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The complementary role of egocentric and allocentric spatial navigation tasks for the diagnosis of Alzheimer's disease: A diagnostic meta-analysis

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ABSTRACT

Spatial navigation impairments represent one of the earliest cognitive changes in patients suffering from Alzheimer's disease (AD), with their underlying neural circuits overlapping regions affected by AD neuropathology. Despite substantial evidence suggesting different navigational impairments across the AD continuum, the diagnostic utility of specific spatial strategies as cognitive markers remains poorly investigated. This diagnostic meta-analysis aimed to systematically evaluate the sensitivity and specificity of egocentric, allocentric, and frame-switching navigation deficits in distinguishing individuals with AD from cognitively healthy controls. First, we carried out a systematic search to identify studies assessing spatial navigation across the AD continuum, compared to cognitively healthy controls or non-AD dementias. Nineteen studies, comprising 1884 participants, were included. Then, meta-analyses quantified diagnostic accuracy (sensitivity, specificity, diagnostic odds ratios) of spatial navigation tasks. Results revealed complementary diagnostic profiles across spatial strategies, supporting their complementary use for AD detection. Allocentric tasks demonstrated balanced diagnostic performance, correctly identifying 84 % of AD cases while accurately classifying 83 % of cognitively healthy individuals. Frame-switching tasks provided high AD detection (84 % sensitivity) but reduced specificity (66 %), making them valuable for excluding AD but less reliable for confirming it. Combined egocentric-allocentric tasks achieved the highest specificity (94 %), while egocentric tasks showed good specificity (81 %) but limited sensitivity (72 %), suggesting that egocentric abilities remain preserved until advanced disease stages. Taken together, these findings suggest that a strategic approach to spatial navigation assessment is crucial for AD detection.

1. Introduction

Spatial navigation is traditionally defined as our ability to determine and maintain a path through the environment. This fundamental cognitive function is essential for survival across species, from basic evolutionary behaviors (such as foraging for food or avoiding predators) to complex human activities in daily life (Ekstrom and Hill, 2023; Patai and Spiers, 2021). Imagine yourself attending an international conference in an unfamiliar city. After the morning session, you explore the city during lunch break. Walking through several streets, you find a restaurant for lunch, and then you need to return to the conference venue. What might appear to be a simple task reveals the complexity of human spatial cognition: you must process both external and internal cues, compute spatial relationships between environmental landmarks, maintain self-orientation, and flexibly alternate between different navigational strategies. Therefore, it is not surprising that declining navigation abilities significantly impact the autonomy and quality of life of older adults (Lester et al., 2017; Moffat, 2009), with spatial navigation deficits representing one of the earliest changes in Alzheimer's disease (AD) and thus offering a particularly relevant cognitive domain for early detection and differential diagnosis (Coughlan et al., 2018; Serino et al., 2014; Tuena et al., 2021).

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A rich body of experimental research has increasingly revealed how we successfully navigate our surroundings - or why we occasionally get lost (Burgess, 2006; Patai and Spiers, 2021; Spiers and Maguire, 2007). Spatial navigation is inherently dynamic and multisensory (Ekstrom et al., 2017; Epstein et al., 2017). When we navigate, we simultaneously process multiple pieces of information to build transient and enduring spatial knowledge (Wolbers and Hegarty, 2010). While environmental visual cues (i.e., landmarks and boundaries) are often preferred during navigation to orient in the environment (Ekstrom, 2015), we also continuously integrate body-based inputs from the vestibular, proprioceptive, and somatosensory systems, as well as motor efference information (Angelaki and Cullen, 2008; Iggena et al., 2023; Ottink et al., 2022). These body-based signals allow for path integration, a process whereby we track our position and orientation by integrating self-motion cues. Crucially, this process accumulates errors over time that can be minimized by using environmental cues, particularly boundaries (Anastasiou et al., 2023; Chersi and Burgess, 2015; Hardcastle et al., 2015). This information is organized into coherent spatial representations via two complementary reference frames – egocentric and allocentric – which support both online (real-time navigation) and offline (memory retrieval) spatial processing (Ekstrom and Hill, 2023). Klatzky (1998) provided a seminal definition of a reference frame, suggesting that we spatially define the position of objects based on two specific anchoring points. Accordingly, in egocentric frames, spatial positions are coded relative to the observer's body (e.g., "*the conference venue is to my left*"), while when we use allocentric frames, spatial relationships between landmarks are coded independent of the observer's position (e.g., "*the conference venue is north of the park*"). When we navigate, these reference frames support different wayfinding strategies that vary both in cognitive demands and flexibility. Response-based navigation, mainly supported by the dorsal striatum, involves a form of egocentric processing through stimulus-response associations (Ekstrom and Hill, 2023). This strategy indeed implies learning sequences of landmarks and associated turning decisions (e.g., "*at the church, turn right; at the grocery store, turn left*") that are useful to guide navigation along a familiar environment. On the other hand, cognitive map-based navigation involves a form of allocentric processing based on spatial relationships between landmarks. This strategy, mainly supported by the medial temporal lobe, requires building an abstract cognitive map (e.g.,"*from the church, cut diagonally across the square to reach the grocery shop two blocks east*"), which enables flexible wayfinding also in unfamiliar environments (Ekstrom and Hill, 2023).

