JNNP Online First, published on December 22, 2014 as 10.1136/jnnp-2014-309477

RESEARCH PAPER

The neural correlates of road sign knowledge and route learning in semantic dementia and Alzheimer's disease

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▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jnnp-2014-309477).

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Received 14 September 2014
Revised 13 November 2014
Accepted 19 November 2014

ABSTRACT

Background Although there is a growing body of research on driving and Alzheimer's disease (AD), focal dementias have been understudied. Moreover, driving has never been explored in semantic dementia (SD).

Methods An experimental battery exploring road sign knowledge and route learning was applied to patients with SD and AD selected in the early-moderate stage of disease and to a group of healthy participants. Neuropsychological data were correlated to cerebral hypometabolism distribution, investigated by means of positron emission tomography.

Results The two dementias showed opposite profiles. Patients with SD showed poor road sign knowledge and normal performance in route learning. By contrast, patients with AD showed low performance in route learning test with preservation of semantic knowledge of road signs. In SD, there was a correlation of semantic knowledge impairment with hypometabolism in the left temporolateral cortex. No correlation between the AD region of interests (ROIs) and the relevant behavioural indices was found, while in the whole-brain analysis there was a significant correlation between route learning and the superior frontal gyrus.

Discussion and conclusions For the first time, driving skills were explored in SD, and it is showed a differential profile from the one detected in AD. We demonstrate that the left anterior temporal cortex is implicated in road sign knowledge, while a distributed cortical network, including the frontal cortex, is likely to process route learning.

INTRODUCTION

Dementia is a well recognised risk factor for unsafe driving.[1 2] A relevant issue to be clarified is whether all forms of dementia invariably lead to impairment of driving abilities. Up to now, there have been no clear data allowing us to characterise the driving profile in the different forms of dementia.[3] Driving performance is analysed on participants affected by unspecified forms of dementia[4 5] or those suffering from Alzheimer's disease (AD).[3 6–11] Nonetheless, since the various forms of dementia show different cognitive profiles, it is unlikely that the pattern of driving impairment detectable in patients with AD is applicable to other forms of dementia.[3] Limited evidence comes from the focal syndromes of the frontotemporal lobe degeneration,[12] which, although less frequent than AD, are the second most common cause of early onset dementias.[13] A single study on case-series was found in the behavioural variant of frontotemporal dementia (FTD).[14] Fifteen patients with a diagnosis of FTD were administered a driving simulation task, and it was found that, compared to controls, patients with FTD received more speeding tickets, ran more stop signs and were involved in more off-road crashes and collisions than controls. Driving performance was correlated with agitated behaviour.

To the best of our knowledge, there are no studies exploring driving in semantic dementia (SD). Nevertheless, from a theoretical point of view, this syndrome, consequent to the circumscribed degeneration of the anterior temporal lobes and characterised by a selective impairment of semantic memory,[15–18] could be of extreme interest in evaluating how semantic knowledge can influence driving.

Episodic memory and spatial orientation are reported to be well preserved in SD.[15–17] By contrast, they are assumed to be the earliest cognitive functions to be impaired in the canonical presentation of AD, with problems in way-finding in unfamiliar environments.[19–21] The underpinning cognitive basis for the early difficulty of patients with AD in way-finding is likely to be multifaceted. Way-finding is a highly complex task that relies on several cognitive functions such as anterograde memory, planning and problem solving, topographical orientation and attention.

The first end point of this study was to explore road sign knowledge and route learning in SD and AD. Stating the current evidence and distinctive cognitive profiles that the two dementias show, a different pattern of impairment in the two diseases is hypothesised. Road signs provide most of the semantic knowledge linked to driving in terms of driving situations (eg, falling rocks) or obeying a conventional rule (eg, stop sign). Since they are part of general conceptual knowledge, they are expected to be altered in SD.

By contrast, since patients with early AD show memory and executive impairment, they are expected to show poor performance in route learning. Although semantic problems are described in AD, they are not usually part of the classical cognitive picture. Therefore, patients with AD are not expected to have problems with route sign recognition. On the other hand, since patients with early SD do not show memory, executive or topographical orientation problems, they are expected to show normal performance in route learning.

To cite: Luzzi S, Cafazzo V, Damora A, *et al*. *J Neurol Neurosurg Psychiatry* Published Online First: [*please include* Day Month Year] doi:10.1136/jnnp-2014-309477

Another relevant issue to be clarified regards the neural correlates of driving in terms of brain circuitries engaged during specific driving tasks.

