.73) and for the control group 45.32 (S.D. = 9.48). Mean years of education was 9.83 (S.D. = 1.77) for the exposed workers and 9.48 (S.D. = 1.91) for the control group. In both groups only 40.3% of the group were native Israelis, 50% were born in North African countries and 9.7% were born in Eastern Europe.

The exclusion criteria which was applied included the use of prescribed drugs affecting the nervous system, poor vision, alcoholism, status

post head trauma, psychiatric disorders in the worker's past and lack of a reasonable command of the language. According to mentioned criteria five workers were excluded (two for lack of a reasonable command of the language, one worker experienced head trauma in the past and one worker was using a prescribed drug affecting the nervous system).

2.2. Tests and procedure

All subjects were tested individually at the health clinic at the work place. Three standard memory tests were administered: Wechsler Memory Scale [revised (WMS-R) (1987)] which includes 13 subtests, each measuring different facets of memory. The following is a detailed list of the WSM-R: information and orientation questions, mental control, figural memory, logical memory, visual paired associate I, verbal paired associate I, visual reproduction I, digit span, visual memory span, logical memory II, visual paired associates II, visual paired associate II and visual reproduction II. Five summary scores are extracted from the test: general memory (MQ), verbal memory, visual memory, delayed memory and attention and concentration. The administration of the full test takes approximately 45 min.The Benton Visual Retention Test (BVRT) (Benton, 1938)A clinical and research instrument designed to assess visual perception, visual memory and visuoconstructive abilities. The test consists of 10 designs, with each design containing one or more figures. The time required for the administration of one form is approximately 5 min.

2.2.1. Rey Auditory Verbal Learning Test — (RAVLT) (Rey, 1964)

The Hebrew version of the test (Vakil and Blachstein, 1993) was administered in standard fashion (Lezak, 1983). The test consists of 15 common nouns, which are read to the subject for five consecutive trials (trials 1–5); participants are asked to remember as many words as possible. Each trial is then followed by free recall. In trial six an interference list of 15 new common nouns is presented, followed by a free recall of these new nouns. In trial seven participants are again asked to recall the first list. Twenty min later participants are once again asked to recall the first list (trial eight). They are then asked to identify the 15 words from the first list out of 50 words presented auditorily (also including the 15 words in the second list and 20 new common nouns) (trial nine).

2.2.2. Questionnaire

The questionnaire includes four sections: personal information, basic information on present work, work history and personal habits.

2.2.3. Exposure levels

The type of solvent exposure was defined by the chemist in the workplace. An occupational hygienist measured levels of personal exposure with Charcoal Tube Absorption/Desorption technique at the same day that the worker was evaluated (Eller, 1994). Since all monitoring levels of exposure in the area of the workers were too low to compute (they came out close to 0), an indirect exposure index was calculated. The workplace was weighted according to exposure intensity during the work process: spraying in an enclosed indoor area (4); spraying near a fume hood (3); rolling (2); and brushing (1). These values were multiplied by the proportion of time spent at that workplace per day and years worked at that specific workplace. The sum of this was multiplied with overall years of exposure to organic solvents. As there had been no significant process or changes at the workplace, stability over time was assumed.

2.3. Data analysis

The performance of the exposed and unexposed groups on the WMS-R and BVRT memory tests was compared using t-test for independent samples. In order to test whether the groups differ in their learning ability (RAVALT 1–5) and retention ability (i.e. trials 5 and 8) we used a repeated measures ANOVA with exposure (exposed and unexposed) as a between factor and trials as a within factor. Pearson's correlation was used to evaluate correlation between exposure index and memory scores of test battery. Finally,

Pearson's correlation was used also to look for a correlation between memory scores and age in the exposed and unexposed groups.

3. Results

As can be seen in Table 1 the performance of the unexposed group was better than that of the exposed group on all the memory measures of the WMS-R and BVRT tests.

