MULTIMODAL SENSORY DISCRIMINATION DEFICITS IN KORSAKOFF'S PSYCHOSIS*

R. G. MAIR,†‡ R. L. DOTY,§ K. M. KELLY,† C. S. WILSON,† P. J. LANGLAIS,†
W. J. McENTEE† and T. A. VOLLMECKE§

†Research Service (151C), Brockton VA Medical Center, Brockton, MA 02401, U.S.A.
‡Department of Psychology, Conant Hall, University of New Hampshire, Durham, New Hampshire, U.S.A.
§Smell and Taste Center, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.

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Abstract—A consistent impairment in odor identification was observed among a group of 21 amnesic patients, diagnosed as having Korsakoff's psychosis. In a subsequent study of eight Korsakoff and matched alcoholic control subjects, a comparable olfactory deficit was again demonstrated, as well as impairment in color discrimination and auditory perception. No such deficit was observed for a picture identification task designed to control for the non-sensory demands of the olfactory test. Step-wise multiple regression analysis showed a significant correlation between odor identification scores and the concentration of the primary metabolite of norepinephrine in lumbar cerebrospinal fluid. The data demonstrate a consistent coincidence between memory impairment and deficient sensory perception among patients with Korsakoff's psychosis.

INTRODUCTION

Global amnesias, such as those associated with Korsakoff's psychosis, are characterized by a selectively impaired ability to form memories of stimulus items that extends across sensory modalities [2, 45]. The occurrence of amnesia has also been related to information-processing deficits. These have been described among patients with Korsakoff's psychosis for measures of semantic encoding [2], as well as for tasks involving dichotic listening [13, 37], embedded figures [12, 45], matching photographs of unfamiliar human faces [8], discriminating the identity of short musical passages [45], and visual backwards masking [36]. Other reports have described deficits in fundamental aspects of olfactory discrimination. Earlier data suggested that Korsakoff's psychosis can: reduce odor recognition memory to chance level [16], impair psychophysical scaling of odor intensity [15, 17], and elevate 'thresholds', derived from magnitude estimation data [15, 17]. MAIR et al. [25] showed that these deficits were not a simple case of anosmia, sensory dulling or memory decay by demonstrating impaired, but above chance level, recognition of easily discriminable odors among 10 Korsakoff patients who exhibited normal detection sensitivity and a lack of decay in short-term odor recognition memory.

Taken together, the data provide evidence of impairments on several measures of odor perception for groups of Korsakoff patients; however, they do not indicate whether such deficits are a consistent symptom of this disease. If the olfactory and memory deficits of

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Korsakoff’s psychosis share a common pathologic basis, then signs of olfactory impairment should be observed consistently among patients rendered amnesic by this disease. It is also not certain whether these sensory discrimination deficits are modality specific. Jones et al. [15, 17] reported deficits in scaling the intensity of tastes and smells, but not of brightness or loudness. On the other hand, we have observed deficits in the consistency of color naming in the Stroop test [27] and color cancellation during McCollough effect testing (White and Mair, unpublished results) that may be indicitive of impaired hue discrimination. We now report that Korsakoff’s disease is consistently associated with deficient odor identification as well as impairments in visual and auditory sensory discrimination.

EXPERIMENT 1

Methods

Subjects. We tested 21 patients with Korsakoff’s psychosis, ranging from 40 to 66 yr old (mean = 57.9). All had a history of an acute episode of Wernicke’s disease or of an amnesia of sudden onset. None had a history of anoxia or showed signs of progressive mental deterioration and none showed evidence of mass or focal lesions on CT scan. All had IQ scores (WAIS) over 85 and an MQ (Wechsler Memory Scale) that was at least 20 points lower than their IQ. All had histories of alcoholism but were abstinent at the time of testing. Control data were obtained by randomly selecting test results for age and gender matched subjects from a large computerized data base [6].

Procedure. Testing took place at the Veterans Administration Medical Centers in Providence, RI and Coatesville, PA. Anosmia was first ruled out by clinical examination and by requiring that subjects discriminate the presence or absence of olfactory stimuli on eight consecutive trials without error (an odorant actually being present on half the trials). Odorants were presented by scratching with sandpaper a Microfragrance strip (3M Company, Minneapolis, MN) taken from the University of Pennsylvania Smell Identification Test (UPSIT), and holding this just under the subject’s nose [6]. To avoid problems associated with exhaustion of odorant by repeated sampling, each Microfragrance strip was sampled once and then discarded. On each of 40 UPSIT trials, subjects were presented with a strip containing a microencapsulated odorant and asked to match the perceived odor to one of four verbal descriptors that were presented at the same time as the odor. Details of the testing procedure have been described elsewhere [6].

