Constraints on the cerebral basis for semantic processing from neuroimaging studies of Alzheimer's disease

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Abstract

Objective—Functional activation studies of semantic processing in healthy adults have yielded conflicting results. The purpose was to evaluate the relative role of the brain regions implicated in semantic processing with converging evidence from imaging studies of patients with impaired semantic processing.

Methods—Semantic memory was assessed in patients with Alzheimer's disease using two measures, and these performance patterns were related to profiles of reduced cerebral functioning obtained with high resolution single photon emission computed tomography (SPECT). Patients with frontotemporal degeneration were similarly evaluated as a control group.

Results—Reduced relative cerebral perfusion was seen in parietal and posterior temporal brain regions of patients with Alzheimer's disease but not patients with frontotemporal degeneration. Impairments on semantically guided category membership decision tasks were also seen in patients with Alzheimer's disease but not those with frontotemporal degeneration. Performance on the semantic measures correlated with relative cerebral perfusion in inferior parietal and superior temporal regions of the left hemisphere only in Alzheimer's disease. Relative perfusion was significantly lower in these regions in patients with Alzheimer's disease with semantic difficulty compared with patients with Alzheimer's disease with relatively preserved semantic processing.

Conclusion—These findings provide converging evidence to support the contribution of superior temporal and inferior parietal regions of the left hemisphere to semantic processing.

However, other activation studies have associated semantic decisions with inferior frontal regions of the left hemisphere.⁷⁻⁹ One way to resolve conflicting claims about the anatomical basis for semantic processing is to seek converging evidence from another source. The purpose of this study was to determine whether one of these areas of cerebral recruitment corresponds to the anatomical distribution of reduced brain activity associated with compromised semantic processing in patients with a semantic impairment.

Alzheimer's disease often results in significant difficulty appreciating the meaning of individual words and pictures.¹⁰⁻¹⁴ Impaired semantic processing in patients with Alzheimer's disease thus interferes with performance on lexical measures such as semantic category membership judgments¹⁵⁻¹⁷ and semantically guided category naming fluency tasks.^{18, 19} A similar pattern of semantic errors on semantic category membership judgments of pictures^{16, 17} and a semantically guided category drawing task¹⁹ has been reported as well. Importantly, Alzheimer's disease is a heterogeneous clinical disorder, and a deficit for word and picture meaning such as this is evident in about half of the patients with Alzheimer's disease.^{16, 20, 21}

Single photon emission computed tomography (SPECT) is an inexpensive and widely available technique that can identify defects in regional cerebral perfusion in neurodegenerative diseases that do not have obvious structural abnormalities. The diagnostic utility of SPECT has been shown in Alzheimer's disease,²²⁻²⁴ and SPECT has been validated in Alzheimer's disease through direct comparisons with more expensive and less available techniques such as PET.^{25, 26} Correlative functional imaging studies have associated impaired language with perfusion defects in the left hemisphere of unselected groups of patients with Alzheimer's disease,²⁷⁻³² and a preliminary study on a few patients with Alzheimer's disease has related reduced glucose metabolism measured by PET in inferior parietal and superior temporal regions of the left hemisphere to impaired semantic memory.³³ We hypothesised that SPECT will associate reduced left superior temporal and inferior parietal brain activity with impaired semantic processing in Alzheimer's disease, and that this deficit will be most evident in the subgroup of patients with Alzheimer's disease with semantic memory difficulty.

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Functional neuroimaging studies in healthy adults have related decisions about the meaning of words to activation of the heteromodal association cortex in inferior parietal and superior temporal regions of the left hemisphere.¹⁻⁶

Table 1 Mean (SD) demographic features of patients with Alzheimer's disease and frontotemporal degeneration

	Age (y)	Education (y)	Duration (months)	MMSE (30 point scale)
Alzheimer's	72.84 (8.45)	13.79 (3.86)	22.47 (16.84)	19.79 (6.97)
Frontotemporal	70.13 (10.42)	14.62 (3.16)	24.87 (24.43)	22.06 (6.96)

Analyses of variance showed that the patient groups did not differ in age ($F(1,33)=0.73$; NS), education ($F(1,33)=0.48$; NS), disease duration ($F(1,33)=0.12$; NS), or overall dementia severity according to the MMSE ($F(1,33)=0.92$; NS).

