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Conditional discrimination and reversal in amnesia subsequent to hypoxic brain injury or anterior communicating artery aneurysm rupture

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Abstract

Human anterograde amnesia can develop following bilateral damage to the hippocampus and medial temporal lobes, as in hypoxic brain injury, or following damage to the basal forebrain, as following anterior communicating artery (ACoA) aneurysm rupture. In both cases, the mnestic deficit may be similar when assessed by standard neuropsychological measures. However, animal and computational models suggest that there are qualitative differences in the pattern of impaired and spared memory abilities following damage to hippocampus versus basal forebrain. Here, we show such a dissociation in human amnesia using a single two-stage task, involving conditional discrimination and reversal. Consistent with a prior study, 10 individuals with anterograde amnesia subsequent to hypoxic brain injury were spared on acquisition but impaired at reversal. However, 10 individuals with amnesia subsequent to ACoA aneurysm showed the opposite pattern of impaired acquisition but spared reversal. The differences between groups cannot be easily ascribed to severity of mnestic or cognitive deficit, since the two amnesic groups performed similarly on neuropsychological tests of memory, intelligence and attention. The results illustrate qualitative differences in memory impairments in hypoxic and ACoA amnesics and highlight the importance of considering etiology in evaluating mnemonic deficits in amnesic populations.

Keywords: Amnesia; Hypoxia; Hippocampus; Basal forebrain; Memory; Attention

1. Introduction

Hypoxic brain injury may result in relatively selective bilateral neuropathology in the hippocampus (e.g. Fig. 1A; Kesner & Hopkins, 2001; Manns, Hopkins, Reed, Kitchener, & Squire, 2003b; Manns, Hopkins, & Squire, 2003a). Such individuals generally display a "pure" amnestic syndrome with dense memory impairments but relative sparing of non-mnemonic functions such as intelligence and attention (e.g. Hopkins, Myers, Shohamy, Grossman, & Gluck, 2004; Press, Amaral, & Squire, 1989). Depending on the duration and severity of the hypoxic episode, there may also be non-specific degenerative neuropathology throughout the brain leading to impairments in non-mnemonic function (e.g. Fig. 1B; Bachevalier & Meunier, 1996; Gale & Hopkins, 2004; Hopkins et al., 1995).

The anterograde amnesia syndrome can also be observed in populations with very different underlying brain damage such as individuals who survive aneurysm and rupture of the anterior communicating artery (ACoA) (see DeLuca &

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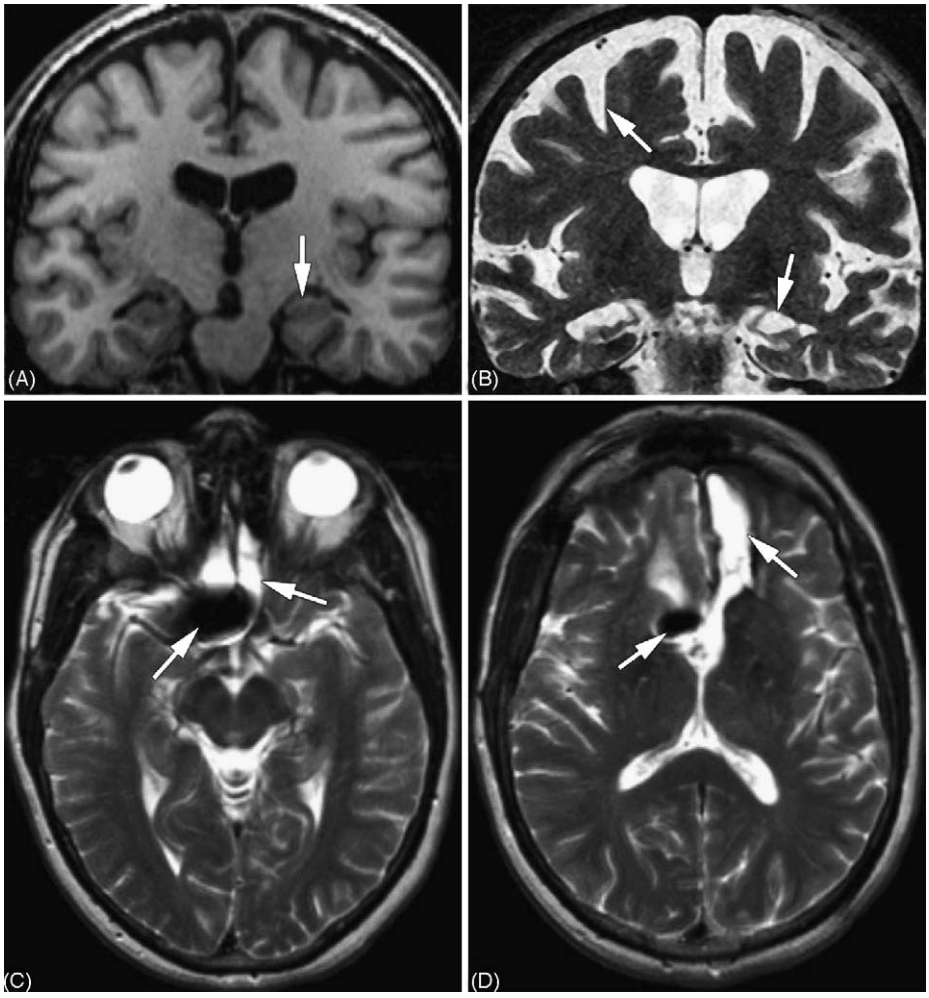

