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Neurochemical Specificity of Learning: Dopamine and Motor Learning

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In previous reports of studies of patients with alcoholic Korsakoff's psychosis, data were presented showing significant correlations between neuropsychometric measures of amnesia and the CSF levels of the major brain metabolite of norepinephrine (NE), which was consistently reduced among a large group of experimental subjects. Dopamine (DA) metabolite concentrations in the CSF of this same patient population were also significantly lowered but to a lesser degree and less consistently than the NE metabolite. CSF levels of the DA metabolite did not correlate with any measures of amnesia but did significantly correlate with performance on the Digit-Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale (WAIS), which involves psychomotor skill learning. DSST performance did not correlate with CSF levels of the NE metabolite. These findings led to the hypothesis that the acquisition of motor learning skills is related to brain DA activity.

In this study, we tested the hypothesis by correlating the ability of a group of Korsakoff patients to learn two different motor tasks (rotary pursuit and mirror tracing) with the concentrations of CSF metabolites of NE, DA, and serotonin. For both tasks, improvement in performance over three daily testing sessions significantly correlated only with the DA metabolite levels. The data are consistent with the hypothesis of a specific role for DA in motor learning.

INTRODUCTION

A large number of molecules have been implicated as being important for learning and memory, but investigations into relationships between molecule and specific aspects of these cognitive functions are lacking. During the course of a nine-year study of the role of brain monoamines in the learning and memory impairments of patients with Korsakoff's psychosis, we have reported consistently reduced levels of 3-methoxy-4 hydroxyphenylglycol (MHPG), the major brain metabolite of norepinephrine (NE), in the cerebrospinal fluid (CSF) of Korsakoff patients, which correlate with psychometric measures of amnesia [1–3]. The data also demonstrated a less consistent but significant reduction of CSF homovanillic acid (HVA), the major metabolite of dopamine (DA), among a large group of Korsakoff patients [2]. CSF HVA levels did not correlate with any psychometric measures of amnesia, however, but did predict performance on the Digit-Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale (WAIS), a measure which did not correlate with the concentration of CSF MHPG among our experimental subjects [3]. This double dissociation is to our knowledge the first evidence in which two measures of neurochemical activity differ significantly in their ability to predict performance on different behavioral tasks within the same group of human subjects.

A large component of the DSST measures psychomotor learning ability, and it is generally recognized that Korsakoff patients usually (but not always) perform poorly on this neuropsychometric test. Patients with Parkinson's disease also show significant deficits in performance on the DSST [4] and have reduced concentrations of CSF HVA [5–7]. Inasmuch as psychomotor speed is also a component of the DSST, the poor performance of parkinsonian patients on this test could be attributed to the innate motor disabilities of the illness, particularly hypokinesia. However, signs of Parkinsonism have not been observed in any of the Korsakoff patients we have studied, even in those with CSF HVA levels well below the mean control value [2,3]. Thus, the reported correlation between DSST performance and concentration of CSF HVA in Korsakoff patients [3] has led to the hypothesis that motor learning abilities are related to levels of central DA activity. To examine this hypothesis further, we measured performance of a group of patients with Korsakoff's psychosis on tests which require a greater degree of psychomotor skill than the DSST. We now report the results of these experiments.

MATERIALS AND METHODS

Subjects

Eight patients, all white men, who were admitted to the Providence, RI V.A. Medical Center between July 1981 and January 1983 with a diagnosis of alcoholic Korsakoff's psychosis, were selected for the study. All had histories of long-term heavy alcohol consumption in addition to a verified occurrence of Wernicke's encephalopathy or an abrupt onset of amnesia at least six months earlier. None demonstrated evidence of progressive deterioration of cognitive or intellectual function nor, on CT scan, signs of focal or mass lesion. None had histories of anoxic episodes, other psychiatric illness, or impairment of coordination of the upper extremities. Their average age was 57.9 years. Before proceeding with any experiments, a full explanation of all procedures was given to each subject and informed consent was obtained.

