Shuffled DNA 

Students of brain and behavior have long recognized that double dissociations (1) provide the strongest evidence for separating the functions of brain systems. Recent work with experimental animals has dissociated hippocampal and dorsal striatal learning systems (2). Rats with lesions of the hippocampus or related anatomically related structures were impaired on tasks thought to require spatial, relational memory, but they were intact at tasks of habit learning that require the gradual, incremental learning of associations. Lesions of the dorsal striatum produced the opposite pattern of results. 

Evidence for separate memory systems has also been obtained in humans (3). For example, amnesic patients are profoundly impaired on conventional tests of declarative (explicit) memory that assess recall and recognition, but they are intact at a variety of nondeclarative (implicit) memory tasks that assess skill learning, simple forms of

**A Neostriatal Habit Learning System in Humans**

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Amnesic patients and nondemented patients with Parkinson’s disease were given a probabilistic classification task in which they learned which of two outcomes would occur on each trial, given the particular combination of cues that appeared. Amnesic patients exhibited normal learning of the task but had severely impaired declarative memory for the training episode. In contrast, patients with Parkinson’s disease had learned the probabilistic associations but, despite having intact memory for the training episode, this double dissociation shows that the limbic-diencephalic regions damaged in amnesia and the neostriatum damaged in Parkinson’s disease support separate and parallel learning systems. In humans, the neostriatum (caudate nucleus and putamen) is essential for the gradual, incremental learning of associations that is characteristic of habit learning. The neostriatum is important not just for motor behavior and motor learning but also for acquiring nonmotor dispositions and tendencies that depend on new associations.
conditioning, and the phenomenon of priming (4). However, the human data, which are based largely on single (one-way) dissociations (5), are subject to an alternate interpretation that has been difficult to discount completely. Namely, there is a single memory system, and in amnesia, some tasks are simply more sensitive at detecting whatever residual memory ability remains (6). In addition, it is not always clear how the memory distinctions proposed in humans relate to findings in experimental animals. In particular, a neostriatal habit learning system like the one identified in rodents (2) has not been demonstrated in humans (7). In the present study, we tested for a double dissociation between declarative memory and habit memory in humans, seeking a parallel to the reports in experimental animals.

We tested 12 amnestic patients who had bilateral damage to the hippocampal formation or diencephalic midline (8), and 20 nondemented patients with Parkinson's disease (PD) (9), which causes neuronal degeneration within the substantia nigra and loss of a major input to the neostriatum. We also tested 15 controls matched to the patient groups with respect to age and education (10).

Two tasks were administered, a task of probabilistic classification learning and a multiple-choice questionnaire (11). In the first task (Fig. 1), individuals learned gradually which of two outcomes would occur on each trial, given the particular combination of cues that appeared. Each cue was independently and probabilistically related to the outcome, and the two outcomes occurred equally often. The probabilistic structure of the task appears to defeat the normal tendency to try to memorize a solution, and individuals can learn without being aware of the information they have acquired. Information about a single trial is not as useful as information accrued across many trials. In this sense, the task is akin to the kind of gradually acquired, habit learning tasks that depend on the dorsal striatum in experimental animals (2). The second task assessed declarative memory for the classification task by means of eight multiple-choice questions about the cues, the layout of the computer screen, and the training episode (four alternatives, chance = 25% correct).

Across 50 training trials, the amnestic patients learned the classification task as well as controls (Fig. 2A). Both groups began near 50% correct (the score that would be achieved by guessing) and reached a level of about 70% correct in trials 41 through 50 (12). In contrast, the PD patients did not learn the task (Fig. 2A). Impaired learning was particularly evident in the 10 PD patients with the most severe symptoms [Hoehn and Yahr Scale score was ≥3 (9)]. Across the five trials blocks (trials 1 through 50), these 10 patients performed worse than both the control group [analysis of variance (ANOVA), F(1,23) = 11.4, P < 0.01] and the amnestic patients [F(1,20) = 5.0, P < 0.04]. In addition, their score in the fifth trial block (trials 41 through 50) was at chance (50.2% correct), worse than the corresponding score of the controls [Student's t test, t(23) = 2.70, P < 0.01], and marginally worse than the score of the amnestic patients [t(20) = 1.92, P < 0.07].

