Regional Cerebral Perfusion and Amytal Distribution During the Wada Test

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The distribution of sodium amytal and its effect on regional cerebral perfusion during the intracarotid amytal (Wada) test were investigated using high-resolution hexamethyl propyleneamine oxime (HMPAO) SPECT coregistered with the patient's MRI dataset. **Methods:** Twenty patients underwent SPECT after intravenous HMPAO injection, and 5 patients had both intravenous and intracarotid injections in a double injection-acquisition protocol. **Results:** All patients had hypoperfusion in the territories of the anterior and middle cerebral arteries. Basal ganglia perfusion was preserved in 20 of 25 patients. Hypoperfusion of the entire mesial temporal cortex was seen in 9 of 25 patients. Partial hypoperfusion of the whole mesial cortex or hypoperfusion of part of the mesial cortex was seen in 14 of 25 patients. In 2 of 25 patients, mesial temporal perfusion was unaffected. In 5 patients, the double acquisition showed a distribution of HMPAO delivery matching that of hypoperfusion, except for the following: (a) HMPAO was delivered to the basal ganglia and insula, where there was no hypoperfusion; (b) HMPAO was not delivered to the contralateral cerebellum, which did show hypoperfusion; and (c) in 1 patient, perfusion of the mesial temporal cortex was preserved despite intracarotid delivery of HMPAO. **Conclusion:** Some degree of hypoperfusion of medial temporal structures occurs in the great majority of patients during the Wada test. Partial inactivation of memory structures is therefore a credible mechanism of action of the test. The double acquisition protocol provided no evidence that mesial temporal structures are inactivated remotely by diaschisis. Perfusion in the basal ganglia and insular cortex is not affected by amytal.

Key Words: Wada; amytal; regional cerebral perfusion; hexamethyl propyleneamine oxime SPECT; memory; diaschisis

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The intracarotid amytal, or Wada, test (*1*) is used to assess speech and memory function as part of the presurgical work-up for temporal lobe surgery. Its basis is that the amytal renders structures involved in memory and speech function inactive, thus lateralizing speech function and predicting the results of a resection on memory function. A substance injected into the carotid artery will usually be delivered to Broca's area but not to the hippocampus (*2*), and some studies have indicated that cerebral hypoperfusion induced by amytal does not usually involve the mesial temporal cortex (*3*). What then is the mode of action of the test? We have hypothesized that the test works either by producing partial inactivation of mesial temporal structures or by inactivating mesial temporal structures indirectly (i.e., by diaschisis).

To test these hypotheses, it is necessary to have clear and precise images of perfusion in the mesial temporal cortex. (Jeffery et al. [*4*] pointed out the difficulty of doing this with conventional slicing). It is also necessary to have measures both of the distribution of structures to which amytal is delivered and of the distribution of structures rendered hypoperfused, because diaschisis effects would be expected to manifest as areas of hypoperfusion where no amytal is delivered. The Wada has a test-retest variability (*5*), so it is important that both amytal delivery and amytal-induced hypoperfusion are assessed during the same test.

We have therefore performed hexamethyl propyleneamine oxime (HMPAO) SPECT in 25 patients undergoing the Wada test. To achieve a precise definition of the extent of mesial temporal hypoperfusion, we have used high-resolution SPECT with slices angled in the long axis of the temporal lobe, in combination with coregistration with the patient's MRI dataset, to ensure accurate identification of anatomic structures (e.g., the identification of the boundaries between temporal lobe, insula and basal ganglia may present problems even on high-resolution SPECT images) and accurate assessment of the anteroposterior extent of hypoperfusion in the mesial temporal cortex.

To identify areas of mismatch between amytal delivery and amytal-induced hypoperfusion, we have, in a subset of 5 patients, performed SPECT with both intravenous and intracarotid injection of HMPAO during the same Wada test, using a double injection-acquisition protocol.

MATERIALS AND METHODS

The participants were 25 consecutive patients (age range 19–38 y, mean 25.3 y) undergoing assessment for temporal lobectomy for medically intractable temporal lobe epilepsy. All participants had grossly normal cerebral anatomy, as assessed by MRI. All patients had interictal regional cerebral perfusion (rCP) SPECT as a baseline for this study. Patients with marked hypoperfusion (asymmetry index [AI] > 15%) of any structure were excluded. The

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study was performed with the approval of the Institute of Neurological Sciences Research Ethics Committee. It was considered that leaving the intracarotid catheter in place while the second acquisition was performed constituted a small added risk to the patient, so the double acquisition study was restricted to 5 patients.