Most studies have been performed on healthy participants. There is evidence from functional MRI and positron emission tomography (PET) studies[22–24] that orbitofrontal and anterior cingulate cortex activation are present during driving and correlate with speed, while activation of the visual association/cerebellar cortex is present during both driving and watching a driving situation. Other studies[25 26] found that an activity specifically associated with driving was only the sensorimotor cortex and the cerebellum.

Limited neuroimaging evidence is available on degenerative dementias. A few SPECT studies are available and show that changes in temporoparietal and frontal regions can differentiate patients who drive alone safely from the ones that show driving problems.[27] In a study of near-infrared spectroscopy performed on healthy participants and patients with AD during a collision avoidance task on the simulator, AD drivers showed a less prominent increase in oxyhaemoglobin levels in the right lateral prefrontal cortex compared with controls.[28]

The second aim of this study was to explore the neural correlates of road sign knowledge and route learning by assessing whether the neural loss detected in specific brain areas is associated with the impairment of specific driving tasks. Since the anterior temporal cortex is a strategic area involved in storing general semantic knowledge, a correlation between performance in road sign knowledge and the anterior temporolateral cortex is expected. It is more difficult to make predictions about route learning. This task entails several cognitive functions such as long-term memory, topographical knowledge, space orientation, decision-making and executive control. This implies that many brain circuitries are presumed to be involved. It is expected that impaired performance in route learning should correlate with hypometabolism in the frontal and temporoparietal cortex.

METHODS

Subjects

The following inclusion criteria were applied:

- All participants were required to have a valid driver's license and current automobile and health insurance and to go for a drive at least once a week. Participants were enrolled if they showed a non-increased risk of unsafe driving measured by means of the *Family or caregiver questionnaire*.[1] This allowed us to select patients at an early stage of potential driving impairment. In this regard, it should be underlined that *The family or caregiver questionnaire* is a screening questionnaire which is aimed at detecting increased risk of crashes or unsafe driving behaviour. This means that the presence of sporadic errors during driving are not necessarily judged relevant to alter the score of this screening questionnaire. A detailed exploration of the driving performance of the participants revealed the presence of subtle errors in three patients with SD and four patients with AD (details are provided in online supplementary appendix 1);
- Patients with AD and SD were selected in the mild–moderate stage of disease based on their general cognitive status (Mini-Mental State Examination, MMSE score >18/30). Patients with SD were also selected in the mild–moderate stage of language impairment;[29]
- Absence of ophthalmological, physical or neurological disorders that might impair driving abilities;
- PET imaging performed within a 6-month interval (max 3 months before and 3 months after) of the administration of the experimental battery.

Twenty-two patients with SD and 73 patients with AD were screened to meet the inclusion criteria. Finally, there were 10 patients with SD and AD who were included in the study.

Diagnosis of SD or AD was performed according to international criteria[17 30 31] and was based on clinical history, neurological and neuropsychological assessment, and neuroimaging (TC or RM scan). A group of 16 healthy controls were recruited from those who had undergone PET imaging for causes different from dementia.

Patients with AD (7 males/3 females) and normal controls (9 males/5 females) were selected whose age range and education level were similar to the that of the SD group (8 males/2 females). The SD mean age was 69.3 (±6.7), the AD mean age was 67.9 (±7.6), and the controls mean age was 63.6 (5.2). The SD mean education was 9 (±4.6), the AD mean age was 10.8 (±5.3), and the controls mean age was 10.9 (±4.4).

The Kruskal-Wallis test and χ^2 test showed no significant differences in the demographic variables between the groups.

Patients and healthy controls gave their written consent to take part in the study which was conducted according to the declaration of Helsinki and approved by the local scientific board.

A detailed neuropsychological evaluation (table 1) was performed to explore the main cognitive domains.

As expected, the two diseases showed different neuropsychological profiles. Patients with SD showed poor language and impaired semantic association, whereas patients with AD showed long-term memory impairment and a dysexecutive syndrome.

Experimental driving battery

Two tests exploring road sign knowledge were applied. A third test explored route finding. Twenty-eight road signs (listed in online supplementary appendix 2) were selected from three categories of road signs: *regulatory signs* (eg, yield sign), *warning signs* (eg, falling rocks) and *guide and informational signs* (eg, refuelling).

