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Bilateral Frontal Lobe Disease and Selective Delayed Response Deficits in Humans

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The performance of patients with frontal lobe disease was compared with that of amnesic patients (with etiology of alcoholic Korsakoff's disease or surgically treated ruptured anterior communicating artery aneurysm) on tasks known to be sensitive to frontal lobe damage in nonhuman primates: delayed alternation (DA) and delayed response (DR). Alcoholic patients with no clinical memory impairment served as controls. Results showed that bilateral frontal lobe damage in humans is associated with impairment on both tasks. In addition, there was no relation between performances on DA and DR and performance on standardized tests of memory, a result strengthening the suggestion that the former tasks are not sensitive to anterograde amnesia in humans.

The study of neurological behavioral dysfunction in humans with experimental paradigms adopted from the animal literature has been well established to be of value for identifying impairments in brain-damaged patients (Oscar-Berman, 1984; Oscar-Berman & Zola-Morgan, 1980a, 1980b; Oscar-Berman, Zola-Morgan, Öberg, & Bonner, 1982; Weiskrantz, 1978). The anatomical significance of the deficits in humans, however, remains uncertain. We therefore report our findings on the abnormal performance by human neurological patients on two tasks that are sensitive to frontal lobe damage in monkeys: delayed alternation (DA) and delayed response (DR; Jacobsen, 1935; Jacobsen, 1936; Jacobsen & Nissen, 1937). Deficits on these tasks have been attributed to various factors such as memory loss, hyperreactivity, disinhibition, and abnormal appreciation of spatial cues (Konorski, Teuber, & Zernicki, 1972; Warren & Akert, 1964). To determine the anatomical and functional significance of impaired performance on DA and DR in humans, we evaluated patients with bilateral frontal lobe lesions verified by computerized tomography (CT). In addition, we studied amnesics with alcoholic Korsakoff's syndrome (Talland, 1965) and surgically treated ruptured anterior communicating artery aneurysms (Talland, Sweet, & Ballantine, 1967). The amnesics were included to examine the contribution of anterograde memory loss to performance on DA and DR in view of the finding by Oscar-Berman et al. (1982) that alcoholic Korsakoff subjects do poorly on these tests.

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Method

Patients

Thirty-five males, comprising four diagnostic groups, participated in the study (Table 1). They were selected from patient populations at the Boston and Brockton Veterans Administration Medical Centers. Subsequent to an explanation of the experimental procedures, written informed consent was obtained from the participants and, when appropriate, from their responsible representatives. The first group consisted of 6 patients with bilateral frontal lobe lesions documented on CT scans (described in Results). The frontal patients were further categorized into 3 subjects with good anterograde and retrograde memory and 3 with poor memory functions. The etiologies in the frontal patients with good memory consisted of trauma in 2 and a gunshot wound in 1. In the patients with poor memory, there were 2 with trauma and 1 with a tumor (see Table 2).

The second diagnostic group consisted of 5 patients with amnesia that developed following surgically treated anterior communicating artery aneurysm rupture. Anterograde amnesia ranged from mild to severe. The lesion in this group is thought to be in the basal forebrain (Damasio, Graff-Radford, Eslinger, Damasio, & Kassell, 1985).

The third group consisted of 12 patients with alcoholic Korsakoff's syndrome. All had a history of chronic alcoholism and clinically significant memory impairment.

The fourth group consisted of 12 alcoholic controls. The alcoholics were included to control for the effects of alcohol abuse per se on any deficits observed in the Korsakoff patients. They had been hospitalized for nonneurological problems, such as fractures, urinary infections, and so on, and had no known pathology of the central nervous system.

The Korsakoff and alcoholic patients (except for one of the alcoholics who was dropped because he obtained an error rate on DR

Table 1
Performance of Subjects on Standardized Tests of Intellectual Function

Group	*n*	Age	WAIS	Wechsler Memory Scale	
			Full-Scale IQ	Memory Quotient	Paired Associates
Frontal					
Good memory	3				
M		45.3	89.7	105.7	13.8
SD		20.6	3.5	6.5	2.3
Poor memory	3				
M		53.3	90.3	84.7	8.0
SD		14.2	13.8	4.0	1.4
Korsakoff	12				
M		53.6	104.3	80.3	6.4
SD		9.4	7.4	4.8	1.7
ACoA	5				
M		45.6	109.4	99.6	10.3
SD		10.5	21.0	14.7	1.3
Alcoholic	12				
M		39.7	—	—	13.3
SD		7.6	—	—	4.0

