Disproportionate Impairment in Naming and Comprehension of Nouns with Relative Sparing of Verbs in a Patient who Survived Herpes Simplex Encephalitis

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Abstract: Various studies reported that patients who survived Herpes Simplex Encephalitis (HSE) may show impairments of specific semantic categories: they often show greater difficulty in naming and comprehension of stimuli belonging to "living" entities (animals, fruit and vegetables), as compared to "non-living" entities (such as handmade artifacts).We report a 26-year-old patient (RP) who suffered from HSE and developed an anomic aphasic syndrome, associated with remarkable impairment of episodic memory. Sixteen months post onset, on neuropsychological examination patient RP showed a disproportionate impairment in oral and written naming of nouns as compared to verbs. Likewise, on word-picture matching tasks she was remarkably impaired in the auditory and visual comprehension of nouns, with relative sparing of verb comprehension. Interestingly, on additional tasks of oral naming and auditory comprehension of noun stimuli belonging to either "living" or "non-living" entities, she showed remarkable difficulties in naming and comprehension of noun stimuli belonging to both categories ("living" and "non-living" entities). Single photon emission computed tomography (SPECT) showed a marked cerebral hypoperfusion in the left temporal lobe and moderate hypoperfusion in the orbital and mesial frontal regions of both cerebral hemisheres, with relative sparing of left ventro-lateral/perisylvian frontal areas, including the inferior frontal gyrus. In this patient, a damage mainly involving both semantic and lexical components critical for noun processing might be hypothesized. The relative preservation of verb production and comprehension might be explained by the relative sparing of ventro-lateral frontal areas (including the left inferior frontal gyrus) critically involved in production and comprehension of verbs.

Keywords: Herpes simplex encephalitis, semantics, nouns, verbs, neuroanatomy.

INTRODUCTION

In the last decades, several neuropsychological studies carried out in patients who survived Herpes Simplex Encephalitis (HSE) reported that these patients may often show a selective impairment on tasks of naming and comprehension of items belonging to the semantic broad class of "living" entities or biological entities (such as animals, fruit, vegetables), while they mostly show a relatively better perfomance on tasks of naming and comprehension of non-living entities such as handmade items, including tools, vehicles and furniture [1-6]. It has been suggested that about 55% of patients affected by HSE may show a category-specific semantic deficit for living/biological entities [7]. However, it has been observed that some patients may show unusual patterns of dissociations [8].

Although since several years ago it has been proposed that semantic knowledge is organized by conceptual categories [1, 4], there has been a strong debate about the the organization and representation of conceptual knowledge and about the neural systems underlying such organization [7, 9-13]. In particular, it has been debated whether conceptual knowledge might basically attributable to motor and modality-specific sensory representations [11, 14] according to a

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"sensori-motor model of semantic knowledge" (embodied cognition theory) or, alternatively, to amodal and more abstract representations ("domains of knowledge theory"), organized according to semantic "domains" [15, 16].

It has been suggested that damage to the medial part of the anterior temporal cortices may result in category-specific deficits for living entities [17, 18]. By contrast, damage to the left anterior temporal lobe extending laterally to inferior temporal gyri, does not usually result in a category-specific impairment for living entities but in a more generalized semantic impairment [18].

Furthermore, various studies reported some brain-damaged patients who were disproportionately impaired in naming and comprehension of nouns as compared to verbs, while other brain-damaged patients showed a disproportionate impairment in naming and comprehension of verbs as compared with nouns [19-24]. These latter observations are consistent with the hypothesis of a functional organization of the mental lexicon according to distinct word categories, such as of nouns and verbs [25-28], although such view is not shared by other Authors [29, 30].

Since the early 90's, it has been hypothesized that in the dominant emisphere for language, neural systems located in the temporal lobes might be part of neural circuits critically involved in the production and comprehension of nouns, while neural system located in the posterior regions of the frontal lobes (in particular in the left inferior frontal gyrus) might be part of neural circuits critically involved in the production and comprehension of verbs [21-23]. This hypothesis has been supported by various observations in patients with difficulties in both the production and comprehension of nouns or verbs [23, 31], but also in patients with difficulties restricted only to the production of nouns or verbs [24, 27, 33, 34].

