

having greatly inferior fitness. This distribution is similar to that for homozygous viability⁷. The line means were subjected to an outlier test (the Grubbs test)¹³, and two lines that were significant outliers were identified as severely deleterious. These lines probably carry a mutation with a larger effect than most mutations. The parameter estimates should be more reliable when these outliers are excluded⁷. Estimates of mutational parameters are shown in Table 1. U is an underestimate and the selection coefficient, $(1-h)s$, an overestimate if there is variation in selection coefficients among loci^{7,9}. The values of k assumed were 0.58 and 0.33, as analytical and numerical results show that when $k=0.58$, U is minimized and $(1-h)s$ maximized, and when $k=0.33$, the rate of decline in the mean and increase in the variance of viability closely match the results given in ref. 7.

Our experiments provide a measure of line fitness, that includes a much wider variety of fitness components than egg to adult viability, notably female fecundity and male mating ability¹¹. Previous results suggest that the rate of decline in heterozygous fitness is similar to that for heterozygous viability¹⁴, but our estimates of the rate of decline in mean, and of increase in the variance are substantially larger than for viability, regardless of the assumptions made about k . Our best estimate of the genomic mutation rate for fitness U is similar to the rate given in ref. 7 for viability, suggesting that fitness declines more rapidly than viability because mutations that decrease viability also decrease other components of fitness. This interpretation is consistent with other data collected at generations 33 and 44 of mutation accumulation. These data on early and late female fecundity and female and male longevity (D.H., D.K.H., S.A. and B.C., manuscript in preparation), indicate that mutational correlations between these traits are generally strongly positive, and that the traits are subject to similar mutation rates. This also agrees with results of spontaneous mutations affecting development time and viability^{15,16}, and with those for induced variations affecting a variety of traits⁹.

One assumption we make is that the decline in fitness with time is linear on an arithmetic scale. We justify this by the nearly linear decline in viability over a similar number of generations^{9,17}. But the same experiment later showed evidence that viability declined more rapidly, presumably as a result of interactions among mutations. Alternatively, if fitness is determined multiplicatively, the rate of decline in fitness should decrease over time. Both of these departures would bias our estimates towards higher U and lower $(1-h)s$. In contrast, under reasonable assumptions, the variance of s will cause our limits to be several times too conservative. For instance, if the distribution of s is exponential, the per-genome mutation rate would be twice as high as we estimate⁹. Our overall estimates are therefore probably still conservative, in spite of potential counter-biases.

Our results indicate that the mutation rate per haploid genome for fitness in *Drosophila* is at least $0.10/0.4 = 0.25$, and is more likely to be several times larger. Our estimate of mutation rate agrees with those of the earlier *Drosophila* studies, and with indirect estimates for plants¹⁸. It provides substantial empirical support for the high per-genome mutation rate to detrimental alleles postulated in some theories of the evolution of breeding systems^{2,3} and of mate choice^{2,4,5}. □

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Neural subsystems for object knowledge

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CRITICAL issues in the cognitive neuroscience of language are whether there are multiple systems for the representation of meaning, perhaps organized by processing system (such as vision or language^{1–6}), and whether further subsystems are distinguishable within these larger ones. We describe here a patient (K.R.) with cerebral damage whose pattern of acquired deficits offers direct evidence for a major division between visually based and language-based higher-level representations, and for processing subsystems within language. K.R. could not name animals regardless of the type of presentation (auditory or visual), but had no difficulty naming other living things and objects. When asked to describe verbally the physical attributes of animals (for example, 'what colour is an elephant?'), she was strikingly impaired. Nevertheless, she could distinguish the correct physical attributes of animals when they were presented visually (she could distinguish animals that were correctly coloured from those that were not). Her knowledge of other animal properties was completely intact, regardless of input stimulus. To explain this selective deficit, these data mandate the existence of two distinct representations of such properties in normal individuals, one visually based and one language-based. Furthermore, these data establish that knowledge of physical attributes is strictly segregated from knowledge of other properties in the language system.

