

The von Restorff Effect in Amnesia: The Contribution of the Hippocampal System to Novelty-Related Memory Enhancements

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Abstract

■ The ability to detect novelty is a characteristic of all mammalian nervous systems (Sokolov, 1963), and it plays a critical role in memory in the sense that items that are novel, or distinctive, are remembered better than those that are less distinct (von Restorff, 1933). Although several brain areas are sensitive to stimulus novelty, it is not yet known which regions play a role in producing novelty-related effects on memory. In the current study, we investigated novelty effects on recognition memory in amnesic patients and healthy control subjects. The control subjects demon-

strated better recognition for items that were novel (i.e., presented in an infrequent color), and this effect was found for both recollection and familiarity-based responses. However, the novelty advantage was effectively eliminated in patients with extensive medial temporal lobe damage, mild hypoxic patients expected to have relatively selective hippocampal damage, and in a patient with thalamic lesions. The results indicate that the human medial temporal lobes play a critical role in producing normal novelty effects in memory. ■

INTRODUCTION

The effects of novelty have been examined using a variety of different behavioral paradigms (e.g., Gabrieli, Brewer, Desmond, & Glover, 1997; Stern et al., 1996; Tulving, Markowitsch, Craik, Habib, & Houle, 1996; Tulving & Kroll, 1995; von Restorff, 1933), but, the most extensively studied method for examining the effects of novelty on subsequent memory was developed by von Restorff (Kishiyama & Yonelinas, 2003; Parker, Wilding, & Ackerman, 1998; Hunt, 1995; Kinsbourne & George, 1974; Wallace, 1965; Saltz & Newman, 1959; von Restorff, 1933). In this paradigm, subjects study a list of items that include a small number of items that have a relatively novel characteristic in the context of the list. For example, in a list of yellow objects, one object may be presented in red. In subsequent tests of memory, subjects are found to exhibit a memory advantage for the novel compared with the non-novel items. This effect is quite robust and has been observed when items are made novel on the basis of a number of different stimulus dimensions such as color, size, brightness, and semantic category (e.g., Hunt, 1995; Cimbalo, 1978; Wallace, 1965). Moreover, it is observed in both recall and recognition memory tests (e.g., Parker et al., 1998; Fabiani & Donchin, 1995; Hunt, 1995; Cimbalo, 1978; Wallace, 1965; von Restorff, 1933).

A variety of brain regions are sensitive to novelty, but the regions involved in producing memory-related novelty effects are currently debated (e.g., Parker et al., 1998; Knight, 1996; Tulving, Markowitsch, Kapur, Habib, & Houle, 1994). For example, human brain imaging studies have shown that visually distinctive items and items that are presented for the first time compared with repeated items elicit greater activation in the hippocampus, in the parahippocampal, fusiform and lingual gyri, as well as in the thalamus and prefrontal cortex (e.g., Kirchoff, Wagner, Maril, & Stern, 2000; Menon, White, Eliez, Glover, & Reiss, 2000; Martin, 1999; Gabrieli et al., 1997; Stern et al., 1996; Tulving et al., 1996). Novelty responses have also been observed in the human medial temporal lobes using intracerebral recordings (Fried, MacDonald, & Wilson, 1997; Halgren et al., 1980, 1995). Furthermore, the P3a event-related scalp potential that is associated with novelty is significantly reduced in human patients with medial temporal (Knight, 1996) or frontal lobe damage (Daffner et al., 2000; Knight & Scabini, 1998; Knight, 1984). Moreover, single-unit recording studies in rats and nonhuman primates have identified novelty-sensitive neurons in the hippocampus (Rolls, Cahusac, Feigenbaum, & Miyashita, 1993), in the perirhinal cortex (Fahy, Riches, & Brown, 1993; Riches, Wilson, & Brown, 1991; Brown, Wilson, & Riches, 1987), and in the thalamus (Aggleton & Brown, 1999; Fahy et al., 1993).

These studies, however, do not indicate which structures are critical in producing novelty-related

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enhancements in memory because subsequent memory was not measured. Moreover, the activation studies only indicate which regions are sensitive to novelty; they do not show which regions play a necessary role in producing the novelty advantage in memory. Studies of patients with damage to these regions should prove useful in addressing this issue. One recent lesion study that examined von Restorff effects in nonhuman primates suggested that the perirhinal, frontal, and thalamic regions, but not the hippocampus, were necessary for producing a novelty effect on memory (Parker et al., 1998). They found that lesions designed to isolate the hippocampus (i.e., bilateral amygdala and fornix lesions) did not disrupt the novelty effects, whereas lesions disconnecting the perirhinal and either the frontal lobes or medial dorsal thalamus eliminated the novelty effects. These results are consistent with the earlier studies in indicating that the perirhinal cortex, the thalamus, and the frontal lobes are involved in novelty, but they are in conflict in showing that the hippocampus does not play a necessary role in producing the novelty advantage in memory. However, whether comparable effects will be observed in human subjects is unknown.

The purpose of the current study was to determine if regions damaged in amnesia were necessary for the novelty-related memory enhancements seen in the von Restorff paradigm. Although amnesics are expected to have lower levels of recognition memory than controls, whether or not they still exhibit a normal memory advantage for novel compared with non-novel items remains unknown.