Methods

PATIENTS

We studied 35 patients with a dementia who were recruited from the cognitive neurology clinic at the University of Pennsylvania Medical Center. These patients were judged to have a mild or moderate dementia that would not prevent them from completing the entire battery of tasks. We evaluated 19 patients (11 women, eight men) with probable Alzheimer's disease. We also assessed 16 patients (six women, 10 men) with a frontotemporal form of degeneration as a demented control group. Clinical diagnosis has been confirmed histopathologically in three patients with Alzheimer's disease and in five patients with frontotemporal degeneration who had dementia lacking distinctive histology or Pick's Disease.³⁴ Table 1 shows that the patient groups were matched for age, education, duration of disease, and overall severity of dementia.³⁵ The patient groups were also matched in their episodic memory performance on a supraspan list learning task³⁶ (learning 10 words over three trials: $F(2,40)=1.31$; NS; delayed recognition memory: $F(2,40)=1.11$; NS). None of the patients had been previously diagnosed with a primary psychiatric disorder such as depression, schizophrenia, or bipolar disorder. There was no history of relevant head trauma, intracranial mass lesion, demyelinating disease, movement disorder, or any other neurological condition that could explain a patient's decline. Serum studies ruled out metabolic, infectious, and endocrinological disorders that could mimic a progressive neurodegenerative condition, and there were no medical conditions that could account for the patient's deficits. Patients were not taking sedating medications at the time of evaluation. Clinical examination indicated that none of the patients had visual or auditory sensory limitations that could have compromised cognitive performance.

Patients with probable Alzheimer's disease were diagnosed on the basis of NINCDS-ADRDA criteria.³⁷ There was no history of stroke and the score on the modified Hachinski scale was 2 or less.³⁸ Patients with frontotemporal degeneration were diagnosed on the basis of published clinical criteria derived from clinicopathological studies performed in our laboratory³⁴ and elsewhere.^{39,40} There was no history of stroke, and the score on the modified Hachinski scale was 2 or less.³⁸ The cognitive functioning of the demented patients was compared with age and education matched control subjects who were spouses of the patients or were recruited from the community, as described in detail elsewhere.¹⁶

SPECT IMAGING PROTOCOL

Regional brain functioning was studied at rest with SPECT. The protocol involved intravenous injection of 370 Mbq (20 mCi) ^{99m}Tc-hexamethyl propyleneamine oxime (Amersham Inc) about 60 minutes before imaging. The patient was positioned supine on a tomography table with the patient's head supported by a low attenuation headrest so that the orbitomeatal line was vertical. Images were acquired on a rotating triple headed gamma camera that covered a 360° rotation about the long axis of the patient and was equipped with ultrahigh resolution fan beam collimators (Prism 3000, Picker International, Cleveland, OH, USA). A stop and shoot mode was used to obtain projection data in a 128×128 matrix with a pixel width of 2.11 mm and a slice thickness of 3.56 mm. A total of four rotations, each requiring 12 to 15 minutes, were acquired and then added together, typically yielding 4×10⁶ counts per acquisition. During the 48 minute to 60 minute image acquisition period, the patient rested quietly with eyes open and ears unplugged; the room was darkened, and soft white noise produced by the imaging apparatus could be heard.

The projection data were reconstructed in tomographic planes before a count rate dependent, three dimensional restorative filter was applied.⁴¹ The modulation transfer function used by the filter was determined experimentally from the line spread function for the camera that was actually used to scan the patients.^{42,43} The effects of the reconstruction technique on the accuracy of the data were measured.⁴⁴ Chang's first order correction method was used to compensate for photon attenuation.⁴⁵

The images were down loaded for off line analysis to a graphics workstation (Sun Microsystems, Mountain View, CA, USA), where an interactive, computer based relational template was applied by an experienced operator (FP) under the supervision of a board certified physician in nuclear medicine with expertise in neuroradiology (AA). These investigators were naive to the diagnosis of the patients and the hypotheses under study. Briefly, the mid-sagittal image was identified in the three dimensional SPECT data set using locally developed software (PETView, UGM, Philadelphia, PA, USA). The anterior commissure-posterior commissure (AC-PC) plane was identified, and a transaxial data set was then constructed in this plane with a slice thickness of 3.56 mm. The circumference of the brain was identified on the transaxial images thresholded at 50%. Gross anatomical landmarks were identified, including the mid-sagittal fissure, the sylvian fissure, and the tentorium cerebelli. Based on pilot studies of 10 three dimensional MRI sets and corresponding transaxial MRI sliced in the AC-PC plane, the frontal, parietal, and temporal lobes of each hemisphere were identified and partitioned into contiguous regions of interest (ROIs) (table 2). A detailed description of the algorithm is available from us. The mean counts in each ROI were computed, omitting