Fig. 1. Representative magnetic resonance scans of amnesic participants; all scans shown in the radiologic view (left/right reversal). (A) T1 coronal view through the body of the hippocampus in a representative individual who became amnesic following hypoxic brain injury. There is significant bilateral hippocampal atrophy (arrow points to left hippocampus) and enlargement of the temporal horns of the lateral ventricles. (B) T2 coronal scan of another amnesic individual, whose hypoxic episode resulted in bilateral hippocampal damage (right arrow points to left hippocampus) and extensive enlargement of the temporal horns, cerebral atrophy (left arrow) and ventricular enlargement due to diffuse atrophic changes. (C and D) T2 axial scan of a representative individual who became amnesic following ACoA aneurysm rupture. Right arrow in (C) indicates bilateral damage to basal forebrain and right arrow in (D) shows predominantly left frontal damage. Left arrows in (C) and (D) point to clip artifact.

Chiaravalloti, 2002, for review). In ACoA aneurysm survivors where lesions have been localized, it appears that damage limited to the basal forebrain results in a relatively "pure" amnestic syndrome (e.g. Abe, Inokawa, Kashiwagi, & Yanagihara, 1998; Morris, Bowers, Chatterjee, & Heilman, 1992; Phillips, Sangalang, & Sterns, 1987); damage extending into prefrontal areas may result in additional impairments such as attentional decline and personality changes (Fig. 1C and D; DeLuca & Chiaravalloti, 2002; DeLuca & Diamond, 1995; DeLuca, Bryant, & Myers, 2003). Among these amnesic patients, basal forebrain damage may extend to include the medial septum/diagonal band complex, the lateral septum, the substantia innominata and the nucleus basalis. Amnesia has been observed in patients with damage to the medial septum/diagonal band complex, but sparing other basal forebrain structures such as nucleus basalis (e.g. Morris et al., 1992; von Cramon, Markowitsch, & Schuri, 1993). Although the size and placement of the basal forebrain makes it difficult to localize the nucleus basalis via neuroimaging, the one published case report of an ACoA amnesic who came to autopsy (Phillips et al., 1987) reported that the nucleus basalis was spared. Two other case reports considered amnesic individuals with documented damage to the basal forebrain including the septal area but in whom the nucleus basalis was not involved (Goldenberg, Schuri, Grommінger, & Arnold, 1999) or minimally affected (Abe et al., 1998). Thus, although it is premature to make any definitive statements, it appears that a lesion in the nucleus basalis is not necessary for amnesia in basal forebrain-damaged patients. Rather, the majority of research appears to suggest that the memory impairments following basal forebrain damage in ACoA amnesia can be primarily attributed to damage to the medial septum/diagonal band complex (see also Everitt & Robbins, 1997; von Cramon & Markowitsch, 2000).

All amnesic individuals, regardless of lesion site, by definition have dense memory impairments, most notably accelerated forgetting of new fact and event information. Because of this similarity, it has often been convenient to consider a unified "organic amnesia" syndrome, in which similar dysfunction is expected regardless of lesion site. Similarly, animals with hippocampal region or basal forebrain damage display many common impairments (see Gray & McNaughton, 1983). Despite these similarities, the two lesions are not identical; animal and computational models have suggested that there are qualitative differences in the pattern of impaired and spared memory abilities following hippocampal versus basal forebrain damage (e.g. Myers, Ermita, Hasselmo, & Gluck, 1998; Myers et al., 1996; Ridley, Baker, Harder, & Pearson, 1996; Solomon, Solomon, Van der Schaaf, & Perry, 1983;).

For example, classical delay eyeblink conditioning is spared in rabbits with hippocampal lesions (e.g. Schmaltz & Theios, 1972; Solomon & Moore, 1975) but severely disrupted in rabbits with basal forebrain (medial septal) lesions (Allen, Padilla, & Gluck, 2002; Berry & Thompson, 1979). The same pattern has been obtained in humans: individuals with amnesia resulting from hippocampal damage are spared at delay eyeblink conditioning (Gabrieli et al., 1995; Weiskrantz & Warrington, 1979; Woodruff-Pak, 1993), but ACoA amnesics, with basal forebrain damage, are strongly impaired (Myers et al., 2001). By contrast, once the initial learning is accomplished, animals with basal forebrain (septal) lesions or disruptions are often spared at subsequent transfer tasks, such as reversal, latent inhibition and learned irrelevance, that are disrupted in hippocampal-lesioned animals (see Myers et al., 1996, 1998, for review).