Wada Test Protocol

A catheter was placed in the internal carotid artery just proximal to the circle of Willis, and bilateral internal carotid angiography was performed. The patient was asked to raise both arms, and sodium amytal in a dose of 25 mg/mL was injected at a steady rate of 1 mL every 5 s until the arm contralateral to the injection fell. The injections were left-sided in 14 patients and right-sided in 11. A standard neuropsychological battery was administered to assess memory function.

Protocol 1 (20 Patients): Assessment of the Effect of Amytal on rCP with Intravenous HMPAO SPECT Only. Patients were injected intravenously with 450 MBq ^{99m}Tc HMPAO 45 s after the point of maximum hemiparesis (*6*). The acquisition was performed within 1 h of the injection.

Protocol 2 (5 Patients): Assessment of the Regional Delivery of Sodium Amytal with Intravenous and Intracarotid HMPAO SPECT. Wada protocol and intravenous injection of HMPAO were performed as described previously, after which, the intracarotid catheter was left in situ with a constant low-volume perfusion device connected to it. The patient was taken to the SPECT imager and the first acquisition was performed. Immediately after this, and with the patient remaining immobile in the imager, 50 MBq ^{99m}Tc-HMPAO were injected through the catheter, duplicating the volume and rate of the original amytal injection. The catheter was removed and the second acquisition was performed.

The first acquisition occurred after intravenous injection of HMPAO and produced an image reflecting amytal-induced hypoperfusion. The second acquisition detected the signal that made up the first image (minus a small loss due to radioactive decay) and the additional signal resulting from the intracarotid injection of HMPAO. The dataset from the second acquisition therefore reflected the perfusion pattern resulting from intracarotid amytal injection plus an additional signal resulting from the intracarotid HMPAO injection.

The intracarotid dose of 50 MBq was chosen on the basis that 4% of an intravenous dose of ^{99m}Tc HMPAO, that is, approximately 20 MBq, reaches the brain. A dose of 50 MBq delivered intra-arterially into the territory supplied by the anterior circulation on one side will be much greater than the signal remaining from the intravenous dose, allowing a clear distinction of structures to which amytal has been delivered.

Data Acquisition and Analysis

Images were acquired using a Strichman 810 multidetector tomographic imager (Strichman Medical Equipment, Inc., Medfield, MA). Overlapping 12-mm slices were acquired through the whole volume of the brain and were converted into a three-dimensional dataset, which could be resliced in any plane. Slices in the plane of the long axis of the temporal lobe and in the coronal plane were used in the visual and numerical analysis of images. We coregistered the interictal and Wada SPECT images with their respective MR images using a combination of anatomic landmarks and the automatic coregistration facility supplied with the SPECT Neuro 900 software (Strichman), which uses a least sum of squares paradigm. Coregistration allowed placement of regions of interest (ROIs) according to individual patient anatomy and gave an anatomic frame of reference for visual interpretation of images.

In those patients who had both intravenous and intracarotid HMPAO injections, ROIs were drawn around hypoperfused regions on intravenous (rCP) images and around regions with HMPAO uptake on combined intravenous and intracarotid images, which were then projected onto coregistered MR images, allowing an exact determination of the anatomic extent of each (Figs. 1 and 2).

The images were analyzed visually by three investigators who were unaware of any patient data. Abnormalities were considered as visually significant if they were seen on more than one adjacent slice and were greater in extent than twice the full width at half maximum of the system (i.e., greater than 16 mm). Published data have shown that the aforementioned observers noted abnormalities at asymmetries over 8% (*7*). Changes associated with the Wada test were then assessed by comparison with each patient's interictal (at least 24 h from last seizure) HMPAO SPECT image. Disagreements were resolved by consensus conference.