K.R. was a 70-year-old right-handed retired librarian, with a 10th-grade education (to the age of 16). She developed a subacute neurological illness manifested 12 weeks after onset by impairments in attention and concentration, new learning for verbal and visual material, and naming on visual presentation⁷, found to be specific to the category of animals. This dysnomia and related functions were studied during the next 4 months, with her informed consent. She remained clinically stable during this time, but 3 months after completion of testing she suddenly deteriorated and died.

Box 1 outlines the initial testing used to isolate and characterize her deficit. Her profound deficit in naming, limited to animals (30–60% correct for animals versus 86–99% for other categories), was present despite the input modality (visual or nonverbal sound) or response route (oral or written). Because this deficit was not modality-dependent, it can be attributed to a central processing impairment.

The category-specificity of her dysnomia held even when controlling for frequency, familiarity and visual complexity of the stimuli⁸. Moreover, her naming responses were also quite consistent for each item across multiple administrations (46/61

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BOX 1 PERFORMANCE ON NAMING AND RELATED TASKS

(a) Visual perceptual. Performance on these visual perceptual tasks ruled out any deficits in elementary visual perceptual processing.

Extraocular movements intact
No field deficits
Corrected vision = 20/20
No colour blindness
No colour anomia
Intact performance on Poppelreuter figures
Able to assemble cut-up drawings of 8 objects or animals²⁸

(b) General language tasks. Performance on these tasks showed K.R.'s general language functions to be intact with no deficits in her ability to produce animal names.

Intact spontaneous speech²⁹
Intact repetition of simple sentences²⁹
Intact comprehension of two-step commands³⁰
Intact reading and writing of simple sentences²⁹
Able to produce animal names used in the testing in spontaneous speech, in repetition of single words or sentences (26/26 correct), and in oral reading (65/65 correct).

(c) Oral naming of frequency-matched colour photographs. Naming from the animals category was significantly impaired compared to naming from other categories ($\chi^2 = 7.2$, $P < .05$).

Animals	8/20
Food	20/20
Inanimate objects	20/20

(d) Oral naming of colour photographs

Animals	
Animals (general)	10/25 correct
Land animals	5/18
Water animals	2/5
Birds	1/7
Insects	0/6
	18/61 total

Control categories

Occupations/people	12/12
Plants	20/20
Food	25/25
Fruits and vegetables	30/30
Letters	26/26
Numbers	20/20
Colours	20/20
Body parts	17/17
Clothing	24/25
Musical instruments	9/10
Personal items	15/15
Transportation	20/20
Tools	10/10
Household objects	70/70
Toys	20/20
Buildings	10/10
	348/350 total

(e) Category-specific impairment in oral naming of line drawings⁸, matched for frequency, familiarity and visual complexity. Normative data from Snodgrass and Vanderwart⁸. All available items were used. Matching was by either group means or item-to-item, in which case the matching criterion was ± 0.5 s.d. Significance testing was by Chi-squares; expected frequencies were those of K.R.'s performance on nonanimal categories. The same animal pictures were presented on two separate occasions. The comparisons of animal naming against one other category (inanimate objects) showed significant differences; although the comparisons against two categories showed differences of a similar if not greater magnitude, they had smaller *ns*, and failed to reach significance.

Matching by means; three category comparison

Category	<i>n</i>	Mean frequency	Mean familiarity	Mean visual complexity	Number correct	Per cent correct
Animals (1st admin.)	15	11	2.52	3.36	7 ($P < 0.08$)	47%
Animals (2nd admin.)					8 ($P < 0.12$)	53%
Food	15	10	3.02	3.02	14	93%
Inanimate objects	15	11	2.51	3.28	15	100%

Matching by means; two category comparison

Animals (1st admin.)	35	16	2.55	3.65	17 ($P < 0.002$)	49%
Animals (2nd admin.)	35				21 ($P < 0.02$)	60%
Inanimate objects	35	16	2.55	3.62	33	94%

Matching by items; two category comparison

Category	<i>n</i>	Number correct	Per cent correct
Animals (1st admin.)	28	12 ($P < 0.01$)	43%
Animals (2nd admin.)	28	13 ($P < 0.02$)	46%
Inanimate objects	28	24	86%

(f) Oral naming of nonverbal sounds. K.R. was impaired at identifying nonverbal sounds (such as a dog's bark) that were made by or highly associated with the animals that had been presented for naming.