Table 2 Mean (SD) normalised SPECT relative perfusion in cerebral regions of interest in Alzheimer's disease and frontotemporal degeneration

	Alzheimer's		Frontotemporal	
	Left	Right	Left	Right
Frontal:				
Lateral superior	0.95 (0.11)	0.96 (0.11)	0.93 (0.11)	0.91 (0.10)
Lateral inferior	0.91 (0.10)	0.93 (0.10)	0.84 (0.07)	0.84 (0.04)
Mesial	0.89 (0.09)	0.92 (0.08)	0.81 (0.09)	0.83 (0.10)
Temporal:				
Lateral superior anterior	0.87 (0.11)	0.88 (0.11)	0.86 (0.11)	0.88 (0.08)
Lateral superior posterior	0.92 (0.12)	0.92 (0.11)	0.93 (0.11)	0.94 (0.09)
Lateral inferior anterior	0.90 (0.09)	0.90 (0.10)	0.89 (0.11)	0.90 (0.09)
Lateral inferior posterior	0.91 (0.11)	0.87 (0.13)	0.95 (0.12)	0.92 (0.11)
Mesial	0.73 (0.07)	0.78 (0.05)	0.74 (0.08)	0.77 (0.06)
Parietal:				
Superior	0.86 (0.10)	0.86 (0.10)	0.91 (0.11)	0.90 (0.07)
Inferior	0.87 (0.12)	0.87 (0.12)	0.90 (0.10)	0.90 (0.08)
Occipital:				
Lateral	0.89 (0.08)	0.87 (0.09)	0.92 (0.08)	0.91 (0.08)

the first and last axial slice on which an ROI could be visualised in an attempt to minimise the effects of volume averaging. We report the ratio of activity in an ROI to cerebellar activity.

COGNITIVE MATERIALS

The subjects were evaluated on a 30 minute battery that included measures of semantic judgments, overall dementia severity, and episodic memory. These measures were administered by experienced technicians (TW-D, KO) who were blinded to the clinical diagnosis of the patient and the hypotheses under study. The materials were presented in a quiet testing room counterbalanced for their order of presentation. Briefly, the following tasks were carried out.

Semantic category membership judgments: words¹⁶

Patients judged whether each of 24 printed words are instances of a familiar superordinate category. The words were printed in black ink on 12.5×20 cm white cards with lower case arial font using letters 2 cm in height. The stimuli were presented in a blocked fashion for each of two superordinates (VEGETABLE and TOOL). Half of the stimuli for each superordinate were targets and half were foils; half of the foils were semantically related to the target as they overlapped with the target category in many semantic features (for example, "apple" for the target category VEGETABLE), and half were semantically unrelated to the target category as they overlapped with the target category in relatively few semantic features (for example, "chair" for the target category VEGETABLE). The target and foil stimuli were presented in a fixed random order within each block. Difficulty discriminating between the target category and semantically related foils was thought to be particularly sensitive to semantic processing.^{16 17}

Category membership judgments: pictures¹⁶

This was identical to "category membership judgments—words" but the stimuli consisted of photographs of objects. The objects were photographed from a prototypical perspective, and the photos were 10×15 cm glossy colour prints presented on white cards that were 12.5×20 cm in size. There was a single photograph corresponding to each word. Perform-

ance on these visual category judgments was thought to reflect visual semantic processing, and comparison with lexical decisions allowed us to test the modality independent nature of impaired semantic processing.

STATISTICAL ANALYSES

Each patient's performance on each cognitive measure was converted to a z score based on the performance of age and education matched control subjects, as described elsewhere.¹⁶ Mean performance of each patient group was compared using these z scores as well as raw accuracy scores. Parametric statistical tests such as analysis of variance (ANOVA) and planned *t* tests were performed to examine differences in cognitive performance and in regional brain function profiles across groups of demented patients. Correlation analyses related cognitive performance to functional brain imaging.