Count densities were measured in mesial temporal (anterior and posterior ROIs each included half the mesial temporal cortex extending from anterior extent of the amygdaloid nucleus to the anterior level of the brain stem), lateral temporal, frontal, parietal, occipital, cerebellar and basal ganglia ROIs. For each ROI, the count density was compared with the contralateral homotopic ROI using the formula $(L - R)/((L + R)/2) \times 100$ to calculate an asymmetry index. These calculations were performed on each ROI in both the interictal and Wada states (intravenous injection only datasets), and the figures were subtracted to give the change in AI associated with the injection of amytal.

RESULTS

Angiography

No crossover of contrast to vessels contralateral to the injection was seen in any of these patients. No abnormalities in circulation were seen, although 5 patients had dominant posterior communicating arteries.

Visual Analysis of Images

With respect to the interictal SPECT dataset, all 25 patients had changes in perfusion associated with intracarotid injection of sodium amytal that corresponded to the usual distribution of the anterior and middle cerebral arteries, with the following variations:

1. There was complete or partial preservation of perfusion in the basal ganglia (caudate, putamen or both) and insular cortex in 20 of 25 patients (80%) (Fig. 1).
2. In 9 of 25 patients, perfusion of the whole of the mesial temporal cortex decreased to a similar degree to that in neocortical structures (four left-sided and five right-sided injections), with 14 of 25 patients showing partial preservation of mesial temporal perfusion. In 4 of 14 patients, mesial hypoperfusion was limited to the anterior mesial temporal cortex, whereas in 3 of 14 patients, only the posterior mesial cortex was hypoperfused. Seven of 14 patients showed some degree of