Why should there be a difference between medial septum and hippocampal lesion? To explain these and related results, Myers et al. (1996, 1998) developed a computational model of hippocampal–basal forebrain interaction. This model assumes that the hippocampus and associated medial temporal structures are important for developing representations of environmental regularities, including stimulus–stimulus associations and the context in which learning occurs. These new representations can then be incorporated into ongoing stimulus–response learning in other brain areas such as cerebellum and striatum. Thus, the model correctly accounts for the findings that hippocampal lesion spares simple stimulus–response learning, but disrupts learning that requires knowledge of stimulus–stimulus and contextual regularities (see also Gluck & Myers, 1993; Myers & Gluck, 1994). Human data, where available, also seem to fit this pattern: for example, amnesic patients with bilateral hippocampal damage may be spared on initial discrimination learning but subsequently impaired when challenged to reverse the learned stimulus-outcome mappings (e.g. Carrillo et al., 2001; Myers, Hopkins, Kesner, Monti, & Gluck, 2000).

In this model, the basal forebrain—specifically the medial septum/diagonal band complex—operates in a loop with hippocampus and modulates the rate at which the hippocampus stores new information (see also Hasselmo & Schnell, 1994; Rokers, Mercado, Allen, Myers, & Gluck, 2002). As a result, septal lesion serves to disrupt hippocampal function, slowing initial learning; however, because the hippocampus is anatomically intact, hippocampal-dependent learning is not abolished, only retarded. The model thus correctly accounts for findings that medial septal lesion in animals slows simple stimulus–response learning but that hippocampal-dependent processing survives (see Myers et al., 1996, 1998).

One question is whether a similar distinction holds in human patients with bilateral hippocampal or basal forebrain damage. If so, this would be an initial dissociation between the qualitative pattern of mnestic deficits in these two amnesic populations.

To address this question, the current study directly contrasts hypoxic and ACoA amnesic patients on a single task: conditional discrimination and reversal (based on an original design by Daum, Schugens, Channon, Polkey, & Gray, 1991). Previously, we had demonstrated that amnesic individuals with hypoxic brain injury could acquire this task as quickly as controls but were impaired at reversal (Myers et al., 2000); we expected to replicate this pattern in the current study with a new group of hypoxic subjects. By contrast, we expected the ACoA group to show the opposite pattern: slow learning followed by little or no impairment on reversal. If so, this would represent a double dissociation of amnesic etiologies within a single learning task.

2. Methods

2.1. Participants

Ten individuals (five males and five females) with anterograde amnesia subsequent to hypoxic brain injury participated in the experiment. Demographic and etiology information for these individuals is shown in Table 1. Structural neuroimaging, available in six hypoxic patients, confirms that three patients had bilateral medial temporal lobe damage while in three patients, the damage extended to include diffuse brain atrophy. All hypoxic participants were at least 1 year post-injury at time of testing. Hypoxic participants were tested at LDS Hospital, Salt Lake City, Utah, and at the Memory Disorders Project, Rutgers University, Newark, NJ.

A second group of amnesic participants (six males and four females) with anterograde amnesia resulting from anterior communicating artery aneurysm rupture formed the ACoA group. Table 1 shows that these individuals were somewhat older than the hypoxic group (independent-samples *t*-test, $t(18) = 2.41$, $p = .027$) but did not differ in education level ($t(18) = 1.18$, $p = .255$). All ACoA participants were at least 6 months post-surgery at time of testing. ACoA participants were tested at Kessler Medical Research Rehabilitation and Education Corporation, West Orange, NJ.

The presence of a surgically implanted metal clip to control bleeding in many ACoA aneurysm survivors prevents

Table 1
Demographic and etiology information for the hypoxic (H13–H28) and ACoA (A1–A10) participants, with brain CT and MR findings where available

