

Title: Diagnostic relevance of spatial orientation for vascular dementia - a case study

Authors: Gillian Coughlan¹, Emma Flanagan¹, Stephen Jeffs¹, Maxime Bertoux¹, Hugo Spiers², Eneida Mioshi³, Michael Hornberger^{1,4}

Affiliations:

¹*Norwich Medical School, University of East Anglia, Norwich, UK*

²*Institute of Behavioural Neuroscience, Department of Experimental Psychology, University College London, London, UK*

³*School of Health Sciences, University of East Anglia, Norwich, UK*

⁴*Dementia and Complexity in Later Life, Norfolk and Suffolk NHS Foundation Trust, Norwich, UK*

Corresponding author:

Prof. Michael Hornberger, Norwich Medical School, University of East Anglia, NR4 7TJ,
Norwich, UK

Tel: +44 1603 593540; Fax: +44 1603 593752; Email: m.hornberger@uea.ac.uk

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ABSTRACT.

Background: 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.

Keywords: Spatial orientation, egocentric, allocentric, vascular dementia, VAD, executive function, neurodegeneration

INTRODUCTION

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 (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 (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 hypercholesterol, stage 2 hypertension, a BMI of 30 and life-long cigarette smoking. There was a strong family history of hypercholesterol (both parents and siblings) and heart disease-related death in both parents.

Procedures. RK underwent clinical and cognitive assessments over two sessions. The first session included a one hour in-depth neuropsychological assessment (see Table 1) while the second session included a clinical interview and evaluation. The clinical presentation reported by the patient and his caregiver included 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 his 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 one-hour spatial test battery was administered and test scores were evaluated against a control sample ($N = 14$). Tests were chosen based on their previous utility to detect spatial impairments, or in the case where current validated test did not examine an area of interest within the boundaries of the human navigation system, additional lab-developed tests were administered.

The Supermarket task is an ecologically valid tool previously shown to reliably dissociate between egocentric and allocentric heading orientation deficits and spatial memory impairments in differing groups of dementia patients (1,2). 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 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(1,2).

The Statue Test is a lab developed task that 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 one of the walls (permanent landmark); ii) the statue is closest to the stool (transient landmark); iii) which of the three statues 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). No computed tomography or magnetic resonance imaging data was available for the current analysis.

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 (12,13), resulting in a Z-case-control (z_{cc}) 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, proverbs), 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 ($t = -9.529$, $p < .000$, $z_{cc} = -9.889$), 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 ($t = -2.983$, $p = 0.01$, $z_{cc} = -3.095$). By contrast, allocentric information, i.e. indicating the place location in the supermarket test, was not significantly different from the control group ($t = -1.537$, $p > 0.05$, $z_{cc} = -0.206$).

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 ($t = -3.085$, $p = 0.01$, $z_{cc} = -3.160$) and stool ($t = -2.590$, $p = 0.02$, $z_{cc} = -2.687$) condition only, showing visual judgments 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 ($t = -2.965$, $p = 0.01$, $z_{cc} = -3.077$) 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, RK shows a typical neuropsychological profile of VaD that includes executive function impairments, as well as memory deficits indicating frontal lobe dependant executive symptomology (14,15). These deficits are accompanied by hypercholesterol, elevated BMI and stage 2 hypertension (16). Normal performance on allocentric orientation measures associated with the medial temporal lobe (17–21) corroborate intact episodic memory after cueing. Deficits in egocentric orientation, dependent mainly on the medial parietal cortex (6,22,23), denote a clear and isolated spatial impairment. More specifically, RK performed worse than controls only on the egocentric portions of the spatial tasks. By contrast, standard neuropsychological visuospatial tasks failed to detect these spatial deficits, despite being one of the RK's main symptoms and causing his family significant concern.

Diagnostically, patients with early AD disease usually exhibit both allocentric and egocentric deficits (1,2,5,24), while RK had specific egocentric difficulties. Therefore, detecting only egocentric deficits along with executive function impairments would not only suggest underlying VaD pathophysiology, but may also allow the diagnostic differentiation of AD from VaD. This suggestion needs to be verified in future group and AD comparison studies. Further MRI and CT studies should also look at the sites of vascular lesions that may elucidate the neural correlates of a selective spatial impairment profile. Nevertheless, our findings reported here form a promising step towards advancing diagnostic tests for VaD, for which cognitive testing is currently very limited and non-specific (25,26). More generally, spatial testing has a promising future as it is highly ecological, resulting in high patient test

compliance but also involving very little verbal material. For these reasons, spatial tests are ideal for cross-cultural testing and are potentially less vulnerable to the impact of educational attainment.

Overall, we report a VaD case with selective egocentric spatial orientation deficits, which tap into the medial parietal changes that are typically associated with this condition. Spatial orientation therefore promises to complement executive testing in VAD to detect the underlying disruption of frontoparietal networks.

