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Testing of navigation in pre-dementia Alzheimer’s disease using immersive virtual reality

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Introduction

In Alzheimer’s disease(AD), the entorhinal cortex (EC) is one of the first region to show neurodegeneration¹

- Grid cells² and head direction cells³, are implicated in path integration (PI)⁴
- Testing for EC dysfunction can aid diagnosis of early stage AD and help stratification of at-risk individuals for future interventional therapies.

We created a navigation task in immersive virtual reality (VR) to assess path integration function in patients with mild cognitive impairments, a stage prior to dementia onset in AD.

- Performances will differentiate patients with MCI above and beyond cognitive declines due to ageing effects

Methodology

- 45 total MCI patients
 - 11 MCI+ (positive AD biomarkers via CSF)
 - 14 MCI- (negative AD biomarkers via CSF)
- 29 healthy aged-matched controls (OC)
- 30 young healthy controls (YC; age=21.35±1.34)

Neuropsychological

	Healthy Control (n=30)	Mild Cognitive Impairment (MCI) (n=45)		
		MCI (n=20)	Positive (n=11)	Negative (n=14)
Age	*65.45 (±7.69)	70.96 (±8.70)	75.51 (±7.80)	69.55 (±8.69)
Females	F=12 (66.6%)	F=8 (66.6%)	* F=4 (36.36%)	F=7 (50%)
Years in Education	15.12 (±7.59)	14.31 (±3.24)	14.20 (± 4.07)	14.90 (±4.59)
ACE-R	*98.07 (± 2.43)	84.73 (±14.93)	83.1 (±10.53)	87.36 (±7.69)
MMSE	29.74 (±0.54)	27.89 (±5.49)	25.8 (±1.79)	27.90 (± 2.66)
NART Errors	5.85 (±3.25)	*17.11 (±11.26)	9.1 (±6.8)	13.1 (±8.9)
Rey Figure Recall	Copy	35.95 (±0.31)	34.13 (±2.66)	34.4 (±1.95)
	iRecall	21.62 (±7.88)	16.36 (±9.83)	*10.9 (±9.53)
	dRecall	20.74 (±8.05)	15.52 (±11.31)	*9.5 (±10.13)
FCSRT immediate	Free	35.2 (±5.91)	24.38 (±11.05)	*15.2 (±11.66)
	Total	46.85 (±5.37)	44.88 (±4.89)	37.4 (±10.49)
FCSRT delayed	Free	*13.8 (±1.71)	8.72 (±4.94)	*5 (±5.12)
	Total	16 (± 0)	15.5 (± 3.25)	12.6 (±3.74)
Trails B seconds	*77.70 (±41.71)	148.05 (±75.33)	146.85 (±79.15)	127.6 (±37.2)
Digit Symbol correct	*65.42 (±14.19)	48.66 (±13.91)	44.90 (±12.26)	46.9 (±5.44)
4MT correct	10.67 (±2.06)	9.16 (±3.12)	7.1 (±2.33)	6.6 (±2.91)

* indicate group significantly differs from at least one other group. Abbreviations: ACE-R-Addenbrookes Cognitive Examination-Revised; MMSE -Mini-Mental State Examination; FCSRT = Free & Cued Selective Reminding Test; 4MT –Four Mountains Test.

Immersive virtual reality (iVR) path integration (PI) task

- Navigation in immersive open field environments (Fig 1).
- Walking along L-shaped outbound path (Fig 2; from location 1 to 2 to 3)
- Returning to starting location(Fig 2; location 1).
- 9 trials in 3 unique environments (total of 27 trials).