A. *Road sign naming:* 28 road signs were shown one by one to the participant who was asked to name each sign. Answers were classified as right or wrong.
B. *Road sign comprehension:* a name-to-picture matching test was used. The participant had to match the name of a sign to the picture of the sign which was presented together with a 'same category distractor' (eg, if the target was a 'warning sign', the distractor was another 'warning sign'), a 'different category distractor' (eg, if the target was a 'warning sign', the distractor was a 'regulatory sign' or a 'guide and information sign') and a 'visual distractor', that is, an unreal sign that was visually similar to the target. Targets and distractors were randomly distributed across the four positions in the page. Answers were classified as correct or incorrect.
C. *Route learning test:* each participant was shown a videotape showing a route. The videotape was recorded from the driver's cabin. The route that the car followed was approximately 8 km and included 10 intersections or choice points. At each intersection, it was possible to turn right or left. At each intersection, a different landmark was present (eg, a yellow house, a church, etc). Verbal information (ie, signals showing the name of a town, etc) was not present along the road. Before viewing the videotape, the participants were instructed that they would see a film of a trip by car and that they should pay attention to the route that was followed. In particular, they were instructed to pay attention to all intersections and to try to keep in mind which direction

Table 1 Neurocognitive profile in the two dementia groups studied

Test (maximum score)	SD	AD	Mann-Whitney U (p value)
General abilities			
MMSE (30)	23.4 (6.4)	22.5 (3.1)	27.5 (n.s.)
Perceptuo-spatial skills			
VOSP			
Shape detection test (20)	19.8 (0.3)	20 (0)	24.5 (n.s.)
Incomplete letters (20)	16.6 (2.4)	16.5 (2.8)	18 (n.s.)
Silhouettes (30)	4.7 (4.6)	14.2 (4.6)	24.5 (0.006)
Object decision (20)	12.1 (3.6)	13.1 (4.1)	25.5 (n.s.)
Dot counting (10)	9.6 (0.7)	9.7 (0.4)	31 (n.s.)
Number location (10)	9.1 (0.7)	8.6 (2.2)	21 (n.s.)
Position discrimination (20)	18.6 (3.5)	17.6 (3.9)	19.5 (n.s.)
Cube analysis (10)	9.2 (1.7)	8.6 (1.8)	24 (n.s.)
Ideomotor praxis			
Left upper limb (20)	20 (0)	19.8 (0.6)	45 (n.s)
Right upper limb (20)	20 (0)	19.7 (0.7)	45 (n.s.)
Constructional praxis			
Rey figure B Copy (31)	28.2 (3.8)	27.4 (4.2)	43 (n.s.)
Memory			
Bisyllabic word span	5.2 (0.9)	4.7 (0.9)	35 (n.s.)
Corsi blocks	5.3 (1.2)	3.5 (0.8)	4 (0.01)
Rey figure B: delayed recall (31)	13.4 (8.9)	6.6 (6)	24.5 (0.04)
Executive functions			
Letter fluency (F,A,S)	17.4 (10.5)	24.5 (14)	28.5 (n.s.)
Luria's motor sequences (50)	47.1 (4)	38.3 (10)	16.5 (0.055)
Stroop test (errors)	5.8 (4.8)	16 (12.3)	15.5. (0.04)
Language			
Verbal fluency (3 categories, 1 min each)	19.9 (9.4)	30.4 (7.7)	21.5 (0.03)
'Easy' picture naming (40)	16 (12.7)	35.1 (2.3)	1 (0.002)
'Easy' picture reading (40)	37.7 (0.5)	40 (0)	20 (n.s.)
'Easy' word-picture matching (40)	32.4 (7.7)	40 (0)	4 (0.002)
PPTT (verbal version)	17.3 (7)	28 (1.4)	4 (<0.0001)
PPTT (non-verbal version)	15.9 (5.9)	28.3 (1.2)	0 (<0.0001)

AD, Alzheimer's disease; SD, semantic dementia.

was followed by the car. The test phase was initiated 2 min after the final viewing of the videotape. The tape was started and allowed to run until reaching the first intersection in the route. At that point the tape was stopped and the participant was asked to indicate the direction the car had followed in the videotape they were shown before. If a participant reported being uncertain about making a decision at a particular intersection, he was asked to make a guess. Answers were classified as correct or incorrect.