Note. WAIS = Wechsler Adult Intelligence Scale; ACoA = anterior communicating artery disease.

that was greater than three standard deviations above the mean of other patients) were the same patients described in previous articles (Oscar-Berman & Zola-Morgan, 1980a, 1980b; Oscar-Berman et al., 1982). They had all been subjects for the DA and DR tasks already reported (Oscar-Berman et al., 1982). Therefore, the results for these patients were extracted from previously published data (with revised criteria, as described in Method).

Table 1 presents a summary of the performance of the patients on two standardized tests of intellectual function, the Wechsler Adult Intelligence Scale (Wechsler, 1955) and the Wechsler Memory Scale (Wechsler, 1945). The Korsakoff and alcoholic patients had not received the complete Wechsler Memory Scale (Oscar-Berman et al., 1982). For these groups, scores on paired-associate learning are reported as a representative measure of memory (Walsh, 1978). Table 3 presents a summary of the performance of the frontals and the patients with anterior communicating artery disease on the Wisconsin Card Sorting Test (Berg, 1948; Grant & Berg, 1948) which was given to assess perseveration of previous response patterns. The Korsakoff and alcoholic patients had not received this test when they were studied (Oscar-Berman et al., 1982).

Table 3
Performance on Wisconsin Card Sorting Test

Group	No. sorts	% correct	% errors attributed to perseveration	
			Category[a]	Consecutive[b]
Frontal				
M	2.5	48.3	14.0	71.3
SD	2.1	14.0	9.1	13.6
n	6	6	4	6
ACoA				
M	4.4	61.6	13.5	78.4
SD	2.3	19.5	2.7	10.5
n	5	5	5	5

Note. ACoA = anterior communicating artery disease.
[a] Errors characterized by a sort according to the dimension of the previous correct category. [b] Errors characterized by a sort according to the same dimension as immediately preceding incorrect sort.

Apparatus and Procedure

The DA and DR tests were given in a modified version of the Wisconsin General Test Apparatus adapted for use with human subjects and described by Oscar-Berman and Zola-Morgan (1980a, 1980b). The investigator and the patient sat facing each other across a table and were separated by a wooden frame approximately 61 cm wide and 53 cm high. A black curtain was anchored to the frame in such a way that it could be raised to reveal a stimulus board (53 × 28 cm) containing two reinforcement wells. The wells were 24 cm apart from center to center and were covered by identical black square stimulus plaques (7.6 × 7.6 × 0.5 cm). When the curtain was in the lowered position, the patient could see neither the stimuli nor the investigator. When the curtain was raised for each trial, the patient could see the stimuli and the hands of the investigator, but not the investigator's face.

The DA and DR tasks were carried out essentially as previously described (Oscar-Berman et al., 1982). The patient was seated opposite the investigator, with the curtain lowered between them. The investigator then explained to the patient in very general terms the requirements of the task:

> Mr. J., I'm going to show you two black plaques. Underneath one of them is a penny. I want you to try to get the penny every time the curtain goes up. When you find a penny, put it in the box next to you, and at the end of the session you may keep all the money you've made. If you want to stop at any time, we can. All right? Remember, your task is to try to get the penny

Table 2
Clinical Profile and DA and DR Performance of Frontal Subjects

Frontal subject/patient no.	Etiology	Age	WAIS	Wechsler Memory Scale		DA	DR
			FSIQ	MQ	Paired Associates (subtest score)		
Good memory							
1	gunshot wound	47	90	99	12.5	5	0
2	blunt trauma	65	93	112	12	20[a]	18[b]
3	blunt trauma	24	86	106	17	3	0
Poor memory							
4	blunt trauma	37	106	84	9	6	0
5	meningioma	63	80	89	9	11	2
6	blunt trauma	60	85	81	6	33[a]	32[b]

Note. DA = delayed alternation; DR = delayed response; WAIS = Wechsler Adult Intelligence Scale; FSIQ = Full-Scale IQ.
[a] Reached failure criterion on DA. [b] Reached failure criterion on at least one delay interval.

every time the curtain goes up. There will always be a penny under one of these black plaques. Any questions?

