Diagnostic relevance of spatial orientation for vascular dementia
A case study

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ABSTRACT. Spatial orientation is emerging as an early and reliable cognitive biomarker of Alzheimer’s disease (AD) pathophysiology. However, no evidence exists as to whether spatial orientation is also affected in vascular dementia (VaD). Objective: To examine allocentric (map-based) and egocentric (viewpoint-based) spatial orientation in an early stage VaD case. Methods: A spatial test battery was administered following clinical and neuropsychological cognitive evaluation. Results: Despite the patient’s complaints, little evidence of episodic memory deficits were detected when cueing was provided to overcome executive dysfunction. Similarly, medial temporal lobe-mediated allocentric orientation was intact. By contrast, medial parietal-mediated egocentric orientation was impaired, despite normal performance on standard visuospatial tasks. Conclusion: To our knowledge, this is the first in-depth investigation of spatial orientation deficits in VaD. Isolated egocentric deficits were observed. This differs from AD orientation deficits which encompass both allocentric and egocentric orientation deficits. A combination of egocentric orientation and executive function tests could serve as a promising cognitive marker for VaD pathophysiology.

Key words: spatial orientation, egocentric, allocentric, vascular dementia, VaD, executive function, neurodegeneration.

DIAGNÓSTICA DE RELEVANCIA DA ORIENTAÇÃO ESPACIAL PARA O DIAGNÓSTICO DE DEMÊNCIA VASCULAR: UM ESTUDO DE CASO

RESUMO. A orientação espacial está emergindo como um biomarcador cognitivo precoce e confiável da fisiopatologia da doença de Alzheimer (DA). No entanto, não existe evidência de que a orientação espacial também seja afetada na demência vascular (DVs). Objetivo: Examinar a orientação espacial alocêntrica (baseada em mapas) e egocêntrica (baseada no ponto de vista) em um caso de DVa em fase inicial. Métodos: Uma bateria de testes espaciais foi administrada após avaliação clínica e neuropsicológica cognitiva. Resultados: Apesar das queixas do paciente, poucas evidências de déficits de memória episódica foram detectadas quando foram fornecidas pistas para superar a disfunção executiva. Da mesma forma, a orientação alocêntrica mediada pelo lobo temporal medial estava intacta. Em contrapartida, a orientação egocêntrica mediada pela região parietal medial estava comprometida, apesar do desempenho normal em tarefas visuoespaciais padrão. Conclusão: Pelo nosso conhecimento, esta é a primeira investigação aprofundada dos déficits de orientação espacial na DVa. Foram observados déficits egocêntricos isolados. Isso difere dos déficits de orientação da DA que abrangem déficits de orientação alocêntricos e egocêntricos. Uma combinação de orientação egocêntrica e testes de função executiva poderia servir como um marcador cognitivo promissor para a fisiopatologia de DVa.
Palavras-chave: orientação espacial, orientação egocêntrica, orientação alocêntrica, demência vascular, função executiva, neurodegeneração.

Deficits in spatial orientation are an emerging early marker for Alzheimer’s disease (AD) pathophysiology.1-5 They have been strongly linked to medial temporal and intra-parietal regional changes in incipient and present AD pathophysiology.6,7 However,
at this stage it is not clear if vascular dementia patients also display any spatial orientation deficits. Such a distinction is important as vascular dementia (VaD) is the second most common form of dementia and the diagnostic differentiation of both dementias is challenging with patients commonly complaining of generic memory complaints.\textsuperscript{8,9} Importantly, VaD patients often show intact medial temporal lobe function, while frontal and parietal regions are compromised due to white matter lesions in the superior frontal fasciculus.\textsuperscript{10,11} Therefore, apparent memory problems in VaD are more likely due to frontal executive and parietal visuospatial deficits than medial temporal memory mediated processes. In the current case study, we explored whether spatial orientation performance could help detect VaD and generate a different profile to AD. We hypothesised that if the case shows spatial orientation deficits, these should be limited to egocentric parietal orientation problems but that allocentric medial temporal processes should remain intact.

**PARTICIPANT**

We report the case of RK, a 65-year-old married man, with six years of secondary education, who worked as a truck driver and window cleaner. A diagnosis of VaD was made in March 2017, he then presented at our dementia research clinic with memory complaints. He reported a short history of behavioural and psychological symptoms including apathy, depression and agitation/aggression. His medical history also revealed hypercholestrol, stage 2 hypertension, a BMI of 30 and life-long cigarette smoking. There was a strong family history of hypercholestrol (both parents and siblings) and heart disease-related death in both parents.

