

## BRIEF REPORT

# Learning and Generalization Deficits in Patients With Memory Impairments Due to Anterior Communicating Artery Aneurysm Rupture or Hypoxic Brain Injury

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Human anterograde amnesia can result from a variety of etiologies, including hypoxic brain injury and anterior communicating artery (ACoA) aneurysm rupture. Although each etiology can cause a similarly severe disruption in declarative memory for verbal and visual material, there may be differences in incrementally acquired, feedback-based learning, as well as generalization. Here, 6 individuals who survived hypoxic brain injury, 7 individuals who survived ACoA aneurysm rupture, and 13 matched controls were tested on 2 tasks that included a feedback-based learning phase followed by a transfer phase in which familiar information is presented in new ways. In both tasks, the ACoA group was slow on initial learning, but those patients who completed the learning phase went on to transfer as well as controls. In the hypoxic group, 1 patient failed to complete either task; the remaining hypoxic group did not differ from controls during learning of either task, but was impaired on transfer. These results highlight a difference in feedback-based learning in 2 amnesic etiologies, despite similar levels of declarative memory impairment.

*Keywords:* learning and memory, generalization, hippocampus, basal forebrain

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Anterograde amnesia is an impairment in declarative (fact and event) learning with relative sparing of other cognitive functions. One etiology that can cause anterograde amnesia is hypoxic brain injury (Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Manns, Hopkins, & Squire, 2003; Press, Amaral, & Squire, 1989). Hypoxic brain injury can cause bilateral neuropathology of the hippocampus and associated medial temporal (MT) areas (Kesner & Hopkins, 2001). Depending on the duration and severity of the hypoxic episode, there may also be nonspecific degenerative neuropathology throughout the brain leading to nonmnemonic cognitive impairments (Bachevalier & Meunier, 1996; Gale & Hopkins, 2004; Hopkins et al., 1995).

Anterograde amnesia can also be observed in individuals who survive anterior communicating artery (ACoA) aneurysm rupture (DeLuca & Chiaravalloti, 2002; DeLuca & Diamond, 1995). This etiology damages the basal forebrain, leading to memory impairments (Everitt & Robbins, 1997; von Cramon & Markowitsch, 2000). Damage may also extend into the ventromedial prefrontal cortex, leading to attentional deficits and personality changes (DeLuca & Chiaravalloti, 2002; DeLuca & Diamond, 1995).

In patients with anterograde amnesia subsequent to hypoxic brain injury or to ACoA aneurysm rupture, the neuropsychological profile may appear superficially similar; for example, both groups by definition have accelerated forgetting of new declarative information. It remains an open question whether hypoxic and ACoA amnesic patients, equated for declarative memory deficits, might show qualitative differences in other learning domains.

One prior study examined two amnesic participants, one with basal forebrain damage and one with medial temporal lobe damage; both patients were similarly impaired on explicit memory measures (Rajaram & Coslett, 2000). Both patients were intact on perceptual priming, but only the basal forebrain patient showed generalization to information containing conceptually related targets. Although care must be taken when extrapolating group characteristics from the performance of two participants, these data suggest that generalization tasks may be a fruitful domain for exploring possible differences between memory impairments in patients with amnesia due to hypoxic brain injury or ACoA aneurysm rupture.

Another prior study considered incrementally acquired feedback-based learning in hypoxic versus ACoA amnesic patients (Myers, DeLuca, Hopkins, & Gluck, 2006). In this study, the two patient groups had similar declarative memory impairments on tests of prose and figural recall. Patients were tested on a conditional discrimination, followed by an unsignaled reversal. The hypoxic group acquired the discrimination as quickly as a control group, but was impaired at the reversal; in contrast, the ACoA group was impaired on discrimination learning but could reverse as quickly as controls.

