

## Long-term Perseveration in Alzheimer's Disease: A Case Report

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The most common clinical sign of Alzheimer's disease (AD) is progressive memory loss. Presented here is a case of AD who, despite ultimate profound dementia with severe amnesia, showed retention of a perseverative response she developed during 26 encounters, over 4.5 years, with the Brown–Peterson distractor test. From Test 9 onwards, she responded from the first distractor-filled trial with one consonant trigram, appearing in none of the seven test forms given her. At Test 26, she could not repeat heard trigrams yet faithfully responded with her perseverative trigram. The trigram, ostensibly declarative information, apparently became part and parcel of the task's procedure. Although perseveration is a form of impairment probably resulting from Alzheimer pathology involving frontal and parietal cortex, it may also reflect a form of preserved memory, albeit distorted, supported by posterior cortical regions spared in AD.

### Introduction

The most common clinical sign of Alzheimer's disease (AD) is progressive memory loss. In rigorous tests of memory, poor scores of AD patients are fraught with omissions and perhaps more interestingly with intrusions and perseverations (Fuld *et al.*, 1982). Perseveration refers to a response, which had been elicited to an earlier-occurring stimulus but is inappropriately elicited again to a different, later-occurring stimulus. The occurrence of intrusive and perseverative errors implies that information is not entirely forgotten, but rather that it is retained in part or whole but reused incorrectly. This observation suggests that the contextual cues required to evoke an answer to a new, specific situation are ignored. Perseveration may represent a special form of memory not fully considered by prevailing theories of memory. Presented here is a case of AD who developed an incorrect, perseverative response with repeated exposure to a memory test over a period of months and used it during testing for years.

### Case Report

*History.* The patient was enrolled in a longitudinal study, which incorporated a series of drug treatment studies, at the Clinical Research Center of the Massachu-

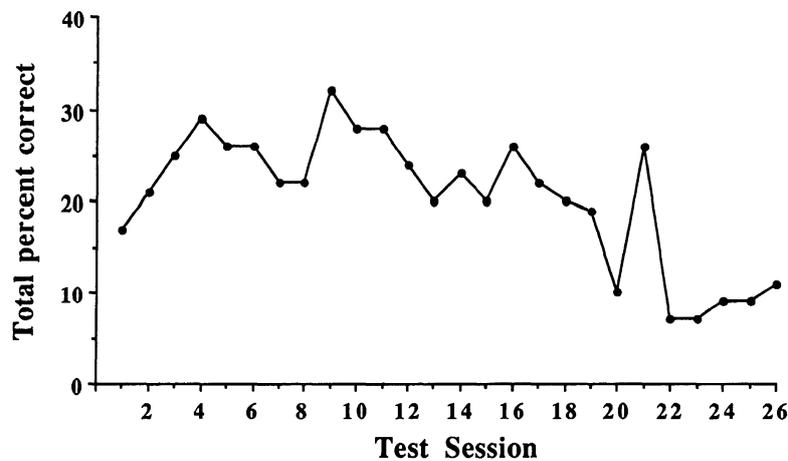


FIG. 1.

setts Institute of Technology. When first studied, she was 56 years old, had symptoms of AD for about 2 years, and was mildly demented as assessed by clinical criteria (Corkin, 1982). Her initial symptoms included memory loss and spatial disorientation. She had 12 years of education and was right handed. She died at age 65. A CT scan revealed marked cortical atrophy, enlarged ventricles, and prominent Sylvian fissures.

*Procedure.* During her many test sessions over the course of 4.5 years, she was administered the Brown–Peterson distractor test of short-term memory (STM) 26 times (Brown, 1958; Peterson and Peterson, 1959). She received the STM test under a variety of interoceptive and exteroceptive conditional changes: she was tested by five examiners, in four testing rooms, with seven forms of the test, under six drug states (lecithin, oral and i.v. physostigmine, tryptophan, and hydergine and their respective placebos), with six retention intervals, and during progressive stages of the disease (mild to profound).