**Procedures**

RK underwent clinical and cognitive assessments, including neuropsychological assessments (Table 1). Both RK and his carer reported memory problems, such as misplacing keys and forgetting appointment. These issues are most likely due to attentional and executive demands, as recent family events were recalled without difficulty. Problems related to executive function, such as misplacing medication and poor finance management, were also reported. Importantly, spatial orientation difficulties were a central concern for both RK and the carer, and included complaints of disorientation on previously familiar routes and when using public transport, which had led to significant safeguarding concerns by the family. Based on these concerns, an additional spatial test battery was administered. The spatial battery consisted of three spatial measures: The Supermarket task, The Statue task and the Clock test. The Supermarket task is an ecologically valid tool adopted to assess the integrity of egocentric and allocentric heading orientation and spatial memory in dementia. Participants are shown short video clips (7 seconds) of a virtual reality supermarket, whereby the person in the video is navigating from the entrance to a finishing location automatically (Figure 1). Once the video clip stops, participants are asked to indicate in real-life the direction of their starting point (egocentric

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**Figure 1.** Screenshots from the Supermarket task, showing i) start viewpoint; ii) movement during an example video clip; iii) end location of an example video clip; iv) ‘onscreen instructions prompting the participant to indicate the direction of their starting point’; v) the supermarket map participants use to indicate their finishing location and their heading direction when the video clip ends.
Table 1. Physical and neuropsychological background.