To further explore possible contrasts in feedback-based learning and generalization in these patient groups, we here report on two tasks that each involve learning a series of stimulus discriminations, followed by a transfer phase in which participants are challenged to generalize based on this prior learning. One task is a discrimination-and-transfer task, in which participants learn six concurrent visual discriminations, and then receive an unsignaled transfer test in which irrelevant stimulus features are altered. The second task is an acquired equivalence task, in which participants learn several stimulus-outcome mappings, in which some stimuli are "equivalent" in the sense that they are mapped to the same outcome; later, when some of these stimuli are mapped to new outcomes, this learning should generalize to the other, "equivalent" stimuli.

Previous studies have shown that nondemented older individuals with hippocampal atrophy are unimpaired relative to nonatrophied peers on the learning phases of both tasks, but are impaired on the transfer phases (Myers et al., 2002, 2003). We expected to observe a similar pattern of spared learning but impaired transfer in the hypoxic group. We expected that the ACoA group, as in the previous reversal study, would show the opposite pattern of impaired learning but spared transfer.

## Method

### Participants

The hypoxic group included one woman and five men with hypoxic brain injury ( $M$  age = 37.0 years,  $SD$  = 2.2;  $M$  education = 12.5 years,  $SD$  = 0.8). Structural neuroimaging was available on four of these patients and confirmed selective reduction of

hippocampal volumes bilaterally, as compared to age-appropriate normative data (Bigler et al., 1997).

The ACoA group included four women and five men who had survived ACoA aneurysm rupture ( $M$  age = 64.7 years,  $SD$  = 6.2;  $M$  education = 13.1 year,  $SD$  = 2.3). All were at least 6 months postsurgery and clean of confabulation. Surgical notes confirmed basal forebrain damage for all seven patients in this group. Structural neuroimaging was available for five patients, and confirmed basal forebrain damage, variable degrees of additional ventromedial frontal damage, and no visible hippocampal damage.

A group of five female and eight male healthy adults served as the control group ( $M$  age = 51.0 years,  $SD$  = 15.2;  $M$  education = 13.8 years,  $SD$  = 2.0). All controls were free of any past or present neurological or psychiatric conditions, were free of any medication that could affect cognition (including anticholinergics and antidepressants), and had no history of alcohol or drug abuse.

The three groups differed significantly in age,  $F(2, 23) = 8.03$ ,  $p < .01$ ; post hoc Scheffé tests confirmed that the hypoxic and ACoA groups differed from each other ( $p < .01$ ) but the control group differed from neither the hypoxic group ( $p = .10$ ) nor the ACoA group ( $p = .08$ ). There were no significant group differences in education level,  $F(2, 23) = 2.51$ ,  $p = .104$  or gender,  $\chi^2(2) = 2.24$ ;  $N = 26$  (13 healthy controls, 7 ACoA patients, 6 hypoxic patients),  $p = .33$ .

Informed consent was obtained from all participants prior to the initiation of any testing. Procedures followed guidelines of the Federal Government, Rutgers University, Brigham Young University, and Kessler Medical Research Rehabilitation and Education Corporation for the protection of human subjects.

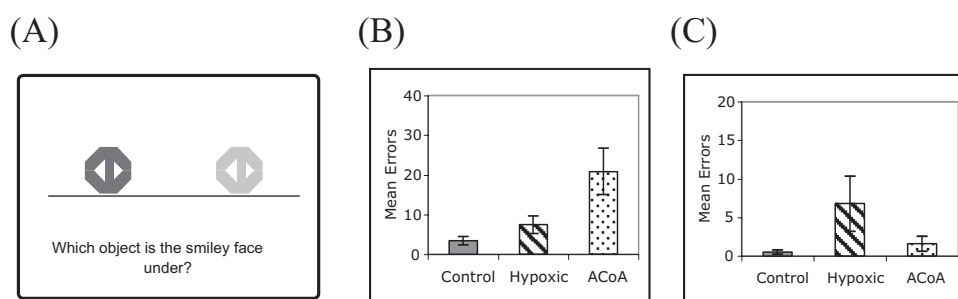
### Neuropsychological Testing

All participants received a series of standard neuropsychological tests, including the logical memory (LM) subtest of the Wechsler Memory Scale–Revised (Wechsler, 1987), the North American Adult Reading Test (NAART; Spreen & Strauss, 1998), the Controlled Word Association Test (COWAT–FAS; Spreen & Strauss, 1998), and the digit span subtest of the Wechsler Adult Intelligence Scale–III (Wechsler, 1991).