Neuropsychometric Testing

All subjects were given the WAIS and Form I of the Wechsler Memory Scale, which determined their suitability for inclusion in the study according to the criteria of McEntee and Mair [1]. The results of these and a number of other tests which measured a variety of cognitive and perceptual functions are reported elsewhere [3]. For the purpose of this study, the eight patients were given two tasks requiring considerable psychomotor skill and effort to perform. One subject dropped out of the study after finishing only one of the tasks. None of the subjects had prior exposure to either task.

Task 1, Rotary Pursuit (RP): The test was conducted with a Rotary Pursuit apparatus, model number 2203, Lafayette Instrument Co., Lafayette, IN (School of Aviation Medicine specifications). With the turntable rotating at 60 rpm, the subject was instructed to keep the tip of the stylus in contact with the metal target as long as possible for each 20-second trial. Time on target was automatically recorded with a Gerbrands digital millisecond clock/counter, model number 1270. Subjects were given thirty 20-seconds trials each day for three consecutive days with a 20-second rest between each trial. Performance was graded by subtracting the mean time on target on day one from the mean time on target on day three.

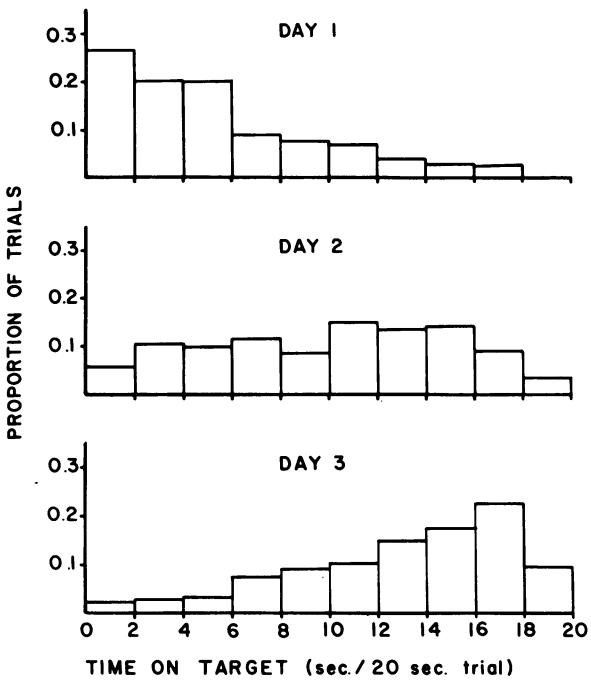

FIG. 1. Performance on RP. Histogram shows the mean time on target for the eight subjects for all 20-second trials over the three-day testing period. Improvement in performance is linear.

Task 2, Mirror Tracing (MT): Using a Mirror Tracing apparatus, model number 2705, Lafayette Instrument Co., Lafayette, IN, the subject was required to trace the outline of an object, in this case a six-pointed star, while looking into a mirror. Performance was measured by recording the time, in seconds, required to trace the target accurately within the prescribed boundaries. Subjects were given ten consecutive trials on three consecutive days. Learning performance was graded by dividing the mean time to trace on day three by the mean time to trace on day one.

Analyses of CSF

Lumbar puncture was performed on all subjects following psychometric testing. Patients were allowed to move about freely without restriction and ate a standard hospital diet. Spinal taps were performed between 10 and 11 A.M. Although most patients underwent lumbar puncture more than once, only data from the CSF specimen obtained following the initial psychometric battery were used. Motor learning testing was done up to several weeks following lumbar puncture but the results of monoamine metabolite assays were unknown to the tester. Monoamine metabolite assays were done on the first two ml of CSF collected from each patient. Specimens were promptly frozen and stored at −70° C for no longer than six months until analyzed. CSF samples were analyzed for free-MHPG, HVA, and 5-hydroxy indoleacetic acid (5-HIAA) by the high-performance liquid chromatography method of Langlais et al [8], which does not require internal standards.

RESULTS

Figure 1 shows the mean performance of the eight patients on RP over the three-day testing period. There was a significant increase in mean time on target across the three

Table 1
Performance of Individual Subjects on RP and MT and Respective CSF Monoamine Metabolite Measurements (ng/ml)
(Subjects are listed in descending order of performance on RP. Ages of subjects at time of testing are in parentheses.)