| Physical and neuropsychological background          | Age | Nationality | Blood pressure | Heart rate | Height | Weight | Body Mass Index | Medication management | General Cognitive Ability Test | Visuospatial functioning | Episodic Memory | Language Ability | Executive Function / Mental Flexibility | Social Cognition Mini-SEA |
|----------------------------------------------------|-----|-------------|----------------|------------|-------|--------|----------------|------------------------|-----------------------------|--------------------------|----------------|----------------|------------------------------------------|--------------------------|
| Age                                                | 69  | British     |                | 55 bpm     | 175 cm| 91 kg  | 30             |                         | Addenbrooke’s Cognitive Examination – III (ACE) |                      |                |              |                                           |                          |
| Nationality                                        |     |             |                |            |       |        |                |                         | 18                          | Visual Object and Space Perception Battery (WOSP) |                  |                |              |                                           |                          |
| Blood pressure                                     |     |             |                |            |       |        |                |                         | 18                          |                          |                |              |                                           |                          |
| Heart rate                                         |     |             |                |            |       |        |                |                         | 04*                      |                          |                |              |                                           |                          |
| Height                                             |     |             |                |            |       |        |                |                         | 26                          |                          |                |              |                                           |                          |
| Weight                                             |     |             |                |            |       |        |                |                         | 16                          |                          |                |              |                                           |                          |
| Body Mass Index                                    |     |             |                |            |       |        |                |                         | 82                          |                          |                |              |                                           |                          |
| Medication management                              |     |             |                |            |       |        |                |                         | Clopidogrel (75 mg)        |                          |                |              |                                           |                          |
| Medication management                              |     |             |                |            |       |        |                |                         | Simvastatin (40 mg)        |                          |                |              |                                           |                          |
| Medication management                              |     |             |                |            |       |        |                |                         | Losartan potassium (100 mg) |                          |                |              |                                           |                          |
| Medication management                              |     |             |                |            |       |        |                |                         | Bendroflumethiazide (2.5 mg) |                          |                |              |                                           |                          |
| General Cognitive Ability Test                     |     |             |                |            |       |        |                |                         | ACE attention              |                          |                |              |                                           |                          |
| General Cognitive Ability Test                     |     |             |                |            |       |        |                |                         | ACE memory                  |                          |                |              |                                           |                          |
| General Cognitive Ability Test                     |     |             |                |            |       |        |                |                         | ACE fluency                 |                          |                |              |                                           |                          |
| General Cognitive Ability Test                     |     |             |                |            |       |        |                |                         | ACE language               |                          |                |              |                                           |                          |
| General Cognitive Ability Test                     |     |             |                |            |       |        |                |                         | ACE visuospatial            |                          |                |              |                                           |                          |
| General Cognitive Ability Test                     |     |             |                |            |       |        |                |                         | ACE total                  |                          |                |              |                                           |                          |
| Visuospatial functioning                           |     |             |                |            |       |        |                |                         | Dot counting                |                          |                |              |                                           |                          |
| Visuospatial functioning                           |     |             |                |            |       |        |                |                         | Position                   |                          |                |              |                                           |                          |
| Visuospatial functioning                           |     |             |                |            |       |        |                |                         | Cube                        |                          |                |              |                                           |                          |
| Visuospatial functioning                           |     |             |                |            |       |        |                |                         | Rey Complex Figure (ROCF)  |                          |                |              |                                           |                          |
| Visuospatial functioning                           |     |             |                |            |       |        |                |                         | Construction               |                          |                |              |                                           |                          |
| Visuospatial functioning                           |     |             |                |            |       |        |                |                         | Reconstruction (3-minute delay) |                          |                |              |                                           |                          |
| Episodic Memory                                    |     |             |                |            |       |        |                |                         | Free immediate recall       |                          |                |              |                                           |                          |
| Episodic Memory                                    |     |             |                |            |       |        |                |                         | Cued immediate recall       |                          |                |              |                                           |                          |
| Episodic Memory                                    |     |             |                |            |       |        |                |                         | Free delayed recall         |                          |                |              |                                           |                          |
| Episodic Memory                                    |     |             |                |            |       |        |                |                         | Cued delayed recall         |                          |                |              |                                           |                          |
| Language Ability                                    |     |             |                |            |       |        |                |                         | Naming                      |                          |                |              |                                           |                          |
| Language Ability                                    |     |             |                |            |       |        |                |                         | Comprehension and repetition|                          |                |              |                                           |                          |
| Language Ability                                    |     |             |                |            |       |        |                |                         | Semantic association        |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | INECO Frontal Screening Test|                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Motor series                |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Interference sensitively   |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Inhibitory control          |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Digit backwards             |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Verbal working memory       |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Spatial working memory      |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Proverbs                    |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Hayling test                |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Working memory index        |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Total                       |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Trail Making Task           |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Part A | Time (sec) | 79 | 117 | 2 | 2 |                          |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Errors | 0 | 2 | 2 |                          |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Social Cognition Mini-SEA  |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Non-Faux-pas                |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Faux-pas (ToM)              |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | All stories                 |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Control                      |                          |                |              |                                           |                          |
| Executive Function / Mental Flexibility            |     |             |                |            |       |        |                |                         | Facial Emotion Recognition  |                          |                |              |                                           |                          |

*Significant differences. Standard mean score and standard deviation representing an aged-matched control group are in parenthesis. Note control scores were only available for the ACE-III and the ROCF test.
orientation). In a second step, participants are given a map of the Supermarket and are asked to indicate where they are on the map (allocentric orientation) and what direction they are facing in the supermarket (heading orientation). More details can be found here.\textsuperscript{1,2}

The Statue Test requires participants to make spatial judgements for a room with 3 statues and a small stool (Figure 2). Participants are asked to indicate i) the statue closest to the wall (permanent landmark); ii) the statue is closest to the stool (transient landmark); iii) identify which statue moved its location after a delay. Each of these sub-tasks includes an easy, medium, and hard condition. The landmark decisions are thought to rely on intra-parietal lobes, whereas the memory condition is typically thought to rely on the medial temporal lobe.

The Clock test requires participants to imagine they are standing in the centre of a large clock facing, e.g., the number 12. Participants are asked to then point in real-life to different numbers on the clock face. For example, “Can you point to the number 9?” (Answer: pointing left). The questions increase in complexity across the test and require medial parietal mediated mental imagery, rotation and egocentric processes, with no episodic memory demand. The study was approved by the UK National Research Ethics Service (NRES: 16/LO/1366).

RESULTS

Analysis

We compared the case to a control sample (\(N = 13\)) with a mean age of 63 (SD = 4.8), who underwent similar testing. RK was contrasted against the controls via a modified paired sample t-test developed by Crawford and colleagues,\textsuperscript{12,13} resulting in a Z-case-control (\(z_c\)) score as an interval estimate of the effect size.