For inclusion in the hypoxic or ACoA group, participants were required to score  $>1$   $SD$  below control group means on the delayed recall component of the LM.

### Behavioral Testing

The discrimination-and-transfer task is similar to that described in Myers et al. (2002). At the start of Phase 1, the computer screen shows a pair of objects (Figure 1A); one is raised to show a smiley face hidden underneath. On subsequent trials, participants see the same two objects, in randomized left–right position, and choose one by pressing a keyboard key labeled *LEFT* or *RIGHT*. The chosen object is lifted and, if the participant has chosen the correct object, the smiley face appears underneath. Once participants reach criterion performance on this pair (two consecutive correct responses), a new object pair is shown, and trials then continue intermixing this new pair and the old pair until the participant has reached criterion on both pairs (four consecutive correct responses). This process is repeated with four new object pairs, until the participant is responding correctly to six pairs (12 consecutive correct responses) or to a maximum of 72 trials.



*Figure 1.* (A) On each trial of the discrimination-and-transfer task, a pair of objects is presented; the participant learns to choose the correct object from each pair. (B) In Phase 1, in which six such object pairs are trained, the ACoA group but not hypoxic group is impaired. (C) In Phase 2, a transfer test in which irrelevant object features are altered, the hypoxic group is impaired but the ACoA group generalizes well.

Within each pair, the objects differ in either color or shape but not both; half of the six pairs differ in color (e.g., red cats-eye vs. gold cats-eye) and the others differ in shape (e.g., brown frame vs. brown mushroom). Thus, within each pair, one stimulus feature is relevant and predictive, and one is irrelevant.

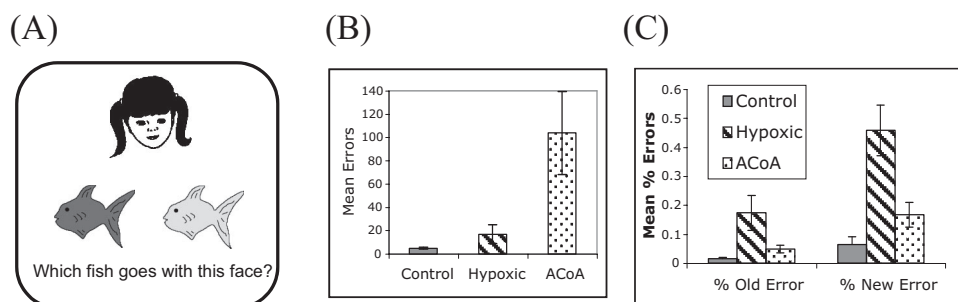
For those participants who successfully complete Phase 1, Phase 2 then begins without warning to the participant. In this phase, relevant features remain the same in each pair but irrelevant features are changed. Thus, pairs might now include a red cross versus a gold cross and a green frame versus a green mushroom. Original valences remain unchanged: thus, if the red object was rewarded in Phase 1, it is also rewarded in Phase 2, regardless of its new shape. None of the new colors or shapes had previously appeared in Phase 1. Phase 2 continues to a criterion of 12 consecutive correct responses or to a maximum of 72 trials.

The acquired equivalence task is similar to that described in Myers et al. (2003). On each trial, the participant sees a cartoon face and a pair of colored fish, and uses the *LEFT* or *RIGHT* keys to guess which of the two fish belongs with that face (Figure 2A). During trials in Phase 1, the computer shows face A along with two fish (Fish1 and Fish2) that can appear in either left–right order. The participant presses a key to select a fish; the selected fish is

highlighted. The correct choice for face A is Fish1. If the subject chooses correctly, the word “Correct” appears at the bottom of the screen; otherwise “Incorrect” appears. Once the participant has mastered this discrimination, trials with the trained pair begin to alternate with trials involving a new face B and the same two fishes; face B is to be mapped to Fish2. Once the participant is responding to both of these faces correctly, new trials are intermingled with the same two fish but with a new face C that is to be mapped to Fish1, and a new face D that is to be mapped to Fish2. At this point, faces A and C are equivalent, in the sense that both are mapped to Fish1, and faces B and D are likewise equivalent in the sense that both are mapped to Fish2.