Each STM test session comprised at least three practice trials and 24 test trials, with four trials at each of six retention intervals. The tests were run in blocks of increasing length: 0, 3, 6, 9, 15, and 30 sec. The memory items were consonant trigrams prerecorded on tape. For each trial, the patient heard a trigram, repeated it, heard a three-digit number, repeated it and subtracted 3 or 1 from it, depending upon her current ability. After a retention interval, the patient attempted to recall the trigram from that trial and was encouraged to guess; 10 sec was allotted for responding. Trials were separated by 15 sec in order to minimize proactive interference (Kincaid and Wickens, 1970).

*Results.* On all 26 STM tests the AD patient was impaired. She completed the test on all occasions, except the third because of nausea and vomiting resulting from an infusion of physostigmine (0.5 mg). She showed slight fluctuations in scores over the first 19 tests, followed by a consistent drop over the last five tests (Fig. 1). From Test 1 to 9, forgetting fell to asymptote at the 3- or 6-sec retention interval; thereafter, the asymptote generally occurred at the 3-sec interval. By contrast, healthy elderly subjects reach asymptote at 9 sec (Corkin, 1982; Sullivan *et al.*, 1986).

The first time the AD patient produced her perseverative response, "KLX," was on Trial 9 of Test 3, which was 1.5 months after her first test. This trigram had never appeared as a test item nor was it presented in any of the test forms she received subsequently. From Test 9 to 21, which occurred over the course of 2 years and 10 months, she responded with this trigram on virtually every trial, except for trials at the 0-sec retention interval; importantly, at this interval, her responses approximated or replicated the given test trigrams. Furthermore, perseverative recall persisted even though this patient accurately repeated the trigrams upon hearing them. In the last five tests, however, she was so aphasic that she could not repeat the test trigrams correctly. Despite this disability in language production, she responded exclusively and without dysphasia with the perseverative trigram, KLX. She herself usually expressed enthusiasm for going this particular test of the battery because she felt she knew *how* to do it. Examples of her responses appear in Table 1.

### Discussion

This patient seemed to rely upon her perseverative response at times when her recall of trigrams was difficult: at long retention intervals and when she was no longer able to repeat given test items. Once perseveration started reliably, she virtually never made errors of omission even though she had done so, particularly at the long retention intervals, prior to Test 9. Moreover, her perseverative response abided by the rules of the task at hand: she always produced a response within the 10-sec recall period and the response met the requirements that it contain three consonants.

The reliance upon perseverative responses when recall becomes difficult was noted previously by Shindler *et al.* (1984). They hypothesized that when long-term memory (LTM) failed, information available in STM would be used in responding. In the present case, the reverse seemed to be true: when STM or working memory failed, stable information from some form of LTM store was retrieved.

In seeking reasons why the perseverative response was "KLX" specifically, it is important to consider the practice trial trigram, "LCK," which was given at each test session. The practice trigram and the patient's perseverative trigram shared two letters but in reversed order and with an intervening letter. Repeated exposure to the practice trigram may have enhanced trace strength for those letters and thus may have acted as a priming agent. It is curious, however, that the only time she would use the perseverative trigram was during the recall interval, and never during the repetition interval; thus, her response was not merely an automatism (cf. Fuld *et al.*, 1982). Alternatively, one could argue that this patient did not understand that she was to recall the just given (and newly repeated) trigram during the retention interval. Performance at the 0-sec retention interval, however, provided evidence that she did understand this aspect of the test because she typically recalled the exact trigram or a close approximation at this interval for the first 19 test sessions (see Table 1 for such instances).