Subject	DSST	RP	MT	HVA	MHPG	5-HIAA
1(40)	65	11.0	.183	52.3	6.8	19.7
2(59)	32	9.7	.218	42.1	8.9	28.8
3(58)	42	7.6	.204	52.4	9.1	72.9
4(62)	31	7.4	.284	28.5	9.4	20.5
5(63)	36	5.4	.313	16.2	5.4	40.1
6(62)	28	4.8	—	27.5	4.8	14.5
7(59)	37	4.3	.231	22.3	8.1	12.0
8(60)	24	3.5	.289	18.4	3.5	23.1

DSST is age-corrected scaled score.
Performance on RP graded: mean time (seconds) on target on day 3 minus mean time on target on day 1
Performance on MT graded: mean time to trace (seconds) on day 3 divided by mean time to trace on day 1
Mean CSF monoamine metabolite levels (ng/ml) for 17 non-neurological control subjects [2]:
HVA = 39.46 ± 1.78; MHPG = 10.98 ± 0.74; 5-HIAA = 22.20 ± 1.38
(DSST data is summarized in [3].)

test days [F (2,14) = 35. 13, $p < .001$)]. Thus the Korsakoff patients were capable of learning the task over time. Figure 2 shows that all subjects learned the MT task over the three-day testing period with significant savings between testing days [F (2,12) = 35.24, $p < .001$]. Individual differences among the subjects, as to the level of acquisition of the MT task, are evident in Fig. 2.

Table 1 shows the data from the monoamine metabolite measurements and the performance grades for RP and MT for individual subjects. Table 2 lists the simple correlation coefficients between CSF monoamine metabolite levels and the three tests which are presumed to measure psychomotor learning abilities, namely, the DSST, RP, and MT. Stepwise multiple regression analysis showed that only CSF HVA significantly correlates with RP [(F (1,6) = 14.33, $p < .01$] and MT [F (1,5) = 16.97, $p < .01$] but not DSST [F (1,6) = 5.00, $p = .065$], while significant correlations are not demonstrated between CSF MHPG or 5-HIAA and any of these behavioral measurements. Table 2 also shows the simple correlation coefficients between performances on each of the three motor learning paradigms which significantly correlate with one another.

Table 2
Simple Correlation Coefficients (r =) Between Performance on RP, MT, and DSST and the CSF Levels of Each of the Three Monoamine Metabolites and Between Performances on Each of the Three Behavioral Tests

	MHPG	HVA	5-HIAA	RP	MT	DSST
RP (n = 8)	.56	.84**	.18		.68*	.70*
MT (n = 7)	.48	.89**	.14			.69*
DSST (n =8)	.24	.68*	.12			

*$p < .05$
**$p < .01$

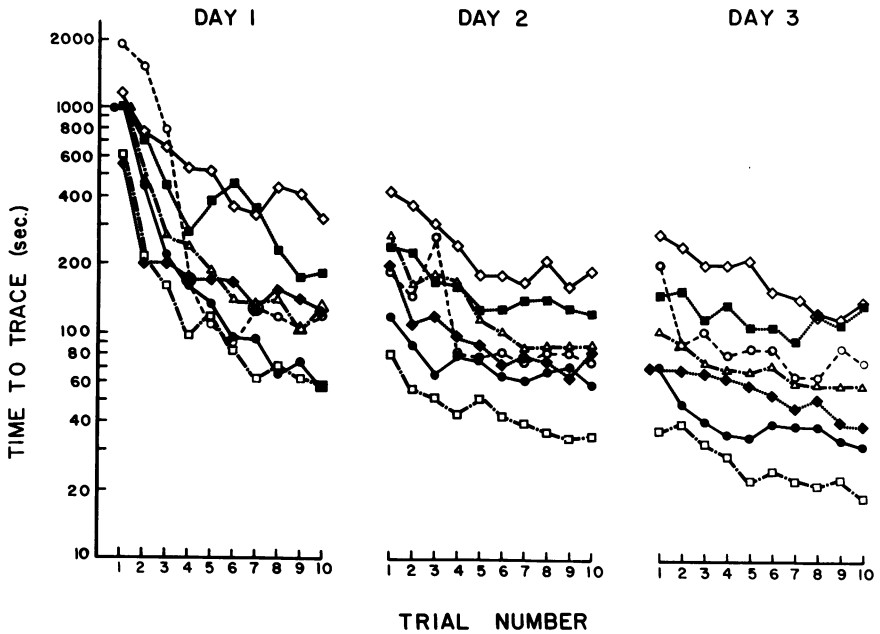

FIG. 2 Performance on MT. Logarithmic plot of time to trace for each of the seven subjects, who completed the task, on each trial for the three-day test period.

