

1 Path integration changes as a cognitive marker for vascular 2 cognitive impairment? – a pilot study

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20

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22 impairment₆, vascular-dementia₇

23 **ABSTRACT**

24 Path integration spatial navigation processes are emerging as promising cognitive markers for
25 prodromal and clinical Alzheimer's disease (AD). However, such path integration changes
26 have been little explored in Vascular Cognitive Impairment (VCI), despite neurovascular
27 change being a major contributing factor to dementia and potentially AD. In particular, the
28 sensitivity and specificity of path integration impairments in VCI compared to AD is unclear.
29 In the current pilot study, we explore path integration performance in AD and VCI patient
30 groups and hypothesise that i) medial parietal mediated egocentric processes will be more
31 affected in VCI and ii) medial temporal mediated allocentric processes will be more affected
32 in AD. This retrospective cross-sectional study included early stage VCI patients (n=9), AD
33 patients (n=10) and healthy age-matched controls (n=20). All participants underwent
34 extensive neuropsychological testing, as well as spatial navigation testing. The spatial
35 navigation tests included the virtual reality 'Supermarket' task assessing egocentric (body-
36 based) and allocentric (map-based) navigation as well as the 'Clock Orientation' test
37 assessing egocentric and path integration processes. Results showed that egocentric path
38 integration processes are only impaired in VCI, potentially distinguishing it from AD.
39 However, in contrast to our prediction, allocentric path integration was similarly impaired for
40 VCI and AD. These preliminary findings suggest limited specificity of allocentric path
41 integration deficits between VCI and AD. By contrast, egocentric path integration deficits
42 emerge as more specific to VCI, potentially allowing for more specific diagnostic and
43 treatment outcome measures for vascular impairment in dementia.

44
45 **INTRODUCTION**

46 Vascular cognitive impairment (VCI) is the second most prevalent cause of cognitive decline
47 after Alzheimer's disease (AD) and is thought to account for ~20% of all dementias
48 (Goodman et al., 2017; van der Flier et al., 2018). Although, individuals with mixed (AD and
49 VCI) pathology are estimated to account for up to 70% of all dementia cases (Toledo et al.,
50 2013). Despite the high prevalence of vascular impairment, its cognitive correlates are still
51 being explored. Clinically, VCI is considered to involve a decline in executive function and
52 higher order cognition such as information processing, planning, set-shifting and working
53 memory (Hachinski et al., 2006; Sachdev et al., 2014). These changes are mostly attributed to
54 micro and macro infarcts in subcortical and cortical regions, as well as their connecting white
55 matter tracts (Beason-Held et al., 2012; van der Flier et al., 2018), in particular affecting
56 fronto-parietal networks. Nevertheless, attributing such executive changes to VCI specifically
57 has remained challenging, as executive function can also present as part of AD or related
58 pathophysiology (Girard et al., 2013; Guarino et al., 2018; Neufang et al., 2011). However,
59 the recent development of novel spatial navigation cognitive markers for AD show promise
60 in being more specific to underlying disease pathophysiology (Coughlan et al., 2018a) and
61 may help to identify cognitive decline specific to VCI. A clear distinction between VCI and
62 AD is critical as with appropriate intervention VCI can be slowed or halted whereas AD has a
63 fixed and terminal prognosis.

64
65 Spatial navigation is a fundamental cognitive skill that requires the integration of egocentric
66 (body-based) and allocentric (map-based) frames of orientation. Both frames are required for
67 everyday navigation with egocentric and allocentric processes shifting as a function of
68 navigational demands (McNaughton et al., 2006). Path integration is integral to spatial
69 navigation as it allows an individual to keep track of and return to their starting location on
70 the basis of visual, self-motion, vestibular and proprioceptive feedback which represent
71 current position and heading direction in references to a permanent location (Etienne and
72 Jeffery, 2004; Knierim, Neunuebel and Deshmukh, 2014; McNaughton et al., 2006). This

73 process involves translating distance travelled with changes in direction of movement either
74 relative to our allocentric or egocentric orientation (Burgess, 2006). Multisensory (visual,
75 self-motion, vestibular and proprioceptive) feedback combine egocentric and allocentric
76 frames of reference, allowing path integration to continuously update this information,
77 allowing one to keep track of one's position in space (Coughlan et al., 2018a; Rieser, 1989).
78

79 Egocentric orientation relies more on the prefrontal and parietal cortex to localise the position
80 of objects relative to the body (Arnold, Burles, bray, Levy and Giuseppe, 2014; Goodale &
81 Milner, 1992), the precuneus then uses these location cues to form the basis of an egocentric
82 representation of the surrounding space, integrating self-motion cues with the egocentric
83 reference frame (Woblers and Weiner, 2014). While, allocentric orientation is reliant on the
84 formation of maps using place, grid and boundary vector cells situated mainly in the medial
85 temporal lobe (Coughlan et al., 2018a; Lester et al., 2017). The integration of egocentric and
86 allocentric frames occurs in the retrosplenial cortex (RSC), which is a critical interface
87 between the medial temporal and medial parietal regions (Alexander & Nitz, 2015). Dorsal-
88 medial regions of the RSC are thought to be implicated in orientating and recalling unseen
89 locations from a current position in space, whilst ventro-lateral portions were more linked to
90 updating and integrating scene information (Burles, Slone and Giuseppe, 2017).
91

92 Tasks that tap into path integration therefore provide a promising ecological, cognitive
93 framework to detect medial temporal and medial parietal pathophysiology. Not surprisingly,
94 path integration has been already explored in AD (Morganti et al, 2013; Ritchie, 2018; Serino
95 et al., 2014; Vlcek & Laczo, 2014) and the advent of VR based testing has allowed such tests
96 to be clinically available (Morganti et al., 2013; Parizkova et al., 2018; Plancher et al., 2012).
97 We have developed previously such a test, the Virtual Supermarket task, which is now used
98 across many large cohorts and drug trials as it can reliably detect path integration differences
99 in preclinical and clinical dementia populations (Tu et al., 2017; Tu et al., 2015). The VR task
100 reliably measures spatial processes of: i) egocentric self-reference navigation; ii) allocentric
101 map-based navigation and iii) heading direction. For example, we have previously shown
102 that the test allows distinction of behavioural variant fronto-temporal dementia (bvFTD) from
103 AD, with AD showing particularly problems in switching between egocentric and allocentric
104 frames during path integration (Tu et al., 2017). Importantly, these switching problems in AD
105 were associated with grey matter atrophy in the RSC (Tu et al., 2015).
106