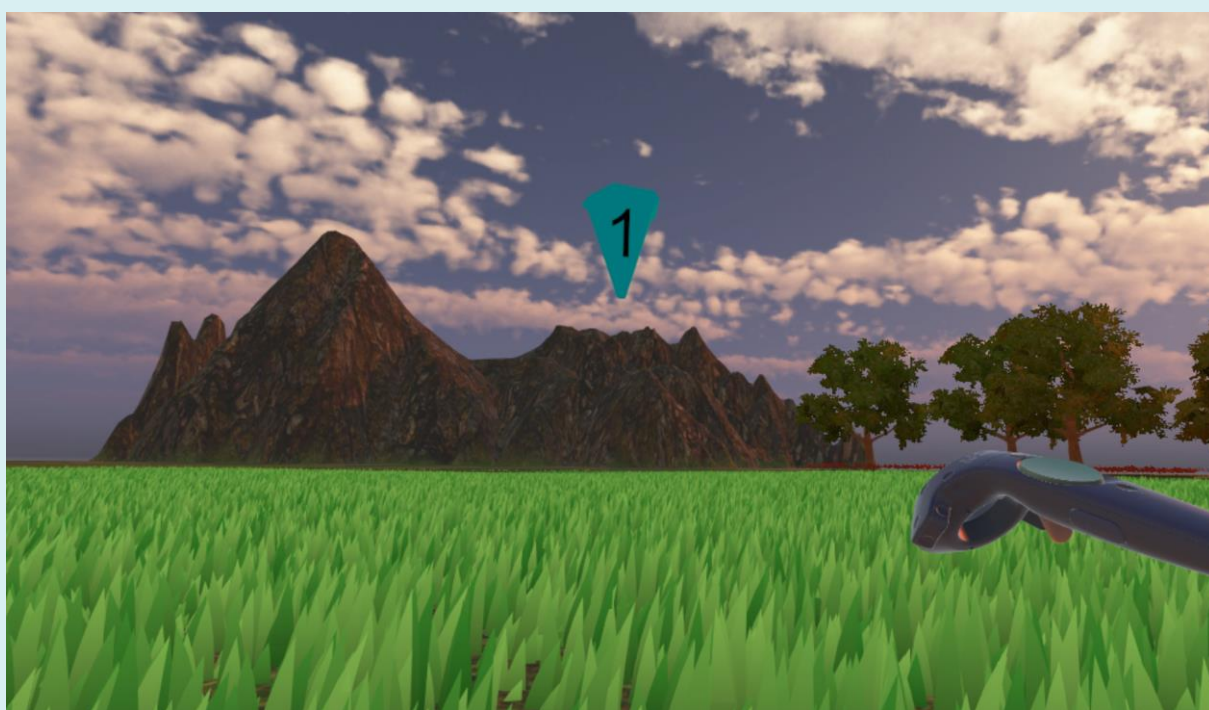


Figure 1. Participant point of view

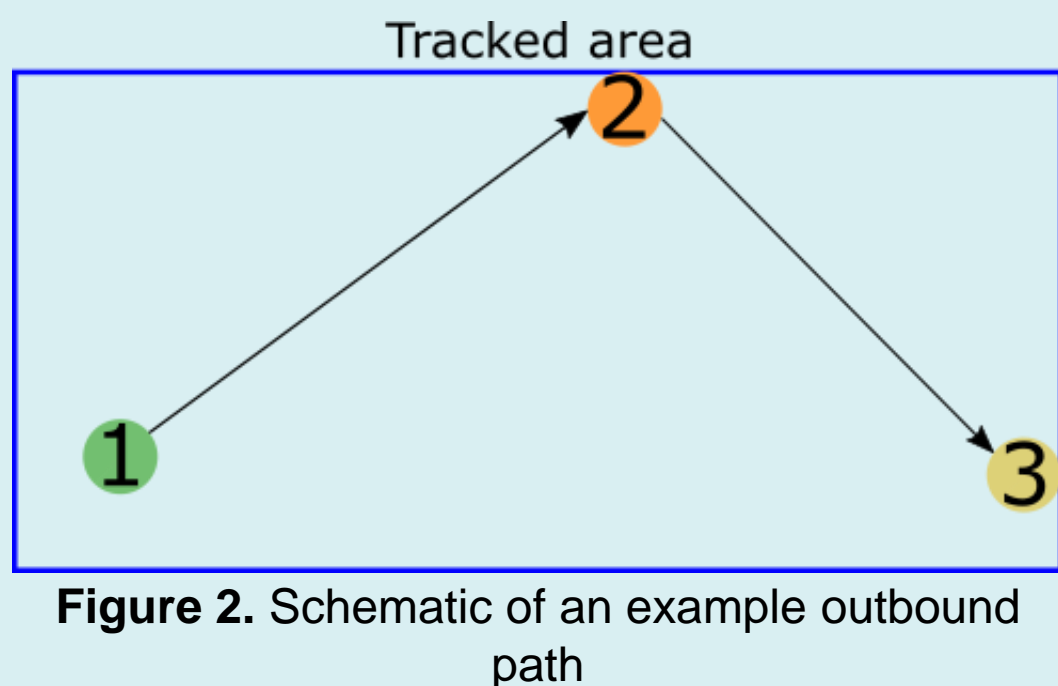


Figure 2. Schematic of an example outbound path



Figure 3. Demonstration of the VR equipment

Outcome measures

Performance were assessed using three different outcome measures.

