

Semantic profiles in mild cognitive impairment associated with Alzheimer's and Parkinson's diseases

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Summary

The temporal and the prefrontal cortices have different roles in semantic information processing: the temporal lobe is where knowledge is stored (Graham and Hodges, 1997), whereas the prefrontal cortex is more specifically involved in executive aspects of semantic processing.

Relatively little is known about the semantic profiles of mild cognitive impairment (MCI) in Alzheimer's disease (AD) and Parkinson's disease (PD). This observational study investigated naming and semantic questionnaire performances in three groups of subjects: 10 patients with the amnesic-type MCI prodrome of AD (aMCI), 10 patients with early-stage executive-type MCI in PD (MCI-PD), and 10 normal subjects.

The MCI-PD subjects demonstrated inferior performances on a semantic questionnaire, whereas the aMCI group displayed modest difficulties in a naming task. These differences may be explained by topographical differences in pathological involvement. Since the frontal areas are more functionally impaired in PD, we hypothesize that the semantic deficit may be a consequence of a deficiency in control of semantic processing. On the other hand, the semantic deficit in aMCI may be related to a lexical-semantic storage dysfunction resulting from pathological involvement of the temporal lobe.

KEY WORDS: Alzheimer's disease, lexical damage, mild cognitive impairment, Parkinson's disease, semantic damage

Introduction

Semantic memory is a term that "refers to a permanent store of representational knowledge, including facts, objects, words and their meanings" (Giffard et al., 2008). The neural basis of semantic processing has been investigated in numerous studies that describe a large and distributed network of semantic representations (Duffau et al., 2005; Hart et al., 2007; Cappa, 2008).

Two cortical areas are considered to play important roles in the processing of semantic information: the temporal and prefrontal cortices. The temporal lobe is where knowledge is stored (Graham and Hodges, 1997), whereas the prefrontal cortex (PFC) is more specifically involved in executive aspects of semantic processing, in other words, the retrieval, selection and control of semantic information (Noppeney et al., 2004). Semantic memory impairment is observed early in Alzheimer's disease (AD) and is related to the presence of medial temporal lobe pathology (Hodges and Patterson, 1995). Semantic profile alterations in AD seem to be due to a breakdown of the semantic storage system or to difficulty in accessing information. It is still debated whether the semantic deficit in AD is category-specific, affecting differentially the ability to name living and non-living things (Laws et al., 2007). Patients with Parkinson's disease (PD) frequently show a cognitive deterioration characterized primarily by a dysexecutive syndrome due to the pathological involvement of the frontal and prefrontal cortices and basal ganglia (Verbaan et al., 2007). Different hypotheses have been advanced to account for the semantic impairment found in these patients: a deficiency of semantic representation activation due to storage impairment, a dysfunction in semantic retrieval processes or increased spreading activation in lexical-semantic networks (Raskin et al., 1992; Auriacombe et al., 1993; Watters and Patel, 1999; Foster et al., 2008).

A publication investigating cognitive functions in AD and PD patients with dementia (Song et al., 2008) found (with the exception of episodic memory) a similar neuropsychological pattern: both groups of patients showed the same difficulty in the task evaluating semantic knowledge.

In order to ascertain the presence of any semantic difference, however, it is necessary to study patients at

an early disease stage when the pathology is still restricted to specific areas.

Amnesic mild cognitive impairment (aMCI) is considered a transitional state between normal aging and AD. Patients with aMCI have relatively good general cognitive abilities and daily functioning, but their declarative memory functions are impaired compared to those of age-matched controls, presumably due to impaired long-term memory function (Collie and Maruff, 2000; Petersen et al., 2001; Alladi et al., 2006; Portet et al., 2006). Conversion rates of 15 to 20% from mild cognitive impairment (MCI) to frank dementia over two years have been reported (Petersen, 2004; Gauthier et al., 2006; Mauri et al., 2012).

Neuropathological findings in MCI patients are characterized by significant structural changes in the ventromedial temporal lobe (Markesbery et al., 2006), known to be involved in semantic memory (Davies et al., 2004), which correlate with a subtle clinical semantic deficit (Duong et al., 2006; Kraut et al., 2007; Gardini et al., 2013).

Recently the concept of MCI has also been applied to PD and the entity MCI-PD (mild cognitive impairment in Parkinson's disease) has been proposed (Litvan et al., 2011). MCI is not uncommon in PD, and is heterogeneous in nature (Janvin et al., 2006; Aarsland et al., 2010).