In contrast, the PD patients, including the subgroup with the most severe symptoms, performed entirely normally on the test that assessed declarative memory for the classification task (t values < 1.0, Fig. 2B). The amnestic patients, however, performed more poorly than each of the other groups (t values > 6.0, P values < 0.001). Together these results demonstrate a double dissociation of memory function between the brain structures damaged in amnesia (13) and the brain structures damaged in Parkinson's disease. Probabilistic classification learning depends on the neostriatum but not on the medial temporal lobe or diencephalon, and the opposite is the case for declarative memory.

With training extended for an additional 100 trials, the PD patients gradually improved their performance, achieving a score of 60.9 ± 3.1% correct for trials 51 through 100 and 61.9 ± 3.7% for trials 101 through 150 (14). The amnestic patients achieved a
Previous studies of patients with basal ganglia disorders, such as Huntington’s disease and Parkinson’s disease, have documented learning impairments in procedural tasks, notably, those that require the generation of motor programs (23). The present findings show that a neostriatal system in humans is important not just for motor learning but also for acquiring nonmotor habits that depend on new associations (24). These nonmotor habits presumably include a wide range of dispositions and tendencies, which are shaped by reward, specific to particular stimuli, and which guide behavior and cognition.

REFERENCES AND NOTES

1. In a double dissociation, one lesion group is intact at task A and impaired at task B, relative to a second lesion group that is impaired at task A and intact at task B. H.-L. Teuber, Annu. Rev. Psychol. 9, 267 (1958); L. Weiskrantz, in Analysis of Behavioral Change, L. Weiskrantz, Ed. (Harp- er & Row, New York, 1968), pp. 85–110, and T. Shal- tile, From Neuropsychology to Mental Structure (Cambridge Univ. Press, Cambridge, 1988).


8. Seven (six men, one woman) of the 12 patient’s median temporal lobe amnesia and five (three men, two women) had diencephalic amnesia. Damage to the hippocampal formation or diencephalon was confirmed by quantitative neuroimaging for 11 of the 12 patients (in = 8; A. P. Shimamura, T. L. Jenning, L. R. Squire, J. Neurosci. 8, 4400 (1988); L. R. Squire, D. G. Amaral, G. A. Press, ibid., 10, 3106 (1990); J. Pollack and L. R. Squire, Behav. Neurophysiol. 86, 408 (1993); for n = 3, L. R. Squire, unpublished observations). The remaining patient was suspected to have hippocampal damage on the basis of etiology (anoxia), and he was assessed 65 years of age (range, 54 to 77) with an average of 14.0 years of education. They averaged 104.3 on the Wechsler Adult Intelligence Scale—Revised (WAIS-R; mean subcale score: the information subcale and 53.0 for the vocabulary subcale), and they averaged 101.3, 72.4, 79.0, 66.5, and 53.0 on the five indices of the Wechsler Memory Scale—Revised (attention-concentration, verbal memory, nonverbal memory, general memory, and delayed memory). These scores have a mean of 100 in the normal population (standard deviation = 15).

9. The diagnosis of Parkinson’s disease (17 men and 3 women) was confirmed by a senior staff neurologist at the University of California Medical Center, San Diego. The patients averaged 69.2 years of age (range, 46 to 79) and an average of 16.0 years of education. They scored 54.2 and 25.1 on the vocabulary and information subcales, respectively, of the WAIS—R subcales and scored 75.0 on the Dementia Rating Scale was 137.7, indicating an absence of dementia Illness (maximum score = 144, S. Mattis, in Geriatric Psychiatry, R. Ballack and B. Keren, Eds. (Grune and Stratton, New York, 1978). The mean severity of Parkinson’s symp- toms was stage 2.5 as rated by the Hoehn and Yahc Scale: 1 = least severe (M. M. Hoehn and M. D. Yahr, Neurology 17, 427 (1967), and was 10.5 as rated by the Unified Parkinson’s Disease Rating Scale, hand and foot subscale, 0 = normal, 30 = most severe (S. Fahn et al., in Recent Developments in Parkinson’s Disease, S. Fahn, C. D. Marsden, M. Goldstein, D. B. Calne, Eds. (Macmil- lain, New York, 1987). The mean score on the Beck Depression Inventory was 19.7 (range, 7–45) indicating an absence of clinical depression (A. T. Beck, C. H. Ward, M. Mendelson, J. Mock, I. Er- baugh, Arch. Gen. Psychiatry 56, 591 (1961). At the time of testing, all patients were under the care of a neurologist and were optimally medicated. All of the patients were receiving dopamine precursor treat- ment (Sinemet). In addition, 12 patients were taking a monoamine oxidase inhibitor (Eldepryl), 8 were taking a dopamine enhancing drug (Parlodel, Permax, or Armanilatin), and 3 were taking an anticholinergic drug (Artane). Removing the latter three patients did not change the results.