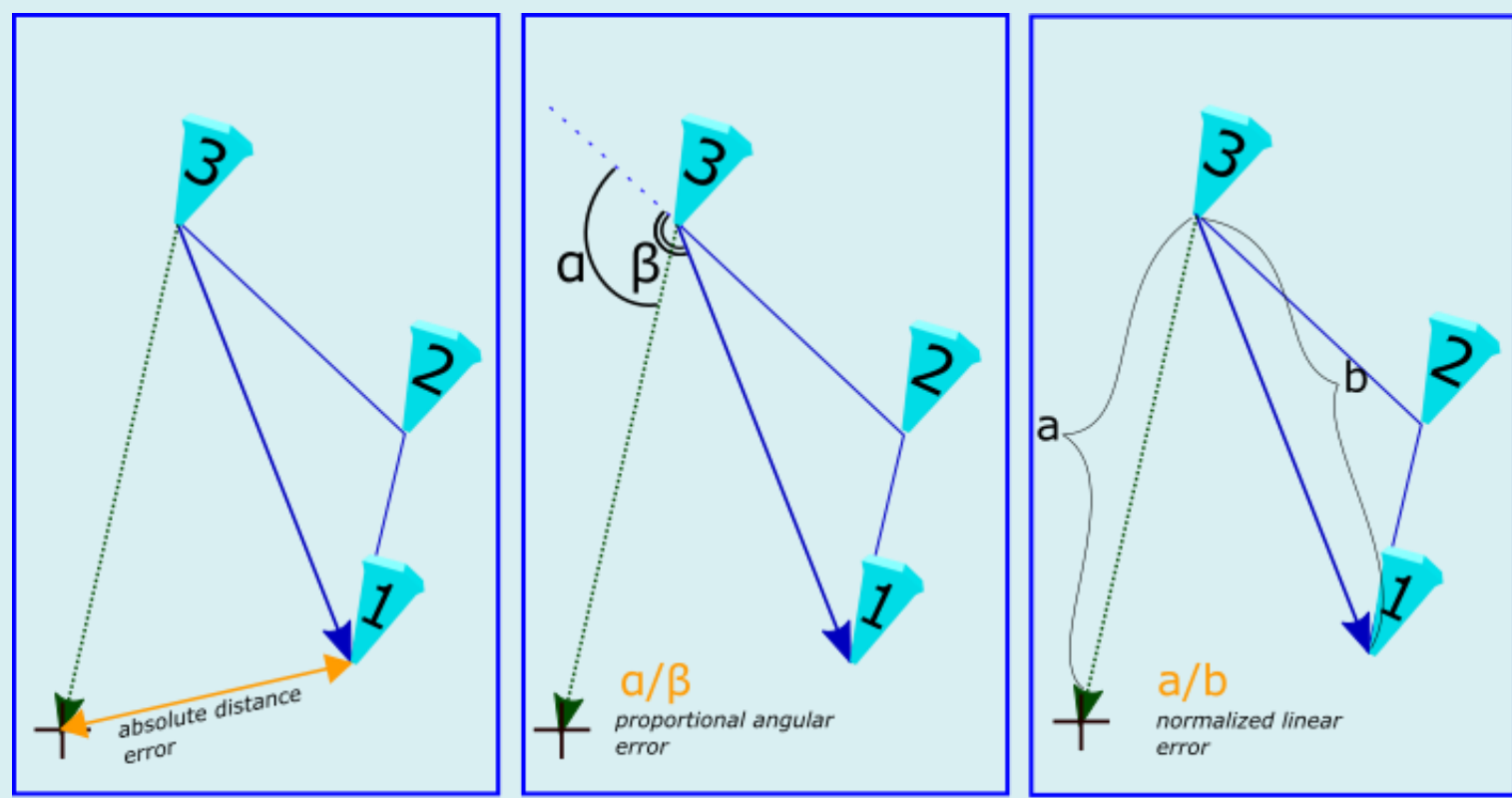


Figure 4. Outcome measures

- **Absolute distance error (Fig 4a):** distance between the indicated location and the real return location.
- **Proportional angular error (Fig 4b):** ratio between participant turn and real turn to face the correct return location.
- **Proportional linear error (Fig 4c):** ratio between the length of walked return path and the length of the real return path.

Results

PI performances

MCI patients show larger errors than YC ($p<0.001$) and OC ($p<0.001$) (Fig 5a) participants in estimating the position of location 1 suggesting an impairment in the MCI patients. In particular, MCI have more difficulties rotating towards the return location (i.e. larger angular errors) compared to OC and YC ($p<0.001$) rather than in estimating the amount of walked distance (i.e. linear error) (Fig 5b, 5c).