To determine which regions were most critical for novelty encoding, we contrasted the memory performance of amnesic patients with different types of lesions. In particular, we compared patients with extensive temporal lobe damage (the H+ group) to patients

with damage expected to be relatively restricted to the hippocampus (the H group). The H+ group included posterior cerebral infarct patients and anterior temporal lobectomy patients with damage to the hippocampus and the surrounding temporal lobe cortex (Figure 1A and B). The H group consisted of a group of cardiac arrest patients who suffered from mild hypoxia (i.e., brief loss of oxygen). The hypoxic patients had defibrillators, thus they could not be scanned in order to conduct volumetric analysis. However, because they suffered only very mild hypoxic events (i.e., less than 10 min), and their impairments were mild and limited to memory (see Methods), their damage is expected to be limited to the hippocampus. In severe hypoxia, other brain regions such as the watershed regions in the cerebral cortex and cerebellum can also be influenced (Markowitsch, Weber-Luxemburger, Ewald, Kessler, & Heiss, 1997; Schmidt-Kastner & Freund, 1991). However, in cases in which the hypoxic event is brief and the cognitive deficits are restricted primarily to memory, volumetric neuroimaging (Vargha-Khadem et al., 1997; Kartsounis, Rudge, & Stevens, 1995), and postmortem neuropathological analyses (Rempel-Clower, Zola, Squire, & Amaral, 1996; Cummings, Tomiyasu, Read, & Benson, 1984) indicate that the hippocampus is the primary region influenced by hypoxia and is the most likely cause of the memory impairments.

Besides the H and H+ groups, we also had the opportunity to examine the performance of an amnesic infarct patient with bilateral thalamic lesions (Figure 1C). Although it is difficult to draw strong conclusions on the basis of a single subject, the results from this patient provided a preliminary test of the prediction derived from neuroimaging studies (e.g., Tulving et al., 1996) that the thalamus is critical for normal novelty-related memory enhancements.

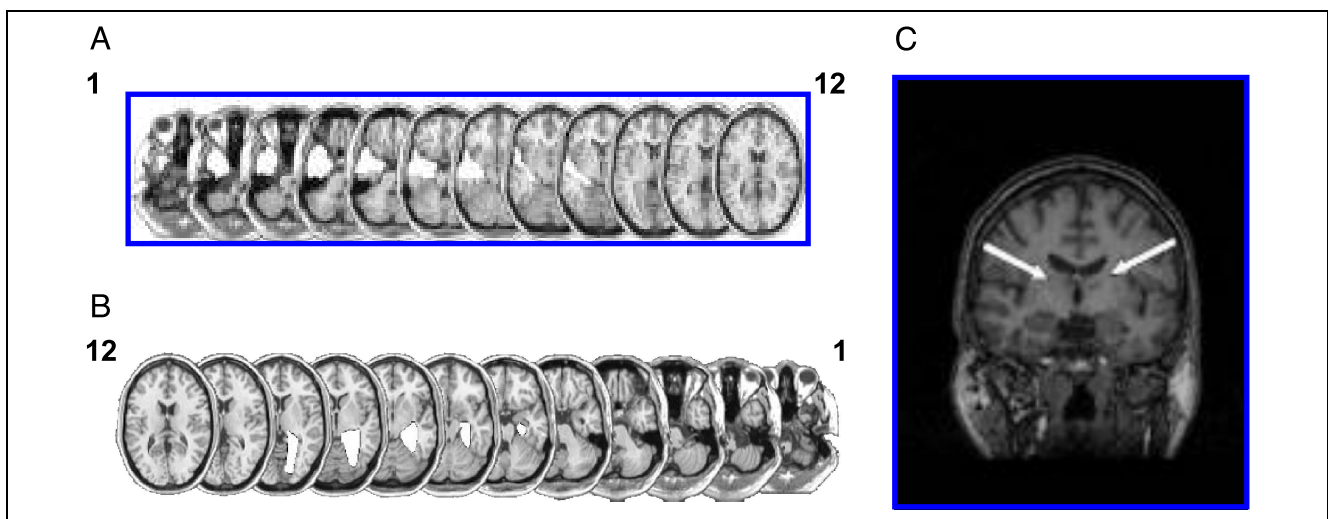


Figure 1. Lesion reconstructions for temporal lobectomy (A) and posterior cerebral artery infarct patients (B). MR scan of a patient with bilateral thalamic infarcts (C).

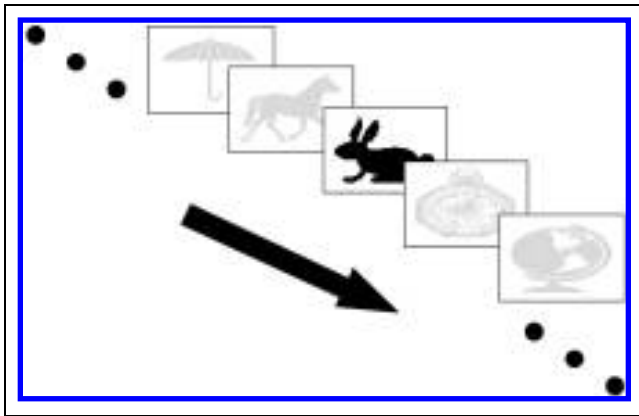


Figure 2. Example of the isolation-by-color technique used in the von Restorff paradigm. Black objects represent objects presented in red and gray objects represent objects presented in yellow.