PET imaging acquisition

PET imaging was performed in a silent room, with the participant's head fixed to a head holder with a plastic spacer to minimise the participant's head movement. The participants received a mean dose of [^{18}F] 2-deoxy-2-fluoro-D-glucose (FDG) of 185±10 MBq (5±0.27 mCi).

The PET emission scan started approximately 30 min after the FDG injection using a GE Discovery PET/CT 690 VCT scanner, with spatial resolutions of 4.8, 4.8 and 5.0 mm at full-with-half-maximum (FWHM) in radial, tangential and axial directions, respectively. A three-dimensional emission scan was performed for 15 min, and a postinjection transmission scan was performed using CT for tissue attenuation correction (Helical Full 0.6 s, 3.75 mm, 47 slices). PET imaging data were corrected for tissue attenuation. PET imaging data were reconstructed into 256×256 matrices based on an Iterative Reconstruction Algorithm: VPFX-S (VUE Point FX, 3.2 mm, 32/8).

Statistical analysis

Behavioural data analysis

Neuropsychological data were examined by means of non-parametric tests because of the small group numbers and non-normal data distribution. The Kruskal-Wallis and Mann-Whitney tests were used to explore differences between the groups and Spearman's test was used to examine correlations. The Bonferroni correction was applied to the correlation analysis ($p<0.0045$).

PET data analysis

Imaging analysis was performed using SPM8. Preprocessing included rigid-body transformation (realignment) to correct for head movement. The images were then normalised to the MNI space using non-linear warping implemented in SPM8 and finally smoothed with a Gaussian filter of 12 mm FWHM to increase the signal-to-noise ratio and to facilitate group analyses. Finally, individual global counts were normalised by proportional scaling to a mean value of 50 mg/100 mL/min. Linear contrasts were used to test for regionally specific differences

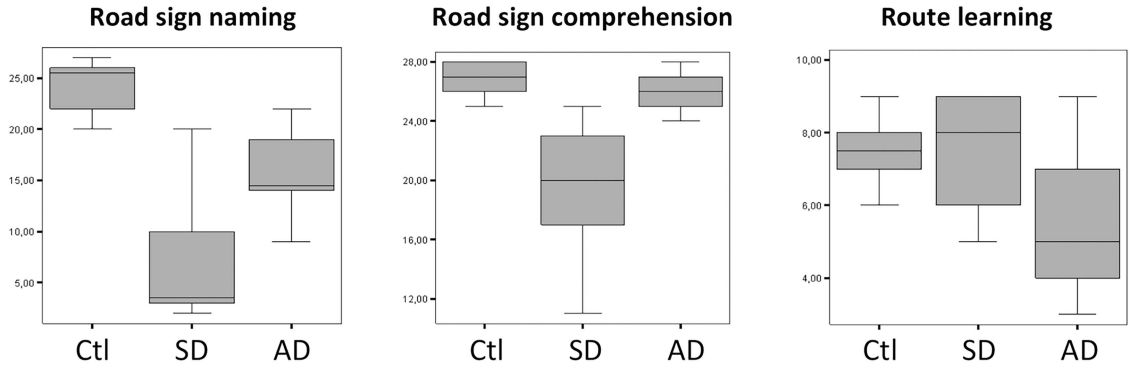

Figure 1 Performance on the three experimental tests in the three groups studied (ctl, controls; SD, semantic dementia; AD, Alzheimer's disease).

between groups, producing t-statistic maps in the MNI standard space. We considered significant effects having $p<0.05$ Familywise error (FWE) corrected for multiple comparisons at the cluster level. Clusters were identified by using a voxel level threshold $p<0.001$ not corrected for multiple comparisons.

For Region of Interest (ROI) analyses, we considered as relevant all clusters identified in the comparisons between pathological groups (SD and AD) and the healthy control group. The mean signal in relevant ROIs was extracted by using the SPM toolbox MarsBar.