ID	Sex	Age	Ed.	Etiology and imaging
H13	M	51	18	Anoxia: CRA; MR scans show bilateral medial and anterior temporal lobe damage
H16	F	37	12	Anoxia: drug overdose; CT, MR scans show bilateral medial temporal lobe damage
H19	M	19	12	Hypoxia: ARDS; MR scans show bilateral damage limited to hippocampus
H22	F	28	12	Hypoxia: ARDS; no imaging available
H23	M	17	11	Anoxia: hemlock poisoning; MR scans show generalized brain atrophy
H24	M	34	14	Hypoxia: CO poisoning; MR scans show generalized brain atrophy
H25	M	18	12	Hypoxia: ARDS; no imaging available
H26	F	42	12	Hypoxia: ARDS; CT scans show generalized brain atrophy
H27	F	57	14	Hypoxia: ARDS; no imaging available
H28	F	78	12	Hypoxia: ARDS; no imaging available
Mean (S.D.)		37.3 (17.9)	12.9 (1.0)	
A1	M	62	12	ACoA aneurysm rupture; damage in basal forebrain confirmed by surgical report
A2	F	45	12	ACoA aneurysm rupture; damage in basal forebrain confirmed by surgical report
A3	F	64	12	ACoA aneurysm rupture; damage in basal forebrain confirmed by surgical report
A4	F	29	16	ACoA aneurysm rupture; CT scans confirm basal forebrain lesion
A5	M	50	18	ACoA aneurysm rupture; CT scans confirm basal forebrain lesion and small right frontal-parietal lesion
A6	F	67	12	ACoA aneurysm rupture; CT & MR scans confirm basal forebrain lesion
A7	F	58	12	ACoA aneurysm rupture; CT scans confirm basal forebrain lesion
A8	M	66	18	ACoA aneurysm rupture; damage in basal forebrain confirmed by surgical report
A9	M	61	14	ACoA aneurysm rupture; damage in basal forebrain confirmed by surgical report
A10	M	53	15	ACoA aneurysm rupture; damage in basal forebrain confirmed by surgical report
Mean (S.D.)		55.5 (11.7)	14.1 (2.5)	

Age and education (Ed.) in years; CRA, cardiac/respiratory arrest; ARDS, acute respiratory distress syndrome; CO, carbon monoxide poisoning; CT, computed tomography and MR, magnetic resonance.

MRI imaging; in addition, in many cases, the clip creates a large artifact on neuroimaging, making it difficult to visualize much of the basal forebrain. The four ACoA participants for whom brain scans were obtained confirm basal forebrain lesions; in the remaining cases, ACoA aneurysm rupture and basal forebrain damage were confirmed by surgical report; there is also the possibility of basal forebrain plus additional frontal lobe damage in these participants, as the ACoA vascularizes other frontal lobe regions in addition to the basal forebrain (e.g. participant A5).

Twenty healthy adults (10 males and 10 females) served as the control group. These individuals were matched for age and education to the amnesic groups. The 10 controls matched to the hypoxic group had an average age of 37.3 years (S.D. 17.8) and education of 12.9 years (S.D. 0.99), neither of which differed from the hypoxic group (independent-samples *t*-tests, all $p > .300$). The 10 controls matched to the ACoA group had an average age of 49.5 years (S.D. 15.7) and education of 13.3 years (S.D. 1.34), neither of which differed from the ACoA group (independent-samples *t*-tests, all $p > .500$). All healthy controls were screened to exclude presence of prior neurologic or psychiatric history, including depression or presence of any medication known to affect cognition. Control participants were tested at the Memory Disorders Project, Rutgers University, Newark, NJ.

2.2. Procedure

All control and amnesic participants signed statements of informed consent before initiation of any (neuropsychological or behavioral) testing. Procedures conformed to guidelines established by the Federal Government and were approved by the IRB at participating institutions.

Amnesic participants were administered a battery of neuropsychological tests, including the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Wechsler Memory Scale-Revised (WMS-R) and the Rey-Osterrieth Complex Figure Test (ROCFT).

All participants were then administered the conditional spatial discrimination task. This task was based on Myers et al. (2000) and took the form of a computerized game in which the participant guided an animated mouse in a T-maze. The game was implemented on Macintosh ibook or equivalent computers, programmed in the SuperCard language. Participants were seated at a comfortable viewing distance from the screen. The keyboard was masked except for two adjacent keys, labeled “left” and “right”, which the participant used to enter responses. The computer screen displayed the following instructions: “*You are a hungry mouse in a maze. Direct your mouse left or right to eat as much cheese as possible. Press the button to begin*.” The experimenter read these instructions aloud to the participant, demonstrated the “left” and “right” response keys and pressed the computer mouse button to begin the experiment.

On each trial, a T-maze was displayed with a black square at the end of each arm serving as a visual blocker. The mouse appeared in the start box at the bottom of the screen (Fig. 2A) and ran to a choice point in the center of the maze (Fig. 2B). The mouse hesitated there, wavering back and forth, until the participant pressed a key to send it into the left or right