Neuropsychological evaluation (Table 1)

RK achieved a score of 82 on the ACE-III, and cognitive deficits on free recall (immediate and delayed), executive function (spatial working memory, digital backwards, proverb), social cognition and verbal fluency measures were observed. Importantly, on the FCSRT, his deficits were only present in free recall; once semantic cues were provided, RK could recall all verbal material, indicating executive dysfunction as the main contributor to the episodic memory deficits. Similarly, for visual episodic memory, the planning of the ROCF copy was disorganised due to executive deficits, which resulted in low recall score. RK’s performance on the theory of mind (ToM) subset of the mini-SEA further suggests a partial deficit in social cognition. Importantly, basic visuo-perception and spatial discrimination (VOSP) were in the normal range, indicating no basic visual problems. Language skills were also in the normal range.

Spatial orientation performance (Table 2)

On the Supermarket task, RK showed significant egocentric navigational impairments (\(t = -9.529, p < .000, z_c = -9.889\)), i.e. failing to point back to the starting point correctly. Similarly, heading orientation (correct judgement of facing direction after travel period) was also impaired, albeit less severely (\(t = -2.983, p = 0.01, z_c = -3.095\)). By contrast, allocentric information, i.e. indicating the place location in the supermarket test, was not significantly different from the control group (\(t = -1.537, p > 0.05, z_c = -0.206\)).

On the statue task, RK showed no significant differences for performance on the easy and hard versions of all conditions, due to ceiling and floor effect. However, in the medium condition, abnormal scores were detected on both the wall (\(t = -3.085, p = 0.01, z_c = -3.160\)) and stool (\(t = -2.590, p = 0.02, z_c = -2.687\)) condition only, showing deficits on visual judgements for permanent and transient objects. RK’s memory performance was comparable to healthy controls.

Finally, the patient’s clock test scores were significantly lower than those of controls (\(t = -2.965, p = 0.01, z_c = -3.077\)) reflecting poor higher visual (mental rotation) and egocentric processing abilities.

DISCUSSION

To our knowledge, this is the first description of human spatial orientation deficits in a VaD case. As predicted,
Table 2. Total scores, standard deviations (SD), Z-case-control (Zcc) scores and confidence intervals (CI) from a modified paired sample t-test for patient and control group on the spatial test battery.

| Spatial measures | Condition               | Patient score mean (N = 13) | Control sample (SD) | t–value | p value | Effect size (Zcc) | 95% CI        |
|------------------|-------------------------|-----------------------------|---------------------|---------|---------|------------------|---------------|
| Statue test      | Wall Easy               | 4                           | 4                   | 0       | NS      | −0.00            | −0.544 to 0.544|
|                  | Wall Medium             | 1                           | 2.6                 | 0.5     | −3.085  | 0.01*            | −3.160 to −1.789|
|                  | Wall Hard               | 0                           | 0.3                 | 0.6     | −0.000  | NS               | −0.00 to −1.083|
|                  | Stool Easy              | 4                           | 3.7                 | 0.4     | −0.723  | NS               | −0.750 to 0.119|
|                  | Stool Medium            | 0                           | 2.2                 | 0.8     | −2.590  | 0.02*            | −2.687 to −1.484|
|                  | Stool Hard              | 0                           | 0.3                 | 0.6     | −0.482  | NS               | 0.500 to 0.1088|
|                  | Memory Easy             | 4                           | 3.9                 | 0.2     | −0.483  | NS               | 0.500 to 0.1088|
|                  | Memory Medium           | 2                           | 2.5                 | 0.6     | −0.623  | NS               | 0.525 to 1.563 |
|                  | Memory Hard             | 0                           | 0.2                 | 0.7     | −0.321  | NS               | −0.886 to 0.233|
| Supermarket test | Ego-centric navigation  | 4                           | 12.9                | 0.9     | −9.529  | <0.001**         | −13.825 to −5.949|
|                  | Allocentric memory      | 1.5                         | 8.1                 | 3.2     | −0.201  | NS               | −0.206 to −3.028|
|                  | Heading Direction       | 6                           | 12.5                | 2.1     | −2.983  | 0.01*            | −3.095 to −1.746|
| The Clock test   | Cardinal (Verbal Response) | 1                          | 3.9                 | 0.9     | −3.105  | <0.01*           | −3.222 to −1.829|
|                  | Right angle (pointing response) | 1                          | 3.6                 | 0.6     | −4.176  | <0.001**         | −6.120 to −2.532|
|                  | Lateral, behind, (mixed response) | 1                          | 3.9                 | 1.7     | −1.644  | NS               | −1.706 to −2.558|
|                  | Total Score             | 3                           | 11                  | 2.6     | −2.965  | 0.01*            | −3.077 to −1.736|