Animal	1/8 (12%)
Objects	7/8 (88%)

(g) Written naming of colour photographs

Animals	11/20
Food	10/10
Objects	10/10

TABLE 1 Property judgments: direct question task (number correct/number administered)

	Physical attributes				Nonphysical attributes and functional properties			
	Colour	4 legs	Not 4 legs	Size	Land/air/sea	Woods/farm/jungle	Food	Pet
Visual words								
Animals	11/30	21/21	14/21	21/30	30/30	41/42	42/42	42/42
Objects	15/15			30/30	30/30			
Auditory words								
Animals	16/34	21/23	7/15	29/37	38/38	38/38	37/38	38/38
Fruits and veg.	10/10	10/10	10/10	10/10				
Vehicles		10/10		10/10	10/10	Carries >10 people 10/10		
Line Drawings								
Animals	2/14*	27/28†	4/13	8/13‡	15/16	16/16	16/16	16/16
Fruits and veg.	10/10	10/10	10/10	10/10				
Vehicles		10/10		10/10	10/10	Carries >10 people 10/10		

These questions were given to four normal age-matched controls. Their performance was intact, except for one error by one normal control in the woods/farm/jungle questions, and one error in the pet questions. Thus, K.R.'s results were not dependent on item selection.

* The colour of the animals was not provided in any of the line drawings.

† The legs were removed from the animal line drawings for these stimuli. The '4 legs' heading refers to the score on animals that had 4 legs and the 'Not 4 legs' heading for those that did not. There is a suggestion from her performance of a tendency for saying animals had 4 legs.

‡ All line drawings were matched to be of roughly the same size in terms of surface area.

items elicited a consistent response on multiple administrations of visual confrontation naming with oral responses), and across response modalities (27/33 items consistent for oral versus written naming)⁹⁻¹¹. K.R. had no overt lexical comprehension disorder, even for the animal names she could not produce¹¹. She scored 100% (65/65) on picture-word matching, with either auditory or visual stimuli, short (5 s) or long (30 s) presentation intervals¹⁰, and with semantically related or semantically and visually related distractors.

K.R.'s residual knowledge of the properties of animals, but not control categories, showed a significant but selective impairment whether tested by direct questioning (such as 'what is the colour of an elephant?') or forced-choice recognition (Tables 1 and 2). She had a deficit for the physical attributes of animals (colour, number of legs and size; for example, answering that an elephant was orange; Table 1), but not for nonphysical attributes of animals, or for any properties of the control categories, including those physical attributes that were impaired for animals. She was not impaired for any functional properties of animals (for example, 'Is an elephant edible? Is it a pet?'),

even for animals she could not name, or describe the physical attributes of, from line drawings.

Cuing of confrontation naming of animal pictures was tested, using auditory or visual word stimuli as cues^{2,10}. Most importantly, cuing with physical attributes (colours or parts, such as 'udder' for a cow) did not facilitate naming (35% versus 40% correct for the uncued condition; $\chi^2 = 0.107$, $P > 0.5$). But cuing with nonvisual perceptual properties ('moo'), or functional properties ('milk') improved K.R.'s naming abilities (95% and 90% and $\chi^2 = 13.80$, $P < 0.001$ and $\chi^2 = 10.99$, $P < 0.001$, respectively). Therefore neither explicit nor implicit tests showed K.R. to have verbal ('language-based') knowledge of the physical attributes of animals, although her knowledge of nonvisual perceptual properties and of other associated functional properties of animals was intact by both types of measures.