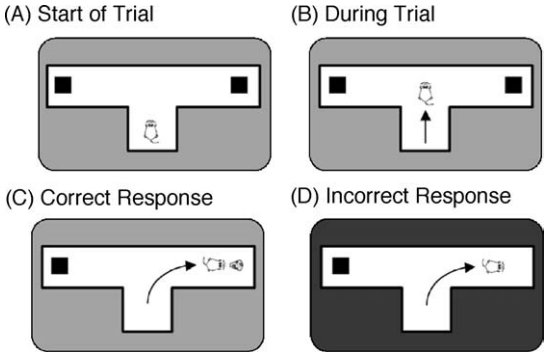

Fig. 2. Screen events during one trial of the discrimination task. (A) At the start of a trial, an animated rat appears at the bottom of a T-maze and runs up to the choice point and wavers there until the participant presses a key to guide the rat into the left or right maze arm. (C) If the response was correct, a piece of cheese is revealed and a "happy" sound is played and (D) otherwise, there is no cheese and a "sad" sound is played. Placement of cheese on a given trial depends on screen background brightness; here, light gray signals that cheese is available in the right arm, and dark gray signals that cheese is available in the left arm.

maze arm. If the participant chose correctly (Fig. 2C), then when the mouse reached the end of the maze arm, the blocker was removed to reveal cheese and a "happy" mouse sound was played through the computer speakers. If the participant chose incorrectly (Fig. 2D), then when the mouse reached the end of the maze arm, the blocker was removed to reveal no cheese and a "sad" mouse sound was played through the computer speakers.

On each trial, cheese was present in either the left or right maze arm; its placement depended on the background screen brightness (unbeknownst to the participant). Thus, cheese was located in the right-hand arm if the background was light gray and in the left-hand arm if the background was dark gray. Trials were pseudorandom but fixed, with the constraint that the cheese never occurred in the same arm more than three times in a row.

This initial acquisition phase lasted until the participant made eight consecutive correct responses or to a maximum of 50 trials. If the acquisition criterion had not been reached, the program terminated. Otherwise, the reversal occurred: the color-cheese mapping was reversed so that cheese was in the left-hand arm for a light gray background and in the right-hand arm for a dark gray background. The participant was given no indication that a reversal had occurred. This reversal phase continued until the participant made eight consecutive correct responses or to a maximum of 50 trials. The total experiment took approximately 10–15 min to complete.

3. Results

3.1. Neuropsychological testing

Table 2 shows the results of neuropsychological testing in the two amnesic groups. The WAIS-R VIQ is a measure of verbal intelligence with an expected normal mean of 100 (S.D. 15). Most of the amnesic participants scored

Table 2
Neuropsychological test scores for the hypoxic and ACoA group

	WAIS-R VIQ	WAIS-R PIQ	WMS-R Gen.	WMS-R Attn/Conc.	WMS-R Delay	ROCFT Copy	ROCFT Delay
H13	102	88	84	72	58	30	10
H16	104	117	88	108	71	36	3
H19	111	77	65	96	50	33	10
H22	84	88	86	63	76	28	14
H23	92	71	50	69	50	32	2
H24	85	80	76	69	50	34	12
H25	93	74	77	75	50	28	3
H26	87	79	78	75	85	12	9
H27	82	84	70	63	78	34	22
H28	91	74	81	69	97	13	0
Mean (S.D.)	94.2 (11.5)	87.0 (12.0)	72.3 (12.2)	79.1 (19.2)	66.5 (17.2)	28.0 (8.6)	8.5 (6.7)
A1	93	87	85	80	53	12	4
A2	82	78	60	72	57	34	26
A3	87	96	60	50	50	24.5	6
A4	80	78	70	78	57	34	22
A5	88	75	65	70	57	35	21
A6	105	108	78	103	50	36	13.5
A7	119	100	70	50	63	36	8
A8	95	88	94	91	76	33	14
A9	95	70	58	101	63	22	4
A10	98	90	83	96	82	28	15
Mean (S.D.)	93.1 (9.6)	83.2 (13.2)	72.3 (12.2)	79.1 (19.2)	60.8 (10.7)	29.5 (7.9)	13.4 (7.8)

WAIS-R and WMS-R scores are shown as index scores with a mean of 100 and standard deviation of 15 with higher scores indicating better performance. The ROCFT copy and delay recall are shown as raw scores (range 0–36) with higher scores indicating better performance. WMS-R, Wechsler Memory Scale-Revised; WAIS-R, Wechsler Adult Intelligence Scale-Revised; ROCFT, Rey-Osterrieth Complex Figure Task; Gen., general memory index; Attn/Conc., attention/concentration index and Delay, delay memory index.

within the normal to low–normal range. WAIS-R PIQ, a measure of non-verbal intelligence, was slightly lower than VIQ in most amnesic participants. These two measures did not differ significantly between hypoxic and ACoA groups (independent-samples *t*-tests, all $p > .500$). Both groups also showed evidence of frontal dysfunction, as indexed by WMS-R attention/concentration score, but this likewise did not differ between groups ($p > .500$).

Both amnesic groups showed severe impairments on the delay memory components of both the WMS-R and ROCFT, consistent with their classification as amnesics. However, there was no significant difference between groups on these measures, nor on the WMS-R general memory or ROCFT copy score (independent-samples *t*-tests, all $p > .100$). There were also no significant differences on any of these measures between patients with available neuroimaging and those for whom neuroimaging was not available (independent-samples *t*-tests, all $p > .200$).