Significant differences are marked bold. P value representing a two-tailed probability that case score differs from controls.
More generally, spatial testing has 17-21 These deficits are accompanied 14,15 25,26

diagnostic differentiation of AD from VaD. This suggestion in vascular cognitive impairment: a state-of-the-art review. BMC Medicine 2016;14(1):174.

Coughlan et al. 11. Schuff N, Matsumoto S, Knieck J, Studholm C, Du AT, Ezekiel F, et al. Cerebral Blood Flow in Ischemic Vascular Dementia and Alzheimer’s Disease By Arterial Spin Labeling MRI. Alzheimer’s Dementia. 2004;1(3):462-72.

Ahnergard et al. 17. Schneider JA, Brown SM, Wallace RB, Storandt M. Cerebral Blood Flow in Ischemic Vascular Dementia and Alzheimer’s Disease. Brain Cogn [Internet]. 1996;31(2):269-82.

Kertesz A, Clydesdale S. Neuropsychological deficits in vascular dementia vs. Alzheimer’s disease. Arch Neurol. 1994;51(12):1226-31.

Kertesz A, Clydesdale S. Neuropsychological deficits in vascular dementia vs. Alzheimer’s disease. Arch Neurol. 1994;51(12):1226-31.

Schneider JA, Brown SM, Wallace RB, Storandt M. Cerebral Blood Flow in Ischemic Vascular Dementia and Alzheimer’s Disease. Brain Cogn [Internet]. 1996;31(2):269-82.

Kertesz A, Clydesdale S. Neuropsychological deficits in vascular dementia vs. Alzheimer’s disease. Arch Neurol. 1994;51(12):1226-31.

Kertesz A, Clydesdale S. Neuropsychological deficits in vascular dementia vs. Alzheimer’s disease. Arch Neurol. 1994;51(12):1226-31.

Kertesz A, Clydesdale S. Neuropsychological deficits in vascular dementia vs. Alzheimer’s disease. Arch Neurol. 1994;51(12):1226-31.

Kertesz A, Clydesdale S. Neuropsychological deficits in vascular dementia vs. Alzheimer’s disease. Arch Neurol. 1994;51(12):1226-31.

Kertesz A, Clydesdale S. Neuropsychological deficits in vascular dementia vs. Alzheimer’s disease. Arch Neurol. 1994;51(12):1226-31.

Kertesz A, Clydesdale S. Neuropsychological deficits in vascular dementia vs. Alzheimer’s disease. Arch Neurol. 1994;51(12):1226-31.

Kertesz A, Clydesdale S. Neuropsychological deficits in vascular dementia vs. Alzheimer’s disease. Arch Neurol. 1994;51(12):1226-31.
the formation and use of cognitive maps. Behav Brain Res. 2009; 196(2):187-91.

21. Hartley T, Lever C, Burgess N, O’Keefe J. Space in the brain: how the hippocampal formation supports spatial cognition. Philos Trans R Soc B Biol Sci. 2013;368(1683):20120510.

22. Vann SD, Aggleton JP, Maguire EA. What does the retrosplenial cortex do? Nat Rev Neurosci [Internet]. Nature Publishing Group; 2009; 10(11):792-802.

23. Spiers HJ, Barry C. Neural systems supporting navigation. Current Curr Opin Behav Sci. 2015;1:47-55.

24. Weniger G, Ruhleder M, Lange C, Wolf S, Irl E. Egocentric and allocentric memory as assessed by virtual reality in individuals with amnestic mild cognitive impairment. Neuropsychologia. 2011;49(3):518-27.

25. Karantoula S, Galvin JE. Distinguishing Alzheimer’s disease from other major forms of dementia. Expert Rev Neurotherapy. 2012;11(11):1579-91.

26. Sachdev P, Kalaria R, O’Brien J, Skoog I, Alladi S, Black SE, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. Alzheimer Dis Assoc Disord. 2014;28(3):206-18.