More recently, it has been proposed [32] that neural networks critical for verb processing might involve various cortical areas, with an important role played by the inferior frontal gyrus, but within networks also involving the parietal lobe (mainly the left supramarginal gyrus) and the temporal lobe (mainly the middle temporal gyrus) [22, 23, 27, 35-39].

We report here a patient who survived HSE and developed a severe impairment of episodic memory associated with a marked anomic aphasia, characterised by a much more severe impairment in the production and comprehension of nouns as compared to verbs.

CASE HISTORY

Patient RP, a woman with 8 years of schooling, developed HSE at the age of 26 years. On admission, she presented with headache, fever and increasing confusion. A computed tomography (CT) scan showed low density areas in both temporal lobes, more marked on left. A CSF analysis revealed a positivity for HSV IgG, while a PCR analysis was positive for HSV-1 DNA. About 24 hours after the beginning of neurological symptoms she started treatment with intravenous acyclovir 10 mg/kg t.i.d., which was administered for 10 days.

Since the early stages of recovery she developed a severe amnesic syndrome (with remarkable difficulties in remembering recent events), difficulties in focusing attention, and a marked anomic aphasia, mainly characterised by remarkable word-finding difficulties. Moreover, since early stages of recovery she developed behavioural symptoms (apathy, episodes of agitation associated to oppositional behavior). Four months post onset of HSE, Magnetic resonance imaging (MRI) showed on T2 weighted images large areas of increased signal intensity mainly in temporal and limbic structures (inferior temporal cortex, temporal pole, amygdala, hyppocampal formation and enthorinal cortex), bilaterally, but most marked in the left cerebral hemisphere. Some additional lesions were also detected in the anterior cingulate gyrus and the adjacent mesial frontal regions of both cerebral hemispheres. A repeated MRI one year post onset confirmed these findings. Single photon emission computed tomography (SPECT) showed a marked cerebral hypoperfusion in the left temporal lobe and moderate hypoperfusion in the orbital and mesial frontal regions of both cerebral hemispheres, with relative sparing of left perisylvian ventro-lateral frontal areas, including the inferior frontal gyrus. An elementary neurological examination performed in our hospital sixteen months post onset was unremarkable. On admission, the patient was still presenting remarkable difficulties in remembering recent events, anomic aphasia (with marked word-finding difficulties) and behavioural symptoms: she showed apathy, rare episodes of agitation, occasional oppositional behavior, bulimia and other inappropriate behaviours (she was inclined to hide food and subsequently eat such food secretly).

METHODS

The patient underwent an extensive general neuropsychological examination, including the Mini-Mental State Examination (MMSE) [40] and several tasks [41] assessing verbal episodic long-term memory (Rey Auditory Verbal learning test), non-verbal abstract reasoning (Raven's Progressive Matrices '47), executive functions such as problem-solving and set-shifting abilities (temporal rule induction), costructional praxic abilities (copying of drawings), visual short-term memory, verbal short-term memory (digit span forward and backward) [42], selective visual attention [43].

Linguistic functions were evaluated by means of an extensive language battery (Battery for analysis of aphasic deficits, BADA, [44]), including tasks of phonemic discrimination, sublexical processing (reading, repetition, writing of non-words), auditory and lexical decision tasks in which the subject is asked to discriminate between non-words and words (including nouns, verbs, adverbs and adjectives), transcoding tasks on words (reading, repetition, writing of words), tasks of oral and written confrontation naming of nouns and verbs, tasks of auditory and visual comprehension of nouns and verbs, tasks of auditory and visual comprehension of sentences.