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Tables

TABLE 1: PHYSICAL AND NEUROPSYCHOLOGICAL BACKGROUND

| | | |
|---|-------------------------------------|---------------|
| Age | 69 | |
| Nationality | British | |
| Blood Pressure | | |
| Systolic | 165mmHg (lying), 158mmHg (standing) | |
| Diastolic | 100mmHg (lying) 101mmHg (standing) | |
| Heart Rate | 55bpm (lying) 61bpm (standing) | |
| Height | 175cm | |
| Weight | 91kg | |
| Body Mass Index | 30 | |
| Medication Management | | |
| Clopidogrel (75mg) | | |
| Simvastatin (40mg) | | |
| Losarten potassium (100mg) High dosage | | |
| Bendroflumethiazide (2.5mg) | | |
| General Cognitive Ability Test | Patient Score | Control Score |
| Addenbrooke's Cognitive Examination – III (ACE) | | |
| ACE attention | 18 | (17 / 1.9) |
| ACE memory | 18 | (23 / 2.7) |
| ACE fluency | 04* | (12 / 2.0) |
| ACE language | 26 | (25 / 0.9) |
| ACE visuospatial | 16 | (14 / 1.0) |
| ACE total | 82 | (92 / 4.7) |
| Visuospatial functioning | | |
| Visual Object and Space Perception Battery (VOSP) | | |
| Dot counting | 09/10 | |
| Position | 20/20 | |
| Cube | 10 /10 | |
| Rey Complex Figure (ROCF) | | |
| Construction | 25* | (33.7 / 1.6) |
| Reconstruction (3-minute delay) | 09 | (19 / 4.5) |
| Episodic Memory | | |
| Free and Cued Selective Reminding Test (FCSRT) | | |
| Free immediate recall | 15/48* | |
| Cued immediate recall | 33/48 | |
| Free delayed recall | 06/16 * | |
| Cued delayed recall | 10/16 | |
| Language Ability | | |
| Sydney Language Battery | | |
| Naming | 29/30 | |
| Comprehension and repetition | 10/10 | |
| Semantic association | 28/30 | |
| Executive Function / Mental Flexibility | | |
| INCO Frontal Screening Test | | |
| Motor series | 3/3 | |
| Interference sensitively | 2/3 | |

| | | |
|------------------------|---------------|---------------|
| Inhibitory control | 2/3 | |
| Digit backwards | 2/6* | |
| Verbal working memory | 1/2 | |
| Spatial working memory | 1/4* | |
| Proverbs | 0.5/3* | |
| Hayling test | 5/6 | |
| Working memory index | 3/10* | |
| Total | 16.5* | |
| Trail Making Task | <i>Part A</i> | <i>Part B</i> |
| Time (sec) | 79 | 117 |
| Errors | 0 | 2 |

Social Cognition Mini-SEA

| | |
|----------------------------|--------|
| Non-Faux-pas | 10/10 |
| Faux-pas (ToM) | 21/30* |
| All stories | 31/40 |
| Control | 19/20 |
| Facial Emotion Recognition | 30/35 |

Significant differences are marked with a *. 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.

| <i>SPATIAL MEASURES</i> | <i>CONDITION</i> | <i>PATIENT SCORE</i> | <i>CONTROL SAMPLE MEAN (N = 13)</i> | <i>(SD)</i> | <i>T-VALUE</i> | <i>P VALUE</i> | <i>EFFECT SIZE (Z_{CC})</i> | <i>95% CI</i> |
|-------------------------|--|----------------------|-------------------------------------|-------------|----------------|--------------------|-------------------------------------|--------------------------|
| STATUE TEST | Wall Easy | 4 | 4 | 0 | 0.00 | NS | -0.00 | -0.544 to 0.544 |
| | Wall Medium | 1 | 2.6 | 0.5 | -3.085 | 0.01* | -3.160 | -4.511 to -1.789 |
| | Wall Hard | 0 | 0.3 | 0.6 | -0.000 | NS | -0.00 | -1.083 to 0.091 |
| | Stool Easy | 4 | 3.7 | 0.4 | -0.723 | NS | -0.750 | 0.119 to 1.357 |
| | Stool Medium | 0 | 2.2 | 0.8 | -2.590 | 0.02* | -2.687 | -3.869 to -1.484 |
| | Stool Hard | 0 | 0.3 | 0.6 | -0.482 | NS | 0.500 | -1.069 to 0.088 |
| | Memory Easy | 4 | 3.9 | 0.2 | -0.483 | NS | 0.500 | -0.088 to 1.069 |
| | Memory Medium | 2 | 2.5 | 0.6 | -0.623 | NS | 0.622 | 0.525 to 1.563 |
| | Memory Hard | 0 | 0.2 | 0.7 | -0.321 | NS | 0.333 | -0.886 to 0.233 |
| SUPERMARKET TEST | Egocentric navigation | 4 | 12.9 | 0.9 | -9.529 | <0.001** | -9.889 | -13.825 to -5.949 |
| | Allocentric memory | 1.5 | 8.1 | 3.2 | -0.201 | NS | -0.206 | -3.028 - 1.070 |
| | Heading Direction | 6 | 12.5 | 2.1 | -2.983 | 0.01* | -3.095 | -4.422 to -1.746 |
| THE CLOCK TEST | Cardinal (Verbal Response) | 1 | 3.9 | 0.9 | -3.105 | <0.01* | -3.222 | -4.596 to -1.829 |
| | Right angle (pointing response) | 1 | 3.6 | 0.6 | -4.176 | <0.001** | -4.333 | -6.120 to -2.532 |
| | Lateral, behind, (mixed response) | 1 | 3.9 | 1.7 | -1.644 | NS | -1.706 | -2.558 to -0.826 |
| | Total Score | 3 | 11 | 2.6 | -2.965 | 0.01* | -3.077 | -4.398 to -1.736 |

Significant differences are market bold. P value representing a two-tailed probability that case score differs from controls.

Figure captions

Fig. 1 Screenshots from the Supermarket task, showing i) start viewpoint; ii) movement during an example the video clip; iii) end location of an example video clip; iv) onscreen instructions for the participant to point towards the starting point; iv) map of the supermarket, on which the participant has to mark the end location for each video clip.

Fig. 2 Screenshots from wall, stool and memory subtasks of the Statue test. Participants view images and are asked i) identify the statue closest to the wall (permanent landmark), ii) identify the statue closest to the stool (transient landmark), iii) identify which statue moved its location. Note, red circled figures are only shown for illustration purposes to identify the correct choice for each example, which was not shown to the participants.