The first trial was initiated by raising the curtain while the investigator reminded the patient again: "Remember, you want to get a penny every time."

There was one 5-s DA problem administered. On the first trial of the DA problem, both plaques were baited with pennies. For the second trial, the penny was put under the side not chosen on the preceding trial. A correction procedure was used on this task such that a penny remained on one side until the patient made a correct response (thus completing a trial). On the trial following a correct response, the opposite side was baited. There was a 5-s intertrial interval, and learning criterion was 12 consecutive correct responses. Failure criterion was 45 trials. This differed from the failure criterion of 400 trials previously used by Oscar-Berman et al. (1982).

There were four DR problems with 0-, 10-, 30-, and 60-s delays, respectively. The same black plaques used for DA were used in the DR tasks. With two plaques in position covering the wells and with the curtain raised, the investigator explained that a penny was going to be placed underneath one of the plaques and that as soon as the penny was covered with one of the plaques, the curtain would be lowered. The investigator stated that after the curtain was raised again, the patient could move the plaque and take the penny. The plaques were baited, in full view of the patient, according to a modified random schedule (Gellermann, 1933). Learning criterion on each DR problem was 9 correct responses in a block of 10 trials. Failure criterion was 40 trials, which differed from the 50 trials used by Oscar-Berman et al. (1982). For the 0-s delay, the curtain was lowered for a very brief instant and then quickly raised again. For the 10-, 30-, and 60-s delays, the investigator explained that the patient would have to wait a bit before taking the penny. After baiting the appropriate plaque in full view of the patient, the curtain was lowered. At the end of the delay interval, the curtain was raised, which permitted the patient to retrieve the penny from under the plaque thought to be correct. A noncorrection procedure was used for all four DR problems.

Results

DA and DR Tasks

Figure 1 shows the number of errors made on DA and DR. On the DR problems, errors were summed across DR tests and entered as a single score per subject. Due to the large inequality of between-groups variance in DA and DR scores, a square-root transformation ($x = \sqrt{x + 1/2}$) was performed on the raw data prior to statistical analysis to make the variances more homogeneous. The ½ was added because many scores were 0 (Winer, 1971).

Despite the wide variability in the data (even after the square-root transformation), individual comparisons were made with t tests in order to explore the nature of the apparent differences suggested by the results from DA and DR tasks.

The frontal patients were significantly impaired on both DA, $t(16) = 2.3$, $p < .03$, and DR, $t(16) = 2.44$, $p < .03$, relative to alcoholic controls. The Korsakoff patients were significantly impaired only on DA, $t(22) = 3.8$, $p < .001$, whereas the amnesics with anterior communicating artery disease did not differ significantly from the alcoholic controls on either DA or DR. Although the amnesics with anterior communicating artery disease had a relatively large error score on DA (Figure 1), their impairment was not statistically significant because of the large variance within the error scores.

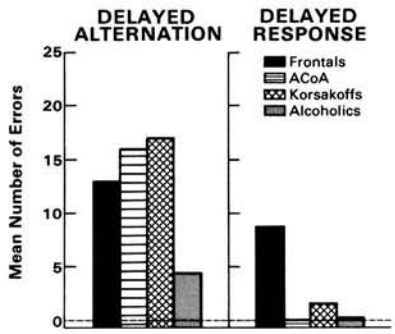

Figure 1. Performance by the groups on the 5-s DA task and on the DR task. (ACoA = anterior communicating artery disease.)

Two of the frontal patients performed much worse than the other frontals. One had a good memory (Patient 2, Wechsler Memory Scale score 112), and the other had poor memory function (Patient 6, Wechsler Memory Scale score 81). In order to further evaluate the relation between anterograde memory and performance on DA and DR, Pearson's product-moment correlations were performed between DA and DR and the paired associate subtest of the Wechsler Memory Scale. These were not significant (DA, $r = -.30$; DR, $r = -.24$).