K.R.'s deficit did not involve her visually based knowledge of the physical attributes of animals¹²⁻¹⁴, as demonstrated by tests using essentially the same items as the verbal tasks. She was intact in visually matching animal bodies to their respective heads^{13,14} (8/8 correct), pointing to the parts of animals in

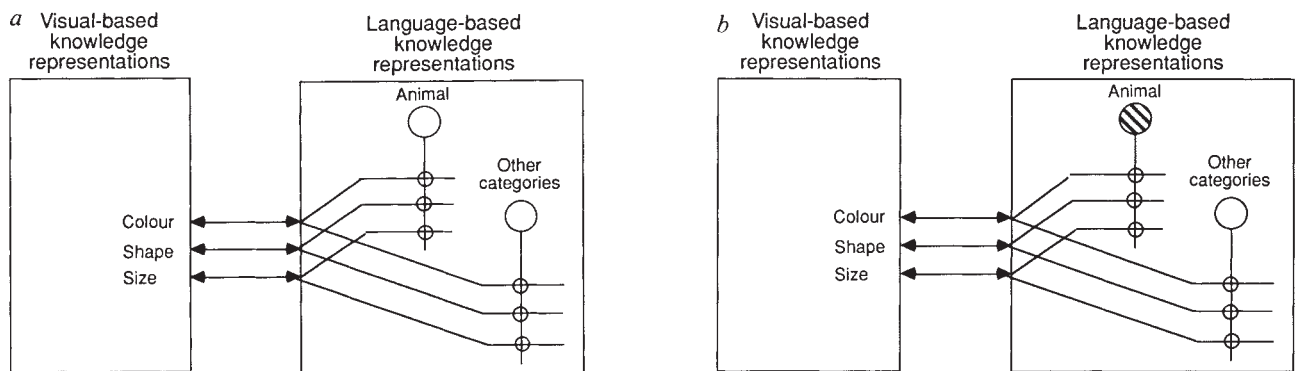


FIG. 1 Hypothetical basis of category specificity in K.R. a, The normal (unlesioned) scheme of knowledge processing. Visual physical attribute information coming from the visual system is divided into many parallel streams for processing in the language system, with the streams organized by semantic categories. The visual physical attribute information inherent

in the language system is similarly organized in these streams. The flow of information in a stream is gated or regulated by activation of a category-level node. b, In K.R.'s case, damage has selectively affected her category-level node for animals, impairing the processing of visual property data that was normally facilitated by that node.

TABLE 2 Property judgments for animals: forced choice task (number correct/number administered)

	Physical attributes				Nonphysical attributes and functional properties			
	Colour	4 legs	Not 4 legs	Size	Land/air/sea	Woods/farm/jungle	Food	Pet
Visual words								
Choice between error on direct question task and correct response	1/19		0/7	0/9				
Choice between correct response on direct question task and distractor error	11/11	21/21	14/14	21/21	15/15	15/15	15/15	15/15
Line drawings								
Choice between error on direct question task and correct response	0/12		0/3	0/5				
Choice between correct response on direct question task and distractor error	2/2	8/8	2/2	8/8	10/10	10/10	10/10	10/10

The task used items on which the patient had made errors on the direct recall task, as well as a subset of the items she had answered correctly. The choices were between her prior errors and the correct answers ('Is an elephant orange or grey?'). The impairment noted on open-ended recall was much more evident on this forced-choice task, although it would have been thought to be easier.

pictures (for an elephant, 'show me the trunk') (27/27 correct)¹⁵, and naming animal body parts from pictures (16/16 correct), even for animals that she could not name. She was also 100% correct (14/14) at discriminating between pictures of animals that showed the proper colour of those animals (grey elephant), versus those pictures that were not colour-appropriate for that particular animal although they were colour-appropriate for animals in general (grey lion). But she could not say which colours were correct for animals that were incorrectly coloured. Clearly, she had no impairment in her internal visual representations of the colours, parts, or general form of animals.