Semantic memory in MCI-PD patients has been investigated using a variety of tasks, addressing aspects such as priming, naming, semantic verbal fluency, concept formation and sentence comprehension, and the patients' performances were found to be modestly impaired (Watters and Patel, 1999; Portin et al., 2000; Arnott et al., 2001).

In a recent study PD patients showed greater impairment in semantic fluency than in phonemic fluency and this aspect seemed to be related to a deficit in semantic memory storage (Henry and Crawford, 2004). Other authors hypothesize that poor performance on semantic tasks is due to a failure of aspects of executive functioning specific to semantic processing which are responsible for retrieving, maintaining, monitoring and manipulating semantic representations stored elsewhere (McDonald et al., 1996; Watters and Patel, 1999; Longworth et al., 2005). Another hypothesis suggests that a decreased signal-to-noise ratio in the semantic network due to dopamine depletion may play a role (Angwin et al., 2005).

The aim of this observational study was to investigate lexical semantic processing through a detailed evaluation of two groups of MCI subjects with different underlying pathologies (aMCI, MCI-PD) in order to: i) explore whether the two groups exhibit semantic deficits; ii) assess the nature of the impairment (storage vs control processing); iii) investigate the semantic category effect.

Materials and methods

Three groups of patients were selected. The first group was composed of 10 patients affected by

MCI-PD selected according to the relative Movement Disorder Society Task Force Criteria (Litvan et al., 2012), namely: a diagnosis of PD, a gradual decline in cognitive ability reported by the patient or informant or observed by the clinician, a cognitive deficit on formal neuropsychological testing, no significant interference with functional independence, and absence of dementia and morbid conditions that significantly influence cognitive testing. We selected only patients presenting with isolated executive dysfunction on neuropsychological assessment.

The second group was composed of 10 patients affected by aMCI, fulfilling the criteria of Petersen et al. (2001), which include a memory complaint, preferably corroborated by an informant, impaired memory function for age and education, preserved general cognitive function, intact activities of daily living, and absence of dementia.

The third group was a control group comprising 10 normal subjects.

All the groups were native Italian speakers with no reported history of cerebrovascular accidents, head injuries, cerebral tumors or abscesses, psychiatric disorders, substance abuse, chronic use of psychoactive medication, coexisting neurological diseases, or speech/language disorders. The MCI-PD patients were evaluated in the on-medication state.

The protocol of this observational study complied with the principles of the Declaration of Helsinki and all the patients gave their written informed consent to participate.

All the patients underwent a neuropsychological screening battery (Table I) to exclude dementia. The control group was also tested to verify the presence of normal cognitive functioning.

The presence of MCI in patients meeting the clinical criteria for MCI-PD (executive type) and aMCI was confirmed by the following neuropsychological indices:

- Mini-Mental State Examination score >24;
- Clinical Dementia Rating scale score =0.5;
- At least two impaired executive tests for MCI-PD, according to the MDS guidelines (Litvan et al., 2012); at least one impaired long-term memory test for aMCI according to Petersen's criteria (Petersen et al., 2001);
- Normal scores in the other cognitive domains.

Semantic memory was further investigated using two subtests of Laiacona's Semantic Battery (Laiacona et al., 1993), namely, i) Figure naming and ii) Semantic feature question task.

Figure naming: the subject is asked to name the objects depicted in 80 line drawings. The drawings are by Snodgrass and Vanderwart and are presented by the examiner one by one, framed in 9.5 cm x 5.5 cm cards.

These stimuli are divided into living and non-living categories, and there are 10 stimuli for each living category (fruits, vegetables, body parts and animals) and 10 stimuli for each non-living category (furniture, vehicles, tools and musical instruments).

We analyzed the total number of errors (0-80) and dis-

tinguished between the living and non-living categories, in order to verify the presence of a category effect.

Semantic feature question task: the subject, through a double or multiple choice procedure, is asked to give semantic judgments (e.g. is a butterfly an animal, a vegetable, or an object? Is it a four-footed animal, a bird or an insect? Does it have transparent wings, multicolored wings or no wings at all? Is it lighter than a frog? Does it jump, fly or run? Does it live in winter, summer or both winter and summer?).

For the sake of simplicity, we selected 40 stimuli among the original 80: 10 animals and 10 fruits from the living categories and 10 vehicles and 10 items of furniture from the non-living categories.