10. The controls (seven men and eight women) aver- aged 65.1 years of age (range, 54 to 77) and 14.2 years of education. They scored 54.0 and 20.3 on the vocabulary and information subcales of the WAIS-R, respectively.


12. The amnesic patients and controls performed 67.2 and 70.3% correct, respectively, during trials 41 through 50, which was well above chance levels (8 values > 3.3, P-values < 0.01). Learning was evident in each group across the five trial blocks (analysis of linear trend for amnesic patients; R(1,11) = 5.9, P < 0.05 for controls, R(1,11) = 4.0, P < 0.05). Data for the controls and 10 of the 12 amnesic patients were reported in (11).


14. Both scores were above the level that would be expected by guessing ([19] values > 3.2, P-values < 0.01). The 10 patients with severe symptoms also learned with extended training (47.5 ≤ 3.9%) correct for trials 1 through 50, 61.1 ± 4.5% correct for trials 101 through 150.

15. Ten of the 12 amnesic patients were given trials 1 through 150. The probability matching rule is conceptually the most nearly equivalent to the patient’s performance. They can navigate “probability matching,” whereby indi- viduals come to select each alternative in proportion to its reinforcement history [W. K. Estes, J. Am. Stat. Assoc. 67, 81 (1972)]. In our task, probability matching would result in a maximum score of 79% correct.

17. The 20 patients with Parkinson’s disease achieved 3.7 categories (maximum = 6) on the Wisconsin Card Sorting Test (WCST) with an average of 19.2% perseverative errors, that is, errors that would have been correct responses in the previous phase of the test [R. K. Heath, G. Chelune, J. Talley, K. Gay, G. Curtiss, Wisconsi Card Sorting Test Manual (Psychological Assessment Resources, Odessa, FL., 1993)]. Individuals from the Haton et al. normative sample (n = 169, age = 50 to 79 years) achieved 4.6 ± 0.1 categories correct with 15.1 ± 7.4% perseverative errors.

18. The patients with frontal lobe lesions (six men and four women) averaged 88 years of age (range, 62 to 76 years); six had sustained right frontal lesions, three had sustained right frontal lesions, and one had bilateral frontal lobe lesions. On the WCST (17), they achieved 3.6 categories and made 32.8% perseverative errors, marginally more than the Parkinson patients, t(28) = 1.76, P = 0.09. For reconstructions of the frontal lesions and examples of their impaired performance on other tests, see J. S. Janowsky, A. P. Shimamura, K. M. Rice, L. R. Squire, Behav. Neurosci. 103, 543 (1989) (patients JD, MD, IV); A. P. Shimamura, P. J. Jurado, J. A. Mangels, F. B. Gershberg, R. T. Knight, J. Cogn. Neurosci. 7, 144 (1995) (patients EB, AL, MM, RM); J. A. Mangels, F. B. Gershberg, A. P. Shimamura, R. T. Knight, Neuropsychology 10, 32 (1999) (patients OA, JOX, LL, Chao and R. T. Knight, Neuroreport 6, 1605 (1995) (patient JC).

19. In addition, analysis of variance (severe PD patients compared with frontal patients and three 5-trial blocks, 51 through 50, 51 through 150) revealed a significant group x trial block interaction (F(2,34) = 5.52, P < 0.04). The interaction resulted from the fact that the frontal patients, like the amnesic patients and controls, scored about the same overall in each of the three 5-trial blocks (frontals: 60.5, 56.5, and 66.1%; amnesics: 58.5, 61.2, and 62.2%; controls: 65.9, 57.3, and 69.6%). In contrast, the severely affected PD patients scored 47.8% correct (at chance) on trials 1 through 50, 58.2% correct trials 51 through 100, and 61.1% on trials 101 through 150.