Inspection of Figure 1 reveals that the pattern of performance of the groups on DA and DR differed considerably. Group comparisons were made of the differences in error rate between DA and DR. Korsakoff patients showed a significantly greater change in error rate compared with the frontals, $t(16) = 2.51$, $p < .02$. Other group comparisons were not significant. It should be noted that both of the amnesic groups, like the alcoholic group, made very few errors on DR, a result suggesting that this task was easy for them. This ceiling effect on DR may have limited the magnitude of the group differences across the tasks (DA and DR). Perhaps this obscured a reliable task difference among groups.

Relation Between Wisconsin Card Sorting and DA, DR

Measures on the Wisconsin Card Sorting Test (Table 3), representative of number of errors and perseveration, were correlated with the scores on DA and DR. Perseveration on previous category responses, but not consecutive responses, correlated significantly with number of errors on DA ($r = .72$), $F(1, 6) = 6.45$, $p < .05$, and DR ($r = .86$), $F(1, 6) = 16.7$, $p < .01$. There was no difference in perseverative performance on the Wisconsin Card Sorting Test between the frontal patients and the amnesics with anterior communicating artery aneurysm disease.

CT Scan Analysis

Figure 2 shows representative CT scans of the frontal patients. Figures 2a, 2b, and 2c represent the 3 patients with