Table 2 presents the mean number (and standard deviation) of words recalled in the eight trials of the RAVLT. The groups (exposed and unexposed) were compared on the learning (i.e. trials 1–5) and retention (i.e. trials five and eight) measures of the RAVLT.

3.1. Learning

The number of words recalled by the two groups in the first five trials of the RAVLT was submitted to a mixed-design ANOVA with group and learning trials as factors; the first effect being a between subject factor and the second effect being a within subject factor. The groups significantly differed from each other in the overall number of words recalled in the first five trials, $F_{1,60} = 19.63$, $P < 0.001$. There was also a significant increase in the number of words recalled from the first to the fifth trial, $F_{4,240} = 184.48$, $P < 0.001$. The interaction between these two main effects did not reach significance, $F_{4,240} = 1.02$, $P > 0.05$.

3.2. Retention

Retention was measured by comparing the number of words recalled on the fifth trial to the number of words recalled 20 min later on the eighth trial. As above the groups were significantly different from each other, $F_{1,60} = 12.25$, $P < 0.001$ and overall less words were recalled on the eighth trial, as compared to the fifth trial, $F_{1,60} = 106.45$, $P < 0.001$. The interaction between these two main effects did not reach significance, $F_{1,60} = 0.01$, $P > 0.05$.

Correlation is an additional way to analyze the relations between the exposure level to organic solvents and memory performance. Thus, Pearson's correlation was conducted between exposure index and memory test battery. These results are presented in Table 3. The negative correlations indicate that the higher the exposure index the lower the memory scores.

The correlation between age and memory performance was conducted separately for the exposed and unexposed group. As can be seen in Table 4, among workers after long-term exposure to organic solvents there was a significantly higher correlation between age and memory scores in compression to unexposed workers. These correlations included most memory subtests in the

Table 1
Comparison of memory scores of workers exposed to organic solvents and control-unexposed group

Test	Exposed workers		Unexposed workers		d.f.	*t*-test *P*-values
	Mean[a]	S.D.	Mean[a]	S.D.		
WMS-R (overall)	73.77	13.11	90.51	13.90	60	0.001
WMS-R (verbal)	79.35	13.34	93.58	14.56	60	0.001
WMS-R (visual)	77.25	17.72	89.03	14.33	60	0.001
WMS-R (delay)	78.19	8.49	93.38	10.04	60	0.001
WMS-R (attention)	76.96	13.14	86.45	13.74	60	0.007
BVRT (correct)	4.70	3.12	6.22	1.49	60	0.001
BVRT (errors)	8.90	4.65	5.16	2.92	60	0.001

[a]Mean and Standard Deviation.

Table 2
Mean number (and standard deviation) of words recalled in the eight trials of the RAVLT, by the two groups

Test	Exposed workers		Unexposed workers	
	Mean[a]	S.D.	Mean[a]	S.D.
RAVLT (trial I)	5.12	1.50	6.35	1.53
RAVLT (trial II)	7.74	1.98	9.03	1.88
RAVLT (trial III)	9.00	2.22	10.83	1.89
RAVLT (trial IV)	9.93	2.20	11.83	1.44
RAVLT (trial V)	10.41	2.12	12.29	1.61
RAVLT (trial VI)	4.12	1.60	5.51	1.57
RAVLT (trial VII)	8.58	2.71	9.96	2.16
RAVLT (trial VIII)	8.03	2.78	9.93	2.52

[a]Mean and Standard Deviation.

exposed group while only few memory subtests correlated with age among unexposed workers.

4. Discussion

In the present study workers exposed to mixed solvent were significantly impaired in all memory aspects measured compared to the unexposed group. These results are in accordance with previous reports in the literature (Hanninen et al., 1976; Orbaek et al., 1985 Gregersen et al., 1987; Gregersen, 1988; Spurgeon et al., 1992; Altmann et al., 1995; White et al., 1995). Although it is important to note that the groups were not significantly different in the learning rate of words over trials as indicated by the non-significant Group by Learning trials interaction. Suggesting that this memory measure is less sensitive to the effect of organic solvent exposure.