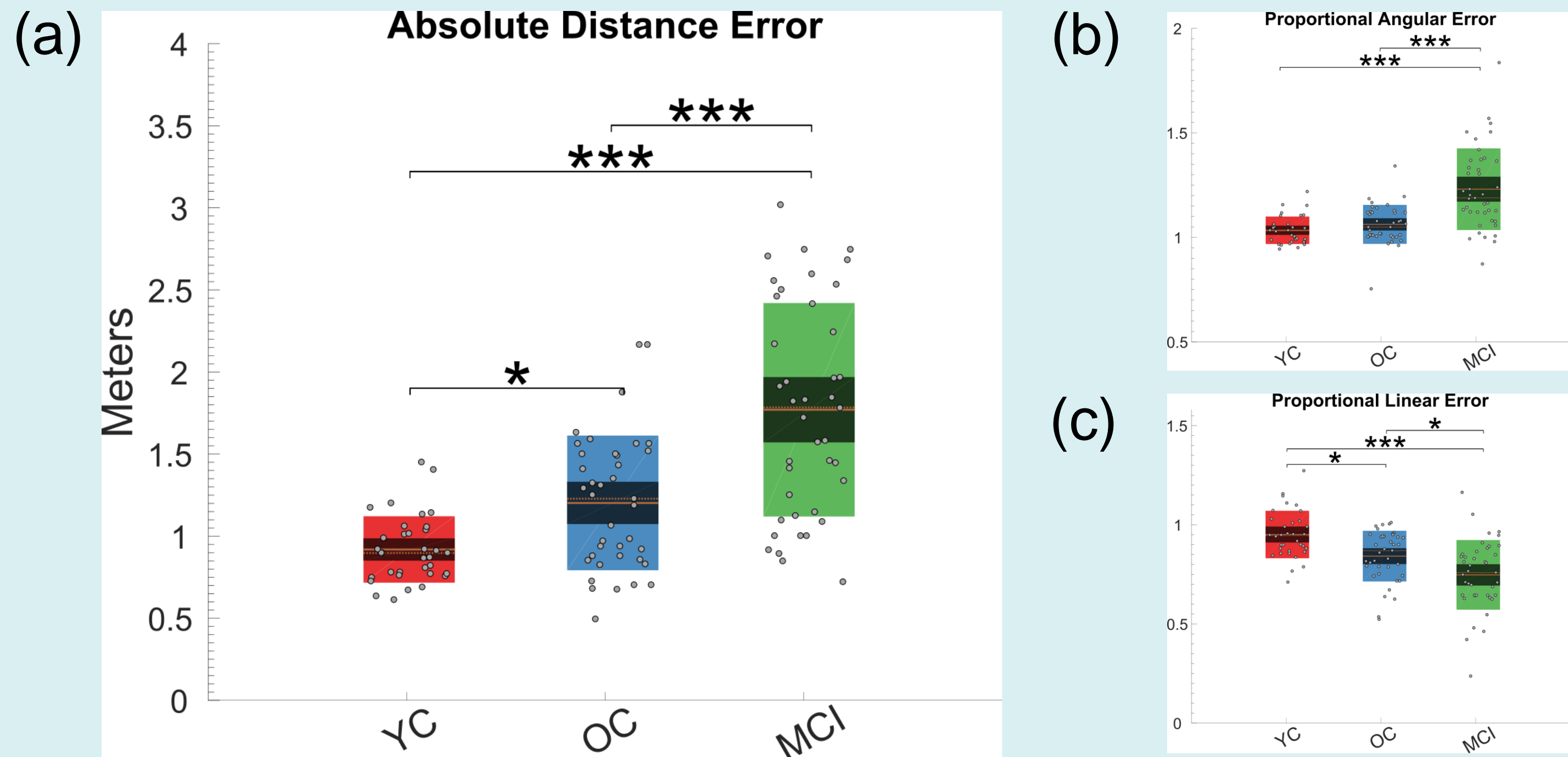


Figure 5. Data distribution per groups. (a) absolute error distance, (b) proportional angular error, (c) proportional linear error

When separated according to the AD biomarker status, MCI+ show larger absolute distance errors ($p<0.001$) compared to MCI- patients (Fig 6a) with contribution to the error given by the angular estimation ($p<0.01$) and linear estimations ($p < 0.001$) (Fig 6b, 6c).