Table 2 Correlations between the driving experimental battery and neuropsychological tests

Test	Road sign naming (r; p)	Road sign comprehension (r; p)	Route learning (r; p)
MMSE	−0.057	−0.042	0.378
	0.811	0.859	0.100
VOSP: silhouettes	0.723*†	0.845*†	−0.419
	0.002	0.0001	0.120
VOSP: number location	−0.229	−0.009	−0.015
	0.451	0.977	0.962
Rey figure B long-term recall	−0.387	−0.236	0.525‡
	0.092	0.317	0.017
Luria's motor sequences	−0.445	−0.187	0.605‡
	0.073	0.472	0.010
Stroop (errors)	0.334	0.215	−0.578‡
	0.190	0.407	0.015
Semantic fluency	0.645*†	0.686*†	−0.213
	0.002	0.001	0.367
Naming	0.671*	0.860*†	−0.265
	0.006	0.0001	0.341
Single word comprehension	0.619‡	0.793*†	−0.473
	0.014	0.0001	0.075
Verbal version of PPTT	0.544‡	0.608*†	−0.527
	0.013	0.004	0.117
Non-verbal version of PPTT	0.550‡	0.612*†	−0.490
	0.012	0.004	0.128

*Correlation is significant at the 0.01 level.
†Correlation is significant according to the Bonferroni correction $p<0.0045$.
‡Correlation is significant at the 0.05 level.
MMSE, Mini-Mental State Examination; VOSP, Visual Object and Space Perception Battery.

RESULTS

Behavioural results

Results are shown in figure 1. The Kruskal-Wallis test revealed a main effect group in the three tests administered:

- *Road sign naming*: Patients with SD obtained very low scores which were significantly worse than those obtained by healthy controls ($U=0.5$; $p<0.0001$) and patients with AD ($U=12.5$; $p=0.004$). Patients with AD obtained significantly lower scores than controls ($U=3$; $p<0.0001$);
- *Road sign comprehension*: Patients with SD obtained significantly lower scores than healthy controls ($U=3$; $p<0.0001$) and patients with AD ($U=11.3$; $p=0.003$). Patients with AD did not show more significant differences than controls ($U=39$; n.s.);
- *Route learning test*: Patients with SD showed a performance similar to that of healthy controls ($U=6.9$; not significant (n.s)) while patients with AD showed a lower performance than that of controls ($U=26.5$; $p=0.01$) and patients with SD ($U=19.5$; $p=0.001$).

Correlation analysis of experimental driving battery with background neuropsychology is shown in detail in table 2.

According to the Bonferroni correction, *Road sign naming* correlated positively with silhouettes from the VOSP and semantic fluency; *Road sign comprehension* showed a positive correlation with silhouettes from the VOSP, namely semantic fluency, single word comprehension and semantic association tasks (PPTT); *route learning* did not correlate with any test from a neuropsychological background.

Neuroimaging results

We first evaluated where in the brain SD and AD groups showed a decrease in FDG uptake compared to a healthy control group of similar age. Patients with SD showed a bilateral decrease in FDG uptake in the temporal pole, the middle temporal gyrus, the anterior part of the parahippocampal gyrus next to the uncus, the fusiform gyrus, the orbitofrontal cortex and in the caudate nucleus (figure 2). As expected, the brain areas involved in patients with AD were different from those observed in patients with SD. Patients with AD showed a widespread bilateral signal drop mainly affecting the lateral frontal, lateral temporal, lateral parietal cortex, posterior cingulate and the precuneus (figure 3).

We then evaluated whether the level of the regional FDG uptake in patients with SD and AD correlated with their

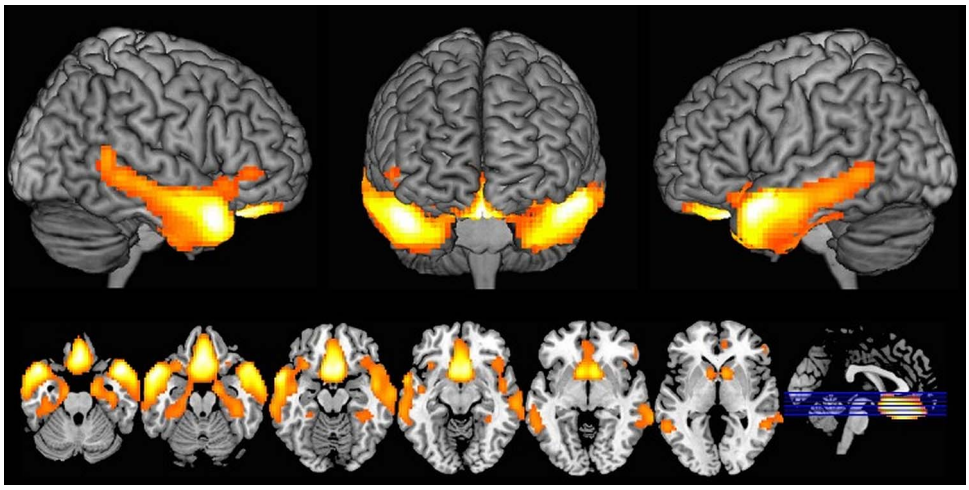

Figure 2 Brain areas with [^{18}F] 2-deoxy-2-fluoro-D-glucose uptake in the semantic dementia group.