107 In contrast to the exciting findings in AD, less is known about path integration in VCI,
108 despite path integration potentially allowing as well to tap into parietal deficits in VCI
109 (Haight et al., 2015; Maguire, 1998; Papma et al., 2012; Wolbers et al., 2004). A previous
110 case study by our group explored path integration in a 65 year old male with VCI. The
111 findings showed that the vascular patient had normal performance on allocentric orientation
112 but a clear and isolated deficit in egocentric and heading direction sub-components of the
113 path integration tasks (Coughlan et al., 2018b). These findings are consistent with fronto-
114 parietal network disruptions typically seen in vascular dementia patients (Beason-Held et al.,
115 2012; Sachdev et al., 2014; van der Flier et al., 2018) and may suggest medial parietal
116 changes impeded the egocentric frame of reference and subsequent path integration.
117

118 The current study leads on from this case study by exploring path integration in a group of
119 VCI patients, and importantly comparing them against a group of AD patients and controls.
120 Navigation will be tested using the Virtual Supermarket task where participants move
121 through the virtual environment to a series of locations and are tested on their egocentric,
122 allocentric and heading direction response. We hypothesise that i) medial parietal mediated

123 egocentric processes will be more affected in VCI; ii) medial temporal mediated allocentric
124 processes will be more affected in AD.

125
126 **MATERIALS AND METHODS**
127

Participants

128 Nine vascular cognitive impairment and 10 Alzheimer's disease patients along with 20
129 healthy controls were recruited to participate in a research study at the University of East
130 Anglia as part of the wider The Dementia Research and Care Clinic (TRACC) study. The
131 study was approved by the Faculty of Medicine and Health Sciences Ethics Committee at the
132 University of East Anglia (reference 16/LO/1366) and written informed consent was obtained
133 from all participants. Clinical diagnosis (VCI or AD) was classified by a consultant at the
134 Norfolk and Suffolk Foundation Trust by interviewing the patient, examining
135 neuropsychological assessment scores, structural clinical MRI scans and the patient's medical
136 history. Disease duration was reported by the person's study partner (a spouse or relative).
137 Participants had no history of psychiatric or neurological disease, substance dependence
138 disorder or traumatic brain injury and had normal or corrected-to-normal vision. All
139 participants underwent neuropsychological screening, including cognitive screening, episodic
140 memory and spatial memory tasks, Addenbrooke's cognitive examination (ACE-III), Rey-
141 Osterrieth Complex Figure Test (RCFT) copy and with 3-min delayed recall, Cube Analysis,
142 Dot Counting and Position Discrimination from the Visual Object and Space Perception
143 Battery (VOSP).

144
145 **Virtual Supermarket Task**

146 The Virtual Supermarket Task has been developed by our group previously and used in
147 symptomatic mild cognitive impairment (MCI), AD, frontotemporal dementia (FTD) and
148 VCI patients (Coughlan et al., 2018b; Tu et al., 2017; Tu et al., 2015). The VR task is an
149 ecological test of spatial navigation abilities designed to simulate navigating through a real-
150 world supermarket. An iPad 9.7 (Apple Inc.,) was used to show participants 20-40 second
151 video clips of a moving shopping trolley in the virtual supermarket (Figure 1A-C). Videos
152 were presented in a first-person perspective and participants are provided with optic flow
153 cues from the moving shopping trolley and changing scenery as it followed different routes to
154 reach a different end point in each trial. The task avoids the use of landmarks or salient
155 features within the environment and limits the demand on episodic memory, reflecting
156 similar tasks in the literature (see, Cushman, Stein and Duffy, 2008; Woblers, Weiner, Mallot
157 and Büchel, 2017; Serino, Morganti, Di Stefano and Riva, 2015). The test taps into path
158 integration processes via three core spatial processes: i) egocentric self-reference navigation;
159 ii) allocentric map-based navigation and iii) heading direction. Once the video clip stops,
160 participants indicate in real-life the direction of their starting point (egocentric orientation;
161 Figure 1D). In a second step, participants indicate their finishing location on a birds-eye view
162 map of the supermarket (allocentric orientation; Figure 1E), performance is calculated using
163 the distance error (mm) between this and the coordinates of the actual finishing location. This
164 map-based component provides an assessment of geocentric encoding of the virtual
165 environment. The participant then indicates their heading direction at the finishing point,
166 which determines the ability to which heading direction was encoded and updated throughout
167 the task. The tasks consists of 14 trials and takes approximately 10 minutes to complete.

168
169 **Clock Orientation test**

170 The Clock Orientation test has also been developed by our lab (Coughlan et al., 2018b) as a
171 bedside clinical test for egocentric orientation. It requires participants to imagine they are
172 standing in the centre of a large clock, facing a particular number, e.g., the number 3.

173 Participants are then asked “which number is directly behind you?” (Answer: number 9).
174 Next participants are asked to point, in real-life, to the positions of different numbers on the
175 clock face in relation to the number that they are currently facing. For example, “You are
176 facing number 12, can you point to the number 3?” (Answer: pointing right). The questions
177 increase in complexity across the test and require medial parietal mediated mental imagery,
178 rotation and egocentric processes, with no episodic memory demand. The test consists of 12
179 trials and takes 5-10 minutes to complete.

180

181 Procedure

182 Participants completed a battery of neuropsychological assessments at their home (see Table
183 1 for list of tasks). In a second session held at the Norfolk and Suffolk Foundation Trust,
184 participants undertook cognitive experimental tests (including the virtual Supermarket task
185 and Clock Orientation test) and completed a clinical interview with the Chief Investigator of
186 the study.