K.R.'s performance obviates several potential problems with interpretation of such deficits. Her deficits must have arisen centrally, because they were present across several input and output modalities. They could not, therefore, be due to task-specific effects. For example, her impairments with the physical attributes of animals were evident whether the task involved recognition, recall, or cueing. Hence they could not be explained by differential dependence on explicit or implicit processing. Finally, the category-specificity of her impairments permits a direct comparison of performance on a task for items from both intact and impaired categories.

K.R.'s pattern of deficits therefore provides unequivocal evidence for at least two distinct representational systems, one language-based and one visually based. Her language-based system must have been responsible for her intact performance with the functional properties of animals, because knowledge of these properties resides only in the language-based system, as described in previous studies^{3,5,12}. Her visually based system must have been responsible for her intact ability to visually recognize the physical attributes of animals, because this information was not in her language system, as the testing showed. No single central representational system that intermingles both types of properties could explain K.R.'s performance.

This demonstration of two distinct representational systems, one subserving visually based knowledge and one for language-based knowledge, is *prima facie* evidence for a distinction already suggested by behavioural and neuroanatomic data^{2,16-18}. But K.R.'s data allow us to go beyond this general specification, claiming that there is, in some cases, a duplication of some types of knowledge for physical attributes across the two systems. It seems apparent that how and in which representational system information is stored depends on both the type of information (particularly the feasibility of forming the appropriate type of code) and individual experience. The visual physical attributes

of objects, as studied in our experiments, must be represented in at least the visual system if they were acquired through visual experience. But they might also be represented in some form in the language system. The congenitally blind may have a reasonably thorough knowledge of visual physical attributes, based entirely in language^{19,20} and acquired exclusively through that system, just as the normally sighted have some knowledge of putatively visual physical attributes in their language system. Some of this information might duplicate that already available visually (albeit in a different code); in other cases, the 'visual' information might be exclusively language-based.

K.R.'s data provide evidence that normally there is a dual representation for visual physical attributes, one visually based and one language-based. This has been suggested by previous studies^{13,21}, but is clearly shown by K.R.'s performance. The best evidence is the dissociation found between K.R.'s intact ability to recognize physical attributes from visually presented pictures, and her impaired ability to verbally describe physical attributes from names, but only for the animal category. K.R.'s performance was consistent with what has been interpreted as a representational deficit rather than an access deficit (degraded representation according to ref. 1)^{2,3,10,11}. Therefore, it would seem that her impairment was a disruption of her language-based representations of the visual physical attributes of animals. Furthermore, we propose that the disruption of her language-based representations also precludes her ability to retrieve this information from the visually based system.

The category-specificity of K.R.'s gap in knowledge of physical attributes is evidence that normally no such gap exists. That is, normally some of the representations of the visual physical attributes of animals can be language-based as well as visually based, and this can be true of some other attributes and items. Alternatively, a less likely explanation for K.R.'s performance is that her verbal representation system was intact, but contained no knowledge of physical attributes and was unable to access this information from the visual representation system, again however, category-specific.

The category-specificity of K.R.'s deficits allows a further conclusion that the language system must contain multiple subdomains of knowledge representation^{1,10,22} (such as visual physical attributes), functionally and, in some sense anatomically, distinguishable. Specifically, K.R. could not identify the colour, size or other visual physical attributes of an animal from its name, but could recall nonvisual or functional properties of the same animal from its name. No deficits in these tasks were seen

with nonanimal categories. It is suggested that category-level information provides a critical gating or facilitative function for property-level knowledge in the language system (Fig. 1).