DISCUSSION

The data reported here suggest that motor learning ability is, at least in part, dependent on the amount of central DA activity. Obviously, the behavorial tests used in this study do not exclusively measure motor learning but require utilization of other cognitive capacities, for example, eye-hand coordination and visual reversal skills. Nonetheless, performances of our subjects on three different tasks, DSST, RP, and MT, all having a large motor learning component, significantly correlate with each other. These correlations, taken together with the significant correlations between patient performance on each of the three tasks and the concentration of CSF HVA but not of CSF MHPG or 5-HIAA, are consistent with the hypothesis of an important role for DA in motor learning. Few would argue against an important role for DA in motor performance as evidenced by the vast amount of scientific data derived from observations of patients with Parkinson's disease, but to our knowledge this is the first report which presents evidence linking DA with motor learning capabilities in humans. Although some of our patients had concentrations of CSF HVA in the range reported for parkinsonian patients [5–7], none showed signs of that illness which could affect performance on the behavioral tests used in the study. Likewise, peripheral neuropathy, a disorder commonly found in association with Korsakoff's disease, did not appear to be a factor in patient performance. In fact, the patient with the most advanced degree of neuropathy was the best performer on all three tests.

Other evidence to support an important role for DA in motor learning comes from the report of Langlais et al. [9] in their study of CSF neurotransmitter metabolites in neurologically normal infants and children. These investigators found CSF HVA levels to be several times higher than that of the average adult during the first two years of

life and still well above the adult level near the end of the first decade of life, suggesting maximal DA activity during the critical period for motor development.

There is general agreement among investigators in the field that most HVA present in lumbar CSF results from striatal DA catabolism. Thus, it might be interesting to speculate that reduced levels of CSF HVA, when found in Korsakoff patients, are related to pathophysiologic involvement of the medial portion of the caudate nucleus. Such a concept is consistent with the characteristic periventricular distribution of lesions associated with the Wernicke-Korsakoff syndrome, although pathologic lesions in the neostriatum have been reported only rarely in patients with Wernicke's encephalopathy [10,11]. Therefore, if significant reduction of CSF HVA, as found among a large group of Korsakoff patients [2], is to be attributed to disease of the medial caudate nucleus, such involvement would not be detectable by the light microscope.

Cohen and Squire [12] have called attention to a dichotomy among amnesics in that they are impaired in their ability to learn factual information while procedural or skill learning is spared. From a neural model viewpoint, Mishkin and Petri [13] propose a dual system for learning; a limbo-diencephalic-neocortical circuit underlying the learning and storage of factual knowledge requiring cognitive processes and a cortico-striatal system for acquisition of procedures or habitual skills. Our results provide support for these concepts in that Korsakoff patients with characteristic diencephalic lesions demonstrate consistent deficits in learning facts. But while they can learn procedures (habitual skills), we suggest the degree of their ability to do so is related to the amount of involvement of striatal dopaminergic pathways as reflected by measurements of CSF HVA, which at present is the most generally accepted *in vivo* method for estimating brain DA activity.

Other examples of the dissociation between factual information and skill learning as they relate to specific neurochemical substrata are the results of two separate drug studies [14,15] in which treatment of two different groups of Korsakoff patients with clonidine, an alpha-2 adrenergic agonist, produced significant improvement in certain measures of anterograde amnesia (factual information) but did not significantly change DSST performance.

The previously reported findings of significant correlations between measures of verbal learning and recall and levels of CSF MHPG [1–3] and improvement of certain measures of anterograde amnesia, but not of DSST performance, in Korsakoff patients treated with clonidine [14,15], taken together with the results of the present study, lead us to conclude that capabilities for factual learning are associated with changes in brain NE activity, while the acquisition of new psychomotor skills is affected by levels of brain DA activity.

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