187

188 Statistical Analysis

189 Statistical analysis was performed using IBM SPSS (Version 25). Chi square and two tailed
190 one-way univariate analysis of variance (ANOVA) were used to test the significance of any
191 demographic or neuropsychological differences between the clinical groups. When
192 quantifying group differences, partial eta squared (η_p^2) was used as a measure of effect size.
193 The Supermarket task has 3 measures -specifically egocentric response, allocentric response
194 and heading direction. Each outcome measure was individually entered into a one-way
195 analysis of covariance (ANCOVA) with group as the independent variable and age and sex as
196 covariates. The Clock Orientation test was also analysed using a one-way ANCOVA with
197 group as the independent variable and age and sex as covariates. Post-hoc pairwise
198 comparisons were conducted using Bonferroni adjustment for multiple comparisons.
199 Sensitivity and specificity of the egocentric supermarket task and clock orientation test
200 performance in VCI and AD were compared using logistic regression and ROC curve
201 analysis. A Z-score of AD performance was computed for 7 missing values for one AD
202 patient in the Virtual Supermarket test.

203

204 (Insert figure 1)

205

206 RESULTS

207 Demographics and Neuropsychology

208 Participant groups were well matched and no significant differences in demographic
209 measures were observed between the VCI, AD and control groups (all p-values > .1).
210 ANOVA of participant groups showed both VCI and AD patients performed significantly
211 lower on a general cognitive screening test (ACE-III) and the memory recall domain of
212 RCFT compared to controls (all p-values < .01). Results showed no significant
213 neuropsychological differences between the VCI and AD patients for the ACE-III, RCFT
214 recall condition, VOSP dot counting and cube analysis sub-sets (all p-values > 0.1. However,
215 VCI patients were significantly more impaired than AD patients in the RCFT copy condition,
216 FCSRT free recall condition and the VOSP position discrimination (all p-values < .1) (see
217 table 1).

218

219 (Insert table. 1)

220

221 Virtual Supermarket Task

222 An ANCOVA with age and gender as covariates revealed a significant differences between
223 egocentric responses on the supermarket test, $F(2, 34) = 8.14, p < .001, n_p^2 = .32$. Post-hoc
224 comparisons revealed significantly greater egocentric impairment in VCI ($M = 3.5, SD = 3.24$)
225 compared to AD ($M = 10.01, SE = 1.11$), $p < .002$, 95% CI [-10, -2.1] and control groups ($M =$
226 8.1, $SD = 3.7$), $p < .009$, 95% CI [-7.95, -1.1]. No other significant group differences were
227 observed ($p > .1$) (see figure 2A).

228
229 Allocentric responses showed a significance difference between groups, controlled for age
230 and gender $F(2, 34) = 10.1, p < .001, n_p^2 = .37$. Post-hoc comparisons showed significantly
231 greater impairments in VCI patients ($M = 68.33, SD = 38.1$) compared to controls ($M = 30.85,$
232 $SD = 14.13$), $p < .001$, 95% CI [16.02, 61.1] but impairments did not reach statistical
233 significance in AD patients ($M = 50.1, SD = 7$), $p = 0.09$, 95% CI [-41.11, 2.1] compared to
234 controls. However, there were no significant groups differences between VCI and AD ($p > .1$)
235 (see figure 2B).

236
237 Heading direction (correct judgement of facing direction after travel period) did not reveal
238 significant group differences when controlling for age and gender $F(2, 34) = 1.11, p > .1, n_p^2$
239 = .06 (see figure 2C).

240
241 Clock Orientation Test
242 An ANCOVA with age and gender as covariates revealed a significant difference between
243 egocentric responses on the Clock Orientation task $F(2, 34) = 13.4, p < .001, n_p^2 = .44$. Post-
244 hoc comparisons showed significantly greater egocentric deficits in VCI patients ($M = 5.42,$
245 $SD = 3.16$) compared to AD ($M = 10.1, SD = 1.21$), $p < .001$, 95% CI [-7.2, -2] and control
246 groups ($M = 9.65, SD = 2.06$), $p < .001$, 95% CI [-6.56, -7.1]. No other significant group
247 differences were observed ($p > .1$) (see figure 2D).

248
249 (Insert Figure. 2)

250
251 Sensitivity and Specificity
252 Sensitivity and specificity of egocentric supermarket and clock test performance in VCI and
253 AD were explored using logistic regression and ROC curves. Logistic regression indicated
254 that the regression model based on egocentric scores of Supermarket and Clock Orientation
255 predictors was statistically significant, $X^2(2) = 16.36, p < .001$. The model explained 77%
256 (Nagelkerke R²) of variance in VCI and AD patients and correctly classified 84% of patients
257 (7 out of 9 VCI; 9 out of 10 AD) into their respective cohorts. ROC curves were computed
258 for the supermarket and clock test predictors in discerning VCI from AD patients. Similarly,
259 Area Under the Curve (AUC) values indicated that egocentric orientation in the Supermarket
260 (AUC = .8, SE = .12; 95% CI [.56, 1]) and Clock test (AUC = .91, SE = .06, 95% CI [.8, 1])
261 had strong diagnostic accuracy in distinguishing VCI from AD patients.

262
263 (Insert Figure. 3)

264
265 **DISCUSSION**
266 Overall, our results indicate that medial parietal mediated egocentric path integration
267 processes are a sensitive and specific cognitive marker selective for VCI. By contrast,
268 allocentric orientation deficits were less sensitive, and not specific to distinguish between the
269 underlying pathologies.

270

271 In more detail, the egocentric path integration measures of the Virtual Supermarket task and
272 Clock Orientation test successfully detect vascular changes in patient populations. More
273 importantly, the measures allowed to reliably distinguish vascular from AD pathophysiology
274 in the patient populations. Notably, egocentric orientation was impaired in VCI, but relatively
275 intact in AD patient groups when controlling for age and gender. This supports findings from
276 our vascular patient case study (Coughlan et al., 2018b) and suggests egocentric impairments
277 indicate a more medial parietal focused change (Weniger et al., 2009) in VCI. Furthermore,
278 the AD patient's egocentric ability remained intact which supports suggestions that MCI and
279 earlier stage AD groups show an undisturbed egocentric orientation (Coughlan et al., 2019).
280 It would be interesting to explore whether more moderate to advanced AD patients might
281 show problems using both allocentric and egocentric orientation, as it is known that medial
282 parietal structures might be affected only later in the disease course (Braak & Del Tredici,
283 2015).