behavioural performance in three tests: the *road sign naming test*, *road sign comprehension test* and the *route learning test*. A *direct* correlation in this context would mean that the more severe the damage to the cortex is, the more severe the functional deficit on the behavioural tests will be. The presence of anatomofunctional correlations was first evaluated in a whole-brain analysis, and later it was evaluated by using a more anatomically focused ROI approach. The ROIs considered were those that showed a decrease in FDG uptake in each pathological group. We did not find any correlation in the whole-brain analysis between FDG uptake and the behavioural indexes considered in the SD group. By contrast, the ROI analyses (figure 4) showed a strong and significant correlation between the average FDG uptake in the left temporal ROI and the *road sign naming test* (r=0.71, p=0.011) and *road sign comprehension test* (r=0.73, p=0.009), but not with the *route learning test* (r=0.1, p=0.39). Furthermore, we found a significant correlation between average FDG uptake in the orbitofrontal ROI and the *road sign comprehension test* (r=0.7, p=0.012), but not with the other behavioural indices (figure 4). No correlation was found for the right temporal ROI with any behavioural index. Finally, we checked how independent the severity of the damage to one ROI compared to the others was. The left lateral temporal and orbitofrontal ROIs shared 60% of the variance (r=78, p=0.004). The left lateral and right lateral temporal ROIs shared a lower proportion of the variance, that is, 42%, but was still significantly higher than 0 (r=0.65, p=0.02). Finally, the right lateral temporal and orbitofrontal ROI only shared 8% of the variance, a level which was not significantly different from 0 (r=0.29, p=0.2).

In the whole-brain analysis for the AD group, we found a correlation between the *road sign naming test* and FDG uptake in a cluster centred on the posterior part of the parahippocampal gyrus close to the lingual gyrus (p=0.04, FWE-corrected at the cluster level). We also found a correlation between the performance on the *route learning test* and the superior frontal gyrus/anterior cingulate (p=0.016, FWE-corrected at the cluster level). No correlation was found with the *road sign comprehension test*. Finally, no correlation significantly different from 0 was found between the AD ROIs and the relevant behavioural indices.

DISCUSSION

The present findings add new insight into the cognitive and neural substrate of driving in SD and AD.

Road sign knowledge and route learning in SD and AD: opposite profiles

To the best of our knowledge, road sign knowledge has never been explored in SD. In AD, a single study explored road sign

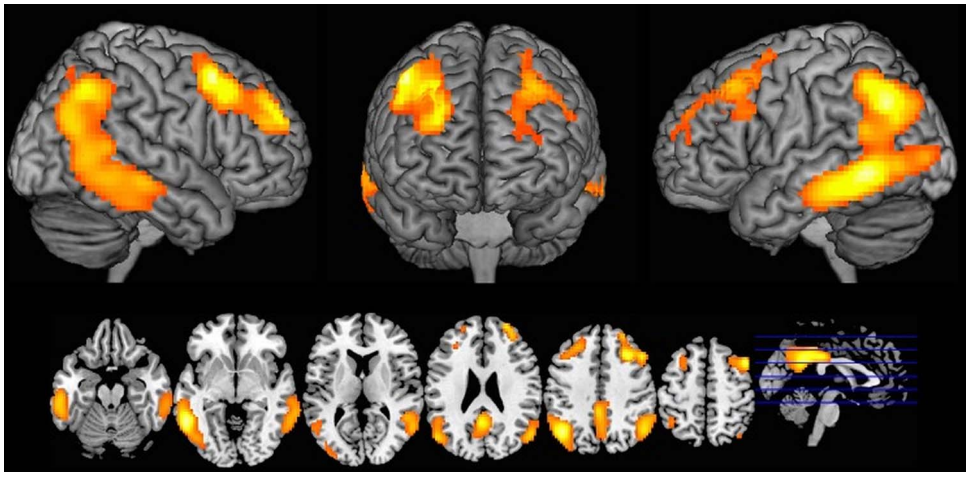

Figure 3 Brain areas with [^{18}F] 2-deoxy-2-fluoro-D-glucose uptake in the Alzheimer's disease group.