The influence of stimulus novelty on recognition memory was investigated using a von Restorff paradigm in which items were made novel on the basis of color (see Figure 2). Recognition memory performance was tested using the remember/know (R/K) procedure (Tulving, 1985) in which subjects were required to indicate whether each recognition judgment was based on conscious recollection of the previous study event or whether it was based on a sense of familiarity in the absence of recollection. Previous experiments have indicated that in normal subjects both recollection and familiarity-based recognition judgments increased for novel compared with non-novel items (Kishiyama & Yonelinas, 2003). Thus, the current study allowed us to determine whether amnesia influenced the novelty effects on either or both of these memory processes. Our expectation was that the extent to which the novelty effects were disrupted would depend on the type of amnesic patient examined. Previous studies of rats and nonhuman primates (Aggleton & Brown, 1999; Eichenbaum, Otto, & Cohen, 1994) and human amnesic patients (Yonelinas, 2002; Yonelinas et al., 2002) have indicated that the hippocampus is critical for recollection, whereas the surrounding parahippocampal gyrus is critical for familiarity. Thus, we expected patients with relatively selective hippocampal damage (the H group) to exhibit reduced novelty effects only on recollection, whereas patients with damage including the hippocampus and the parahippocampus (the H+ group) would show reduced novelty effects in both recollection and familiarity.

RESULTS

Recognition Accuracy

Table 1 presents the average recognition responses for old and new items for the amnesic and control groups, and Figure 3 presents d' measures of overall recognition accuracy. Recognition accuracy was measured using d'

(see MacMillan & Creelman, 1991) such that a hit was defined as the proportion of old items receiving a remember or know response, and the false alarm rate was defined as the proportion of new items receiving a remember or know response. Separate analyses of the remember and know responses are described below. Note that other indices of accuracy such as hits-minus-false alarms and A' were examined but led to similar conclusions. Planned t tests were one-tailed.

Overall recognition accuracy was greater for novel than non-novel items, $F(1, 18) = 5.29, p < .05, MSE = .05$, and was lower for the amnesics than the controls, $F(1, 18) = 14.33, p < .01, MSE = .16$. Most importantly, there was a significant Group \times Item type interaction, $F(1,18) = 8.32, p < .05, MSE = .05$, indicating that the novelty effects were significantly reduced in the amnesics compared with the controls. This was consistent with direct contrasts that indicated that there was a significant novelty effect observed in the control group [$t(9) = 3.11, p < .05$], but not in the amnesic group [$t(9) = 0.53, p = .31$].

Because the amnesics performed more poorly than controls it is possible that their reduced novelty effects were due in part to lower levels of performance. To address this issue, a median split was conducted in which the control subjects were divided into the subjects with the “highest” overall recognition and the subjects with the “lowest” recognition. Because the lowest performing control group ($n = 5$) performed at comparable levels to the amnesic group (see Figure 4), this group served as a performance-matched control group. Note that the d' measurements reported in Figure 4 were derived in the same way as those reported in Figure 3. Importantly, significant novelty effects were observed in overall recognition accuracy in this control group [$t(4) = 2.33, p < .05$], indicating that novelty effects were observed even in control subjects who performed at levels comparable to the amnesics.

Table 1. The Average Probabilities of Remember (R) and Know (K) Responses for Amnesics and Controls.

	<i>Old Items</i>		<i>New Items</i>	
	<i>R</i>	<i>K</i>	<i>R</i>	<i>K</i>
<i>Amnesics</i>				
Novel	.32 (.19)	.31 (.25)	.09 (.07)	.28 (.18)
Non-novel	.41 (.19)	.37 (.23)	.15 (.10)	.36 (.23)
<i>Controls</i>				
Novel	.55 (.18)	.20 (.11)	.07 (.11)	.16 (.09)
Non-novel	.54 (.18)	.24 (.14)	.13 (.10)	.26 (.12)

Standard deviations are presented in parentheses.

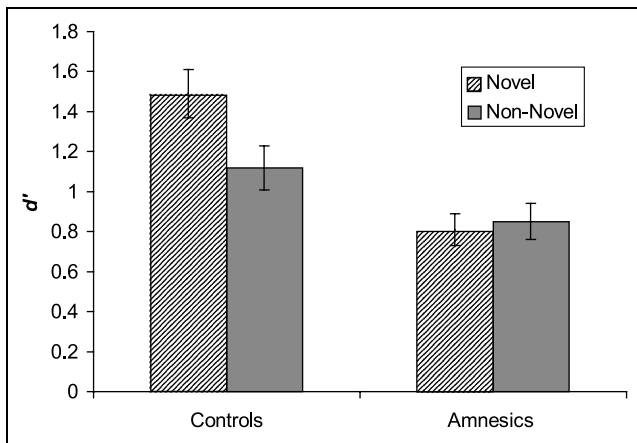


Figure 3. Overall recognition performance for the control and amnesic groups.

In a subsequent analysis, performance was examined separately for the H and H+ groups, and the thalamic patient (Figure 4). As just mentioned, the performance-matched control group exhibited a significant novelty effect. In contrast, there was no evidence of a novelty effect in the H [$t(2) = 0.45, p = .35$] or H+ [$t(5) = 0.23, p = .41$] groups, or in the thalamic patient, indicating that novelty effects were disrupted in all the amnesic subgroups.