Egocentric and allocentric reference frames co-exist and operate in parallel across adulthood. Neurophysiological rodent studies have identified specialized neurons in the hippocampus and medial entorhinal cortex, such as place cells, grid cells, head direction cells, and boundary cells (Boccara et al., 2010; Hartley et al., 2014; Moser et al., 2008; O'Keefe and Dostrovsky, 1971; Tolman, 1948), providing neurophysiological support for allocentric spatial processing. These seminal findings from animal research have been fundamental in shaping theoretical frameworks and experimental paradigms in human spatial navigation research. Importantly, subsequent intracranial recordings in epilepsy patients have confirmed the presence of similar allocentric coding mechanisms in the human medial temporal lobe (MTL) (see, for example, Ekstrom et al., 2003). In parallel, neuroimaging studies have revealed anatomically distinct neural circuits supporting allocentric and egocentric processing. On one side, the dorsal striatum primarily supports response-based navigation through stored egocentric stimulus-response associations that guide navigational choices (Chersi and Burgess, 2015), working with posterior parietal regions that maintain egocentric spatial representations of the environment (Stein, 1992). On the other hand, when navigation requires self-localization and computing flexible spatial relationships to goals, the hippocampus and connected structures in the MTL, including the entorhinal cortex, play essential roles in allocentric cognitive map navigation (Epstein et al., 2017). This neural network extends beyond the MTL: in particular, the parahippocampal cortex supports specific view recognition (Epstein et al., 2007), while the retrosplenial cortex mediates conversion between allocentric representations in hippocampal-entorhinal regions to egocentric representations in the posterior parietal cortex, and *vice versa* (Byrne et al., 2007; Vann et al., 2009; Burgess, 2008). This transformational role of the retrosplenial cortex is also supported by computational models: Bicanski and Burgess (Bicanski and Burgess, 2018) provide a detailed neural network model illustrating how egocentric spatial representations in parietal cortex interface with allocentric representations in the hippocampal formation via the retrosplenial cortex. In their model, "gain-field" neurons in retrosplenial areas use head-direction or gaze signals to transform egocentric inputs into allocentric codes.

Finally, the behavioral dissociation of egocentric and allocentric processing has been progressively refined through methodological advances that moved beyond early paradigms, which often confounded reference-frame use with other cognitive demands (Harris and Wolbers, 2014). The development of controlled real-world and virtual reality (VR) navigation tasks, including shifted-viewpoint paradigms (Burgess et al., 2006; King et al., 2002) and human analogs of the traditional Morris Water Maze (Laczó et al., 2010), has provided increasingly accurate tools for isolating and measuring egocentric and allocentric abilities. These approaches have traditionally supported functional distinctions in both online navigation and spatial memory (Ekstrom and Hill, 2023).

Although egocentric processing is primarily supported by the dorsal striatum and posterior parietal cortex, and allocentric processing by the MTL, this separation is not absolute. For example, Long and colleagues (Long et al., 2025) recently demonstrated that allocentric and egocentric representations coexist within the rodent medial entorhinal cortex - indicating a shared locus of interaction - and Kunz and colleagues (Kunz et al., 2021) identified human 'egocentric bearing cells' in the parahippocampal cortex that mirror allocentric cell types, further highlighting overlapping neural substrates for both reference frames. Within the theoretical framework outlined thus far, literature on spatial navigation deficits in aging has evolved significantly over time. These research efforts have progressively revealed distinct patterns of navigational decline in physiological aging versus Alzheimer's disease (AD), with the neuroanatomical distribution of spatial navigation mechanisms showing remarkable alignment with the progression of AD dementia neuropathology (Braak et al., 2006; Jagust, 2018; McKhann et al., 2011).