We considered the total number of errors (0-240), divided into living and non-living items.

Statistical analysis

Univariate analysis of variance (ANOVA) and the post-hoc Tukey test were used to compare the results of the three groups.

Results

Demographic data

Univariate ANOVA was performed and showed that the three groups were matched for age and education (Table II).

Line drawing naming task

Univariate ANOVA was performed and yielded statistically significant results in total errors ($F= 4.107$; $p<0.028$) and non-living stimuli errors ($F= 4.807$; $p<0.016$). Post-hoc analysis of total errors revealed a significant difference between the aMCI group and the control group ($p<0.031$). The same was also observed with the non-living category of stimuli ($p<0.02$) (Table III).

Semantic feature question task

Univariate ANOVA of the semantic feature question task yielded statistically significant results in total

Table I - Neuropsychological screening battery.

Cognitive domain	Neuropsychological tests
Cognitive level and staging	Mini-Mental State Examination (Folstein et al., 1975) Clinical Dementia Rating scale (CDR) (Hughes et al., 1982)
Attention	Attentive matrixes (Spinnler et al., 1987)
Frontal functions	Phonemic fluency (FAS) (Caltagirone et al., 1995) Stroop's test (Caffarra et al., 2002) Weigl's sorting test (Spinnler et al., 1987)
Short-term memory	Digit span (Spinnler et al., 1987) Corsi's test (Spinnler et al., 1987)
Long-term memory	Rey word list recall (Caltagirone et al., 1995) Prose memory (Spinnler et al., 1987)
Reasoning ability	Progressive matrixes A Ab B (Basso et al., 1987)
Visuo-constructional ability	Copy of figures (Spinnler et al., 1987)
Language	Naming (Capasso et al., 2001) Token test (Spinnler et al., 1987) Animal naming (Capasso et al., 2001)

Table II - Demographic data of patients with mild cognitive impairment and normal controls.

	Controls (n=10)	aMCI (n=10)	MCI-PD (n=10)	
Gender (male:female)	5:5	5:5	5:5	
Age, mean \pm SD	69.60 \pm 3.77	68.60 \pm 2.91	64.30 \pm 11.32	$p=0.225$ n.s. ^a
Education, mean \pm SD	11.90 \pm 4.04	11.60 \pm 4.62	10.30 \pm 4.34	$p=0.685$ n.s. ^a

Abbreviations: aMCI=patients with the amnesic-type mild cognitive impairment prodrome of Alzheimer's disease; MCI-PD=patients with mild cognitive impairment in Parkinson's disease; n.s.=not significant; ^ap-value was obtained from ANOVA results

errors ($F=8.8$; $p<0.001$), living stimuli ($F=7.990$; $p<0.002$) and non-living stimuli ($F= 6.324$; $p<0.006$). The post-hoc analysis of total errors showed significant differences between the MCI-PD group and the control group ($p<0.001$) (Table III).

The same was found for the living stimuli, with the MCI-PD group performing worse than the control group ($p<0.001$) (Table III). The MCI-PD group performed significantly worse in the non-living category than the aMCI patients ($p<0.006$) and control group ($p<0.01$) (Table III).

Discussion

Several key findings emerged from this study. The results replicate those of earlier studies documenting semantic deficits in the early stage of both these neurodegenerative diseases (Portin et al., 2000; Taler and Phillips, 2008; Pereira et al., 2009; Bastiaanse and Leenders, 2009). The new findings emerging from the present study concern differences in the nature of semantic processing and in the category effect between the two pathological groups.

In the aMCI patients, our results confirmed a mild semantic system impairment as shown by the occurrence of relatively few errors mostly concentrated in one of the tasks. These patients showed a specific difficulty in naming visual stimuli: in this task they needed to visually process the picture, access the semantic system, search for a central representation, and retrieve the verbal label. They did not encounter difficulties when they were presented with semantic probes. In this case the subjects needed to syntactically process the question, search for a central representation within their semantic memory, compare information contained in the question with that contained in the semantic memory, and decide whether the possible answers were true or false. Instead, the impaired performances in naming could have been due to a difficulty in accessing the semantic system through visual object recognition or to a problem with the activation of the lexical label of the said object. In either case, it is likely that the strength of activation

would probably be low and increase when cueing is supplied, as in the semantic question task.