284

285 The egocentric demands in the virtual Supermarket requires the individual to form an
286 accurate representation of the starting point by integrating virtual self-motion with heading
287 direction to reach their end destination. Path integration plays an important role in updating
288 spatial orientation during self-motion but this process is accumulative, therefore can be liable
289 to directional errors with respect to the original starting position (McNaughton et al., 2006),
290 which may be responsible for problems observed across both egocentric tasks. The Clock
291 Orientation test also demands path integration to configure the position of numbers on a
292 clock face relative to the individual's current position. Both tasks rely on accessing scene
293 construction, mental rotation and imagery translated from an egocentric orientation. At the
294 neural level, translation of these egocentric processes depend mainly on medial parietal
295 cortex (Coughlan et al., 2018a; Galati et al., 2000; Goodale & Milner, 1992; Zaehle et al.,
296 2007) as well as prefrontal cortex (Bird et al., 2012; Spiers, 2008; Spiers & Barry, 2015),
297 indicating potential disruptions in fronto-parietal structures typically seen in vascular patients
298 (Beason-Held et al., 2012; Heiss et al., 2016; van der Flier et al., 2018; Vipin et al., 2018).
299

300

300 Medial parietal mediated egocentric deficits appear to characterise VCI patients. This is
301 consistent with emerging evidence suggesting the earliest signs of dysfunction appear in
302 medial frontal and anterior cingulate regions in at VCI-risk individuals (Haight et al., 2015;
303 Papma et al., 2012), which is accompanied by a more typical vascular profile of reduced
304 integrity of white matter in the bilateral superior longitudinal fasciculus (Beason-Held et al.,
305 2012). Since egocentric orientation does not deteriorate in healthy aging and early stage AD,
306 compared to medial temporal based cognitive functions (for review, see Colombo et al.,
307 2017) it emerges as a potential powerful cognitive marker to identify early vascular-related
308 pathology. Given the prevalence of vascular related dementia it is surprising that
309 investigation to isolate cognitive deficits unique to this pathology is so sparse. However,
310 based on our findings, it appears that egocentric orientation may be a useful diagnostic tool to
311 discriminate VCI from other neurodegenerative conditions.
312

313

313 Our study suggests allocentric orientation deficits were not statistically present in AD, only
314 VCI showed significant impairments compared to healthy controls. This does not support our
315 prediction that allocentric deficits would be more profound in AD. The literature suggests
316 allocentric deficits are more prominent in preclinical AD (Coughlan et al., 2019) with a loss
317 in selectivity as the disease stage progresses and deficits become more widespread (Braak &
318 Del Tredici, 2015). Yet, in the early stage AD patients in our study results did not reach
319 significance. One potential explanation for the results observed may be provided by the large
320 range in allocentric scores across the VCI group. VCI is a highly heterogeneous disordered in

321 terms of disease pathology and subsequent cognitive impairments which may account for this
322 variation, compared AD pathology and symptoms are more uniform. Indeed, as evident from
323 Figure 2, it is clear that AD patients perform differently from controls but this did not reach
324 statistical significance. VCI patients revealed both egocentric and allocentric orientation
325 problems which is likely to represent a disruption to translational and integration processes
326 where both frames are combined to produce effective navigation. This view also explains the
327 reduced visuospatial performance exhibited by the VCI patients during neuropsychological
328 testing across RCFT copy and position discrimination tasks. It is also important to consider
329 the domain of memory when interpreting our findings. Results from the FCSRT suggest VCI
330 patients had significantly worse memory than the AD and control groups, sub-score results
331 indicate this is driven by reduced performance during free recall. This is likely due to the
332 retrieval demands on pre-frontal and parietal structures (Staresina and Davachi, 2006) which
333 are typically disrupted in VCI. However, when cued VCI patients outperform AD patients.
334 This finding is consistent with evidence that suggests providing a cue has little bearing on
335 improved memory recall in AD (Sarazin et al., 2007; Wagner et al., 2012). This may be
336 relevant to the poor allocentric results observed for VCI patients, as reduced retrieval
337 mechanisms may have disrupted their task performance opposed to pure allocentric (medial
338 temporal) mapping problems, which we would expect to see in the AD patients.
339

340 Despite these exciting findings, our study is not without limitations. First and foremost, the
341 sample sizes for the groups were small and therefore replication in larger patient cohorts
342 would be important. Further, clinical characterisation of VCI subtypes (Skrobot et al., 2017)
343 would help to better classify vascular pathology and determine accompanying cognitive
344 symptoms, this may also help inform the variation of results seen in allocentric performance
345 for the VCI patients. Finally, we did not have neuroimaging biomarker confirmation of
346 vascular or AD pathophysiology. Confirmation of vascular lesions and their locations, as well
347 as AD specific biomarkers would be important in the future to corroborate our cognitive
348 findings.
349

350 Nevertheless, to our knowledge this is the first study to isolate a selective navigational deficit
351 in VCI. This showcases the important role of virtual navigation and spatial tests in the future
352 development of sensitive and specific diagnostic tests for VCI. Further investigation into the
353 cognitive symptoms selective to VCI as well as longitudinal cohort studies in at VCI-risk
354 individuals is critical to identify the emergence of the disease and intervene with therapeutic
355 strategies as early as possible.
356

357 In conclusion, our findings show a distinct egocentric orientation deficit that is specific for
358 VCI relative to AD. This is critical given the lack of specificity in current diagnostic tests and
359 the indistinct diagnostic criteria for cognitive symptoms in VCI. In turn, this will inform
360 diagnostic work-ups and aid personalised treatment pathways to treat underlying vascular
361 changes in patients.
362