In summary, both amnesic groups showed strong memory deficits, with modest cognitive and attentional deficits, but on none of these measures did the two amnesic groups differ from each other.

3.2. Conditional discrimination task

No significant differences on the conditional discrimination task were found between the controls matched to the hypoxic and ACoA groups; data from all controls were, therefore, pooled.

Fig. 3A shows mean trials to criterion during acquisition for each group. Three individuals in the ACoA group, one in the hypoxic group and two in the control group failed to reach criterion within the maximum 50 trials. An analysis of variance (ANOVA) confirmed significant group differences for total number of acquisition trials ($F(2,36) = 5.00$, $p = .012$) with no effect of age ($F(1,36) = 1.77$, $p = .193$). Tukey HSD pairwise tests confirmed that performance in the ACoA group was significantly worse than either the hypoxic or control group (all $p < .05$), while the hypoxic and control group did not differ from each other ($p > .500$).

Fig. 3B shows mean total errors committed by each group during the acquisition phase. Again, there was a significant group effect (ANOVA, $F(2,36) = 4.71$, $p = .015$) with no effect of age ($F(1,36) = 0.61$, $p = .441$). Tukey HSD pairwise tests confirmed that the ACoA group made significantly more errors than the control group ($p = .011$) while the hypoxic and control groups did not differ ($p > .500$). The difference between ACoA and hypoxic groups was not significant ($p = .153$).

Fig. 4A shows mean trials to criterion during reversal for those participants who reached criterion in the acquisition phase. All ACoA and control participants reached criterion on the reversal, while three of the hypoxic participants did not. Again, there were significant group differences (ANOVA, $F(2,30) = 10.74$, $p < .001$) with no effect of age ($F(1,30) = 1.09$, $p = .305$). Now, however, Tukey HSD pairwise tests confirmed that the hypoxic group performed worse than the ACoA and control groups (all $p < .030$), while the ACoA and control groups did not differ ($p > .500$).

A similar pattern emerges from consideration of the mean total errors committed during reversal (Fig. 4B): a significant group effect (ANOVA, $F(2,30) = 17.26$, $p < .001$) with no effect of age ($F(1,30) = 1.02$, $p = .320$). Tukey HSD pairwise tests confirmed that the hypoxic group performed worse than the control and ACoA groups (all $p < .010$) while the control and ACoA groups did not differ ($p > .500$).

Operationally, the reversal phase can be divided into three sub-phases: a perseverative phase consisting of those trials immediately following reversal for which the participant is still using the old (now incorrect) response rule, a mixed phase consisting of some correct and some incorrect responses during which the new rule is acquired and a correct phase consisting of consistently correct responding as per the new rule. During the perseverative phase, participants make a string of consecutive incorrect responses. Fig. 4C shows the mean perseverative errors for each group at the beginning of the reversal phase. Again, there was an effect of group (ANOVA, $F(2,30) = 13.87$, $p < .001$) with no effect of age ($F(1,30) = 0.23$, $p > .500$), with the hypoxic group making more perseverative errors than the control and ACoA groups (Tukey HSD, all $p < .05$) while the control and ACoA groups did not differ ($p = .240$).

Fig. 4D shows mean trials to criterion (not including final eight correct responses) in the subsequent mixed phase,

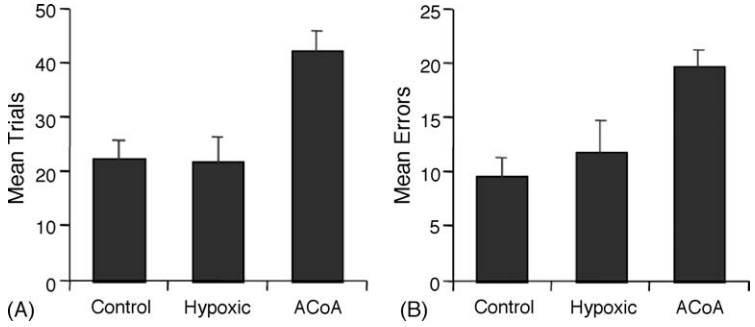

Fig. 3. Performance on the conditional discrimination acquisition for all participants, in terms of (A) mean total trials before criterion of eight-in-a-row consecutive correct responses and (B) mean total errors during this phase. Bars represent standard error.