Results

The Korsakoff patients scored an average of 16.57 ± 1.78 (S.E.M.) items correct on the UPSIT compared to controls who scored an average of 32.86 ± 1.22. This difference was significant (t = 6.459, P = 0.00005). Furthermore the impairment measured by the UPSIT was a consistent finding, with only two of 21 Korsakoff patients scoring 80% correct, a level achieved by 88% of an extensive (N = 1253) normative control group (Fig. 1). Item analysis did not show a significant difference in performance for odorants that are also strong trigeminal nerve stimulants (cf. [6]).

Data were available describing the concentration of the primary metabolites of norepinephrine (MHPG), dopamine (HVA), and serotonin (5-HIAA) in lumbar cerebrospinal fluid (CSF) for 10 Korsakoff patients at the time of their UPSIT testing. These data have been reported elsewhere [30]. Evidence has also been presented relating the concentration of CSF MHPG to the performance of patients with Korsakoff's psychosis on measures of anterograde amnesia, including odor recognition memory [28]. We thus sought to determine whether a similar relationship would exist for UPSIT performance and any of these monoamine metabolites. Stepwise multiple regression analysis showed a strong relationship between UPSIT performance and the concentration of MHPG (partial r = 0.87, P = 0.002) but not for HVA (partial r = −0.58) or 5-HIAA (partial r = 0.16).

Discussion

The results indicate that poor performance on the UPSIT is a consistent feature of
Korsakoff's psychosis. It is not convincing to ascribe the failure of the Korsakoff subjects to simple anosmia. All were able to detect consistently the presence or absence of odorants released from scratched Microfragrance strips and most individuals performed well above chance, yet worse than controls on the UPSIT (Fig 1). Finally, other patients with Korsakoff's psychosis have been shown to have odor discrimination deficits even though they perform normally on tests of absolute olfactory sensitivity [25].

It is striking that UPSIT performance should correlate with the concentration of CSF MHPG, the primary metabolite of norepinephrine, in much the same fashion as odor recognition memory and other measures of anterograde memory [28]. Although correlational analyses cannot establish causality, the association of these measures with the same monoamine metabolite supports the notion that they may share a common neuropathologic basis.

The results of Experiment 1 raised several questions. Can the failure of Korsakoff patients on the UPSIT be ascribed to a general inability to match sensory stimuli to verbal descriptors? Is the discrimination deficit apparent in this and other experiments [15–17, 25] limited to stimuli in the olfactory modality? Is the history of chronic alcohol abuse, common among the Korsakoff patients tested, a sufficient explanation for any observed perceptual deficits? Experiment 2 was undertaken to answer these questions.
EXPERIMENT 2

Methods

Subjects. Eight Korsakoff and eight alcoholic control subjects were tested in this experiment. Korsakoff subjects met the criteria described for Experiment 1. Two of the Korsakoff subjects had been included in Experiment 1, the others had not previously been included in olfactory experiments. The alcoholic control subjects had a minimum history of 10 yr of ethanol abuse, ranged between 51 and 64 yr old (mean = 59.7), 11.8 yr of education, and had averaged age-corrected scaled scores of 11.38 and 11.12, respectively, on the Information and Vocabulary subtests of the WAIS [47]. The Korsakoff subjects could not provide reliable drinking histories, ranged between 53 and 66 yr of age (mean = 60.6), averaged 10.3 yr of education, and had mean age-corrected scaled scores of 10.44 and 11.50, respectively, on the same two WAIS subtests. Compared to the controls, Korsakoff patients had lower mean peer-scaled scores [34] on the Memory Passage (7.40 compared to 11.37) and Associative Learning (7.55 compared to 13.37) subtests of the Wechsler Memory Scale. The differences between the groups were significant for Memory Passages (t = 2.69, P = 0.017) and Associative Learning (t = 7.64, P < 0.001) but not for Information (t = 0.796, P = 0.44) or Vocabulary (t = 0.320, P = 0.69).

Procedure. After screening for anosmia as in Experiment 1, four sensory tests were administered: the UPSIT, the Picture Identification Test (PIT), the Farnsworth–Munsell 100 Hue Test [10], and the Seashore Measures of Musical Talent [40]. Olfactory testing was carried out as described in Experiment 1. The PIT is a test of identical format to the UPSIT except that the subject is required to match a picture instead of an odor to one of four verbal descriptors. It thus provides a means to control for the non-olfactory cognitive demands of the UPSIT. Except for the modality of stimuli, testing procedures were the same for the PIT and the UPSIT. The Farnsworth–Munsell 100 Hue Test involves comparison of simultaneously presented hues selected to be 'just easily noticeable' as different colors by normal subjects. This test was carried out and scored following standard procedures [10]. Hue samples were illuminated by two 122 cm long, full spectrum Daylite 65 bulbs (Duro Test Corporation) positioned 50 cm above the color chips. The Seashore test requires subjects to discriminate between successive auditory stimuli on the basis of different aspects of sound (pitch, loudness, rhythm, time, timbre, and tonal memory). Series A of the Seashore Measures of Musical Talent was presented by earphones via a Sony BM11 tape recorder. Standard testing procedures were followed [40] with the modification that instructions were repeated after every 10 items.