363 **AUTHOR CONTRIBUTION**

364 EL and MH contributed to the conception and design of the study, statistical analysis and the
365 intellectual contribution to the writing of the manuscript. VP, GC and SJ contributed to the
366 data collection and intellectual contribution to the manuscript.
367

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370

371 **CONFLICT OF INTEREST**

372 There are no known conflicts of interest.

373

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377 **REFERENCES**

378 Alexander, A., & Nitz, D. (2015). Retrosplenial cortex maps the conjunction of internal and
379 external spaces. *Nat Neurosci*, 18(8), 1143-1151. doi:10.1038/nn.4058

380 Beason-Held, L., Thambisetty, M., Deib, G., Sojkova, J., Landman, B., Zonderman, A., et al.,
381 (2012). Baseline cardiovascular risk predicts subsequent changes in resting brain
382 function. *Stroke*, 43(6), 1542-1547. doi:10.1161/STROKEAHA.111.638437

383 Bird, C. M., Bisby, J. A., & Burgess, N. (2012). The hippocampus and spatial constraints on
384 mental imagery. *Frontiers in human neuroscience*, 6, 142.
385 doi:10.3389/fnhum.2012.00142

386 Braak H, Del Tredici K. The preclinical phase of the pathological process underlying
387 sporadic Alzheimer's disease. *Brain* 2015; **138**(Pt 10). doi: 2814-33.
388 10.1093/brain/awv236

389 Burles, F., Slone, E., & Iaria, G. (2017). Dorso-medial and ventro-lateral functional
390 specialization of the human retrosplenial complex in spatial updating and
391 orienting. *Brain Structure and Function*, 222(3), 1481-1493.

392 Burgess, N. (2006). Spatial memory: how egocentric and allocentric combine. *Trends Cogn
393 Sci*, 10(12), 551-557. doi:10.1016/j.tics.2006.10.005

394 Colombo, D., Serino, S., Tuena, C., Pedroli, E., Dakanalis, A., Cipresso, P., et al., (2017).
395 Egocentric and allocentric spatial reference frames in aging: A systematic review.
396 *Neurosci Biobehav Rev*, 80, 605-621. doi:10.1016/j.neubiorev.2017.07.012

397 Coughlan, G., Coutrot, A., Khondoker, M., Minihane, A. M., Spiers, H., & Hornberger, M.
398 (2019). Toward personalized cognitive diagnostics of at-genetic-risk Alzheimer's
399 disease. *Proc Natl Acad Sci U S A*, 116(19), 9285-9292.
400 doi:10.1073/pnas.1901600116

401 Coughlan, G., Flanagan, E., Jeffs, S., Bertoux, M., Spiers, H., Mioshi, E., et al., (2018b).
402 Diagnostic relevance of spatial orientation for vascular dementia: A case study.
403 *Dement Neuropsychol*, 12(1), 85-91. doi:10.1590/1980-57642018dn12-010013

404 Coughlan, G., Laczo, J., Hort, J., Minihane, A. M., & Hornberger, M. (2018a). Spatial
405 navigation deficits - overlooked cognitive marker for preclinical Alzheimer disease?
406 *Nat Rev Neurol*, 14(8), 496-506. doi:10.1038/s41582-018-0031-x

407 Etienne, A. S., & Jeffery, K. J. (2004). Path integration in mammals. *Hippocampus*, 14(2),
408 180-192.

409 Galati, G., Lobel, E., Vallar, G., Berthoz, A., Pizzamiglio, L., & Le Bihan, D. (2000). The
410 neural basis of egocentric and allocentric coding of space in humans: a functional
411 magnetic resonance study. *Exp Brain Res*, 133(2), 156-164.
412 doi:10.1007/s002210000375

413 Girard S, Baranger K, Gauthier C, Jacquet, M., Bernard, A., Escoffier, G., et al., (2013).
414 Evidence for early cognitive impairment related to frontal cortex in the 5XFAD
415 mouse model of Alzheimer's disease. *J Alzheimers Dis*; 33(3): 781-96.
416 doi:10.3233/JAD-2012-120982

417 Goodale, M., & Milner, A. (1992). Separate visual pathways for perception and action.
418 *Trends in Neurosciences*, 15(1), 20-25. doi.org/10.1016/0166-2236(92)90344-8

419 Goodman, R., Lochner, K., Thambisetty, M., Wingo, T., Posner, S., & Ling, S. (2017).
420 Prevalence of dementia subtypes in United States Medicare fee-for-service
421 beneficiaries, 2011-2013. *Alzheimers Dement*, 13(1), 28-37.
422 doi:10.1016/j.jalz.2016.04.002

423 Guarino A, Favieri F, Boncompagni I, Agostini F, Cantone M, Casagrande M. Executive
424 Functions in Alzheimer Disease: A Systematic Review. *Front Aging Neurosci* 2018;
425 10: 437. doi: 10.3389/fnagi.2018.00437

426 Hachinski, V., Iadecola, C., Petersen, R., Breteler, M., Nyenhuis, D., Black, S., et al. (2006).
427 National Institute of Neurological Disorders and Stroke-Canadian Stroke Network
428 vascular cognitive impairment harmonization standards. *Stroke*, 37(9), 2220-2241.
429 doi:10.1161/01.STR.0000237236.88823.47

430 Haight, T., Bryan, R., Erus, G., Davatzikos, C., Jacobs, D., D'Esposito, M., et al. (2015).
431 Vascular risk factors, cerebrovascular reactivity, and the default-mode brain network.
432 *Neuroimage*, 115, 7-16. doi:10.1016/j.neuroimage.2015.04.039

433 Heiss, W., Rosenberg, G., Thiel, A., Berlot, R., & de Reuck, J. (2016). Neuroimaging in
434 vascular cognitive impairment: a state-of-the-art review. *BMC Med*, 14(1), 174.
435 doi:10.1186/s12916-016-0725-0

436 Knierim, J. J., Neunuebel, J. P., & Deshmukh, S. S. (2014). Functional correlates of the
437 lateral and medial entorhinal cortex: objects, path integration and local-global
438 reference frames. *Philosophical Transactions of the Royal Society B: Biological
439 Sciences*, 369(1635), 20130369.