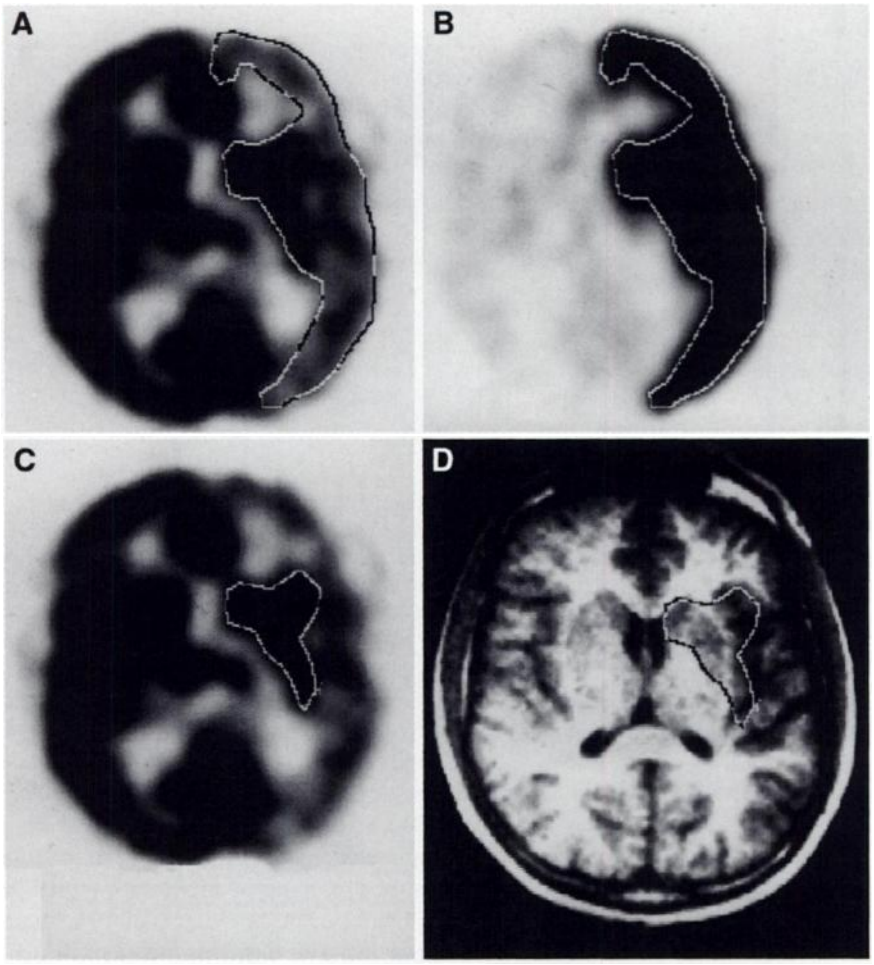

FIGURE 1. Equivalent axial slices through basal ganglia from two SPECT datasets in same patient, plus equivalent coregistered MR slice. (A) Wada test with intravenous HMPAO injection. This acquisition followed intravenous injection of 450 MBq ^{99m}Tc-HMPAO. Injection was performed 45 s after left intracarotid injection of 125 mg sodium amytal. Image shows hypoperfusion involving left frontal and temporal cortex but sparing basal ganglia and insula. (B) Wada test with intracarotid HMPAO injection. Immediately after acquisition in (A), 50 MBq ^{99m}Tc-HMPAO were injected into left internal carotid artery through angiographic catheter that had been left in situ after Wada test. Second acquisition was then performed without moving patient. Image shows signal that appears on original acquisition (A), which appears as ghost image of perfusion in right side of brain. Superimposed on this is signal resulting from left intracarotid injection of HMPAO, seen on left of brain (right side of image). Note that intravenous image appears fainter than (A) because of decay of radioactivity in time taken to complete two acquisitions and because image intensity has been adjusted downward to allow clear visualization of extent of structures perfused by left intracarotid HMPAO injection. ROI has been drawn around this area. (B) ROI has been drawn around high signal resulting from intracarotid HMPAO. This has then been projected onto (A), showing that two areas match, except in basal ganglia and insula. (C) Second ROI has been drawn around area of mismatch. This is then projected onto equivalent coregistered MR slice (D), which shows that mismatch involves caudate nucleus, putamen and insular cortex.

hypoperfusion in both areas. In 2 of 25 patients, the whole of the mesial cortex remained unchanged. (Table 1, Fig. 2).

3. The cerebellar hemisphere contralateral to the amytal injection was hypoperfused in 10 (48%) of those 21 cases in which the cerebellum was adequately visualized.

The results of visual analysis of these three regions are presented in Table 1.

Numerical Analysis of Images

Changes in asymmetry indices with respect to indices measured on the interictal SPECT dataset are assessed using the Mann-Whitney U test and are presented in Table 2. Significant changes were demonstrated in most areas perfused by the middle and anterior cerebral arteries and in the cerebellum. In the temporal lobe, the greatest changes in AI were seen in the lateral cortex and pole (10.69% −18.72%). The anterior mesial temporal ROI showed a greater mean change in AI than the posterior mesial ROI (9.38% versus 7.98%) but with a wide spread of values, so that the change over the group as a whole was not significant.

Significant changes in perfusion were demonstrated in the caudate ($P = 0.001$) but not in the putamen or in the thalamus.