Results

SPECT REGIONAL BRAIN ACTIVITY

A multivariate analysis of variance (MANOVA) evaluated relative cerebral perfusion in brain regions with a group (Alzheimer's disease, frontotemporal degeneration)×ROI (22) design. This disclosed a significant main effect for ROI ($F(21,693)=16.72$; $P<0.0001$) and a significant group × ROI interaction effect ($F(21,693)=2.29$; $p<0.001$). The absence of a main effect for group ($F(1,33)=0.01$; NS) indicates that the patient groups did not differ in their overall relative cerebral perfusion. Table 2 shows that patients with Alzheimer's disease had reduced relative cerebral perfusion compared with patients with frontotemporal degeneration in all but one (91.7%) of the parietal, posterior temporal, and occipital ROIs with non-zero differences ($P<0.003$, binomial test), but patients with frontotemporal degeneration had reduced relative cerebral perfusion compared with patients with Alzheimer's disease in all (100%) of the frontal and anterior temporal ROIs with non-zero differences ($P<0.003$, according to the binomial test). These findings confirm that patients with Alzheimer's disease have reduced relative cerebral perfusion in parietal and posterior temporal regions.

SEMANTIC JUDGMENT PROFILES

Figure 1 summarises the overall semantic judgment profiles of patients with Alzheimer's

Figure 1 Mean z score of overall semantic judgment accuracy for words and pictures in Alzheimer's disease and frontotemporal degeneration.

Table 3 Mean (SD) clinical and cognitive characteristics of Alzheimer patient subgroups with impaired semantic processing or preserved semantic processing

	Age (y)	Education (y)	MMSE (30 point scale)	Learning/memory (z score)*
Alzheimer's + sem	72.62 (10.91)	13.00 (2.98)	17.75 (7.59)	-3.62 (2.05)
Alzheimer's - sem	73.00 (6.72)	14.36 (4.43)	21.27 (6.43)	-3.27 (1.89)

* Compared with age and education matched control subjects. *t* Tests comparing subgroups of patients with Alzheimer's disease with impaired semantic processing (+ sem) and preserved semantic processing (- sem) failed to show differences for age ($t=0.08$), education ($t=0.75$), mini mental state examination ($t=1.09$), or learning and memory ($t=0.39$).

disease and frontotemporal degeneration. Only patients with Alzheimer's disease were significantly impaired in their category membership judgments of words and their category membership judgments of pictures, at least at the $P<0.01$ level. We analysed semantic judgment performance in Alzheimer's disease and frontotemporal degeneration in greater detail to determine the basis for this impairment and to identify an appropriate cognitive variable that we could relate to the relative cerebral perfusion patterns seen on SPECT. Figure 2 shows that patients with Alzheimer's disease did not differ from random in their judgments of word foils and picture foils that are semantically related to the target category, although they were better than random in their judgments of word foils and picture foils that are

Figure 2 Mean accuracy judging semantically related and semantically unrelated word and picture foils in Alzheimer's disease and frontotemporal degeneration.

Figure 3 Mean accuracy judging semantically related and semantically unrelated word and picture foils in subgroups of patients with Alzheimer's disease with impaired semantic processing (AD+sem) and preserved semantic processing (AD-sem).

not semantically related to the target category (words $t(18)=5.40$; pictures $t(18)=5.14$; $P<0.01$). Patients with Alzheimer's disease also had significantly greater difficulty in their judgments of related foils than unrelated foils (words $t(18)=3.85$; pictures $t(18)=3.71$; $P<0.01$). These differences were equally evident for natural items such as vegetables and manufactured artifacts such as tools. By comparison, patients with frontotemporal degeneration consistently differed from random in their judgments of both semantically related foils (words $t(15)=3.13$; pictures $t(15)=3.64$; $P<0.01$) and semantically unrelated foils (words $t(15)=5.84$; pictures $t(15)=6.81$; $P<0.01$), and patients with frontotemporal degeneration did not differ in the accuracy of their judgments of semantically related foils and semantically unrelated foils. These findings suggest that Alzheimer's disease and patients with frontotemporal degeneration differ in their performance on semantic category membership judgments.