440 Lester, A. W., Moffat, S. D., Wiener, J. M., Barnes, C. A., & Wolbers, T. (2017). The aging
441 navigational system. *Neuron*, 95(5), 1019-1035. doi:10.1016/j.neuron.2017.06.037

442 Maguire, E., Burgess, N., Donnett, J., Frackowiak, R., Frith, C., & O'Keefe, J. (1998).
443 Knowing where and getting there: a human navigation network. *Science*, 280, 921-
444 924. doi: 10.1126/science.280.5365.921

445 McNaughton, B., Battaglia, F., Jensen, O., Moser, E., & Moser, M. (2006). Path integration
446 and the neural basis of the 'cognitive map'. *Nat Rev Neurosci*, 7(8), 663-678.
447 doi:10.1038/nrn1932

448 Morganti, F., Stefanini, S., & Riva, G. (2013). From allo- to egocentric spatial ability in early
449 Alzheimer's disease: a study with virtual reality spatial tasks. *Cogn Neurosci*, 4(3-4),
450 171-180. doi:10.1080/17588928.2013.854762

451 Neufang S, Akhrif A, Riedl V, Forstl, H., Kurz, A., Zimmer, C., et al., (2011). Disconnection
452 of frontal and parietal areas contributes to impaired attention in very early
453 Alzheimer's disease. *J Alzheimers Dis*; 25(2): 309-21. Doi: 10.3233/JAD-2011-
454 102154

455 Papma, J., den Heijer, T., de Koning, I., Mattace-Raso, F., van der Lugt, A., van der Lijn, F.,
456 et al., (2012). The influence of cerebral small vessel disease on default mode network
457 deactivation in mild cognitive impairment. *Neuroimage Clin*, 2, 33-42.
458 doi:10.1016/j.nicl.2012.11.005

459 Parizkova, M., Lerch, O., Moffat, S., Andel, R., Mazancova, A. F., Nedelska, Z., et al.,
460 (2018). The effect of Alzheimer's disease on spatial navigation strategies. *Neurobiol
461 Aging*, 64, 107-115. doi:10.1016/j.neurobiolaging.2017.12.019

462 Plancher, G., Tirard, A., Gyselinck, V., Nicolas, S., & Piolino, P. (2012). Using virtual reality
463 to characterize episodic memory profiles in amnestic mild cognitive impairment and
464 Alzheimer's disease: influence of active and passive encoding. *Neuropsychologia*,
465 50(5), 592-602. doi:10.1016/j.neuropsychologia.2011.12.013

466 Rieser, J. (1989). Access to knowledge of spatial structure at novel points of observation.
467 *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 15(6), 1157-
468 1165. doi:10.1037/0278-7393.15.6.1157

469 Ritchie, K., Carrière, I., Howett, D., Su, L., Hornberger, M. (2018). Allocentric and
470 egocentric spatial processing in middle-aged adults at high risk of late-onset
471 Alzheimer's disease : the PREVENT Dementia study. *Journal of Alzheimer's
472 Disease*, 65(3), 885. doi:10.3233/JAD-180432

473 Sachdev, P., Kalaria, R., O'Brien, J., Skoog, I., Alladi, S., Black, S., et al., (2014). Diagnostic
474 criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc
475 Disord*, 28(3), 206-218. doi:10.1097/WAD.0000000000000034

476 Sarazin, M., Berr, C., De Rotrou, J., Fabrigoule, C., Pasquier, F., Legrain, S., ... & Verny, M.
477 (2007). Amnestic syndrome of the medial temporal type identifies prodromal AD: a
478 longitudinal study. *Neurology*, 69(19), 1859-1867.

479 Serino, S., Cipresso, P., Morganti, F., & Riva, G. (2014). The role of egocentric and
480 allocentric abilities in Alzheimer's disease: a systematic review. *Ageing Res Rev*, 16,
481 32-44. doi:10.1016/j.arr.2014.04.004

482 Skrobot, O., O'Brien, J., Black, S., Chen, C., DeCarli, C., Erkinjuntti, T., et al., (2017). The
483 Vascular Impairment of Cognition Classification Consensus Study. *Alzheimers
484 Dement*, 13(6), 624-633. doi:10.1016/j.jalz.2016.10.007

485 Spiers, H. (2008). Keeping the goal in mind: prefrontal contributions to spatial navigation.
486 *Neuropsychologia*, 46(7), 2106-2108. doi:10.1016/j.neuropsychologia.2008.01.028

487 Spiers, H., & Barry, C. (2015). Neural systems supporting navigation. *Current Opinion in
488 Behavioral Sciences*, 1, 47-55. doi:10.1016/j.cobeha.2014.08.005

489 Staresina, B. P., & Davachi, L. (2006). Differential encoding mechanisms for subsequent
490 associative recognition and free recall. *Journal of Neuroscience*, 26(36), 9162-9172.

491 Toledo, J., Arnold, S., Raible, K., Brettschneider, J., Xie, S. X., Grossman, M., et al., (2013).
492 Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative
493 disease cases in the National Alzheimer's Coordinating Centre. *Brain*, 136(Pt 9),
494 2697-2706. doi:10.1093/brain/awt188

495 Tu, S., Spiers, H. J., Hodges, J. R., Piguet, O., & Hornberger, M. (2017). Egocentric versus
496 Allocentric Spatial Memory in Behavioral Variant Frontotemporal Dementia and
497 Alzheimer's Disease. *J Alzheimers Dis*, 59(3), 883-892. doi:10.3233/JAD-160592

498 Tu, S., Wong, S., Hodges, J., Irish, M., Piguet, O., & Hornberger, M. (2015). Lost in spatial
499 translation - A novel tool to objectively assess spatial disorientation in Alzheimer's
500 disease and frontotemporal dementia. *Cortex*, 67, 83-94.
501 doi:10.1016/j.cortex.2015.03.016