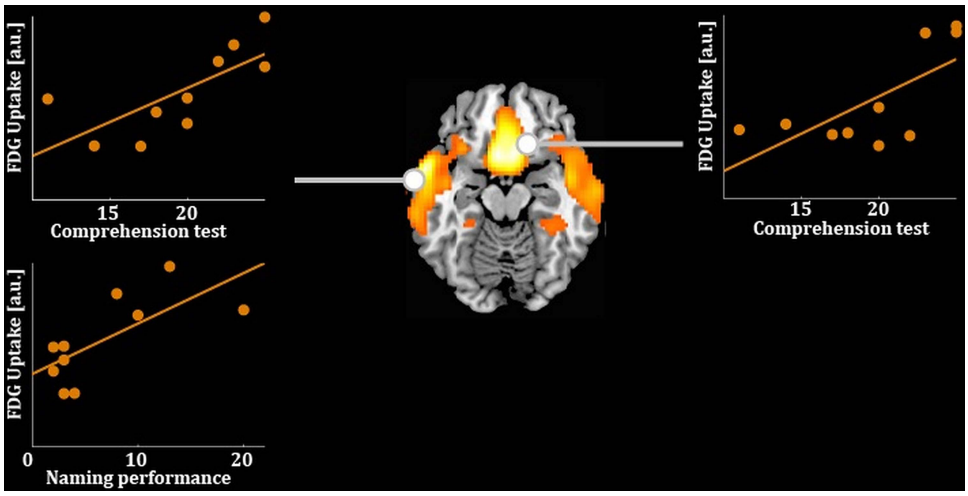

Figure 4 Correlation between neuropsychological tests and [^{18}F] 2-deoxy-2-fluoro-D-glucose uptake in the whole-brain analysis for the Alzheimer's disease group.

naming by means of a screening test (10 road signs were presented) which showed that patients with AD had a lower performance than normal participants.[32]

In this study, patients with SD and AD showed problems in road sign naming when compared to normal participants. The magnitude of naming impairment was significantly greater in patients with SD than in patients with AD. In contrast, road sign comprehension was normal in patients with AD, while in patients with SD it was very poor.

The present finding supports the view that in SD, performance reflects a primary semantic breakdown with impaired road sign recognition, while patients with AD seem to show prominent lexical impairment. They show difficulty in naming the road signs and preserved sign comprehension. In route learning, there were differences in the two dementia groups as well. Patients with SD performed this test flawlessly, while patients with AD were impaired.

There are no data in the literature exploring route learning in SD. The present data show that in the early-moderate stages of disease, the possibility that these patients can be disoriented in familiar and unfamiliar routes seems unlikely. On the contrary, the present data support the notion that way-finding constitutes an early problem in AD.

In this regard, we would like to point out that the experimental battery was able to catch the early signs of driving impairment in the patients examined. Although the patients enrolled were judged as safe drivers by means of the well-known *Family or caregiver questionnaire*,[1] an accurate driving history revealed minor errors in the day-to-day driving of some patients. According to the findings in the experimental battery, semantic errors, that is, errors in road sign comprehension, were reported in three patients with SD, while four patients with AD showed way-finding problems in unfamiliar routes. It could be interesting to apply the present experimental battery to larger samples of patients to verify whether it can detect the earliest impairment of specific driving skills.

Growing efforts have been made over the past decades to understand the impact of dementia on driving. It is well established by accumulating evidence[1 2 33 34] that after the onset of AD, patients show a significantly increased annual risk for automobile accidents in comparison with other drivers. During the first 3 years after the onset of AD, the risk of crashes for patients with AD is within the accepted range of other drivers.[1]

From this study, it emerges that the well characterised driving impairment profile identified in AD is not applicable to other forms of dementia and, consequently, the general rules (eg, the 'three-year rule') applied to patients with AD could not be valid for all forms of dementia.

This finding should encourage future research to study in detail driving abilities in the non-AD types of dementia to acquire dementia-driven information about a patient's driving profile which may have important implications in a clinical setting and driving management.