Moreover, she was administered various additional lexical–semantic tasks aimed at specifically assessing lexical-semantic processing of nouns and verbs [20]: a confrontation naming task requiring naming of 48 pictures depicting nouns and a confrontation naming task requiring naming of 48 pictures depicting verbs, in which the subject is asked to name picture depicting stimuli corresponding to nouns or verbs, matched for word frequency and length; a word-picture matching task of auditory comprehension of nouns, in which the examiner reads aloud a noun and the subject is required to point to one out of 3 alternative pictures (a target-picture and two distractors showing a stimulus semantically related to the target-word or a stimulus not related to the target-word, respectively); a word-picture matching task of auditory comprehension of verbs, in which the examiner reads aloud a verb and the subject is required to point to one out of 3 alternative pictures depicting actions (a target-picture and two distractors showing a stimulus semantically related to the target-word or a stimulus not related to the target-word, respectively); a word-picture matching task of visual comprehension of nouns, in which the subject is asked to read aloud a written noun and to point to one out of 3 alternative pictures (the corresponding target-picture and two distractors showing a stimulus semantically related to the target-word or a stimulus not related to the target-word); a word-picture matching task of visual comprehension of verbs, in which the subject is asked to read aloud a written verb and to point to one out of 3 alternative pictures (the corresponding target-picture and two distractors showing a stimulus semantically related to the target-word or a stimulus not related to the target-word).

Finally, the patients was administered three additional lexical-semantic tasks aimed at specifically assessing lexical-semantic processing of noun stimuli belonging to either living/biological entities or to non-living entities [45]: a confrontation naming task, a single-word comprehension task requiring an inter-categorical matching, a single-word comprehension task requiring an intra-categorical matching. In such three tasks, a set of ten stimuli for each out of 4 living categories (animals, fruits, vegetables, body parts) and of ten stimuli for each out of 4 non-living categories (tools, furnitures, vehicles, musical instruments) was selected from Snowdgrass and Vanderwarts set [46], with stimuli matched for various variables (word frequency, age of acquisition, prototipicality and familiarity). In the auditory word-picture matching task requiring an inter-categorical matching, the examiner reads aloud a word and the subject has to choose among five alternative pictures belonging to semantic categories not related to the target-word (for example, if the target-word is an apple, the subject is shown 4 distractor pictures showing a motorcycle, a lamp, a nail, a giraffe). In the auditory word-picture matching task requiring an intra-categorical matching, the examiner reads aloud a word and the subject has to choose among five alternative pictures belonging to the same semantic category as the target-word word (for example, if the target word is a pear, the subject is shown 4 distrator pictures showing a lemon, an apple, a water mellon, grapes).

For each task, statistical comparisons between number of errors versus correct responses across different grammatical categories (nouns versus verbs) and semantic categories (living versus non-living entities) were carried out by means of Chi-square test and Fisher's exact tests.

RESULTS

General Neuropsychological Examination

Patient RP showed a severely impaired performance on tasks of verbal episodic long-term

Table 1: Performance of Patient R.P on General Neuropsychological Evaluation [41]. Scores Below the Normal Range are Reported in Bold

Neuropsychological task	Raw and (adjusted) scores	Cut-off score
MMSE	**10**	
Episodic memory		
RAVLT immediate recall	**15 (5.93)**	28.52
RAVLT delayed recall	**0**	4.69
Visual memory		
Immediate visual memory	19 (18.3)	13.85
Praxis		
Limb praxis	18	18
Costruxional praxis (Copying drawings)	12 (12)	7.18
Working memory		
Digit Span forward	5 (4.50)	4.26
Digit span backward	4 (3.50)	2.65
Abstract reasoning		
Raven progressive Matrices '47	23 (19.15)	18.96
Selective visual attention		
MFTC accuracy	1	0.838
MFTC false	0	2.77
MFTC time (s)	60 (64.94)	135.73
Executive functions		
Temporal rule induction	5 (6.5)	<15

memory (Table **1**) and on the MMSE. By contrast, her performance was nearly in the normal range on tasks assessing verbal and visual short-term memory, non-verbal abstract reasoning (Raven's Progressive Matrices '47), executive functions (problem-solving and set-shifting abilities), oro-facial, limb and costruxional apraxia.