502 van der Flier, W., Skoog, I., Schneider, J., Pantoni, L., Mok, V., Chen, C., et al., (2018).
503 Vascular cognitive impairment. *Nat Rev Dis Primers*, 4, 18003.
504 doi:10.1038/nrdp.2018.3

505 Vipin, A., Loke, Y., Liu, S., Hilal, S., Shim, H., Xu, X., et al., (2018). Cerebrovascular
506 disease influences functional and structural network connectivity in patients with
507 amnestic mild cognitive impairment and Alzheimer's disease. *Alzheimers Res Ther*,
508 10(1), 82. doi:10.1186/s13195-018-0413-8

509 Vlcek, K., & Laczo, J. (2014). Neural correlates of spatial navigation changes in mild
510 cognitive impairment and Alzheimer's disease. *Front Behav Neurosci*, 8, 89.
511 doi:10.3389/fnbeh.2014.00089

512 Wagner, M., Wolf, S., Reischies, F. M., Daerr, M., Wolfsgruber, S., Jessen, F., ... & Hampel,
513 H. (2012). Biomarker validation of a cued recall memory deficit in prodromal
514 Alzheimer disease. *Neurology*, 78(6), 379-386.

515 Weniger, G., Ruhleider, M., Wolf, S., Lange, C., & Irle, E. (2009). Egocentric memory
516 impaired and allocentric memory intact as assessed by virtual reality in subjects with
517 unilateral parietal cortex lesions. *Neuropsychologia*, 47(1), 59-69.

518 Wolbers, T., Wiener, J. M., Mallot, H. A., & Büchel, C. (2007). Differential recruitment of
519 the hippocampus, medial prefrontal cortex, and the human motion complex during
520 path integration in humans. *Journal of Neuroscience*, 27(35), 9408-9416.

521 Wolbers, T., & Wiener, J. M. (2014). Challenges for identifying the neural mechanisms that
522 support spatial navigation: the impact of spatial scale. *Frontiers in human
523 neuroscience*, 8, 571.

524 Wolbers, T., Weiller, C., & Buchel, C. (2004). Neural foundations of emerging route
 525 knowledge in complex spatial environments. *Brain Res Cogn Brain Res*, 21(3), 401-
 526 411. doi:10.1016/j.cogbrainres.2004.06.013
 527 Zaehle, T., Jordan, K., Wustenberg, T., Baudewig, J., Dechent, P., & Mast, F. W. (2007). The
 528 neural basis of the egocentric and allocentric spatial frame of reference. *Brain Res*,
 529 1137(1), 92-103. doi:10.1016/j.brainres.2006.12.044
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 531

532 **Table 1.** Demographic characteristics and Neuropsychological Performance.

	VCI	AD	Control	<i>Sig post-hoc VCI vs. AD comparisons</i>
	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	
<i>n</i>	9	10	20	
Sex (F/M)	3/6	2/8	9/11	<i>ns</i>
Age	70.22 (4.57)	69.91 (7.7)	69.6 (6.45)	<i>ns</i>
Disease duration	3.13 (2.64)	2.81 (2.21)	n/a	<i>ns</i>
General cognition				
Total ACE-III	69.44 (12.9)	72.1 (22.41)	95.1 (3.13)	<i>ns</i>
ACE: Attention	13.5 (.72)	15.75 (.72)	17.6 (.45)	<i>ns</i>
ACE: Memory	13.5 (1.73)	17.13 (1.17)	24.3 (.74)	<i>ns</i>
ACE: Fluency	7.13 (.59)	8.12 (.59)	11.7 (.37)	<i>ns</i>
ACE: Language	21.77 (2.44)	22.33 (3.04)	25.6 (.61)	<i>ns</i>
ACE: Visuospatial	11.5 (1.19)	16.67 (1.12)	15.8 (.75)	*
Visuospatial ability				
RCFT: Copy	22.1 (7.17)	28.4 (8.92)	32.72 (3.23)	*
RCFT: Recall	7 (5.65)	11.8 (8.12)	17.55 (5.43)	<i>ns</i>
Dot Counting	9.5 (0.71)	9.8 (0.42)	10 (0)	<i>ns</i>
Position Discrim	18.87 (1.27)	19.7 (0.67)	19.85 (0.37)	*
Cube Analysis	8.11 (2.62)	8.7 (1.88)	9.8 (0.52)	<i>ns</i>
Memory ability				
Total FCSRT	29.21 (2.84)	42.91 (2.63)	47.92 (2.01)	**
FCSRT: Free recall	8.83 (7.94)	17.14 (8.83)	26.83 (4.17)	<i>ns</i>
FCSRT:Cued recall	25.7 (4.94)	20.5 (7.2)	23.35 (4.87)	<i>ns</i>
Supermarket test				
Egocentric	3.44 (3.24)	9.4 (2.27)	8.1 (3.7)	**
Allocentric	69.1 (38.11)	48.41 (12.17)	30.2 (14.13)	<i>ns</i>
Head direction	4.8 (1.33)	5 (3.41)	7.1 (0.9)	<i>ns</i>
Clock test	5.43 (0.81)	10.1 (1.2)	10.1 (0.51)	***