Recollection and Familiarity

Estimates of recollection and familiarity based on R/K responses (Yonelinas & Jacoby, 1995) are presented in Figure 5. Note that all estimates in this figure were significantly above chance ($p < .01$), indicating that both recollection and familiarity supported recognition in each experimental condition. The estimates in Figure 5 were reported in d' values, and these estimates were derived from the proportions of hit and false alarm rates

for remember and know responses. Because subjects were instructed to respond remember whenever an item was recollected, the probability of a remember response was used as an estimate of recollection (i.e., $R = \text{“remember”}$). To incorporate false alarm rates, accuracy was measured using d' , such that the proportion of correct and incorrect remember responses were used as hits and false alarms. Because subjects were instructed to respond “know” when an item was familiar in the absence of recollection [i.e., “know” = $F(1 - R)$], familiarity was estimated as the probability of a know response given the item was not recollected [i.e., $F = \text{“know”}/(1 - R)$]. As with the recollection estimates, the estimates of familiarity for old and new items were used as hits and false alarms in order to derive d' estimates of familiarity accuracy. Note that using other indices of accuracy, such as hits minus false alarms, led to similar conclusions.

There was a significant Item (novel vs. non-novel) \times Group (amnesic vs. control) interaction, $F(1,36) = 5.40, p < .05, SEM = .096$, reflecting the finding that the novelty effects were significantly reduced in the amnesics compared with the controls. The Group \times Item \times Process (recollection vs. familiarity) interaction did not approach significance ($F < 1$), indicating that the same pattern of results was observed for both recollection and familiarity. Moreover, the Item \times Process interaction did not approach significance ($F < 1$), indicating that novelty had similar effects on recollection and familiarity. Planned comparisons indicated for the control subjects that novelty led to a significant increase in recollection [$t(9) = 3.98, p < .01$], and a similar although only marginally significant effect on familiarity [$t(9) = 1.61, p = .07$]. In contrast, for the amnesic patients, novelty did not influence estimates of recollection [$t(9) = 0.04, p = .48$] or familiarity [$t(9) = 0.53, p = .30$].

Separate analyses of recollection and familiarity estimates in the H and H+ subgroups did not reveal any

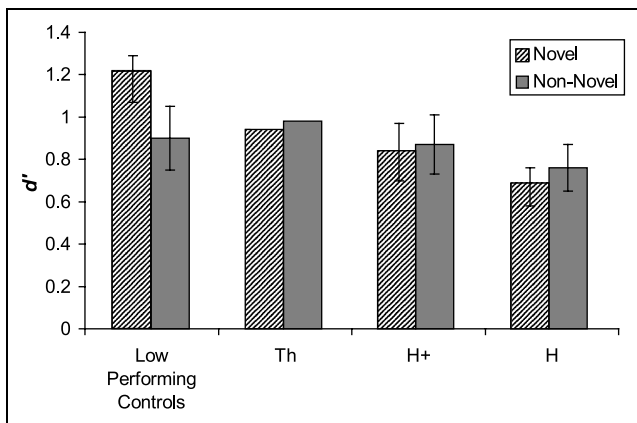


Figure 4. Overall recognition performance for the lowest performing control group, the thalamic patient (Th), the H+ patients, and the H patients.

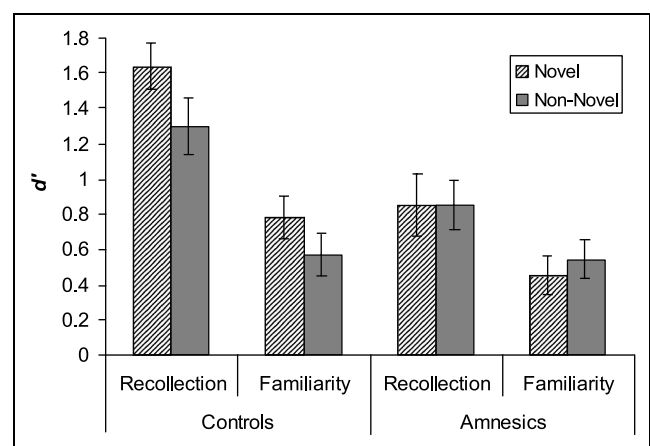


Figure 5. Recollection and familiarity performance for the control and amnesic groups.

significant effects of novelty on recollection or familiarity (all t 's < 1), and there was no evidence of novelty effects on either process in the thalamic infarct patient. Thus, novelty did not influence estimates of either recollection or familiarity in any of the amnesic groups.

DISCUSSION

Healthy control subjects exhibited better recognition memory for novel compared with non-novel items in the von Restorff paradigm. Consistent with prior work, comparable novelty effects were observed on recollection and familiarity-based recognition responses (Kishiyama & Yonelinas, 2003). The novelty advantage, however, was significantly reduced, and no longer significant, in the amnesic patients. Moreover, no evidence of a novelty effect appeared in either the patients with extensive medial temporal lobe damage, in hypoxic patients expected to have more selective hippocampal damage, or in a patient with thalamic damage. These results indicate that the human hippocampal system plays a critical role in producing novelty-related memory effects. The fact that the novelty effects were eliminated in the hypoxic patients and in the thalamic patient indicates that the human hippocampus and the thalamus play critical roles in novelty processing. The novelty effects, however, were eliminated in both recollection and familiarity in all the amnesic groups. This disconfirms our expectation that the extent to which the novelty effects were disrupted would depend on the type of amnesic patient.