Language Assessment

General assessment of language (Table **2**) was carried out by means of the BADA [44]. Spontaneous speech was fluent, normally articulated, and without grammatical errors, but it was characterised by very marked word-finding difficulties associated with frequent circumlocutions. Performance on tasks of phonemic discrimination and repetition of words and non-words was accurate. On tasks of reading, writing to dictation and repetition of regular words and non-words, her performance was quite good, except for some difficulties just on irregular words. On both auditory and visual lexical decision tasks, her performance was mildly impaired, mainly due to difficulties in rejecting non-words (auditory lexical decision: error rate on words = 5%; error rate on non-words =22%; visual lexical decision: error rate on words = 7%; error rate on non-words =12%). On both lexical decision tasks, when performance on specific categories of words was analysed, there was no difference in the error rate between nouns (error rate: 10%) and verbs (error rate: 10%). Auditory and visual comprehension of sentences was spared.

As to the naming tasks of the BADA, she showed a severely impaired performance, with greater impairment on nouns than on verbs on both an oral confrontation task (error rate on nouns: 100%; error rate on verbs: 71%) and a written confrontation naming task (error rate on nouns: 100%; error rate on verbs: 32%). As to the single-word comprehension tasks of the BADA, the patient showed a less severely impaired performance, with greater impairment on nouns than on verbs on both an auditory single-word comprehension task (error rate on nouns: 25%; error rate on verbs: 10%) and a visual single-word comprehension task (error rate on nouns: 25%; error rate on verbs: 10%).

Table 2: Performance of Patient RP on Language Tasks of the Battery for the Analysis of Aphasic Deficits [44]. Scores Below the Normal Range are Reported in Bold

Neuropsychological task	no. of errors/overall no of. items (%)
Phonemic discrimination	0/60 (0%)
Transcoding Tasks on Non-words	
Repetition of non-words	0/35 (0%)
Reading of non-words	4/45 (8.8%)
Writing-to-dictation of non-words	1/25 (4%)
Lessical Decision tasks	
Auditory Lexical decision	11/80 (14%)
Words (n=40) error 5%	
Non-words (n=40) error 22%	
Visual Lexical decision	5/80 (6%)
Words (n=40) error 7%	
Non-words (n=40) error 12%	
Trascoding Tasks on Words	
Repetition of words	0/45 (0%)
Reading of words	19/92 (20.65%)
Writing-to-dictation of words	0/46(0%)
Single-word Comprehension tasks	
Auditory comprehension of nouns	10/40 (25%)
Auditory comprehension of verbs	2/20 (10%)
Visual comprehension of nouns	10/20 (25%)
Visual comprehension of verbs	2/20 (10%)
Naming tasks	
Oral confrontation naming of nouns	30/30 (100%)
Oral confrontation naming of verbs	20/28 (71%)
Written confrontation naming of nouns	22/22 (100%)
Written confrontation naming of verbs	7/22 (32%)
Naming of noun stimuli on verbal description	6/16 (37%)
Sentence Comprehension tasks	
Auditory comprehension of sentences	2/60 (3.3%)
Visual comprehension of sentences	1/45 (2.2%)
Additional Grammatical tasks	
Visual Grammatical Judgements	3/24 (12.5%)
Sentences repetition	0/20 (0%)
Sentences reading	0/6 (0%)

Performance of patient RP on the additional lexical–semantic tasks aimed at specifically assessing lexical-semantic processing of nouns and verbs is reported in Table **3**. On the whole, she was more severely impaired on naming tasks than on single-word comprehension tasks. On an oral confrontation naming task (Miceli *et al*., 1988), she was significantly more impaired ($\chi 2 = 12.9$ $p = 0.03$) in the production of nouns (error rate = 81%) as compared to verbs (error rate =45%). Unfortunately, when she was asked to undergo a further written confrontation naming task involving the presentation of pictures depicting stimuli corresponding to 48 nouns or 48 verbs (Miceli *et al*. 1988), the patient refused to undergo such task due to her oppositional behavior in such circumstance.