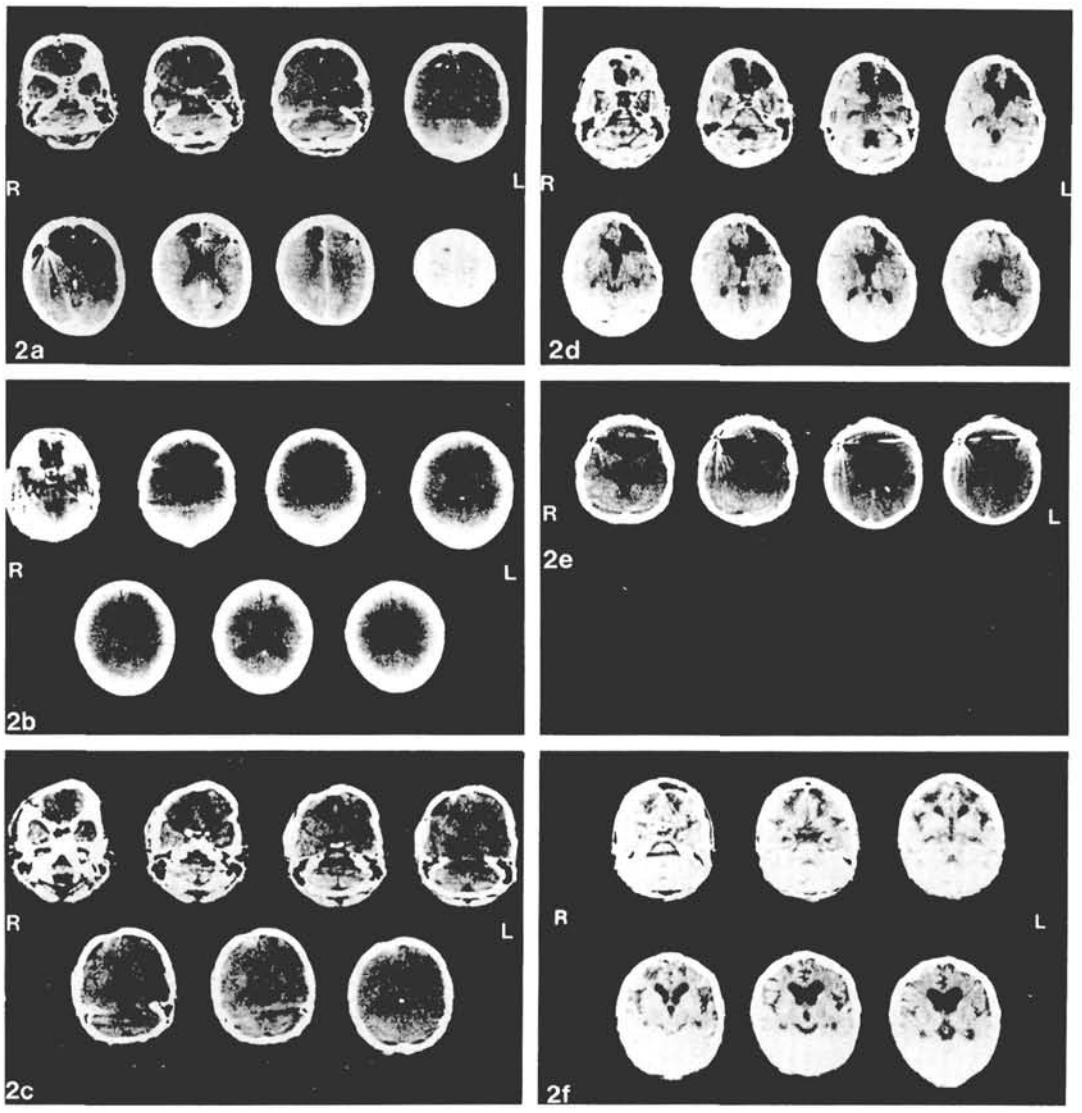

Figure 2. Computerized tomographic scans of the patients with frontal lesions. (Figures 2a, b, and c represent patients with good memory, and Figures 2d, e, and f are from patients with poor memory. See Plate C.)

preserved anterograde and retrograde memory, and Figures 2d, 2e, and 2f are from the patients with severe amnesia.

Patient 1 (Figure 2a). There was an extensive low-density prefrontal lesion involving the orbitofrontal, medial, and dorsolateral regions on the left. On the right, there was a low-density, patchy lesion in the orbitofrontal area which became more extensive in the medial and dorsolateral regions.

Patient 2 (Figure 2b). The acute scan showed bilateral frontal lobe hemorrhages. The present scan showed a large left low-density lesion in the orbitofrontal region which extended upward to involve approximately the lower half of the frontal lobe anterior to the frontal horn. On the right, there was a smaller, residual low-density orbitofrontal lesion.

Patient 3 (Figure 2c). There was a relatively small low-density lesion on the lowest CT slice on the left at the frontal pole. This became bilateral at the level of the frontal horns. A larger low-density lesion was present on the right in the dorsolateral region.

Patient 4 (Figure 2d). There were large bilateral low-density lesions. On the left, there was involvement of the orbitofrontal, medial, and dorsolateral regions extending over the lower two thirds of the prefrontal lobe. On the right, the lesion involved the orbitofrontal and medial areas in the lower one third of the frontal lobe, with extension to the dorsolateral surface anteriorly.

Patient 5 (Figure 2e). There was a meningioma in the interhemispheric fissure anterior and superior to the frontal horns of the lateral ventricles, affecting the medial frontal areas bilaterally.

Patient 6 (Figure 2f). There were large bilateral, patchy, low-density lesions beginning in the orbitofrontal regions and extending upward to involve approximately the lower half of

the prefrontal lobe. Some extension to the dorsolateral surface was present. The lesion was slightly larger on the right.

Discussion

The results show that bilateral frontal damage in humans is associated with impairment on both DA and DR. The deficits on DA and DR are, moreover, not related to associated memory loss. This was illustrated by the fact that among the frontal patients, the most impaired subjects on both DA and DR were those with the highest and lowest Wechsler Memory Scale scores, respectively (Patients 2 and 6). The absence of a relation within the frontal group between memory loss and impairment on DA and DR suggests that these tests are not sensitive to amnesia within the delay intervals studied. Further support for this statement comes from the lack of a significant correlation between performance on the paired-associate subtest of the Wechsler Memory Scale and error rate on DA and DR across all groups.

The data therefore support the view that deficits in alcoholic Korsakoff's syndrome on DA (Oscar-Berman et al., 1982) are due to associated frontal system pathology. The evidence that the frontal systems are implicated in Korsakoff's syndrome comes from the results of clinical/neurobehavioral studies (Oscar-Berman, 1973; Talland, 1965) showing classical frontal lobe signs in this disorder (Lhermitte & Signoret, 1976; Luria, 1980; Milner, 1964) and also from neuropathological data. The dorsomedial nucleus of the thalamus has strong projections to prefrontal cortex (Akert, 1964; Fuster, 1980; Nauta, 1971; Rose & Woolsey, 1948; Walker, 1938) and has been postulated to be a critical lesion site responsible for the amnesia (Victor, Adams, & Collins, 1971).