Once the participant is responding to all four faces correctly, new trials are intermixed in which face A or B is presented with two new fish (Fish3 and Fish4). Face A should be mapped to Fish3 and B to Fish4. Trials continue until the participant has mastered these new discriminations while maintaining good performance on the previously trained discriminations, evidence by reaching a criterion of 12 consecutive correct responses, or to a maximum of 72 trials.

For those participants who successfully reach criterion in Phase 1, Phase 2 follows. This is a testing phase, similar to Phase 1 except that feedback is not given. Phase 2 includes 6 retention



*Figure 2.* (A) On each trial of the acquired equivalence task, the participant sees a face and two colored fish, and must learn to select the fish that goes with that face. (B) In phase 1, in which six such face-fish pairs are trained, the ACoA group is again strongly impaired; the hypoxic group does not differ significantly from control performance. (C) In Phase 2, participants are tested both on old (previously trained) face-fish pairs as well as on new (never-trained) pairs of faces and fish. Here, the ACoA group performs as well as controls, but the hypoxic group is impaired.

trials with each of the trained discriminations in random order. Intermixed with these 36 retention trials are 12 test trials, consisting of six repetitions each of two new discriminations: Face C presented together with Fish3 and Fish4, and Face D presented together with Fish3 and Fish4. Although these discriminations have never been explicitly trained, acquired equivalence predicts that, because face C is equivalent to face A, and because A goes with Fish3, C should also go with Fish3. Similarly, because face D is equivalent to face B, and because B goes with Fish4, D should also go with Fish4.

In both experiments, data were analyzed as total errors in Phase 1 and Phase 2; for the acquired equivalence test, the Phase 2 data were broken down into percent errors on old (previously trained) and new pairs. Analysis of variance (ANOVA) was used to determine whether group differences in these measures were significant, with post hoc Scheffé tests to examine pairwise contrasts. The alpha level for computation of significance was set at  $p < .05$ .

## Results

### Neuropsychological Testing

There were no significant differences between control and patient groups on NAART estimated VIQ (control:  $M = 112.05$ ,  $SD = 11.74$ ; ACoA:  $M = 110.52$ ,  $SD = 6.89$ ; hypoxic:  $M = 98.74$ ,  $SD = 9.21$ ),  $F(2, 23) = 2.28$ ,  $p = .13$ , on COWAT-FAS  $z$  score (control:  $M = 0.05$ ,  $SD = 1.31$ ; ACoA:  $M = -.66$ ,  $SD = 1.26$ ; hypoxic:  $M = -1.18$ ,  $SD = 1.17$ ),  $F(2, 23) = 2.08$ ,  $p = .15$ , or digit span (control:  $M = 15.23$ ,  $SD = 3.96$ ; ACoA:  $M = 13.71$ ,  $SD = 3.04$ ; hypoxic:  $M = 13.17$ ,  $SD = 3.60$ ),  $F(2, 23) = 0.79$ ,  $p = .46$ .

On LM, there were group differences on both immediate recall (control:  $M = 25.7$ ,  $SD = 8.0$ ; ACoA:  $M = 15.0$ ,  $SD = 5.63$ ; hypoxic:  $M = 18.3$ ,  $SD = 9.1$ ),  $F(2, 23) = 4.92$ ,  $p = .02$ , and delayed recall (control:  $M = 21.2$ ,  $SD = 10.0$ ; ACoA:  $M = 4.6$ ,  $SD = 3.2$ ; hypoxic:  $M = 4.0$ ,  $SD = 4.4$ ),  $F(2, 23) = 58.72$ ,  $p < .01$ . Post hoc Scheffé tests confirmed that the ACoA group was impaired relative to controls on both immediate recall ( $p = .02$ ) and delayed recall ( $p < .01$ ); the hypoxic group was impaired relative to controls on delayed recall ( $p < .01$ ) but not immediate recall ( $p = .18$ ). The ACoA and hypoxic groups did not differ from each other on either measure (immediate:  $p = .74$ ; delayed:  $p = .99$ ). Every patient in the ACoA and hypoxic groups scored  $>1 SD$  below the control group mean on LM delayed recall, fulfilling the inclusion criterion.