The results from the current experiment are consistent with previous studies suggesting that the hippocampus and thalamus are sensitive to stimulus novelty. In particular, evidence from neuroimaging (Kirchoff, Wagner, Maril, & Stern, 2000; Gabrieli et al., 1997; Stern et al., 1996; Tulving et al., 1996) and electrophysiological studies (Knight, 1996; Halgren et al., 1995) as well as animal studies using single-unit recordings and lesions (e.g., Aggleton & Brown, 1999; Fahy et al., 1993; Riches et al., 1991) suggests that the hippocampus and thalamus are involved in novelty-related responses. However, subsequent memory performance for novel events was not measured in those studies. To our knowledge, the current study is the first to examine subsequent memory for novel items in amnesic patients, and it thus provides the first evidence that the human hippocampus and thalamus are necessary for normal novelty effects on memory.

The results are partially consistent with the conclusions drawn in a recent nonhuman primate lesion study (Parker et al., 1998). Parker et al. concluded that interactions between perirhinal and frontal as well as between perirhinal and thalamic regions were critical in leading to normal von Restorff effects. This is in agreement with the finding that damage to the thalamus eliminated the novelty effects in the current study.

It is also consistent with the finding that the H+ group in the current study, which included patients with damage to the perirhinal cortex, also exhibited novelty deficits. Although it is important to note that on the basis of the current results alone it is not clear if the novelty deficit in the H+ group was due to hippocampal damage or to the additional damage of the surrounding perirhinal regions.

The most critical discrepancy between the two studies, however, relates to the fact that Parker et al. found that novelty effects were unaffected by lesions designed to disrupt the hippocampus (i.e., bilateral lesions of the amygdala and fornix). Their results suggest that the hippocampus does not play a necessary role in the von Restorff effects, whereas the current results indicate that this region did play a critical role. Based on the existing results, we cannot be sure why this discrepancy arose. One possibility is that there may be inherent differences in how human and nonhuman primates respond to novelty in the von Restorff paradigm. Another possibility is that procedural differences led to the different results. For example, the study list in the current experiment was quite long, whereas in the Parker et al. (1998) experiment a repeated study-test procedure was used in which the length of the study list varied for each animal depending on their performance, and list lengths could be as short as two items. Although the hippocampus appears to be involved in von Restorff effects in tests of long-term memory, it may be less critical when the lists are very short. Another possible explanation for the discrepancy is that the type of lesions differed in the two studies. The hippocampal group in the current study consisted of hypoxic patients who are known to suffer damage to the hippocampus, whereas the group in the Parker et al. study underwent amygdala and fornix resections. Although the fornix represents one major output of the hippocampus, the hippocampus in those lesioned animals may still have been able to support novelty detection and encoding through interactions with other temporal lobe structures. For example, the hippocampus has reciprocal connections with the entorhinal, perirhinal, and parahippocampal cortices (Suzuki 1996; Suzuki & Amaral, 1994), and the perirhinal cortex, in particular, has been implicated as a region critical for novelty detection (Aggleton & Brown, 1999).

Recollection and Familiarity

In control subjects, novelty was found to increase recollection and familiarity-based memory as measured using the R/K procedure (for similar results, see Kishiyama & Yonelinas, 2003). Given that no novelty effects were observed in the amnesics' overall recognition performance, it is perhaps not surprising that neither recollection nor familiarity was influenced by novelty in the amnesic patients. However, it is important to

realize that amnesia need not have eliminated the novelty effects on both processes. In fact, we had expected that hippocampal damage would have selectively disrupted the novelty effects on recollection, but left those on familiarity unaffected. This was based on previous studies indicating that both the hippocampus and the parahippocampal gyrus are sensitive to novelty (e.g., Kirchoff et al., 2000), and on studies indicating that the hippocampus is critical for recollection but not for familiarity (Yonelinas, 2002; Aggleton & Brown, 1999; Eichenbaum et al., 1994). In fact, consistent with these previous findings, in the current study, planned *t* tests indicated that the hypoxic group exhibited significant deficits in recollection ($p < .05$), but not familiarity ($t < 1$). The failure to find differences in the extent to which the novelty effects were reduced between the patient groups may be related to the fact that the H+ patients in the current study suffered unilateral lesions compared with the hypoxic patients who likely suffered bilateral damage.

The fact that hippocampal damage disrupted sensitivity of the familiarity process to stimulus novelty suggests that the hippocampus and the surrounding cortex must interact in producing novelty effects on memory. One possibility is that inferior temporal lobe regions, including the parahippocampal gyrus, are involved in identifying the abstract identity of each object independent of its specific perceptual characteristics (e.g., see Rolls, 2000). As such, when acting alone, this region would not be sensitive to the novelty manipulation used in the present study. However, the detection of novel items in the hippocampus may trigger additional processing in the surrounding temporal lobe regions that are involved in identifying that object and supporting familiarity-based recognition which could then lead to novelty effects on familiarity.