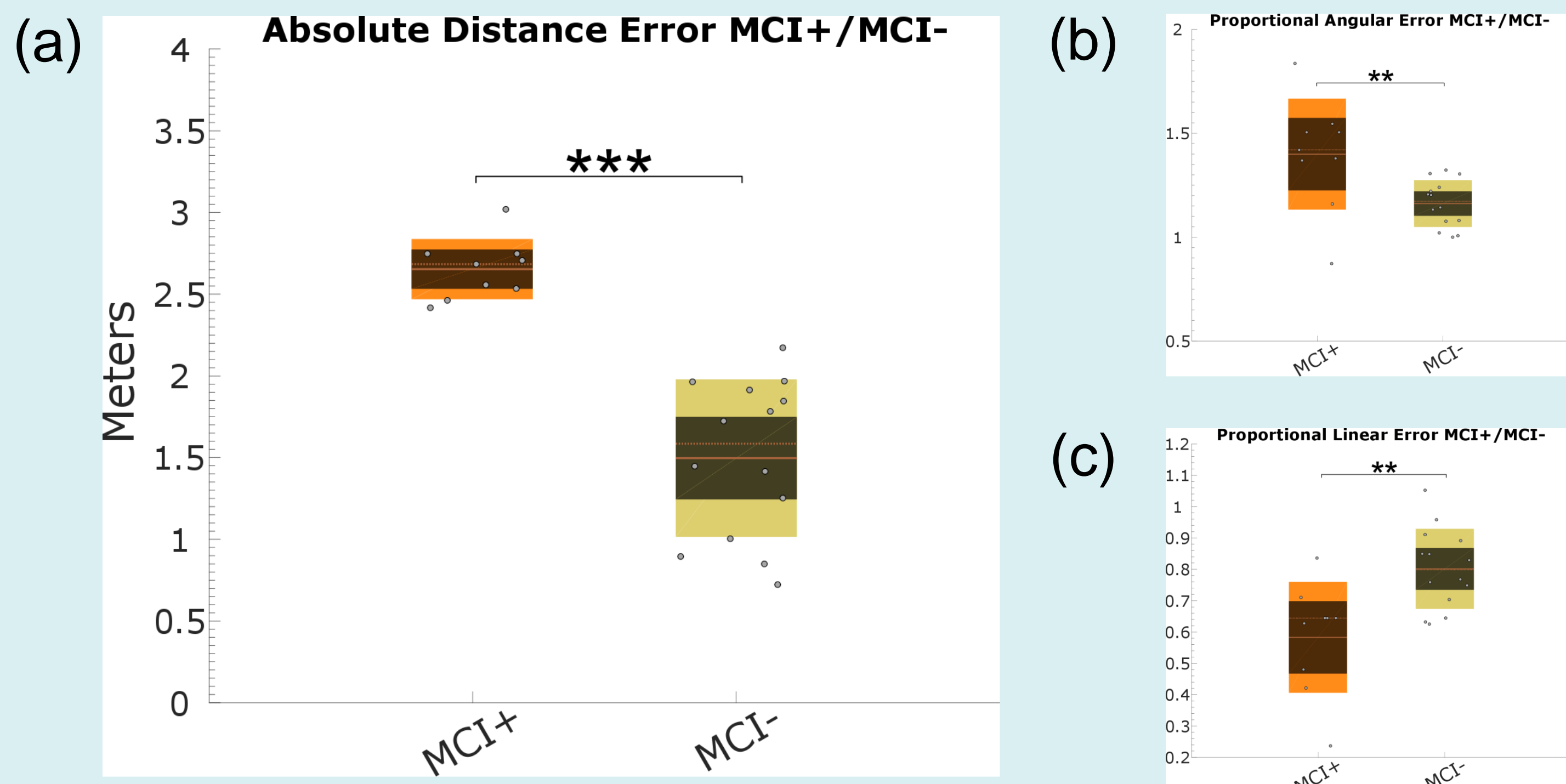


Figure 6. Data distribution for MCI+ and MCI- groups. (a) absolute error distance, (b) proportional angular error, (c) proportional linear error