Research on spatial navigation in healthy aging presents a complex picture: while several studies suggest that older adults increasingly rely on egocentric over allocentric strategies (Colombo et al., 2017; Ladyka-Wojcik and Barense, 2021; Moffat, 2009), recent evidence challenges this traditional view of an age-related decline, specifically in allocentric navigation. On one side, for instance, Schuck and colleagues found that older adults predominantly use landmark information with greater caudate nucleus engagement, indicating a shift from hippocampal-dependent to caudate-mediated navigation strategies (Schuck et al., 2015). However, using a fully immersive virtual Morris Water Maze with free ambulation, McAvan and colleagues (McAvan et al., 2021) revealed that while older adults demonstrated less precise spatial memories for target locations, they maintained crucial navigational abilities: they performed comparably when navigating from both familiar and novel viewpoints and showed comparable reliance on allocentric versus beaconing strategies as younger adults. Critically, healthy older adults show a particular difficulty in switching between reference frames. For instance, Harris and Wolbers (2014) demonstrated that while performance within a single reference frame remains relatively preserved, older adults struggle specifically when transitioning from egocentric to allocentric navigation.

In pathological aging associated with AD dementia, navigational deficits extend beyond age-related changes, including earlier and more pronounced deficits in allocentric navigation, coupled with an eventual

deterioration of the compensatory egocentric strategies. As consistently demonstrated, the hallmark navigational impairment in AD dementia involves constructing and storing allocentric spatial representations (Serino et al., 2014; Tuena et al., 2021; Weintraub et al., 2012). Pioneering evidence came from Burgess and colleagues (Burgess et al., 2006), who developed a desktop-VR shifted-viewpoint task. In their study, a patient with AD dementia learned object locations from a fixed perspective in a virtual town square. When later tested, AD dementia patients could accurately recall object locations when viewing the environment from the original position (egocentric memory) but exhibited a specific difficulty when asked to retrieve the locations from a viewpoint shifted approximately 135° away (allocentric memory). These findings have been consistently replicated (Coughlan et al., 2018; Jheng and Pai, 2009; Kalová et al., 2005; Nedelska et al., 2012; Parizkova et al., 2018; Serino et al., 2015) and extended to earlier disease stages. Importantly, mild cognitive impairment (MCI) has been proposed as a transitional stage from normal aging to dementia (Petersen, 2001), with particularly elevated AD risk in individuals showing objective memory deficits (amnestic MCI or aMCI) compared to those with non-amnestic impairments (Dubois and Albert, 2004). Consistent with the progression model of AD, individuals with aMCI not only report subjective navigational complaints but also manifest objective impairments in allocentric spatial navigation (Boccia et al., 2016; Hort et al., 2007; Laczó et al., 2009), even at these prodromal stages (Lithfous et al., 2013). For example, Laczó and colleagues (Laczó et al., 2023) used a virtual supermarket to differentiate older adults with aMCI who have positive (+) AD biomarkers from those with negative (-) AD biomarkers. After navigating the environment, participants were asked to perform two different tasks: first, indicating their starting position (egocentric heading), and second, indicating both their current position and final heading orientation on an aerial supermarket map (measuring allocentric retrieval). While both egocentric and allocentric navigation tasks revealed impairments in patients with aMCI due to AD from non-AD aMCI, only allocentric performance could differentiate between those conditions. Likewise, the 4 Mountains Test, a hippocampal-dependent allocentric spatial memory assessment requiring landscapes to be recognized from shifted viewpoints, has been demonstrated to be predictive of prodromal mild cognitive impairment due to AD (Wood et al., 2016).