Several potential limitations of the current study must be kept in mind when interpreting these results. First, in the current experiment, the study list was quite long and it is possible that the reduced novelty effects in the amnesics arose in part because they found the task to be particularly demanding. However, the amnesics' overall memory performance was not much worse than the controls—the lower half of the control group performed at levels that were comparable to the amnesics. Moreover, if the amnesics had difficulty remaining oriented to the encoding task, then one might expect to see lower performance overall, rather than reasonable performance coupled with no novelty advantage, as was the case in the current study. Second, even though there was no evidence for a novelty effect in any of the amnesic groups, it is possible that with larger sample sizes a small benefit for novel items over non-novel items might be observed. The critical finding in the current experiment, however, was that the novelty effects were significantly reduced by amnesia. Given the small group sizes, this indicates that the novelty

deficits in amnesia were quite robust. Third, only one form of novelty was examined in the current study (i.e., perceptual novelty using the von Restorff paradigm). It therefore remains unknown if the current results generalize to different manipulations of novelty. However, results from other studies using different novelty paradigms are in agreement in showing that the hippocampus plays an important role in novelty processing, suggesting that the current results may be quite general. For example, orienting responses to novel items are reduced in patients with hippocampal damage (Knight, 1996), and the hippocampus does respond preferentially to a variety of different novelty manipulations (e.g., Kirchoff et al., 2000; Stern et al., 1996).

Conclusions

Our findings show that the human hippocampal system, including the hippocampus and the thalamus, plays a critical role in novelty-related memory enhancements. The results join a growing body of research indicating that these regions are sensitive to stimulus novelty, but extend those results in showing that they play a necessary role in producing novelty-related enhancements in recognition memory. These results indicate that the memory impairments seen in amnesia are due in part to the failure to process and retrieve memory for novel items in the environment.

METHODS

Subjects and Materials

Ten amnesic patients were recruited from the University of California, Davis Medical Center (UCDMC) and the Veteran's Administration Northern California Health Care System (VANHCSS) in Martinez, CA. The age range of the patients was 26–62 years ($M = 44.6$ years, $SD = 11.9$ years), and the mean education level was 14.4 years ($SD = 3.3$). A total of 10 age-matched controls were tested. The age range of the controls was 25–61 years ($M = 45.3$ years, $SD = 11.6$ years), and the mean education level was 15.1 years ($SD = 1.7$). Overall, amnesics and controls did not differ in age [$t(9) = 0.17$, $p = .43$] or education [$t(9) = 0.84$, $p = .21$]. The control subjects were recruited from the Sacramento and Davis communities. All amnesic patients and control subjects were tested for colorblindness (Ishihara, 1998). No patient or control subject was found to be colorblind.

The H+ group consisted of amnesic patients with damage to the hippocampus and the surrounding temporal cortex that was verified on the basis of magnetic resonance (MR) imaging. Three patients had temporal lobectomies (two left hemisphere and one right hemisphere patient). These patients had the anterior 4.5 cm of the temporal lobe, including the hippocampus and rhinal sulcus, surgically removed for

the treatment of epilepsy. Also included in the H+ group were three patients (one left hemisphere and two right hemisphere patients) with unilateral infarction of the posterior cerebral artery resulting in lesions to the posterior hippocampus, fornix, posterior portion of the parahippocampal gyrus extending up to the posterior surface of the amygdala, and the surrounding fusiform and lingual gyri.

The H group consisted of three hypoxic patients who experienced a mild hypoxic episode due to sudden cardiac arrest. Because the patients had defibrillators, MR imaging could not be conducted, but as discussed earlier, previous studies indicate that this type of patient typically has bilateral damage that is limited primarily to the hippocampus.

There was one additional patient included in the amnesic group who had bilateral thalamic lesions (see Figure 1C). An examination of MR scans revealed that the left thalamic lesion was more anterior and lateral, undercutting the anterior thalamic radiation and encroaching on the mammillothalamic tract (MTT), anterior nuclei (AN), and internal medullary lamina (IML). The right thalamic lesion was anterior and medial including all of the AN, the MTT, and the anterior pole of the mediodorsal nucleus. This patient is described in more detail in Kishiyama et al. (in press).

The H group performed normally on tests of intelligence ($M = 107$) and on the attention subscales of the WMSr ($M = 93$), but was impaired on the delayed memory subscales ($M = 74$). The H+ group was normal on tests of intelligence ($M = 101$) and attention ($M = 93$). The right hemisphere patients in this group performed well on the delayed memory subscales ($M = 101$), whereas the left hemisphere patients performed poorly ($M = 81$). Note that full WMSr test scores were not available on two of the H+ patients so delayed memory was estimated on the basis of the delayed logical memory, delayed visual reproduction, and delayed verbal paired associates subtests and attention was estimated on the basis of the forward and backward digit span tests. The thalamic patient was in the low normal range on intelligence (85), normal on attention tests (94), but well below normal on the delayed memory measures (66).

A total of 660 thumbnail object images (see Figure 2) from MasterClips Premium Image Collection (MasterClips, 1998) were used as study and test items (Kishiyama & Yonelinas, 2003). The objects were presented in red against a white background or in yellow against a black background.

Design and Procedure

Subjects were told that a long series of objects would be presented on the computer monitor at a rapid rate, and that they were to try to remember them for a later memory test. They were told that some of the objects

would appear in red and some would appear in yellow, but that color was not important and that they were to try to remember all the objects. During the study phase, subjects were presented with 600 items at a rate of 850 msec per item. Within the study list there were 60 critical study items, 30 were novel and 30 were non-novel items appearing in red and yellow. There were 540 filler items appearing in the same color as the non-novel study items. Items were thus made novel in the sense that they appeared in a less frequent color than the majority of items in the study list. Items were presented in a pseudorandom order such that novel objects were separated by a minimum of 10 intervening non-novel objects. Novel and non-novel items were counterbalanced across subjects.