We identified individual patients with Alzheimer's disease with a semantic impairment by combining each patient's performance across picture and word materials and then partitioning the patients into subgroups based on their relative accuracy judging semantically related foils and semantically unrelated foils. Thus, individual patients with Alzheimer's disease with at least 50% more errors for semantically related foils compared with semantically unrelated foils were considered to have a semantic processing impairment (Alzheimer's disease+sem), whereas patients with Alzheimer's disease with less of a discrepancy between semantically related foils compared with semantically unrelated foils were considered not to have a semantic processing deficit (Alzheimer's disease-sem). Using this technique, eight (42.1%) of the 19 patients with Alzheimer's disease were judged to have impaired semantic processing. Table 3 shows that subgroups of patients with Alzheimer's disease differing in their semantic processing were matched for demographic, memory, and overall dementia characteristics.

Inspection of *z* scores in Alzheimer's disease subgroups disclosed that seven (87.5%) of the eight Alzheimer's disease+sem patients were significantly impaired ($P<0.05$) in their overall semantic judgment performance for words and pictures, but only two (18.2%) of the 11 Alzheimer's disease-sem patients were similarly impaired for word and picture judgments ($\chi^2(1)=8.86$; $P<0.01$). Examination of foil judgments in the Alzheimer's disease patient subgroups (fig 3), showed significantly greater difficulty with semantically related foils in Alzheimer's disease+sem patients than Alzheimer's disease-sem patients ($t(17)=2.39$; $P<0.02$). However, the subgroups did not differ in their judgments of semantically unrelated foils ($t(17)=0.44$; NS). Alzheimer's disease+sem patients also had significantly more difficulty with semantically related foils than their own performance with semantically unrelated foils ($t(7)=8.90$; $P<0.0001$), a difference that was not apparent in Alzheimer's

disease–sem patients. These findings emphasise the different patterns of semantic judgments in Alzheimer's disease+sem patients and Alzheimer's disease–sem patients.

RELATION BETWEEN REGIONAL PERFUSION PATTERNS AND SEMANTIC PROFILES

Correlation analyses were used to test the hypothesis that judgments of semantically related foils are related to perfusion in left posterior perisylvian ROIs. For the purpose of these analyses, we combined performance on semantically related word foils and semantically related picture foils. Anterior ($r(17)=0.69$) and posterior ($r(17)=0.56$) portions of the superior temporal gyrus and the inferior parietal region ($r(17)=0.56$) of the left hemisphere correlated with judgments of semantically related foils in Alzheimer's disease at least at the $P<0.01$ level. Partial correlations between these brain regions and semantic judgments that controlled for demographic characteristics (age, education, disease duration) and disease severity (mini mental state examination) did not reduce the significance of these correlations. There were no significant correlations between judgments of semantically related foils and relative perfusion in left frontal ROIs of patients with Alzheimer's disease, nor between semantic judgments and left frontal or left temporoparietal ROIs of patients with frontotemporal degeneration.

We compared relative perfusion in the brain regions correlated with semantic memory performance in subgroups of patients with Alzheimer's disease. A MANOVA with an Alzheimer's disease subgroup (2)×ROI (3) design disclosed a significant main effect for group ($F(1,17)=4.56$; $P<0.05$), but there was not a significant main effect for ROI or a significant group×ROI interaction effect. Mean (SD) relative perfusion was significantly lower in patients with Alzheimer's disease+sem compared with patients with Alzheimer's disease–sem in the left superior anterior temporal region (Alzheimer's disease+sem = 0.801 (0.10), Alzheimer's disease–sem = 0.917 (0.09); $t(17)=2.55$; $P<0.02$), and differences in the left superior posterior temporal region (Alzheimer's disease+sem = 0.865 (0.11), Alzheimer's disease–sem = 0.961 (0.11); $t(17)=1.88$; $P<0.07$) and the left inferior parietal region (Alzheimer's disease+sem = 0.819 (0.10), Alzheimer's disease–sem = 0.914 (0.11); $t(17)=1.88$; $P<0.07$) approached significance. These findings suggest that the subgroup of patients with Alzheimer's disease with semantic difficulty has reduced relative perfusion in specific brain regions that seem to contribute to semantic processing.