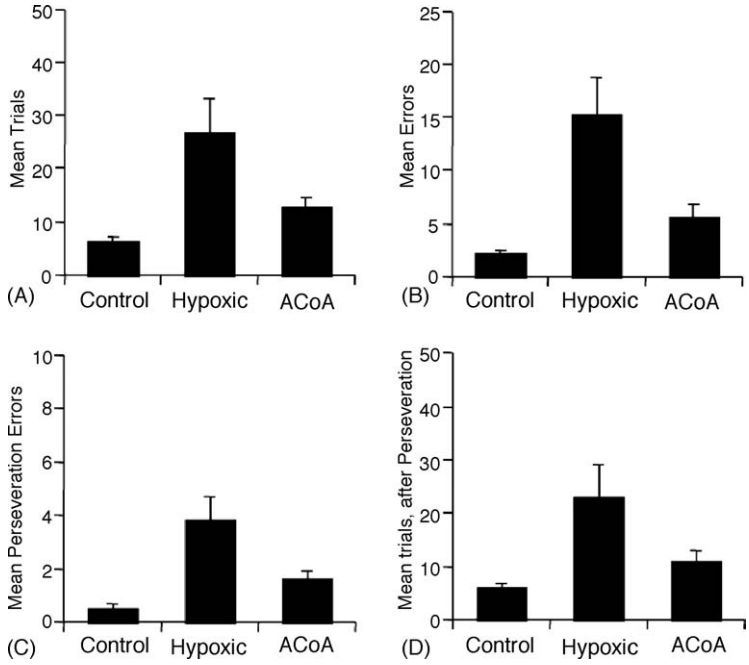

Fig. 4. Performance on the reversal phase, for subjects who completed the acquisition phase, in terms of (A) mean total trials before criterion of eight-in-a-row consecutive correct responses and (B) mean total errors during this phase; (C) shows mean perseverative errors, defined as consecutive incorrect trials immediately following the unsignaled reversal and (D) shows mean number of trials to reacquisition, once subjects stop making perseverative errors. Bars represent standard error.

once perseverative responding stopped. There was still a significant group effect (ANOVA, $F(2,31) = 7.90$, $p = .002$), with the hypoxic group making more errors than the control group (Tukey HSD, $p = .001$). The ACoA and control group did not differ ($p = .515$). Comparison of Figs. 3A and 4D shows that the control group completed the mixed phase of reversal (once perseverative responses are excluded) in significantly fewer trials that it took them to complete acquisition (two-tailed *t*-test, $p < .001$), suggesting a learning set effect. The hypoxics showed no such learning set effect, taking about as long to learn the new rule (after perseveration) as they had taken to learn the original acquisition (two-tailed *t*-test, $p > .500$).

In summary, the ACoA group was slower to acquire the conditional discrimination than controls, with some ACoA participants failing to reach criterion within the maximum 50 trials. However, those ACoA individuals who did reach criterion subsequently reversed as well as controls. In contrast, the hypoxic group acquired the conditional discrimination quickly, but was then impaired at reversal and showed higher level of perseverative responding than the other groups.

4. Discussion

Results from the conditional discrimination task suggest that performance among amnesic groups differs as a result of etiology and lesion site (hippocampus versus basal forebrain). The hypoxic group learned the initial discrimination as quickly as healthy controls, but was impaired at reversal. By contrast, the ACoA group was impaired on acquisition but then went on to reverse well.

The impaired acquisition in the ACoA group cannot be easily ascribed to global cognitive or attentional impairments in the ACoA group, since the hypoxic group had similar levels of impairment (Table 2). The pattern of impaired acquisition but good performance on a subsequent transfer task is consistent with other data in ACoA amnesia (Myers, Bryant, DeLuca, & Gluck, 2002). It is also consistent with the predictions of the computational model of Myers et al. (1998), which expects basal forebrain/medial septal damage to result in slow initial learning but preserved ability to perform subsequent transfer operations, including reversal.

An alternate interpretation of the learning deficit might note that the ACoA variably vascularizes prefrontal areas, and indeed the patient group showed attentional impairments that are consistent with some degree of frontal damage. Petrides (1985) concluded that posterior dorsolateral frontal cortex was the critical frontal region for acquisition of spatial conditional discrimination. However, ACoA patients generally do not show dorsolateral prefrontal damage, nor do they typically show an impairment in tests sensitive to dorsolateral prefrontal function (see Mavaddat, Kirkpatrick, Rogers, & Sahakian, 2002, for review).

By contrast, ACoA patients often display ventromedial prefrontal damage and are often impaired on tests of ventromedial prefrontal function such as decision-making (Mavaddat et al., 2000). Because the ventromedial prefrontal area operates in a loop with striatum, the ACoA impair-

ment might reflect disruption of a striato-frontal loop; patients with caudal dysfunction, such as Parkinson's disease, are impaired on conditional discrimination learning (e.g. Vriezen & Moscovitch, 1990). However, patients with ventromedial prefrontal and/or striatal damage are generally also impaired on reversal of conditional discriminations (e.g. Fellows & Farah, 2003; Freedman & Oscar-Berman, 1989; Hornak et al., 2004), while our ACoA patients did not show reversal deficits. In fact, many researchers in the field now argue that while frontal damage may underlie personality changes in ACoA patients, it is more likely to be basal forebrain projections to medial temporal lobe areas that mediate the memory loss in these patients (e.g. DeLuca, 1993; Selden, Gitelman, Salamon-Murayama, Parrish, & Mesulam, 1998).