Results

One Korsakoff subject was diagnosed as anosmic and was thus eliminated from both the UPSIT and PIT analyses. On average, the Korsakoff subjects were correct on 16.00 ± 2.81 (S.E.M.) items on the SIT and 36.00 ± 1.00 items on the PIT, while alcoholic controls scored 32.75 ± 2.60 and 39.00 ± 0.38 respectively, on these same two tests. Two-way analysis of variance demonstrated a significant effect of group [Korsakoff vs control: F(1, 25) = 24.50, P < 0.001], test UPSIT vs PIT: F(1, 25) = 43.27, P < 0.001], and group x test interaction [F(1, 25) = 11.87, P = 0.002]. Post hoc analysis by the Newman–Keuls test demonstrated a significant difference between Korsakoff and control groups for the UPSIT (P < 0.01) but not the PIT (P < 0.10). Korsakoff patients performed significantly better on the PIT than the UPSIT (P < 0.01) whereas control subjects did not.

Compared to controls, Korsakoff patients were impaired on both the Farnsworth–Munsell 100 Hue Test and the Seashore Measures of Musical Talents. On the Farnsworth–Munsell test, an error score was calculated based on the sum of deviations between adjacent hue samples, as arranged by a given subject [10]. The Korsakoff group ranged between 88 and 820 errors with a mean of 356.8 ± 93.8 (S.E.M.) and the controls ranged between 47 and 311 errors with a mean of 127.8 ± 43.8. The difference between these means was significant (t = 2.29, P = 0.036). Errors were distributed in all areas of the visible spectrum and did not fit the patterns associated with protan, deutan or tritan color blindness for any individual subjects (Fig. 2). Split-plot analysis of variance showed an overall impairment for the Korsakoff patients across the six subtests of the Seashore test [F(5, 42) = 4.403, P = 0.039]. There were no significant interactions between the subtests [F(5, 42) = 0.346] and post hoc analyses did not show a significant deficit for any single subtest when considered alone (Table 1). There were insufficient data describing the concentration of monoamine metabolites in
the lumbar CSF of subjects included in Experiment 2 to carry out correlational analyses like those in Experiment 1.

**Discussion**

The results of Experiment 2 provide a precise replication of the smell identification deficit demonstrated in Experiment 1. The high incidence of impairment of the UPSIT is consistent

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<td>2.7</td>
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<td>Control</td>
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<tr>
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<td><strong>Tonal memory</strong></td>
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with the possibility that the olfactory and memory disorders associated with Korsakoff’s syndrome might result from a common pathologic mechanism. The apparent coincidence of olfactory and memory deficits in this disease is intriguing in view of similar observations made of the well known amnesic H.M. [9]. According to Eichenbaum et al. [9], H.M. is impaired in odor discrimination and identification, but retains a normal ability to detect weak odorants and discriminate differences in odor intensity. The observation of deficient odor discrimination and identification, in face of normal absolute sensitivity, is consistent with results described here and elsewhere [25] for amnesic cases of Korsakoff’s syndrome.

Given the strong performance of Korsakoff patients on the PIT, a test using verbal descriptors identical to the UPSIT, it is not convincing to ascribe their poor performance on the UPSIT to an impaired ability to match verbal descriptors to sensory stimuli. On the other hand, the results of the PIT do not rule out the possibility that Korsakoff patients have visual discrimination deficits. The near-perfect scores of the controls on the PIT suggest that this test may be insensitive to perceptual impairment due to a ceiling effect. The similarity of control scores in Experiments 1 and 2 and the significant difference in the UPSIT scores of Korsakoff and alcoholic control subjects in Experiment 2 argue against the possibility that chronic abuse of ethanol can account for the olfactory deficits described in the present experiments.