Discussion

Our findings showed distinct patterns of cerebral perfusion defects in Alzheimer's disease and frontotemporal degeneration. Patients with Alzheimer's disease had relatively reduced activity in parietal and superior temporal areas, whereas patients with frontotemporal degeneration had relatively reduced perfusion in

frontal and anterior temporal regions. These findings are consistent with previous reports showing different patterns of reduced relative cerebral perfusion in patients with Alzheimer's disease and frontotemporal degeneration.^{46–48}

Functional neuroimaging studies have related non-specific language impairments in Alzheimer's disease to hypoperfusion in the left hemisphere.^{27 28 30–32} In the present study, we sought to relate the pattern of reduced cerebral activity in patients with Alzheimer's disease to a more specific language deficit. Difficulty judging semantically related foils on a semantic category membership judgment task marks impaired semantic processing,^{16 17} and we found that in patients with Alzheimer's disease semantic judgment performance correlates with relative cerebral perfusion in superior temporal and inferior parietal regions of the left hemisphere. A similar pattern was not found in frontotemporal degeneration, indicating that the correlation between semantic processing and left superior temporal and inferior parietal brain regions is not a general property of dementia. Alzheimer's disease is a heterogeneous disorder that interferes disproportionately with certain cognitive processes in a subset of patients with Alzheimer's disease,^{16 20 21} and we attempted to use the heterogeneity in the cognitive profiles and the cerebral metabolic patterns^{31 32} to establish the brain regions related to a semantic processing deficit. We found that the subgroup of patients with Alzheimer's disease with semantic difficulty had reduced relative cerebral perfusion in the left temporoparietal regions compared with patients with Alzheimer's disease with preserved semantic processing. This finding relates this brain area specifically to impaired semantic processing.

It is possible to use findings of brain-behaviour relations in patients with Alzheimer's disease to constrain theories about normal cerebral processing.⁴⁹ The association of inferior parietal and superior temporal regions of the left hemisphere with semantic memory is consistent in part with the results of some PET activation studies in healthy adults that have described recruitment of these cerebral regions during semantic challenges.^{1–6} Such PET activation studies have been difficult to interpret as other brain regions also have been activated during the semantic challenges, possibly due to the automatic recruitment of a fully elaborated neural network for all aspects of lexical processing when a word is presented.^{50 51} Our findings emphasise the role of the left inferior parietal and superior temporal brain regions in the semantic component of these tasks. This is also consistent with some lesion studies in stroke patients that have noted similar semantic processing difficulty after insult to posterior perisylvian regions of the left hemisphere.^{52–54} Posterior heteromodal association areas such as this may be crucial for semantic processing because the connectivity pattern allows these brain areas to integrate information represented throughout modality specific association cortices for the purpose of comparison with a target category.^{2 55–57} Converging evi-

dence from activation imaging studies in healthy adults and functional imaging studies in semantically impaired patients thus provides support for the hypothesis that posterior heteromodal association regions of the left hemisphere contribute to semantic processing.

Left frontal regions have been activated during the "verb generate" paradigm in which the subject produces a verb that is semantically related to a noun prompt.⁷⁻⁹ It has been argued on the basis of these findings that there is a frontal semantic region. Semantic difficulty on category membership judgment tasks occurred rarely in patients with frontotemporal degeneration who have reduced activity in left frontal brain regions, and we did not find a significant correlation between semantic judgments and frontal activity in frontotemporal degeneration. An alternative hypothesis has been forwarded that frontal recruitment during semantic activation studies is related to some strategic aspect of task performance.^{5, 58}

Several caveats must be kept in mind when interpreting our findings. The correlations we found were limited in the proportion of the variance in performance that they could explain, and additional factors thus need to be defined to arrive at a more complete characterisation of the part played by posterior supramodal association cortices in the semantic deficits of Alzheimer's disease. Imaging studies of regional brain function at rest are limited as they do not show which brain regions are not recruited during an appropriate cognitive challenge. Whereas our findings suggest that the frontal cortex may not be crucial to semantic category membership decisions, frontal brain regions may contribute to other aspects of semantic processing that were not assessed in this study. With these shortcomings in mind, our findings provide converging evidence to support the claim that semantic processing is associated with left inferior parietal and superior temporal brain regions.

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