21. The PD patients who performed poorest on the classification task (scores during trials 1 through 50) also obtained the highest Hoehn and Yahr Scale scores of symptom severity (9) correlation coefficient, r = -0.55, P < 0.02. In contrast, in the case of the frontal patients, performance on the first 50 trials of the classification test was slightly and nonsignificantly better for those patients with the more severe frontal symptoms [preclassification, the number of categories achieved correctly on the WCST (17) and by the perchance perseverative error score, r = -0.14 and r = 0.22, respectively]. Interestingly, for the AV patients, poor classification learning also correlated with frontal lobe symptoms (r = 0.63, P < 0.01 for categories; r = 0.69, P < 0.01 for perseverative errors), as would be expected if frontal lobe dysfunction reflects the progression of the primary disease in the neostriatum. However, the overall pattern of correlations suggests that the neostriatal symptoms, not the frontal lobe symptoms, are responsible for this finding. This conclusion depends on the assumption that frontal lobe dysfunction in the AV patients was no more severe than in the patients with frontal lobe lesions. The neuropathological findings (17, 18) are consistent with this idea.


24. Patients with Huntington’s disease also did not learn the probabilistic classification task (B. J. Knowlton et al., Psychophysiology, in press). However, it is difficult to isolate this deficit to the basal ganglia because of the dementia and widespread neuropathology associated with Huntington’s disease.

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A Requirement for Local Protein Synthesis in Neurotrophic-Induced Hippocampal Synaptic Plasticity

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Two neurotrophic factors, brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), are able to produce a long-lasting enhancement of synaptic transmission in the hippocampus. Unlike other forms of plasticity, neurotrophin-induced plasticity exhibited an immediate requirement for protein synthesis. Plasticity in rat hippocampal slices in which the synaptic neuropil was isolated from the principal cell bodies also required early protein synthesis. Thus, the neurotrophins may stimulate the synthesis of proteins in either axonal or dendritic compartments, allowing synapses to exert local control over the complement of proteins expressed at individual synaptic sites.

The cellular changes that underlie both synaptic and behavioral plasticity are usually classified as either (i) short term, because they are based on the modification of preexisting proteins, or (ii) long term, because they require protein synthesis. For example, studies of synaptic plasticity in the hippocampus and in Aplysia have shown that, whereas the short-term phase (0 to 1 hour) of synaptic enhancement is not blocked by inhibitors of protein translation, the long-term phase (>1 hour) is (i) (but see (2)). These cellular studies are paralleled by many studies of behavioral plasticity that also indicate that short-term memories are insensitive to inhibitors of protein synthesis (3). The neurotrophic factors BDNF and NT-3 can enhance synaptic efficacy (4), and we have now examined the temporal sensitivity of the neurotrophin-induced synaptic enhancement to inhibitors of protein synthesis.

Synaptic transmission was examined at the Schaffer collateral–CA1 pyramidal neuron synapse in adult rat hippocampal slices with the use of conventional extracellular recording techniques (5). In control experiments, extracellular application of BDNF (50 ng/ml) or NT-3 (50 ng/ml) elicited a robust enhancement of synaptic transmission (Fig. 1, A and B) (4) [mean percent of baseline: BDNF, 221.4 ± 16.4 (mean ± SEM, n = 7), P < 0.005; NT-3, 231.1 ± 19.5 (n = 8), P < 0.005]. Pretreatment with one of two protein synthesis inhibitors (6), either anisomycin (40 μM) or cycloheximide (40 μM), markedly attenuated the synaptic enhancement induced by either neurotrophin (Fig. 1, C through F and H) [mean percent of baseline: BDNF plus anisomycin, 134.2 ± 8.4 (n = 7), P < 0.05; BDNF plus cycloheximide, 138.7 ± 13.2 (n = 7), P < 0.05; NT-3 plus anisomycin, 130.1 ± 7.6 (n = 9), P < 0.05; NT-3 plus cycloheximide, 118.5 ± 14.0 (n = 7), not significant (NS)]. In contrast to previous studies of synaptic plasticity, the sensitivity to inhibitors of protein synthesis was evident within minutes of neurotrophin application (Fig. 1, C through F). Similar pretreatment of hippocampal slices with an inhibitor of prokaryotic protein synthesis, chloramphenicol (80 μM), did not significantly reduce the synaptic enhancement.