A final remark is about the role of road signs in driving behaviour. Poor road sign knowledge should lead the driver to commit driving errors. Stating the present findings in patients with SD, this seems not to be the case, and it would imply that road signs have a marginal role in actual driving. Nevertheless, it should be underlined that even the patients' relatives reported the patients to have an almost preserved ability to drive in terms of car accident or prescriptions they reported a few errors made by some patients with SD that were potentially interpretable as an indicator of poor road sign knowledge. In the literature, scant evidence is found regarding the issue of the real usefulness of road signs in active driving. Evidence states that the importance of road signs in driving is questionable.[35] In day-to-day life, the driver usually runs along familiar routes, and one may argue that the driver relies more on autobiographical memory or on the general road context in order to modify his/her driving behaviour accordingly, rather than on the road signs. Further evidence coming from driving simulators in which various road signs are presented could help to clarify the nature of the impairment in road sign knowledge documented in this study.

Neural correlates of road sign knowledge and route learning

This study shows that different brain areas correlate to driving abilities in the two types of dementia examined.

In SD, a positive strong correlation between left temporal hypometabolism and road sign naming and comprehension was showed. A positive correlation was also found between orbifrontal areas and road sign comprehension.

For the first time, the neural correlate of driving was explored in SD. Our findings show that a conceptual knowledge of road sign, similar to many other categories of knowledge, relies on the lateral temporal cortex. It is interesting to note that the left temporal lateral cortex plays a prominent role. Since both naming and comprehension of road signs are verbal tasks, it follows that the involvement of the left temporal lateral cortex could reflect the verbal nature of the test. These data support the modality-specific model of organisation of semantic

knowledge (see refs. 36–38 for reviews on this topic) rather than the 'unitary' model of the 'semantic hub'. The right temporal cortex does not have a critical role, even though the data about variance analysis do not allow us to completely rule out a role for this area in the naming and comprehension of road signs. The orbitofrontal cortex is reported to be involved in SD, and the correlation of semantic tasks with this brain area is likely to reflect the spread of the degenerative process.[16]

In AD, the patients' hypometabolism was identified in many cortical areas. Although none of these areas showed any significant correlation with the driving tasks, most likely due to the small sample of patients included, data from an analysis of the whole brain showed two potentially interesting findings. The first is the correlation between the naming of road signs and the posterior part of the parahippocampal gyrus close to the lingual gyrus. The data are in keeping with the previous meta-analysis, which showed that the parahippocampus is implicated in the naming of different categories of knowledge and supports the notion that it is a convergence area implicated in naming processing.[39] The second interesting finding is the correlation between the superior frontal gyrus and the anterior cingulate cortex with route learning, which implies a potential role of the prefrontal cortex in route finding. There is some evidence that the superior frontal gyrus is activated during mental navigation tasks together with the parietal areas and are presumed to reflect the spatial mental imagery components of the tasks.[40]

The route-finding task we applied is aimed at learning a new route, which involves multiple processing systems[41] including the formulation of strategy, problem solving, anticipation and verification that the plan is correct.

Studies on way-finding in AD show[42] that patients with AD fail to reach their destination mainly because of a basic problem-solving deficit. In patients with AD, plans are poorly structured and organised. Learning a new route could most likely be processed by a neural circuit that focuses mainly on the frontal lobe and the anterior cingulate cortex, while way-finding of a familiar route may rely on topographical memory and then on the temporoparietal association cortex. Although these data can be of interest, we would like to stress the fact that the correlations of the superior frontal gyrus with route learning and of the parahippocampal gyrus with the naming task are found in the whole-brain analysis, which makes the finding reported to be less reliable than the correlations with a specific ROI. Evidence from the AD series classified on the basis of the severity of driving impairment is needed to confirm this hypothesis.

Acknowledgements The authors thank the participants and their relatives for their cooperation in this study. CR was supported by the PRIN grant 2010RP5RNM_001 from the Italian Ministry of University.

Contributors SL was involved in the study concept and design, selection of the patients enrolled, analysis and interpretation of data and drafting of the manuscript. VC performed the driving experimental battery. AD created the driving experimental battery. KF performed the background neuropsyhological evaluation. FMF and GA performed PET imaging. MS took part in literature revision. LP performed a critical revision of the manuscript for intellectual content. CR undertook PET imaging analysis and interpretation of imaging data and was also involved the drafting of the manuscript.

Competing interests None.

Ethics approval Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

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J Neurol Neurosurg Psychiatry published online December 22, 2014