Relatively little pathological evidence is available for the anatomical basis of category-specific deficits. Most patients have shown temporal lobe pathology^{1,4,12,14,23} but see also ref. 24. Pathology limited to the frontoparietal lobes has been associated with impairments of the nonliving things categories; however, these cases may also have included temporal lobe pathology^{10,22}. K.R.'s brain showed diffuse, mild inflammation attributable to

a paraneoplastic syndrome that involved the cerebral cortex, including both temporal lobes. This was thought to be the basis for her deficits. Based on K.R.'s neuropathology, and those well studied cases in the literature, this type of category-specific deficit involves: (1) left or both temporal lobes; and generally (2) incomplete or patchy disruption, rather than a complete and sweeping disruption. A number of neural processing architectures (hierarchical^{1,10,25} or distributed networks^{22,26,27}) could produce the processing distinctions and anatomical assignments K.R.'s case requires. □

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Degeneration *in vitro* of post-mitotic neurons overexpressing the Alzheimer amyloid protein precursor

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A PATHOLOGICAL hallmark of Alzheimer's disease is the deposition of amyloid fibrils in the brain. The principal component of amyloid fibrils is β /A4 amyloid protein^{1,2}, which can be generated by the aberrant processing of a large membrane-bound glycoprotein, the β /A4 amyloid protein precursor (APP)³. To test whether overexpression of APP generates abnormally processed derivatives that affect the viability of neurons, we stably transfected full-length human APP complementary DNA into murine embryonal carcinoma P19 cells. These cells differentiate into post-mitotic neurons and astrocytes after exposure to retinoic acid^{4–6}. When differentiation of the APP cDNA-transfected P19 cells was induced, all neurons showed severe degenerative changes and disappeared within a few days. The degenerating neurons contained large amounts of APP derivatives that were truncated at the amino terminus and encompassed the entire β /A4 domain. These results suggest that post-mitotic neurons are vulnerable to overexpressed APP, which undergoes aberrant processing to generate potentially amyloidogenic fragments.

Mouse embryonal carcinoma cells (P19 cells) are multipotential stem cells which differentiate into a variety of cell types (for example, extra-embryonic endoderm, neurons, muscles and epithelia) in response to chemical agents such as

retinoic acid and dimethyl sulphoxide^{4–7}. We have reported previously that neural differentiation of P19 cells markedly increases the abundance of APP messenger RNA⁸. We first characterized APP molecules expressed in neurally differentiated P19 cells by western blotting (Fig. 1a). APP species with apparent relative molecular masses (M_r) of 105,000–120,000 (105K–120K) markedly increased during days 3–12, but declined thereafter. The time course of altered levels of 105K APP was consistent with that of the change in abundance of mRNA encoding APP695 (ref. 3; Fig. 1b, upper panel). The presence of APP species with M_r 105–120K coincided with the existence of viable neurons in mixed P19 cell cultures during neural differentiation (Fig. 1b, lower panel). On the other hand, APP species with M_r 115–130K were detected on days 15 and 17; these APP species may correspond to the modified forms of APP (APP751/770) expressed in non-neuronal cells, including astrocytes and microglia-like phagocytes^{9,10}.

We then stably transfected APP695 and APP770 cDNAs into P19 cells and isolated four clones for each APP cDNA species (Fig. 1c). The undifferentiated transfectants of APP695 cDNA (APN1–4) had APP immunoreactive bands of $M_r \approx 105K$, and those of APP770 cDNA (APG1–4) at $M_r \approx 115K$. The control transfectants APC1–2 showed only weak bands of APP species at M_r 105–110K. The APP levels of all APP695 cDNA transfectants were higher than those of the APP770 cDNA transfectants.

After treatment with retinoic acid, control transfectants differentiated into mixed populations of neurons and non-neuronal cells (presumably astrocyte precursors), whereas the population of neurons in the APP cDNA transfectants was severely reduced during days 3–5 (Fig. 2a–c). In these cultures, non-neuronal cells showed no degenerative changes and grew to the confluent density on days 8–14 (data not shown). In neuron-enriched cultures (Fig. 2d–f), most of the APP cDNA transfectants had severely degenerated; they had numerous vacuoles within their soma, and many of them had disintegrated neuritic processes. The degenerating neurons in all of the APP cDNA transfectants (APN1–4 and APG1–4) completely disappeared by day 8 (data not shown). Neuronal degeneration in mixed cell cultures was quantified by counting surviving neurons during neural differentiation (Fig. 3). All of the APP cDNA