The deficits measured by the Farnsworth–Munsell and Seashore tests, as well as those reported here and elsewhere for olfactory tasks [15–17, 25] indicate that the discrimination deficits associated with Korsakoff’s psychosis encompass a number of sensory systems. These deficits are consistent with the range of impairment reported among Korsakoff patients for more complex measures of perception [2, 8, 12, 13, 25, 27, 28, 35–37, 45]. It has been argued that patients with Korsakoff’s psychosis exhibit signs of frontal lobe pathology [43] and it is thus possible that the Farnsworth–Munsell deficit could reflect an impaired ability to arrange hue samples in a sequence. There are two arguments against this possibility. First, Korsakoff patients perform normally on the Picture Arrangement subtest of the WAIS [2, 30, 45], a task involving a similar sequencing of concurrently presented stimuli. Second, patients with right or left frontal lobectomies are unimpaired in performance on the Farnsworth–Munsell task (Gotman-Jones, personal communication).

Similarly, it is possible that memory impairments contribute to poor performances observed for some perceptual tasks, particularly those (like the Seashore) which require a comparison of successively presented stimuli. However, for others like the Farnsworth–Munsell and the UPSIT, there is no requirement to remember sensory stimuli beyond the span of immediate perception and thus little indication that performance was made worse by memory difficulties. Likewise, for the Seashore and odor recognition tasks [25], stimuli were presented within time limits and under conditions that are not normally associated with a sharp temporal decay in performance.

Jones et al. [15–17] have argued that olfactory perception could be selectively impaired in Korsakoff’s psychosis by the diencephalic lesions that are characteristic of this disease. The dorsomedial (MD) nucleus of the thalamus is the only structure consistently affected by this disease [29, 46] that has been shown to receive an olfactory input [18, 19, 22, 38, 39]. Thus it might be argued that Korsakoff’s disease produces selective olfactory deficits by damaging olfactory processes in MD. There are, however, several problems with this argument. First, it is by no means certain that olfactory projections to MD are affected by Korsakoff’s disease. In the rat, fibers of this transthalamic pathway arise in the endopyriform nucleus and terminate in a restricted zone within the central dorsal region of MD [38, 39]. In man the
location of this pathway is not known. In monkey there is evidence of olfactory input to the 
medial magnocellular zone of MD [1]. Although MD is consistently damaged at 
postmortem in cases of Korsakoff's amnesia there is evidence that these lesions are often 
restricted to the ventral medial portions of MD, sparing the larger part of this nucleus, 
including central and dorsal zones [29, 46]. In the rat, a subacute bout of thiamine deficiency 
can produce behavioral and pathologic changes like those in Korsakoff's disease, including 
lesions of ventral MD, but not in the dorsal regions of MD that receive olfactory input 
[20, 23, 24]. Second, there is no indication that MD lesions produce impairments of simple 
odor discrimination like those attributed to Korsakoff's psychosis. Although MD has 
reciprocal connections with apparent olfactory areas in orbital and insular cortex, there are 
much more direct and robust projections to these same areas from pyriform cortex [22, 38] 
and thus no requirement for a transthalamic relay to transmit olfactory information to 
neocortex. In the rat, MD lesions have been shown to affect higher-order olfactory processes, 
such as reversal learning, without affecting simple odor quality discrimination [42]. Third, 
MD receives robust inputs from multimodal sensory areas, including amygdala, temporal 
cortex, and all areas of frontal granular cortex [18, 19, 33], and thus it is questionable 
whether it should be considered a part of a specific olfactory pathway.

Our results indicate that the sensory discrimination deficits associated with Korsakoff's 
psychosis are not restricted to olfaction. If this is the case, then parsimony requires the 
consideration that there is a generalized impairment in attention or perception that produces 
multimodal deficits in sensation. Others have argued that Korsakoff's psychosis is associated 
with a fundamental impairment of attention [26, 35, 45]. There are at least two possible 
mechanisms that might produce such a deficit. The first involves the 'non-specific' 
intralaminar thalamic nuclei, adjacent to ventral MD. These nuclei have been implicated in 
the control of attention and the promotion of cortical-cognitive processing [41, 44] and are 
located in the same areas as the lesions associated with the amnesias of Korsakoff's psychosis 
[29, 46] and thalamic infarcts [3] in man and thiamine deficiency in the rat [20, 23, 24]. The 
second possibility is that attention is impaired by diminished brain norepinephrine (NE) 
activity. Physiologic studies have provided evidence that NE modulates the activity of 
sensory neurons in olfactory [14, 31], auditory [11], and visual [21, 32] pathways. Other 
studies have provided evidence that NE activity is diminished by Korsakoff's psychosis in 
humans [26–28, 30] or thiamine deficiency in animals [20, 23, 24]. This possibility is 
supported directly by our observations of significant correlations observed between CSF 
MHPG and performance on the UPSIT and odor recognition [28] tasks. It is supported 
indirectly by observations that UPSIT performance is also impaired by other conditions that 
have been associated with diminished brain NE activity, namely aging [4], Parkinson's 
disease [7], and senile dementia of the Alzheimer's type [5].

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