In addition to the one case tested over 4.5 years, two additional AD cases had

TABLE 1. *Examples of the AD patient's responses on the STM distractor test over 4.5 years*

<i>Test 1</i>					<i>Test 9</i>				
<i>Retention interval</i>	<i>Test trigram</i>	<i>Subject's repeat</i>	<i>Recall</i>	<i>Score</i>	<i>Retention interval</i>	<i>Test trigram</i>	<i>Subject's repeat</i>	<i>Recall</i>	<i>Score</i>
0 seconds	XGC	XGC	XGC	4	0 seconds	XGC	XGZ	XZG	4
	PTM	PTM	PTM	6		PTM	PTM	PTM	6
	KBQ	KBQ	P-	0		KBQ	KBQ	KBQ	6
	FLS	FLS	FLS	6		FLS	FLS	FLS	6
3 seconds	BKD	BKD	--	0	3 seconds	BKD	BKD	BKD	6
	SFH	SFH	--	0		SFH	SFH	SKF	3
	BNR	BNR	--	0		BNR	BNR	KNX	2
	MJZ	MJZ	MJ-	4		MJZ	MJZ	KMX	1
6 seconds	HPL	HPL	--	0	6 seconds	HPL	HPL	KLM	1
	XBM	XBM	BMX	3		XBM	XBM	XXM	3
	JQK	JQK	KXM	1		JQK	JQK	KLX	1
	FTC	FTC	XPM	0		FTC	FTC	KLX	0
9 seconds	DSJ	DSJ	--	0	9 seconds	DSJ	DSJ	KLX	0
	ZQL	ZQL	XZ-	1		ZQL	ZQL	KLX	1
	RHB	RHB	X-	0		RHB	RHB	KLX	0
	GPX	GPX	--	0		GPX	GPX	KLX	2
15 seconds	FNB	FNV	--	0	15 seconds	FNB	FNB	KLX	0
	RMC	RMC	--	0		RMC	RMC	KLX	0
	GJV	GJV	--	0		GJV	GJV	KLX	0
	DQS	DQS	--	0		DQS	DQS	KLX	0
30 seconds	LDX	LDX	--	0	30 seconds	LDX	LDX	KLX	3
	BKT	BKT	--	0		BKT	BKT	KLX	1
	NZP	NZP	--	0		NZP	NZP	KLX	0
	HRG	HRG	--	0		HRG	HRG	KLX	0
			Total = 25					Total = 46	

<i>Test 16</i>					<i>Test 26</i>				
<i>Retention interval</i>	<i>Test trigram</i>	<i>Subject's repeat</i>	<i>Recall</i>	<i>Score</i>	<i>Retention interval</i>	<i>Test trigram</i>	<i>Subject's repeat</i>	<i>Recall</i>	<i>Score</i>
0 seconds	QSD	QSD	QSD	6	0 seconds	MCX	M-	--	0
	BKV	BKB	BKC	4		FHR	F-	--	0
	GFN	GFN	GFN	6		LJT	K-	--	0
	FCJ	FCJ	FCJ	6		PKD	key-	KLX	1
3 seconds	CLR	CLR	KLX	2	3 seconds	GTK	G-	KLX	1
	HMK	HMK	KLX	1		JPC	JKkey	dayKL	0
	BSZ	BSZ	BLX	2		BHZ	Bzay	KLX	0
	XPD	XPD	KLX	1		QMF	K-	KLX	1
6 seconds	JXF	JXF	KLX	1	6 seconds	VRL	--	KLX	1
	DMS	DMS	KLX	0		SFQ	--	--	0
	HGL	HGL	KLX	1		NZG	--	KLX	0
	KNC	KNC	KLX	2		DXK	B-	KLX	2
9 seconds	BTL	BTL	KLX	1	9 seconds	HLS	ay	KLX	2
	JQZ	JQZ	KLX	0		QDR	Q-	KLX	0
	XMH	XMH	KLX	1		PCM	K-	KLX	0
	FVR	FVR	KLX	0		VNG	B-	KLX	0
15 seconds	SLG	SLG	KLX	2	15 seconds	NJT	--	KLX	0
	TCN	TCN	KLX	0		BRZ	B-	KLX	0
	RPK	RPK	KLX	1		SPV	--	KLX	0
	VHQ	BHQ	KLX	0		XFQ	--	KLX	1
30 seconds	DJT	DJT	KLX	0	30 seconds	KXB	KLX	KLX	6
	PRF	PRF	KLX	0		GSM	--	KLX	0
	BXQ	BXQ	KLX	1		THL	--	KLX	1
	ZGM	ZGM	KLX	0		ZCJ	--	KLX	0
			Total = 38					Total = 16	