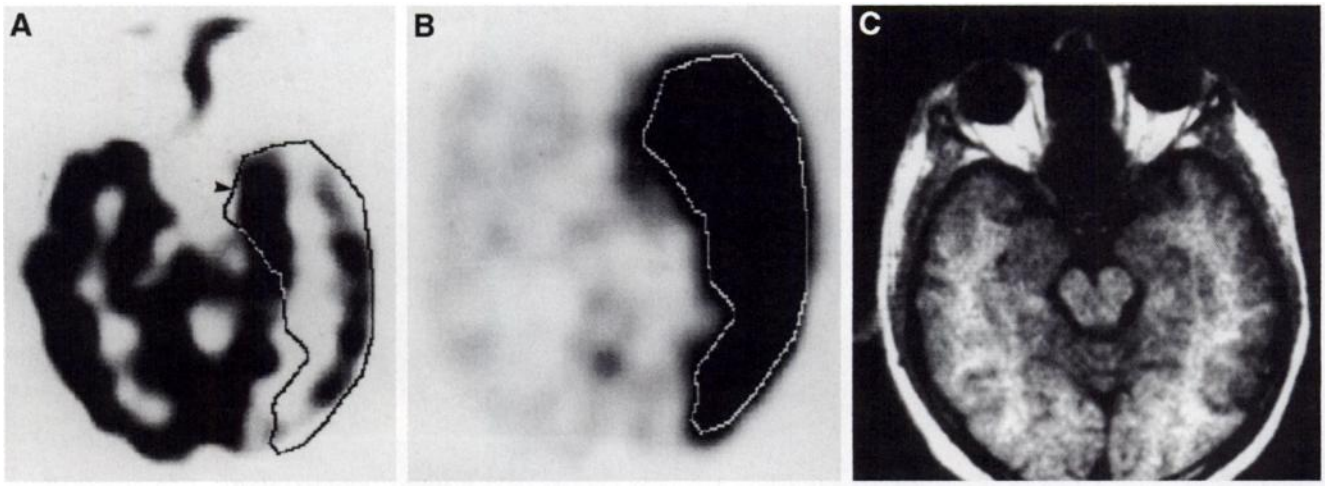

FIGURE 2. Axial slices in long axis of temporal lobe. Same acquisition and analysis protocol has been followed as in Figure 1. (A) Acquisition after intravenous HMPAO injection during Wada test shows hypoperfusion of whole left temporal lobe and lateral occipital cortex. Note preservation of perfusion of most of medial temporal cortex (arrow). (B) Second acquisition after left intracarotid HMPAO injection. ROI has been drawn around high-signal area. Projection of this ROI onto (A) shows good correspondence between hypoperfusion and intracarotid HMPAO uptake, with exception of medial temporal cortex, where perfusion remains similar to contralateral perfusion despite having same additional signal level from intra-arterially injected HMPAO as rest of temporal lobe. (C) Equivalent coregistered MR slice.

Combined Intravenous and Intracarotid HMPAO Injections

In all 5 participants in whom intravenous and intracarotid HMPAO injections were performed, the areas rendered hypoperfused correlated with the distribution of intra-arterially injected HMPAO (and hence, by inference, sodium amytal) with the following exceptions:

1. In all 5 patients, the basal ganglia and insula were only minimally hypoperfused on the intravenous HMPAO images, but the intra-arterial image showed that the basal ganglia had the same delivery of HMPAO as cortical structures that were markedly hypoperfused (Fig. 1A).
2. In all 5 patients, the cerebellar hemisphere contralateral to the injection was hypoperfused on the intravenous HMPAO image, but there was no HMPAO uptake on the intra-arterial image.
3. In 2 patients, discrepancies were seen in the mesial temporal cortex. In 1 patient, there was clear preservation of perfusion in the whole mesial temporal cortex, despite apparent delivery of amytal to the isoperfused area (Fig. 2). In the other patient, a small area of the mesial temporal cortex had relatively preserved perfusion despite having the same delivery of HMPAO as the rest of the temporal lobe.

DISCUSSION

This study found complete mesial temporal hypoperfusion in 9 of 25 (36%) patients, a figure comparable with previous studies (*2–4*), but it also found partial hypoperfusion in a further 14 of 25 patients. Thus, the great majority of patients showed some effect of the amytal injection on perfusion levels in the mesial temporal cortex. The lateral temporal lobe and pole showed most hypoperfusion; the mesial structures showed less. In mesial structures themselves, we found a variable pattern of hypoperfusion, with some patients showing preservation of anterior perfusion and some patients showing preservation of posterior perfusion. Preservation of posterior mesial perfusion makes sense in terms of the vascular anatomy, whereas anterior preservation is more difficult to explain. Four of 5 patients with a dominant posterior communicating artery showed marked posterior mesial hypoperfusion, but the relevance of this would seem doubtful. Comprehensive evaluation was not possible because our angiographic studies were limited to the anterior circulation. Notably, no evidence of crossover of amytal to the contralateral hemisphere was seen in any patient on angiography or on intravenous or intravenous and intracarotid SPECT images.

Our finding of cerebellar diaschisis has been previously noted (*8*) and was expected, as was the fact that it occurred in the absence of cerebellar delivery of amytal. Lack of hypoperfusion in the basal ganglia was not expected, however, and occurred despite the fact that intracarotid HMPAO delivery (and presumably, therefore, amytal delivery) was similar to that of other structures. This apparent resistance to amytal-induced hypoperfusion may be due to the known paucity of GABA(A) receptors that normally bind barbiturate in these structures (*9–11*). This finding is perhaps the more surprising because diaschisis tends to cause basal ganglia perfusion to follow that of the neocortex (*12,13*).