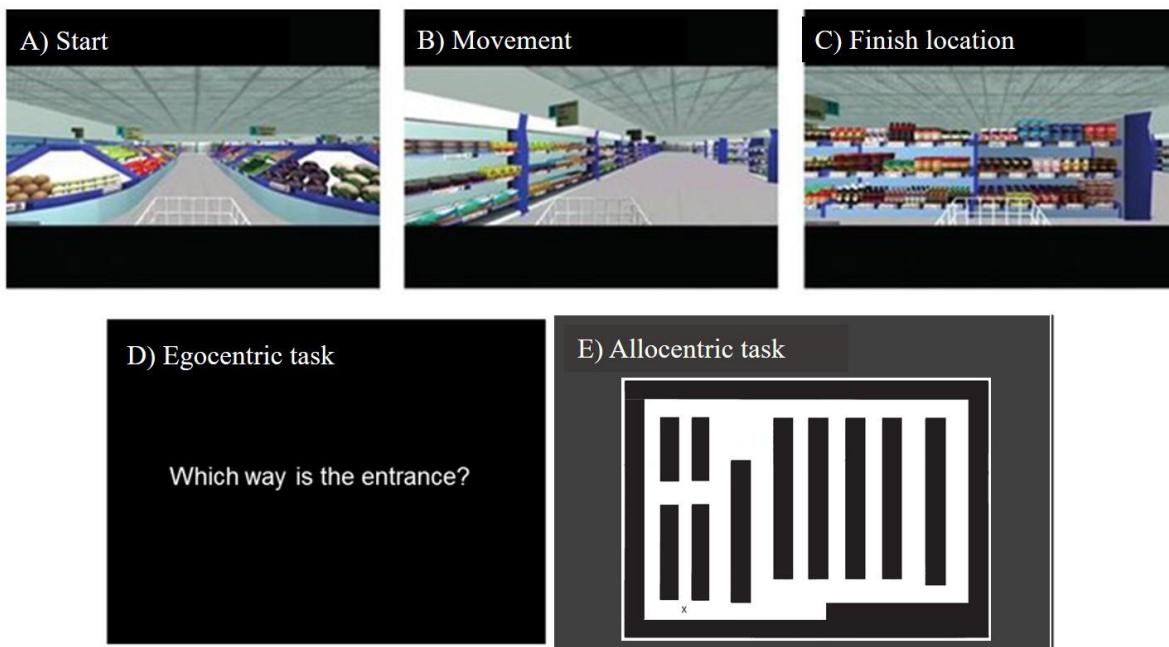
533 * Significant group differences between VCI and AD patients. **p*<.1, ***p*<.01, ****p*<.001.
 534 ACE-III= Addenbrooke's cognitive examination. RCFT: Copy= Rey-Osterrieth Complex
 535 Figure Task, copy condition. RCFT: Recall= Rey-Osterrieth Complex Figure Task, recall 3
 536 minutes after copy. Dot Counting, Position Discrimination and Cube Analysis= sub-sets from
 537 Visual Object and Space Perception Battery (VOSP). FCSRT: free recall= Free and Cued
 538 Selective Reminding, free recall Test condition, FCSRT: free recall= Cued and Cued
 539 Selective Reminding Test, cued condition.

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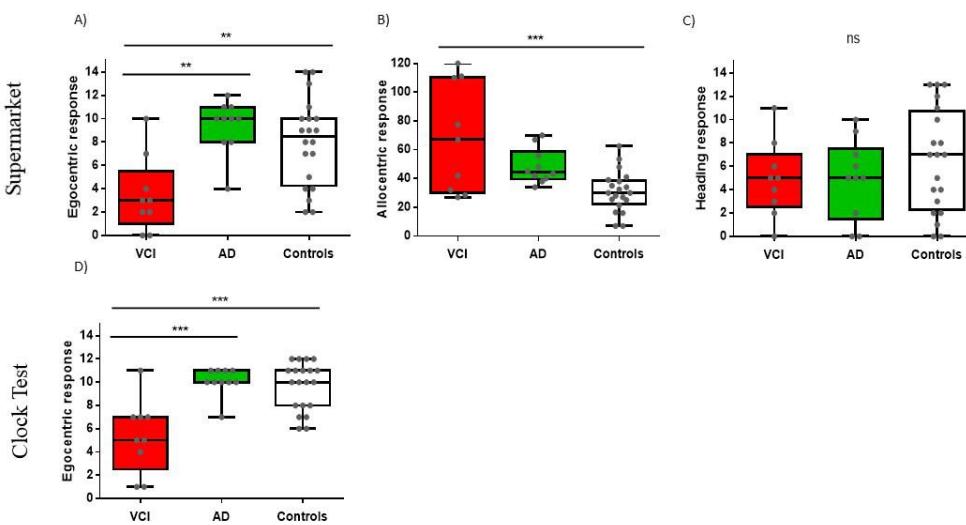
542 **Figure 1.** Screenshots from the supermarket task, showing A) starting viewpoint, B)
 543 movement during example video clip, C) end location of an example video clip, D) onscreen

544 instructions prompting participant to indicate direction of their starting point, E) the
545 supermarket map participants use to indicate their finishing location and their heading
546 direction when the video clip ends.

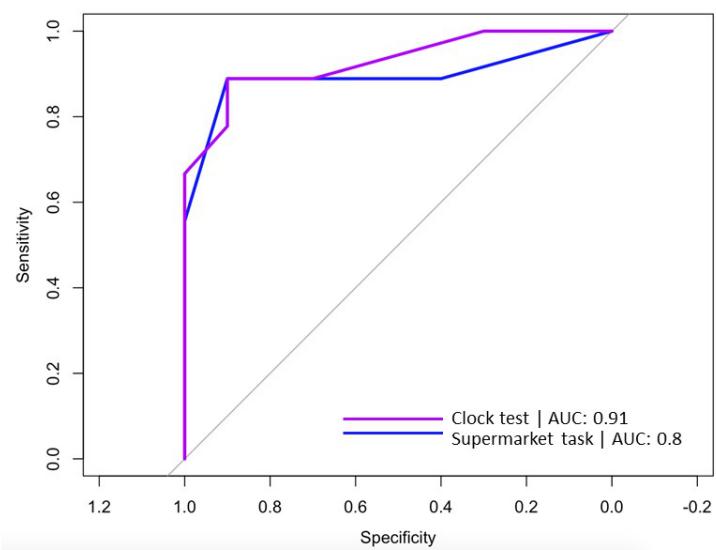


Tu et al (2015, 2017)

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549 **Figure 2.** Spatial orientation performance between VCI, AD and Controls. ** $p < .01$,
550 *** $p < .001$. Supermarket task displays Egocentric response (correct), Allocentric response
551 (error in mm) and Heading response (correct). Clock Orientation test displays Egocentric
552 response (correct).



553
554 **Figure 3.** ROC curves for Supermarket task (blue line) and Clock test (purple line) predicting
555 correct diagnosis (VCI or AD).



556