taken the STM test on multiple occasions: 19 and 22 times over a period of 16 and 21 months. These patients were similar to the featured case by spontaneously creating incorrect, unique perseverative responses that abided by the rules of the test. These two patients differed from the case presented, however, in that they did not carry over a specific trigram to subsequent testing sessions. Thus, their perseverative responses were of the type commonly reported in tests of memory (e.g. Fuld, *et al.*, 1982).

Within the taxonomy of perseveration offered by Sandson and Albert (1984), the type of perseveration most suitable to that described here is *recurrent*, "... the unintentional repetition of a previous response to a subsequent stimulus, involv[ing] an abnormal post-facilitation of memory traces ..." (p. 715). Within Liepmann's classification (1905; reviewed in Sandson and Albert, 1984), it is called *intentional* and refers to motor responses previously performed and reenacted when a different response was intended. On two accounts, this definition does not entirely fit this case. Firstly, there is reason to believe that the patient's responses were not unintentional because she never showed insight into the repetitive nature of her response; by contrast, the other two AD patients did reveal insight into their perseverations, thus suggesting that they were incorrect as well as unintentional. For example, one patient spontaneously offered the following observations about his perseverative responses in three different test sessions: "Now I forget 'JQR' [i.e. the perseverative response] and rest"; "CJP [i.e. the perseverative response], are we still on this?"; and after perseverating on "QST" said several times that "QST" was wrong but that it was his best answer. Secondly, the type of memory traces overly facilitated during perseveration are highly specific and may qualify as fact, declarative, or episodic memory. Fact memory, however, is severely compromised in patients with AD, as it was in the presented case. Consequently, it is difficult to attribute perfect recall, observed in her perseverative response, to an intact fact memory system.

Perseveration can be considered to have a dual character: it is incorrect yet consistent. In an attempt to speculate about the neural basis for perseveration, considered here are compromised brain systems, which may contribute to the production of aberrant responses, and spared brain systems, which may underlie consistent performance. Perseveration has been attributed to poor capacity to use contextual cues, such that new and old stimuli and responses lose their temporal or spatial tags (Buckingham *et al.*, 1981). Temporal contextual memory, as measured by recency discrimination, is impaired in AD (Sagar *et al.*, 1988; Sullivan and Sagar, 1989) and accordingly may contribute to perseveration. That temporal contextual discrimination is also impaired in patients with frontal-lobe lesions but spared in patients with medial temporal-lobe lesions (Milner, 1971; Sagar *et al.*, 1990; Schacter, 1987; Smith and Milner, 1983, 1988) implicates frontal-lobe pathology in perseveration. More direct evidence for a frontal-lobe basis of perseveration abounds in the neuropsychological literature; for example, a high rate of perseverative errors on the Wisconsin Card Sorting Test occurs in patients with lesions invading the dorsolateral prefrontal cortex (Milner, 1964). An important area of additional pathology is probably the hippocampus, which is a common site of dense Alzheimer pathology (e.g. Blessed *et al.*, 1968; Kemper, 1984). While memory test performance of patients with unilateral or bilateral hippocam-