This study confirms that sodium amytal injected into the carotid artery does not normally lead to hypoperfusion of the entire mesial temporal cortex, but it suggests that some hypoperfusion occurs in most patients. Only 2 patients showed no mesial temporal hypoperfusion at all, and in 1 of

TABLE 1
Visual Assessment of Change in Perfusion Associated with Intracarotid Injection of Sodium Amytal

Patient no.	Posterior mesial temporal	Anterior mesial temporal	Caudate	Putamen	Contra-lateral cere-bellum	Wada result
1	1	1	P	P	0	PD
2	0	1	1	0	1	PD
3	1	0	1	1	NV	PD
4	P	1	0	P	1	F
5	1	1	1	1	1	PD
6	1	0	1	1	0	PD
7	0	0	0	0	0	PD
8	P	1	0	0	0	PD
9	1	1	0	1	1	PD
10	1	1	0	0	0	PD
11	1	0	0	0	1	PD
12	1	1	0	0	1	PD
13	P	1	0	P	1	F
14	0	P	0	0	0	PD
15	P	1	0	1	0	PD
16	1	1	0	P	0	PD
17	1	1	P	P	NV	PD
18	1	P	0	0	0	PD
19	0	P	0	1	1	PD
20	1	P	P	P	0	PD
21	1	1	1	1	0	PD
22	0	1	1	P	NV	PD
23	0	0	1	1	NV	F
24	1	1	P	1	1	PD
25	P	1	0	P	1	F

1 = marked decline in perfusion; P = pass; 0 = no change; PD = partial decline in perfusion; NV = structure not visualized; F = fail.

Perfusion change ratings are the change in symmetry of perfusion in the structure concerned in the intra-Wada state compared with the interictal state. They assume that any change is on the side of the amytal injection.

TABLE 2
Median Change in Asymmetry Index (AI) Associated with Intracarotid Injection of Sodium Amytal

Region of interest	n	Median change in AI (%)	Interquartile range	*P*
Posterior mesial temporal	25	7.98	9.1	0.006
Anterior mesial temporal	25	9.38	6.4	0.190
Temporal pole	25	10.69	11.7	<0.001
Anterior lateral temporal	25	19.40	13.4	<0.001
Posterior lateral temporal	25	18.72	11.1	<0.001
Cerebellum	21	11.23	9.7	<0.001
Medial frontal	25	7.94	9.1	0.012
Dorsal lateral frontal	25	10.46	13.2	<0.001
Lateral frontal	25	14.02	10.1	<0.001
Parietal	25	19.40	12.2	<0.001
Caudate	25	9.40	8.6	0.001
Putamen	25	7.28	8.0	0.256
Thalamus	25	7.30	11.3	0.171

those patients (patient 7) hypoperfusion was relatively mild elsewhere in the brain. This patient only had the intravenous protocol, so we do not know whether amytal was delivered to the mesial cortex.

The other patient (patient 23) with preserved mesial temporal perfusion failed the test. He had marked hypoperfusion of the anterior cortex on the intravenous image and had poor baseline psychometry. Structures other than the temporal lobes are involved in some aspects of memory (e.g., the frontal lobes). It may be that in a patient with relatively poor baseline memory function, extratemporal dysfunction is enough to disable memory, thus producing a false-positive result. This patient went on to have Wada with selective posterior cannulation and removal of his temporal lobe with no postoperative worsening of his memory deficit. Recent work in a small group of patients has suggested that selective cannulation provides better correlation between the result of the test and the postoperative deficit (*14*).

Patient 23 also had the intravenous plus intracarotid double acquisition protocol, which showed that he was the only one to have an unequivocal discrepancy between our measure of amytal delivery and perfusion. Complete preservation of mesial temporal perfusion occurred despite clear delivery of amytal. Our sample for the intravenous plus intracarotid protocol was necessarily small, and further study would better define the exact proportion of patients who show such discrepancies between amytal delivery and hypoperfusion.

CONCLUSION

Previous authors have suggested that the amytal test often has no effect on mesial temporal perfusion levels, but empiric data do suggest that the test is effective in predicting postoperative amnesia (*15*). The results of this study may resolve this apparent contradiction. Assuming that perfusion and function remained coupled (*16*), some reduction in mesial temporal function was seen in the great majority of our patients. Memory is a relatively fragile function and is quick to become impaired by many pathological processes (*17*). It would seem credible that a relatively mild effect of amytal in the anterior mesial cortex is sufficient to effectively prevent memory function in that area, particularly if extratemporal memory areas are also affected.

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