This cognitive impairment can be explained anatomopathologically by a degenerative process in the medial temporal lobe (Whitwell et al., 2007). In fact, recent neuroimaging studies have demonstrated that brain atrophy involves the medial temporal lobe three years before AD is diagnosed. This region is responsible for the processes of picture naming and may account for the impaired naming performance in our group (Ruff et al., 2008; Moore and Price, 1999; Kivisaari et al., 2012).

A recent meta-analysis (Laws et al., 2007) revealed no significant difference in large weighted effect sizes for naming pictures of living and non-living items in AD. By contrast, we found a non-living effect on naming performance in aMCI. This could be explained in different ways: it is possible that representation of living items is less vulnerable in the early stage of AD, because living items possess a larger number of inter-correlated attributes (Gonnerman et al., 1997); it is also possible that the non-living effect within the aMCI patient group was due to the inclusion of musical instruments in the non-living category. This category, like the unique entities faces and buildings (landmarks), is processed by a more anterior temporal region (Damasio et al., 2004; Tranel, 2006). aMCI patients have more difficulty in naming unique entities (Ahmed et al., 2008) and therefore they may have an impairment in naming musical instruments too.

In the MCI-PD group, we found normal naming abilities, but a clear semantic impairment in the semantic feature question task. We hypothesize that this pattern of impairment is not due to a semantic storage disorder, because the patients showed normal naming ability and their performances worsened under cueing conditions, such as guiding questions. It can be explained, rather, by a dysfunction in the executive aspects of semantic processing, in other words in the ability to adapt behavior to current demands by promoting task-relevant information in the event of interference or competition (Dreher and Berman, 2002). Clinical, neuropsychological and neuroimaging investigations suggest that different regions of the PFC

Table III - Comparison of performances on naming and semantic feature question tasks (number of errors).

	Controls		aMCI		MCI-PD		p ^a	Group differences ^b
	Mean	SD	Mean	SD	Mean	SD		
Naming								
Total items	0.80	1.13	4.60	3.37	3.90	4.14	0.028	C<aMCI
Living items	0.50	0.84	2.70	2.11	2.00	2.62	n.s.	
Non-living items	0.30	0.48	2.20	1.75	1.90	1.79	0.016	C<aMCI
Semantic feature questions								
Total items	0.90	1.37	3.90	3.31	8.00	5.51	0.001	C<MCI-PD
Living items	0.70	1.25	3.30	2.94	6.20	4.26	0.002	C<MCI-PD
Non-living items	0.20	0.42	0.60	1.07	1.80	1.39	0.01	C<MCI-PD
							0.006	aMCI<MCI-PD

Abbreviations: aMCI=patients with the amnesic-type mild cognitive impairment prodrome of Alzheimer's disease; MCI-PD=patients with mild cognitive impairment in Parkinson's disease; ^ap-value was obtained from ANOVA results; ^bThe differences between groups were obtained from post hoc analysis

mediate between distinct aspects of this control (Sharp et al., 2004). It is hypothesized that the ventrolateral PFC (VLPFC) is specialized in the retrieval of semantic information from semantic storage and in its maintenance within the working memory (Badre et al., 2005; Sabb et al., 2007). The dorsolateral PFC (DLPFC) controls subsequent monitoring and manipulation of maintained information through interaction with the VLPFC (Badre et al., 2005).

In MCI-PD, the functions of the DLPFC are more susceptible to impairment than the functions of the VLPFC, which remain relatively intact (Owen, 2004). This may lead to early impairment in some higher executive functions such as manipulation, strategy and planning (Owen, 2004). Ventral frontal dysfunction may develop with disease progression, leading to impairment in basic memory functions such as maintenance and recall. Since naming is a retrieval task mediated by the VLPFC, our patients showed normal performances as they were in the early stage of the disease.

The semantic probe task requires not only retrieval but also information monitoring and manipulation. These functions are mediated by both the VLPFC and the DLPFC. Our patients' poorer performance in this task could be explained by DLPFC damage. In addition, since the two systems share the same neural resources, we hypothesize a VLPFC dysfunction due to an overriding channeling of neural system resources to the DLPFC (Sabb et al., 2007).

In conclusion, our groups of mildly cognitively impaired patients suggest different patterns of semantic dysfunction in the early stages of two common neurodegenerative diseases. aMCI patients have a pure lexical semantic deficit characterized by difficulty in finding the proper label, whereas MCI-PD patients have impaired performance as a consequence of disruption of the semantic control processes.

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