In contrast to the spared reversal learning in the ACoA group, the hypoxic group did show impaired reversal. These results are consistent with the predictions of our computational model, which expects hippocampal lesion to spare simple stimulus–response learning, but not the additional representational learning that would underlie efficient reversal (Gluck & Myers, 1993). Our prior study with different hypoxic individuals with bilateral hippocampal damage also found a selective reversal deficit (Myers et al., 2000). The hypoxic patients in the current study had somewhat more diffuse brain damage and greater non-mnemonic (attentional and cognitive) deficits than those in the prior study; their reversal deficit was correspondingly somewhat more pronounced. Again, the reversal impairment in the current hypoxic group cannot simply be ascribed to global attentional impairments, since the ACoA group—who reversed well—had similar attentional impairments revealed by neuropsychological testing.

The hypoxic group made more perseverative errors than either the control or ACoA group (Fig. 4C), but their impairment remained even after perseverative errors were subtracted (Fig. 4D). One explanation of this finding is that the hypoxic group may have been more tired or frustrated than the other groups, leading to slower learning simply because they were less motivated. A second possibility is that the mixed phase masks continued perseverative responding in the hypoxic group, a period during which the hypoxic group tried new responses but also occasionally reverted to the old response rule. A third possibility is suggested by comparing Figs. 3A and 4D; excluding perseverative responses, the control group appeared to show a learning set effect—learning a new response rule more quickly in the reversal phase than in the initial acquisition phase—while the hypoxic group did not. This is consistent with the prediction of our intact model that reversal learning should be faster than initial acquisition because stimulus representations formed during initial learning can be used during subsequent reversal and merely mapped to new outcomes (Gluck & Myers, 1993). Because these stimulus representations depend on hippocampal mediation in the model, the model predicts no such reversal facilitation following hippocampal-region damage, which would be consistent with the hypoxic deficit observed in the current results.

Among the hypoxic group, diffuse cortical damage could have included some frontal damage, although specific frontal lesions were not visible on those patients for whom neuroimaging was available. Such an interpretation would be generally consistent with the common finding of reversal deficits in patients with frontal lesions (e.g. Swainson et al., 2000) and with the trend for reversal deficit among frontal patients in the Daum et al. (1991) study. The good acquisition performance of the hypoxic group in the current study would appear to argue against significant dorsolateral frontal damage, since the Petrides (1985) study implicated that brain region in conditional discrimination learning (see also Petrides, 1990); however, it is again possible that ventromedial or diffuse frontal damage could have contributed to the reversal impairment in these patients. Freedman, Black, Ebert, and Binns (1998) have suggested that at least some kinds of perseveration may be associated specifically with medial and orbitofrontal damage and this would be consistent with the increase in perseverative responding among the hypoxic group in the current study as well as the mild (one or two trials) perseveration observed in the frontal patients in the Daum et al. (1991) conditional discrimination study.

In contrast to the mild impairment in their frontal patients, Daum et al. (1991) found that individuals with unilateral (primarily right-side) temporal lobe resection were significantly impaired on acquisition of the conditional discrimination, but were not impaired on the reversal. Petrides (1985) also found impairments on spatial conditional association in patients with right-side temporal lobe damage, but only if that damage extended to include the hippocampus (see also Petrides & Milner, 1982).

Considering those results in combination with the current results, one interpretation is that extrahippocampal cortical areas within the right temporal lobe normally subserve acquisition of this task while the hippocampus subserves reversal learning. According to this view, right temporal lobe patients are slow on learning if forced to use their surviving left temporal lobe but then, having done so, are able to use their surviving hippocampus to mediate reversal. The opposite pattern would obtain in the hypoxic patients, who have bilateral hippocampal damage but relative sparing of extrahippocampal temporal regions; these patients would learn quickly but then not reverse easily. Further studies, and particularly functional imaging of hypoxic and temporal lobectomy patients, may shed further light on how these patients go about solving this type of task and what types of brain system are necessary and sufficient for such learning.

In summary, the results from this study suggest that a simple two-phase task, such as the conditional discrimination and reversal task, can provide a double dissociation between the memory impairments in two amnesic populations: individuals with hippocampal/medial temporal damage resulting from hypoxic brain injury and individuals with basal fore-

brain damage resulting from ACoA aneurysm rupture. These differences occur in spite of the fact that the memory and attentional deficits on standard neuropsychological tests are similar across the two amnesic groups. Understanding these differences may have implications for understanding the normal function of the brain structures involved, as well as in the design of rehabilitation techniques to address each population's pattern of impaired and residual memory abilities.

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