On a auditory word-picture matching task [20], she was significantly more impaired (Fisher's test: $p = 0.02$)

Table 3: Performance on Additional Lexical-Semantic Tasks Aimed at Specifically Assessing Lexical-Semantic Processing of Nouns and Verbs [20, 44]

Neuropsychological task	Objects		Action		Statistical test	p
	No. of items	% error rate	No. of items	% error rate		
Oral Confrontation Naming (Miceli *et al*., 1988)	48	81%	48	45%	$\chi2=12.9$	p=.003
Auditory Word-Picture matching (1 spoken word-3 pictures)	48	31%	48	6%	*Fisher's test*	p=.002
Visual Word picture matching (1 written word-3 pictures)	20	35%	20	15%	*Fisher's test*	p=0.13

in the comprehension of nouns (error rate = 31%) as compared to verbs (error rate = 6%). On a visual word-picture matching task [44], there was only a statistical trend (Fisher's test: p = 0.13) towards a greater impairment in the comprehension of nouns (error rate = 35%) as compared to verbs (error rate = 15%). On both visual word-picture matching tasks, all errors made were semantically related to the target.

Performance of patient RP on lexical-semantic tasks aimed at specifically assessing lexical-semantic processing of noun stimuli belonging to either living/biological entities or to non-living entities [45] is reported in Table **4**. On an oral confrontation naming task, the patient was severely impaired in the production of nouns belonging to both living/biological entities (error rate: 95%) and non-living entities (error rate: 95%). On such tasks, most errors were omissions and circumlocutions. On a single-word comprehension task requiring an inter-categorical matching, the patient was impaired in the comprehension of nouns belonging to both living/biological entities (error rate: 27 %) and non-living entities (error rate: 37%). On a single-word comprehension task requiring an intra-categorical matching, she was impaired in the comprehension of nouns belonging to both living/biological entities (error rate: 50%) and non-living entities (error rate: 42%). As to all such 3 lexical-semantic tasks, no significant difference in performance was observed between living/biological entities and non-living entities.

DISCUSSION

In summary, patient RP suffered from HSE and developed a severe anomic aphasia syndrome and severe deficits of episodic memory, with brain MRI evidence for brain damage mainly involving temporal and limbic structures (inferior temporal cortex, lateral temporal convexity, temporal pole, amygdala, hyppocampal formation and enthorinal cortex) bilaterally, but more markedly in the left cerebral hemisphere. Moreover, brain MRI showed areas of abnormal signal intensity in the anterior cingulate gyrus and the adjacent mesial frontal regions of both cerebral hemisheres. About 24 hours after the beginning of neurological symptoms, treatment with intravenous acyclovir 10 mg/kg t.i.d. was administered for 10 days. When the patient was admitted in our hospital, about sixteen months post HSE onset, patient underwent a neuropsychological examination, including an extensive language assessment.

On lexical-semantic linguistic tasks, she showed an impairment on tasks of naming (oral and written) and comprehension (auditory and visual), which was disproportionately more severe on nouns as compared to verbs. On the whole, she was more severely impaired on naming tasks than on single-word comprehension tasks. She underwent additional lexical-semantic tasks aimed at specifically assessing lexical-semantic processing of noun stimuli belonging

Table 4: Performance of Patient RP on Lexical-Semantic Tasks Aimed at Specifically Assessing Processing of Noun Stimuli Belonging to Either Living/Biological or Non-Living Entities [45]

Neuropsychological task	Living/biological entities		Non-living entities		Statistical test	p
	No. of items	% error rate	No. of items	% error rate		
Oral Confrontation Naming	40	95%	40	95%	*Fisher's test*	p=ns
Word-Picture inter-categorical matching (1 spoken word-5 pictures)	40	27%	40	37%	$\chi2=.91$	p=ns
Word-Picture intra-categorical matching (1 spoken word-5 pictures	40	50%	40	42%	$\chi2=.45$	p= ns

to either living/biological entities or to non-living entities. On tasks of naming of nouns belonging to the two categories of living/biological and non-living entities, the patient was severely impaired to a similar degree on both categories, while on tasks of single-word comprehension of nouns belonging to the two categories of living/biological and non-living entities showed a moderate impairment of similar degree on both categories. This latter pattern of performance is not common in patients who survived HSE, who mostly show on tasks of naming and comprehension a disproprortionate impairment in processing items belonging to the broad semantic category of living or biological entities [7].