At test, subjects were presented with 120 items one at a time, 30 “old” novel items presented in the original color, as well as 30 “new” items presented in the same color as the novel items, mixed with 30 “old” non-novel items presented in their original color, as well as 30 “new” items presented in the same color as the non-novel items. For each item, subjects were required to make a “remember,” “know,” or “new” judgment, and the experimenter recorded the responses. The R/K instructions were adapted from Gardiner (1988). Subjects were told that they were to respond “remember” if they could recollect some qualitative information about the study event. Moreover, they were instructed that they should only respond “remember” if they could, if asked, tell the experimenter what they recollected about that study event. Subjects were told to respond “know” if they thought the item was studied, but they could not recollect any details about the study event. That is, they should respond “know” if the item was familiar but not recollected. They were told to respond “new” if they thought the item was not in the study list. To ensure that subjects understood the test instructions, they were asked to describe the R/K distinction back to the experimenter, and the instructions were repeated if the subject appeared to misunderstand the distinction.

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REFERENCES

- Aggleton, J. P., & Brown, M. B. (1999). Episodic memory, amnesia and the hippocampal–anterior thalamic axis. *Behavioral and Brain Sciences*, *22*, 425–489.
- Brown, M. W., Wilson, F. A. W., & Riches, I. P. (1987). Neuronal

- evidence that inferomedial temporal cortex is more important than hippocampus in processing underlying recognition memory. *Brain Research*, 409, 158–162.
- Cimbalo, R. S. (1978). Making something stand out: The isolation effect in memory performance. In M. M. Grunberg, P. E. Morris, & R. N. Sykes (Eds.), *Practical aspects of memory* (pp. 101–110). New York: Academic Press.
- Cummings, J. L., Tomiyasu, U., Read, S., & Benson, D. F. (1984). Amnesia with hippocampal lesions after cardiopulmonary arrest. *Neurology*, 34, 679–681.
- Daffner, K. R., Mesulam, M. M., Scinto, L. F. M., Acar, D., Calvo, V., Faust, R., Chabrierie, A., Kennedy, B., & Holcomb, P. (2000). The central role of the prefrontal cortex in directing attention to novel events. *Brain*, 123, 927–939.
- Eichenbaum, H., Otto, T., & Cohen, N. J. (1994). Two functional components of the hippocampal memory system. *Behavioral and Brain Sciences*, 17, 449–518.
- Fabiani, M., & Donchin, E. (1995). Encoding processes and memory organization: A model of the von Restorff effect. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 21, 224–240.
- Fahy, F. L., Riches, I. P., & Brown, M. W. (1993). Neuronal activation related to visual recognition memory: Long-term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex. *Experimental Brain Research*, 96, 457–472.
- Fried, I., MacDonald, K. A., & Wilson, C. L. (1997). Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron*, 18, 753–765.
- Gabrieli, J., Brewer, J. B., Desmond, J. E., & Glover, G. H. (1997). Separate neural bases of two fundamental memory processes in the human medial temporal lobe. *Science*, 276, 264–266.
- Gardiner, J. M. (1988). Functional aspects of recollective experience. *Memory and Cognition*, 16, 309–313.
- Halgren, E., Baudena, P., Clarke, J. M., Heit, G., Marinkovic, K., Devaux, B., Vignal, J., & Birabin, A. (1995). Intracerebral potentials to rare target and distractor stimuli: 2. Medial, lateral, and posterior temporal lobe. *Electroencephalography and Clinical Neurophysiology*, 94, 229–250.
- Halgren, E., Squires, N. K., Wilson, C. L., Rohrbaugh, J. W., Babb, T. L., & Crandall, P. H. (1980). Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. *Science*, 210, 803–805.
- Hunt, R. R. (1995). The subtlety of distinctiveness: What von Restorff really did. *Psychonomic Bulletin and Review*, 2, 105–112.
- Ishihara, S. (1998). *The series of plates designed as a test for colour deficiency*. Tokyo: Kanehara & Co.
- Kartsounis, L. D., Rudge, P., & Stevens, J. M. (1995). Bilateral lesions of CA1 and CA2 fields of the hippocampus are sufficient to cause a severe amnesic syndrome in humans. *Journal of Neurology, Neurosurgery, and Psychiatry*, 59, 95–98.
- Kinsbourne, M., & George, J. (1974). The mechanism of the word-frequency effect on recognition memory. *Journal of Verbal Learning and Verbal Behavior*, 13, 63–69.
- Kirchhoff, B. A., Wagner, A. D., Maril, A., & Stern, C. E. (2000). Prefrontal-temporal circuitry for episodic encoding and subsequent memory. *Journal of Neuroscience*, 20, 6173–6180.
- Kishiyama, M. M., & Yonelinas, A. P. (2003). Novelty effects on recollection and familiarity in recognition memory. *Memory & Cognition*, 31, 1045–1051.
- Kishiyama, M. M., Yonelinas, A. P., Kroll, N. E. A., Lazzara, M. M., Nolas, E. C., Jones, E. G., & Jagust, W. J. (in press). Bilateral anteromedial thalamic lesions affect recollection and familiarity-based recognition memory judgments. *Cortex*.
- Knight, R. T. (1984). Decreased responses to novel stimuli after prefrontal lesions in man. *Electroencephalography and Clinical Neurophysiology*, 59, 9–20.
- Knight, R. T. (1996). Contribution of the human hippocampal region to novelty detection. *Nature*, 383, 256–259.
- Knight, R. T., & Scabini, D. (1998). Anatomic bases of event-related potentials and their relationship to novelty detection in humans. *Journal of Clinical Neurophysiology*, 15, 3–13.
- MacMillan, N. A., & Creelman, C. D. (1991). *Detection theory: A user's guide*. New York: Cambridge University Press.
- Markowitsch, H. J., Weber-Luxemburger, G., Ewald, K., Kessler, J., & Heiss, W. D. (1997). Patients with heart attacks are not valid models for medial temporal lobe amnesia. A neurological and FDG-PET study with consequences for memory research. *European Journal of Neuroscience*, 4, 178–184.
- Martin, A. (1999). Automatic activation of the medial temporal lobe during encoding: Lateralized influences of meaning and novelty. *Hippocampus*, 9, 62–70.
- MasterClips [Computer software]. (1998). San Rafael, CA: IMSI.
- Menon, V., White, C. D., Eliez, S., Glover, G. H., & Reiss, A. L. (2000). Analysis of a distributed neural system involved in spatial information, novelty, and memory processing. *Human Brain Mapping*, 11, 117–129.
- Parker, A., Wilding, E., & Ackerman, C. (1998). The von Restorff effect in visual object recognition memory in humans and monkeys: The role of frontal/perirhinal interaction. *Journal of Cognitive Neuroscience*, 10, 691–703.
- Rempel-Clower, N. L., Zola, S. M., Squire, L. R., & Amaral, D. G. (1996). Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *Journal of Neuroscience*, 16, 5233–5255.
- Riches, I. P., Wilson, F. A. W., & Brown, M. W. (1991). The effects of visual stimulation and memory on neurons in the hippocampal formation and the neighboring parahippocampal gyrus and inferior temporal cortex of the primate. *Journal of Neuroscience*, 11, 1763–1779.
- Rolls, E. T. (2000). Functions of the primate temporal lobe cortical visual areas in invariant visual object and face recognition. *Neuron*, 27, 205–218.
- Rolls, E. T., Cahusac, P. M. B., Feigenbaum, J. D., & Miyashita, Y. (1993). Responses to single neurons in the hippocampus of the macaque related to recognition memory. *Experimental Brain Research*, 93, 299–306.
- Saltz, E., & Newman, S. E. (1959). The von Restorff isolation effect: Test of the intralist association assumption. *Journal of Experimental Psychology*, 58, 445–451.
- Schmidt-Kastner, R., & Freund, T. F. (1991). Selective vulnerability of the hippocampus in brain ischemia. *Neuroscience*, 40, 599–636.
- Sokolov, E. N. (1963). Higher nervous functions: The orienting reflex. *Annual Review of Physiology*, 25, 545–580.
- Stern, C. E., Corkin, S., Gonzalez, R. G., Guimaraes, A. R., Baker, J. R., Jennings, P. J., Carr, C. A., Sugiura, R. M., Vedantham, V., & Rosen, B. R. (1996). The hippocampal formation participates in novel picture encoding: Evidence from functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences, U.S.A.*, 93, 8660–8665.
- Suzuki, W. A. (1996). The anatomy, physiology and functions of the perirhinal cortex. *Current Opinion in Neurobiology*, 6, 179–186.