On DR, no significant impairment was found for either the Korsakoff patients or the amnesics with anterior communicating artery disease, relative to the alcoholics. It is of note that Isseroff, Rosvold, Galkin, and Goldman-Rakic (1982) found that monkeys with mediodorsal nucleus of the thalamus lesions were, like the Korsakoff patients, less impaired on DR than DA. However, ceiling effects cannot be ruled out as the reason for this negative finding in the amnesics in our study. In an earlier report based on the same data for the Korsakoffs and alcoholic subjects, Oscar-Berman et al. (1982) did find an impairment in Korsakoff patients compared with aphasic, brain-damaged patients. This discrepancy may be related to the inclusion of a larger number of trials for the failure criterion in the previous study than in the present one.

Earlier studies in humans have produced equivocal evidence about the effects of frontal damage on DA and DR. Our findings are in agreement with those of Pribram, Ahumada, Hartog, and Roos (1964), who found that schizophrenics with bilateral frontal lobotomies performed poorly on DA. This contrasts with the results of Chorover and Cole (1966), who failed to demonstrate deficits on DA in their frontal patients compared with brain-damaged patients with lesions outside the frontal lobes. However, only one third of their frontal patients had bilateral lesions, whereas all of the subjects reported by Pribram et al. (1964) and by us had bilateral damage. Moreover, the majority of Chorover and Cole's nonfrontal brain damaged subjects had tumors which may have affected the frontal lobes through mass effects. This would have blurred the distinction between the frontal and nonfrontal patients and may have contributed to the absence of a difference between the groups. With respect to DR, Ghent, Mishkin, and Teuber (1962) found no deficits associated with frontal lesions. However, only one third of their subjects had bilateral frontal lesions. Also, the DR tasks that they used bore little resemblance to the one employed by us and by others in studies with monkeys. Therefore, factors contributing to the previously reported negative results may include (a) failure to study only patients with bilateral frontal lesions, (b) inclusion of tumor patients in nonfrontal brain-damaged control groups, and (c) type of procedure used to study DR performance.

Analysis of the CT scans in the frontal group was carried out to determine whether any specific lesion site could account for the observed deficits on DA and DR. The two frontal patients (Patients 2 and 6), who performed much worse than the other frontals, had, in common, lesions in the orbitofrontal areas on both sides. Stuss et al. (1982) reported a relation between bilateral orbitofrontal lesions in humans and sensitivity to proactive interference. Although this suggests that proactive interference may be an underlying factor in performance on DA and DR tasks in our patients, the number of frontal subjects in the present study is too small to draw conclusions about critical lesion site and its effects.

In addition to the observation that DA and DR are impaired in bilateral frontal lobe disease, the data support the finding in nonhuman primates that different frontal systems mediate separate aspects of DA and DR (Brutkowski, Mishkin, & Rosvold, 1963; Divac, Rosvold, & Szwarcbart, 1967; Goldman, Rosvold, Vest, & Galkin, 1971; Mishkin, 1957). This point is highlighted by the strikingly different pattern of group performance on DA compared with that on DR. The major source of this difference is the dramatically low number of errors made by the amnesics (in particular, the Korsakoff patients), relative to the frontal patients, on DR. A clue to the exact nature of the functions that are being assessed by DA and DR must lie in the differences in frontal pathology and in the neuropsychological deficits of the amnesics and the frontal patients. This question was not addressed directly by the present investigation but certainly warrants further study.

One factor that was significantly correlated with number of errors both on DA and DR was perseveration on the Wisconsin Card Sorting Test as measured by errors due to responses that would have been appropriate for the immediately preceding category. Perseveration on consecutive items within a category, on the other hand, did not correlate with either DA or DR. The reason for this difference may be that correct responses on previous category items were strongly rewarded by positive feedback from the examiner (subjects must obtain 10 consecutive correct sorts before shifting categories) whereas perseverative errors within a category were never rewarded. The element of reward is also present on the DA and DR tasks (as subjects obtain a penny after every correct response) and may be a critical factor in the impairment on these tasks. Perseveration has also been related to deficits in DA and DR resulting from orbitofrontal lesions (in contrast to dorsolateral lesions) by others (Numan, 1978; Rosenkilde, 1979).

In conclusions, DA and DR appear to be sensitive to bilateral frontal lobe pathology in humans. The homologous findings in humans and in nonhuman primates reinforces the validity of the comparative neuropsychology approach for the study of neurological behavioral disturbances in humans.

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