As to the fuctional locus of damage, the overall pattern of impaired performance of patient RP on various lexical-semantic tasks (impairment not only on naming tasks, but also on single-word comprehension tasks, especially on nouns) seems consistent with a damage mainly of semantic components critical for noun processing. Moreover, since she was more severely impaired on naming tasks than on single-word comprehension tasks, an additional severe damage involving lexical components critical for noun production might be hypothesized in this patient.

It has been suggested that anomic aphasic syndrome is a heterogenous clinical syndrome, shared by patients with different clinical features: in some anomic patients, with word difficulties not associated with language comprehension difficulties, lexical processes involved in noun production might be selectively impaired [47]; in other anomic patients, with word difficulties associated with language comprehension difficulties, semantic processes involved in noun production might be selectively impaired [48]. The extensive language assessment in patient RP was helpful in suggesting that her anomic aphasic syndrome associated with language comprehension difficulties resulted from an impairment of both semantic and lexical processes involved in noun production and comprehension. Nevertheless, such extensive language examination was sometimes frustating for our patient, since she was quite aware of her unsuccessful performance on language tasks.

One limitation of the present study is the use of lexical-semantic tests on nouns and verbs with stimuli matched only for word length and frequency, but not for other variables, such as age of acquisition, degree of imageability, degree of concreteness, visual complexity, morphosyntactic complexity of the stimuli. In order to minimize the influence of confounding variables, differences in performance levels between the dissociating categories need to be large ("strong dissociations") [49]. In a review of the literature, it has been proposed an arbitrary cut-off of 30% for the magnitude of difference in performance on tasks of picture naming of stimuli depicting nouns versus verbs [50]. On the oral confrontation naming task of the BADA [44], patient RP showed a 71% difference between error rate on nouns (100%) versus verbs (29%), while on an additional oral confrontation naming task [20], she showed a 36% difference between error rate on nouns (81%) versus verbs (45%). On the written confrontation naming task of the BADA[44], patient RP showed a 68% difference between error rate on nouns (100%) versus verbs (32%). In conclusion, dissociations between naming of nouns versus verbs were quite strong in our patient.

From a neuranatomical perspective, the observation of semantic deficits involving nouns belonging to both categories of living/biological and non-living entities in our patient (with brain MRI evidence for damage in the temporal lobes, involving inferior temporal cortex, temporal pole, amygdala, hyppocampal formation and enthorinal cortex) is consistent with the hypothesis that damage to the left anterior temporal lobe extending laterally to inferior temporal gyri may result in a more generalized semantic impairment [18], while damage restricted to the medial part of the anterior temporal cortices may result in category-specific deficits for living entities [17,18]. Accordingly, individual differences in anatomical distribution of the lesions among patients who survived HSE may give rise to different patterns of lexical-semantic impairment in different patients [7]: most patients show a sematic impairment affecting disproportionately the category of living entities, while other patients (like patient RP) may show a more generalized semantic impairment, affecting both living and non-living entities.

Furthermore, the observation in patient RP of a disproportionate impairment in naming and comprehension of nouns as a compared with verbs is consistent with the hypothesis that neural systems located in the temporal lobes might be part of neural circuits critically involved in lexical and semantic processes underlying the production and comprehension of nouns [21-23]. The main interest of the present case report, on the other hand, arise from the observation in our patient of a relative preservation of verb production and comprehension. This latter finding might be explained by the relative sparing of

ventro-lateral frontal areas (including the left inferior frontal gyrus), which might be part of neural circuits critically involved in the production and comprehension of verbs [22, 23].

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