### Behavioral Testing

One individual in the hypoxic group made more than twice the errors of any other hypoxic participant, on both tasks, and failed to reach criterion in Phase 1 of either task. This individual's data were excluded from group analysis, leaving five participants in the hypoxic group.

Among the remaining participants, there was a significant group effect on Phase 1 of the discrimination-and-transfer task (Figure 1B),  $F(2, 22) = 7.69$ ,  $p < .01$ . Post hoc Scheffé tests confirmed that the hypoxic group learned as quickly as controls ( $p = .60$ ) but the ACoA group was impaired ( $p < .01$ ). Two ACoA patients failed to reach criterion in Phase 1; all other participants reached criterion and re-

ceived Phase 2 training (Figure 1C). Again there was a significant group difference on phase 2 performance,  $F(2, 20) = 4.29$ ,  $p = .03$ ; specifically, the hypoxic group made significantly more errors than the control group ( $p = .03$ ) but the ACoA group did not differ from controls ( $p = .97$ ).

There was also a significant group effect on Phase 1 of the acquired equivalence task (Figure 2B),  $F(2, 22) = 6.48$ ,  $p = .01$ . Post hoc Scheffé tests confirmed that the hypoxic group again did not differ from controls ( $p = .93$ ) but the ACoA group was impaired ( $p = .01$ ). Three ACoA patients, and one hypoxic patient, failed to reach criterion in this phase; the remaining participants received Phase 2 testing (Figure 2C). On trials involving old (previously trained) discriminations, there was a group effect,  $F(2, 18) = 5.73$ ,  $p = .01$ , with the hypoxic group making more errors than the control group ( $p = .01$ ); the ACoA and control groups did not differ ( $p = .78$ ). On trials involving new (never-trained) discriminations, there was a similar group effect,  $F(2, 18) = 10.88$ ,  $p = .01$ , with the hypoxic group again making more errors than controls ( $p = .01$ ); the ACoA and control groups did not differ ( $p > .99$ ).

## Discussion

On two incrementally acquired feedback-based learning tasks, a group of amnesic individuals with hypoxic brain injury was unimpaired at learning, but was impaired relative to matched controls on a transfer phase when familiar information was presented with new irrelevant features or in new combinations. The opposite pattern obtained in a group of individuals with comparable memory impairments subsequent to ACoA aneurysm rupture.

Because performance in the controls was near ceiling on the acquisition phase of both tasks, it is possible that this masked differences between hypoxic and control groups, and that a hypoxic deficit might emerge with a more difficult version of the test. It is also unclear why one hypoxic patient failed to complete either task; this individual scored well below ACoA group averages on both the COWAT-FAS (age-adjusted  $z = -2.7$ ) and digit span (forward + backward score = 6), suggesting possible executive and/or attentional deficits that might have impaired her ability to attend to the tasks or to master task demands.

However, the absence of a learning deficit in the remaining hypoxic patients is consistent with the prior finding of no hypoxic group impairment on conditional visual discrimination (Myers et al., 2006). Because hypoxic patients often have bilateral hippocampal atrophy, these findings are also consistent with data suggesting that hippocampal damage does not retard simple stimulus-response learning. Specifically, although some early studies suggested that hippocampal-region lesions impaired concurrent object discrimination (e.g., Moss, Mahut, & Zola-Morgan, 1981; Zola-Morgan & Squire, 1985); later studies suggested that the critical substrate was area TE of the inferior temporal cortex (Buffalo, Stefanacci, Squire, & Zola, 1998; Malamut, Saunders & Mishkin, 1984), rather than the hippocampus.