pal pathology is not marked by perseveration, hippocampal and frontal-lobe pathology may provide a critical combination of loss of contextual cues as well as poor recall of past events or responses to produce severe perseveration, which may entail forgetting that a perseverative response has already been used. A third cortical site, the posterior parietal region, may also contribute to recurrent perseveration. Sandson and Albert (1984) reported verbal recurrent perseveration in a patient with a speech disorder and right-sided weakness who had a left hemisphere infarction, and nonverbal recurrent perseveration in a patient with right-sided weakness and mutism who had a left fronto-parietal infarction. In a study by Freedman and Oscar-Berman (1987), AD patients committed significantly more perseverative errors than did demented patients with PD in a tactile reversal of original learning task, which provides a measure of perseveration; the AD deficit was attributed to lesions of the parietal system. Invoking both the dorsolateral prefrontal and posterior parietal cortices as contributing to perseveration is reasonable considering the multiple anatomical connections between these sites documented in monkey (Selemon and Goldman-Rakic, 1988). Thus, the anterior three-quarters of the cortex and medial temporal regions of the brain may be implicated in producing long-term, recurrent perseveration. Indeed AD is commonly marked by pathology in these regions (e.g. Brun and Englund, 1981; Kemper, 1984).

Cortical regions spared in AD include feed-forward areas of the occipital lobes and primary motor cortex (e.g. Brun and Englund, 1981; Kemper, 1984). Extrastriate visual cortex has been hypothesized to subservise, at least in part, the spared learning capacity of repetition priming for visually-presented information in AD (Gabrieli *et al.*, 1991). The role of spared motor cortex has not yet been explored in AD memory research. Priming refers to response facilitation to specific stimuli previously experienced and involves implicit, or unconscious, rather than explicit memory processes (e.g., Gabrieli, 1990; Graf *et al.*, 1984; McAndrews *et al.*, 1984; Tulving and Schacter, 1990; Warrington and Weiskrantz, 1974); it does not merely reflect reactivation of preexisting memories, i.e. pre-morbidly-encoded semantic information (Smith and Oscar-Berman, 1990; Tulving and Schacter, 1990). According to Tulving and Schacter (1990), priming is independent of explicit memory and is "hyperspecific." Clearly the robustness of the perseverative response described here contrasts with the patient's severely impaired explicit memory; furthermore, her perseverative response was linked exclusively to a specific, meaningless trigram retrieved within a specific set of constraints (i.e. the rules of the STM test).

In addition to priming, the perseveration noted here may reflect a form of procedural, or ruled-based, learning because the responses always fell within the rules of the test (Cohen and Squire, 1980). Because the stimuli used in the STM test were auditory and demanded articulated responses, spared capacity to perform this test within a given rule set may be linked to an auditory/articulatory cortical system analogous to the visual system proposed for preserved priming in the visual modality. As with the proposed visual mnemonic system spared in AD, such a system would be presumed to operate presemantically and pre-linguistically. Thus, this system could support preservation of articulation for the primed trigram despite disability in phoneme articulation. Supporting this position is a

report by Morris (1984) demonstrating that the articulatory loop system is intact in AD. This system is a principal component of working memory (Baddeley, 1987) and is defined as "a buffer store of limited duration fed either phonetically or by articulation" (Morris, 1984, p. 144). Such systems may further provide a theoretical basis as to why word reading, as done in the National Adult Reading Test (NART; Nelson and O'Connell, 1978), remains relatively preserved and provides a good estimate of premorbid intelligence through moderate to severe dementia (Stebbins *et al.*, 1990).

The long-term, recurrent perseveration of the AD patient presented here provides evidence for two dissociations: impaired recall with spared, rule-driven performance, and impaired spontaneous and repetitive language production with spared production of a perseverative consonant trigram. The impairment in the form of perseveration may be attributable to pathology of the much of the anterior cortex and medial temporal lobes, and the preservation of performance in the form of perseverative regularity may be attributable to the sparing of primary motor and extrastriate cortices in AD. These observations suggest that despite severe memory impairment for newly-presented facts, the capacity to formulate and remember a strategy that abides by rule constraints can persist in AD. This preservation of capacity to use rules, even though deplete of flexibility and usefulness within normal standards, provides some indication that perseveration, perhaps like rituals and obsessions documented in patients with frontal-lobe pathology, represents an attempt to override the loss of ability to process, use, and remember episodic information. Perseveration, then, might be considered the misuse and misinterpretation of episodic data in terms of procedural knowledge, that is, procedural learning gone awry.

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