Since direct exposure could not have been calculated, an indirect exposure index was used taking into account intensity, proportion of time in a specific workplace, years of exposure and overall exposure to organic solvents. This method is used often in the absence of objective monitoring for solvent exposure. A semi-quantitative exposure index, such as years of employment and/or historical plant production data have sometimes been equated with estimates of solvent usage (Armstrong and Oakes, 1982; Fidler et al., 1987; Baker et al., 1988).

Table 3
Correlations between exposure index of organic solvents and the results of memory scores[a]

Tests	Exposed workers	
	R^2	P
WMS-R (overall)	−0.16	NS[b]
WMS-R (verbal)	−0.12	NS
WMS-R (visual)	−0.30	NS
WMS-R (delay)	−0.11	NS
WMS-R (attention)	−0.31	NS
BVRT (correct)	−0.17	NS
BVRT (omission)	0.30	NS
RAVLT (I)	−0.40	0.02
RAVLT (II)	−0.35	0.04
RAVLT (III)	−0.30	NS
RAVLT (IV)	−0.18	NS
RAVLT (V)	−0.03	NS
RAVLT (VI)	−0.38	0.03
RAVLT (VII)	−0.04	NS
RAVLT (VIII)	−0.00	NS

[a]The correlations were calculated using Pearsons' correlations.
[b]n.s., not significant.

Even though the scores of all memory tests were significant lower among workers following long-term exposure to organic solvents than non-exposed workers, only few subtests showed correlation with exposure index. One possibility for this discrepancy is that the indirect exposure level index used in this study is not a reliable measure. The second possibility is that although memory is affected by long-term exposure to organic solvents as reflected by the group differences, some memory aspects are more sensitive than others. Based on the results presented in Table 3 it seems that verbal memory as measured by the RVALT is the most sensitive memory measure to long-term exposure to organic solvents.

Cross-sectional studies are limited in that subjects are not followed over time to know whether performance deteriorates beyond that attributable to the normal aging process.

The major potential confounder and interacting factors of neurobehavioral performance are age and primary intellectual ability (Grandjean, 1989). In that sense the different effect of age on memory function of the exposed and unexposed

Table 4
Correlations between age and the results of the memory scores[a]

Tests	Exposed workers		Unexposed workers	
	R^2	p	R^2	p
WMS-R (overall)	−0.42	0.01	−0.05	NS[b]
WMS-R (verbal)	−0.19	NS	−0.08	NS
WMS-R (visual)	−0.37	0.04	0.06	NS
WMS-R (delay)	−0.44	0.01	−0.07	NS
WMS-R (attention)	−0.11	NS	−0.16	NS
BVRT (correct)	−0.02	NS	−0.17	NS
BVRT (omission)	0.10	NS	0.25	NS
RAVLT (I)	−0.44	0.01	−0.22	NS
RAVLT (II)	−0.39	0.02	0.04	NS
RAVLT (III)	−0.38	0.03	−0.23	NS
RAVLT (IV)	−0.41	0.02	−0.19	NS
RAVLT (V)	−0.34	0.05	−0.40	0.02
RAVLT (VI)	−0.28	NS	−0.31	NS
RAVLT (VII)	−0.42	0.01	−0.50	0.00
RAVLT (VIII)	−0.31	NS	−0.41	0.01

[a]The correlations were calculated using Pearsons' correlations.
[b]n.s., not significant.

population who were cautiously matched, suggest different age-related changes in memory functions in the exposed population in opposition to the unexposed population. Indeed the results of this study showed that a combination of long-term exposure to organic solvents and age had affected the memory scores of exposed workers.

Personnel reports suggested that this working population was extremely stable. The stable population allowed us to examine long duration of exposure ranging from 5 to 38 years. This was particularly important as solvent-induced central nervous system dysfunction is thought to require 5–10 years of exposure (Bleecker et al., 1991).

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