The reference frame switching deficit appears particularly informative across the AD spectrum, including its prodromal stages (Serino et al., 2014). For instance, Morganti and colleagues (Morganti et al., 2013) compared AD patients with healthy elderly controls using two VR-based spatial tasks: the VR-Maze Task and VR-Road Map Task. Their results demonstrated that AD patients showed specific impairment in performing the allocentric-to-egocentric translation of spatial knowledge during virtual wayfinding. Serino and colleagues (Serino et al., 2015) provided evidence of progressive deterioration in strategy switching across the AD spectrum. After memorizing object locations in a virtual room, participants had to recall these locations on a real map (allocentric retrieval) or start from a different position in an empty version of the virtual room (requiring a switch between spatial representations). Results revealed that aMCI patients showed specific deficits in encoding and storing allocentric viewpoint-independent representations, while AD patients were impaired not only in storing allocentric representations but also, critically, in syncing stored allocentric knowledge with viewpoint-dependent representations during egocentric navigation, indicating a more severe and multifaceted spatial processing deficit. This differential pattern was further investigated by Ruggiero and colleagues (Ruggiero et al., 2018), who compared AD and aMCI patients with cognitively healthy older adults on an Ego-Allo-Switching spatial memory task. Their paradigm assessed the capacity to use switching (Ego-Allo, Allo-Ego) and non-switching (Ego-Ego, Allo-Allo) verbal judgments about relative distances between memorized stimuli. In the switching conditions, participants first judged which object was closer to themselves, then switched to judging which object was closer to a reference object (Ego-Allo); the reverse was done for the Allo-Ego condition, starting with an allocentric judgment, and switching to an egocentric one. Their results revealed a distinct impairment in aMCI and AD patients when switching from allocentric to egocentric reference frames. Importantly, they observed that when the first reference frame was egocentric, the allocentric deficit in aMCI appeared attenuated, suggesting that allocentric deficits might not always be clinically detectable in prodromal stages if testing procedures start with egocentric reference frames. Interestingly, evidence suggests that egocentric impairments are also present across the AD continuum (Bianchini et al., 2014; Hashimoto et al., 2020). Weniger and colleagues (Weniger et al., 2011) provided some of the first evidence for egocentric impairment using virtual navigation tasks. They required participants to find a hidden goal in a maze without any landmarks, primarily involving egocentric processing, and a virtual park task, asking participants to find a hidden goal in an environment containing various landmarks, primarily engaging allocentric processing. Their results suggested that aMCI patients showed significant impairments not only in allocentric but also in egocentric navigation when compared to cognitively healthy controls. Importantly, these egocentric navigation deficits correlated with reduced volumes in the precuneus, highlighting the involvement of medial parietal regions in egocentric navigation impairments even at prodromal stages. Intriguingly, from a recent systematic review (Tuena et al., 2021), patients with hippocampal amnesia compatible with AD exhibited greater egocentric errors in a hidden goal task (HGT) when compared to aMCI patients with frontal amnesia; their performance closely resembled that of individuals with AD dementia. In the same review, aMCI with genetic risk of AD (E4 +) exhibited greater egocentric and allocentric errors in the HGT, like AD dementia performance, when compared to aMCI with frontal amnesia. Together, these findings highlight that the relative contribution of egocentric and allocentric spatial memory deficits in the prodromal phases of AD is still uncertain.

Despite the substantial evidence suggesting different patterns of navigational impairment in healthy aging versus the AD continuum, the diagnostic utility of specific spatial mechanisms as cognitive markers remains poorly investigated (Coughlan et al., 2018). Additionally, quantifying the diagnostic utility of each specific navigational strategy may support the clinical diagnosis of AD, which currently relies primarily on biomarker-based approaches and on neuropsychological assessments (Jack et al., 2018; McKhann et al., 2011). Although these methods are widely accepted, they present some limitations: biomarker-based approaches are often costly, may require invasive procedures, and have limited accessibility, while neuropsychological testing heavily depends on patient and/or caregiver self-reports, introducing potential bias. In contrast, spatial navigation assessments offer the potential for more objective, accessible, and cost-effective screening tools.

This meta-analysis addresses this critical gap in the literature by systematically evaluating the sensitivity and specificity of egocentric, allocentric, and frame-switching navigation deficits in distinguishing individuals within the AD continuum from cognitively healthy controls. Specifically, sensitivity refers to a test's ability to correctly identify individuals with the disease (i.e., minimizing false negatives, namely if the test is negative the disease should be ruled out), whereas specificity indicates its capacity to correctly exclude those without the disease (i.e., minimizing false positives, namely if the test is positive the disease should be ruled in). Based on the evidence reviewed so far, we advance the following hypotheses regarding the diagnostic performance of different spatial navigation strategies. First, we expect that egocentric tasks will provide high specificity but low sensitivity. Since egocentric navigation remains relatively preserved in physiological aging and becomes compromised only in more advanced stages of AD or in specific patient subgroups, we predict that these tasks will correctly classify most cognitively healthy individuals as cognitively healthy (high specificity) but fail to detect many true AD cases (low sensitivity). Second, we