MCI+/- classification

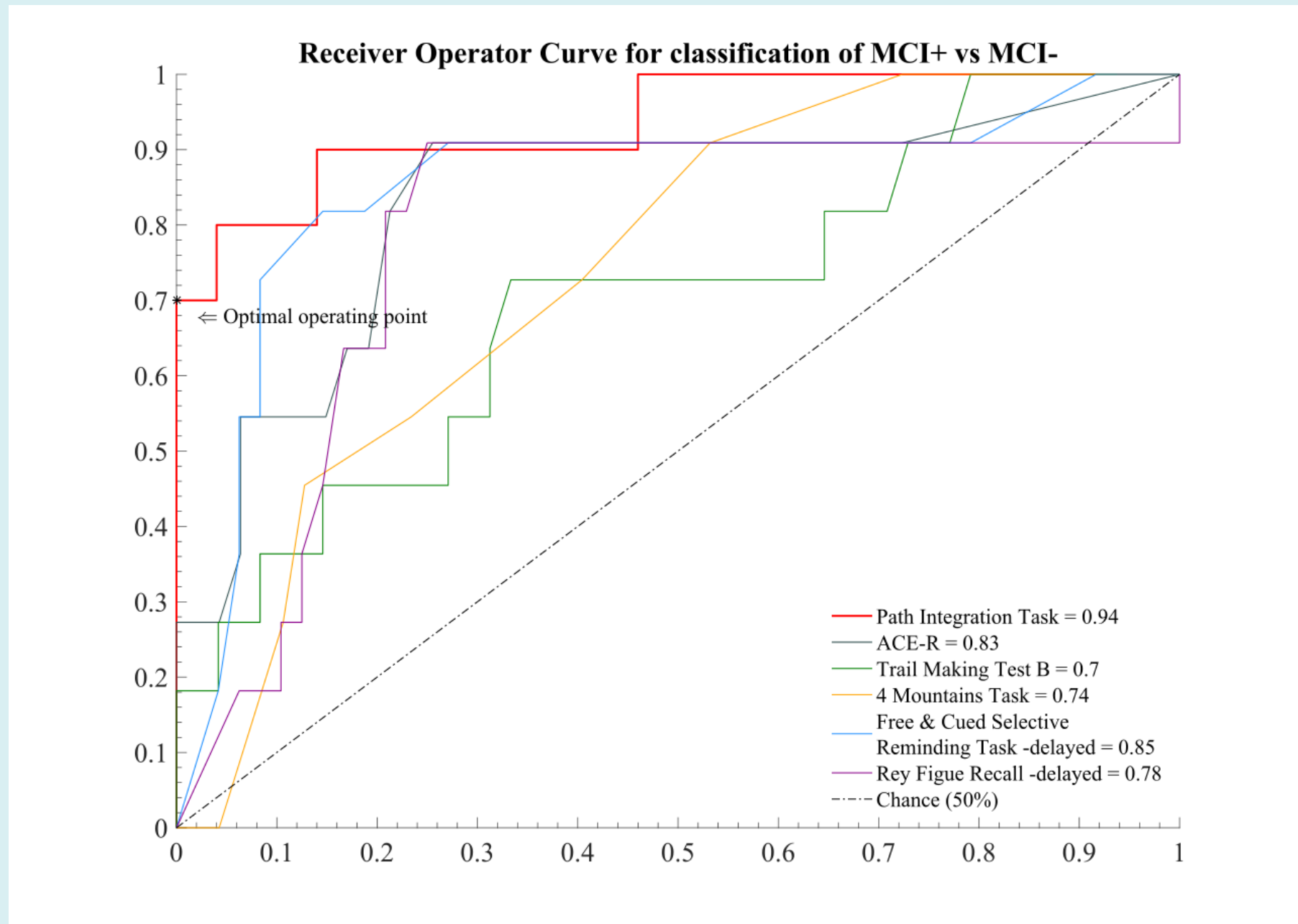


Figure 7. Receiver operating characteristic plot.

- Classification accuracy of this task in delineating MCI+ from MCI-produced an area under the curve of 0.94 (Fig 7; red line). Mean absolute distance error per participant has been used to generate the curve.

- PI task has superior diagnostic sensitivity and specificity compared to the best-in-class neuropsychological tests.

Discussion

All participants concluded the PI task with no tolerability issue, indicating that commercial VR technology is a suitable testing platform for older people.

MCI patients exhibit significant impairments compared to healthy age-matched controls and younger controls suggesting a cognitive decline due to AD that goes beyond the natural ageing decline⁵.

MCI patients with underlying AD exhibit higher degree of impairments when compared to the MCI patients without underlying AD, showing the PI task is able to classify MCI patients with an higher sensitivity than several neuropsychological tests.

These results show that a test of navigation may be of value in the early detection of AD.

¹ Braak H, Brak E (1991). *Acta Neuropathol.* 82 239-59; ² Hafting T, et al (2005). *Nature* 436 801-806; ³ Taube JS, et al (1990). *Journal of Neuroscience* 10 420-435; ⁴ Grieves M, et al (2017). *Behav. Proc.* 135 113-131;

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