- Suzuki, W. A., & Amaral, D. G. (1994). Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. *Journal of Neuroscience*, *14*, 1856–1877.
- Tulving, E. (1985). Memory and consciousness. *Canadian Psychologist*, *26*, 1–12.
- Tulving, E., Markowitsch, H. J., Craik, F. I. M., Habib, R., & Houle, S. (1996). Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cerebral Cortex*, *6*, 71–79.
- Tulving, E., Markowitsch, H. J., Kapur, S., Habib, R., & Houle, S. (1994). Novelty encoding networks in the human brain: Positron emission tomography data. *NeuroReport*, *5*, 2525–2528.
- Tulving, E., & Kroll, N. (1995). Novelty assessment in the brain and long-term memory encoding. *Psychonomic Bulletin and Review*, *2*, 387–390.
- Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., Van Paesschen, W., & Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science*, *277*, 376–380.
- von Restorff, H. (1933). Über die wirkung von bereichsbildungen im spurenfeld. *Psychologische Forschung*, *18*, 299–342.
- Wallace, W. P. (1965). Review of the historical, empirical, and theoretical status of the von Restorff phenomenon. *Psychological Bulletin*, *63*, 410–424.
- Yonelinas, A. P. (2002). The nature of recollection and familiarity: A review of 30 years of research. *Journal of Memory and Language*, *46*, 441–517.
- Yonelinas, A. P., & Jacoby, L. L. (1995). The relation between remembering and knowing as bases for recognition: Effects of size congruency. *Journal of Memory and Language*, *34*, 622–643.
- Yonelinas, A. P., Kroll, N. E. A., Quamme, J. R., Lazzara, M. M., Sauve, M., Widaman, K. F., & Knight, R. T. (2002). Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. *Nature Neuroscience*, *5*, 1236–1241.