Although the hypoxic group could acquire the Phase 1 discriminations well, they were impaired on the Phase 2 transfer tests. Their impairment was qualitatively similar to the transfer impairment shown by elderly individuals with hippocampal atrophy on the same tests (Myers et al., 2002, 2003). These data are consistent with several extant theories suggesting that the hippocampal re-



gion is not strictly necessary for learning new stimulus–response associations, but that the presence of hippocampal-region mediation during such learning allows the information to be acquired in a fashion that supports “generalization” or “flexibility” later, in new situations or contexts other than the ones in which the information was originally acquired (e.g., Cohen & Eichenbaum, 1993; Gluck & Myers, 1993; Schacter, 1985; Squire, 1992).

This interpretation is consistent with several functional neuroimaging studies. In one, healthy elderly participants were tested on Phase 1 of the discrimination-and-transfer test presented here, and bilateral hippocampal activation was revealed (Johnson, Schmitz, Asthana, Gluck, & Myers, 2008). Hippocampal activation also occurs during both acquisition and test phases of an acquired equivalence task similar to the one presented here (Preston, Shrager, Dudokovic, & Gabrieli, 2004), and during a related transitive inference task, in which participants learn a relationship between A and B, and between B and C, and are tested on the inferred (but never explicitly trained) relationship between A and C (Heckers, Zalesak, Weiss, Ditman, & Titone, 2004). Together, these neuroimaging studies are consistent with the view that the hippocampal system may be important during learning of new associations if those associations are to support the ability to generalize or transfer successfully later.

In contrast to the hypoxic group performance, the ACoA group was significantly impaired on the acquisition phase of both behavioral tasks. The acquisition deficit in this group is consistent with the prior discrimination reversal study that found ACoA amnesic patients required about twice as many trials to acquire a simple conditional discrimination, compared with healthy controls or hypoxic patients (Myers et al., 2006). It is also consistent with findings from animal and computer models showing that basal forebrain lesions or disruption can retard simple stimulus–response learning, presumably by disrupting neuromodulatory projections from basal forebrain nuclei to other brain areas (Myers, Ermita, Hasselmo, & Gluck, 1998; Ridley, Baker, Leow-Dyke, & Cummings, 2005; Solomon, Solomon, Van der Schaaf, & Perry, 1983). Although the ACoA patients had variable degrees of frontal damage visible on neuroimaging, the acquisition deficit in these patients is not easily attributable to frontal dysfunction, at least insofar as their scores on neuropsychological measures of attention and executive function did not differ significantly from the control or hypoxic groups.

Despite their impaired learning, those ACoA patients who were able to master the discriminations in Phase 1 went on to transfer as well as healthy controls. This is consistent with the prior study showing that, although a similar ACoA group was impaired at learning a conditional discrimination, those that did reach criterion could subsequently reverse as well as controls (Myers et al., 2006).

Data from animal models of basal forebrain lesion suggest that basal forebrain damage disrupts brain neuromodulatory systems, slowing simple stimulus–response associations, but not necessarily impairing hippocampal-dependent generalization and contextual processing (for review, see Myers et al., 1998). This could account for the current finding that the ACoA group, with basal forebrain damage, was slow to learn a series of stimulus–response associations, but unimpaired on subsequent transfer tests known to be disrupted in individuals with bilateral hippocampal atrophy as well as in the hypoxic group.

The results reported here, together with those from the earlier conditional discrimination and reversal study, suggest that learning of incrementally acquired feedback-based associations may be spared in patients who develop anterograde amnesia due to hypoxic brain injury, but that such learning may not support subsequent transfer when stimuli or contexts change; in contrast, patients who develop anterograde amnesia due to ACoA aneurysm rupture may show retarded learning but, given enough time to complete this learning, their ability to transfer or generalize may be relatively intact. Such results have implications for understanding the memory impairments each etiology, especially in the design of optimal rehabilitation therapies that might be targeted to the unique pattern of impaired and spared learning and memory abilities in each amnesic subgroup.

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