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

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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 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 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 no 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 show 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 hypercholestrol, 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		
INECO 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	*Part A*	*Part B*
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.

SPATIAL MEASURES	CONDITION	PATIENT SCORE	CONTROL SAMPLE MEAN (N = 13)	(SD)	T-VALUE	P VALUE	EFFECT SIZE (Z_{CC})	95% CI
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.