predict that allocentric tasks will have balanced diagnostic performance between sensitivity and specificity. Although physiological aging involves some decline in allocentric navigation abilities, deficits are typically more severe in AD patients. Accordingly, these tasks will capture a moderate proportion of true AD cases (high sensitivity) while excluding most cognitively healthy individuals (high specificity). Finally, we expect that frame-switching tasks will show high sensitivity but relatively lower specificity. The ability to flexibly switch between egocentric and allocentric representations is severely impaired in AD but also shows a significant decline in physiological aging, particularly when patients are asked to switch from egocentric to allocentric strategies. These tasks will successfully detect most AD cases (high sensitivity) but may also misclassify some cognitively healthy individuals as impaired (lower specificity). We will also include comprehensive spatial tasks that integrate both egocentric and allocentric processing without explicitly differentiating between them, providing an ecologically valid comparison to tasks that selectively assess specific spatial reference frames. Overall, we predict that these cognitive processes may represent promising cognitive markers for early AD continuum diagnosis.

2. Methods

2.1. Literature search

This meta-analysis was conducted (initial search July 6, 2023, updated February 12, 2025) following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2009). The review was registered in PROSPERO (registration number: CRD42023400009). Keyword selection followed the population, intervention, comparison, outcome (PICO) framework (Methley et al., 2014), using the following terms: 'specificity' OR 'sensitivity' OR 'AUC' OR 'ROC' AND 'spatial' OR 'navigation' AND 'aMCI' OR 'MCI' OR 'dementia' OR 'Alzheimer'.[1] The comparison term was omitted from our PICO framework to include all studies on spatial memory assessment regardless of the reference standard used. Thus, our guiding PICO question was: "*Are spatial memory and navigation tasks accurate diagnostic tools for AD detection?*". These keywords were searched across PubMed, Web of Science, PsycINFO, and Embase databases. All keywords were queried within the title, abstract, and keyword fields.

Following duplicates removal, two blinded researchers (CSB and GM) utilized a web-based systematic review tool (Ouzzani et al., 2016) to select records according to predefined inclusion/exclusion criteria. The initial screening examined titles and abstracts, categorizing papers as 'included', 'excluded', or 'uncertain'. Similarly, the secondary screening evaluated full-text articles that passed the initial phase. Authors of unavailable full-text papers were contacted. Throughout both screening phases, discrepancies were resolved by researcher consensus, with a third author (CT) consulted for unresolved disagreements.

2.2. Selection criteria

We implemented a hierarchical eligibility framework for both title/abstract and full-text screening (quantitative exclusion data presented in Fig. 1[2]):

1. English language publications.
2. Original research articles (excluding meta-analyses, systematic reviews, editorials, narrative reviews, perspective articles, and conference proceedings).
3. Human studies featuring participants with preclinical (e.g., subjective complaint with positive AD biomarkers), prodromal (mild objective impairment), or clinical (dementia) Alzheimer's syndrome staging, with or without evidence of AD biomarkers or genetic risk (Jack et al., 2018) compared to a control sample of healthy participants or non-AD dementias.
4. Inclusion of real-world, VR, computer-based, or paper-pencil spatial navigation and spatial memory tasks providing diagnostic metrics (e.g., AUC, sensitivity, specificity, true positive [TP], false positive [FP], true negative [TN], false negative [FN]). Crucially, we included only studies that employed experimental paradigms specifically designed to assess distinct spatial representation systems: egocentric reference frames, allocentric reference frames, and the ability to flexibly switch between these frames. Additionally, we included tasks that either engage in multiple spatial reference frames simultaneously or provide a composite score incorporating both egocentric and allocentric performance. In our results section, we refer to these different spatial processing collectively as 'spatial strategies'. As a result, we excluded studies focusing on different or less specific constructs, such as visuospatial memory (e.g., tasks like the Corsi Block-Tapping Test) and constructional praxis (e.g., copying the Rey–Rey-Osterrieth Complex Figure), which, while related to spatial cognition, do not allow for the dissociation or measurement of specific spatial reference frames or frame-switching processes.
5. Diagnostic or assessment studies (excluding RCTs, usability studies, pragmatic trials, case studies)
6. Utilization of a reference standard (established diagnostic criteria for dementia, MCI, and AD pathology) for task outcome comparison.

2.3. Data extraction and synthesis

Two independent authors (CSB and GM) performed data extraction for all included studies, verifying accuracy and comprehensiveness. The extracted variables comprised: (1) sample and setting characteristics (population size, cohort descriptions); (2) detailed spatial cognition task specifications: studies were rated as assessing egocentric, allocentric, switching (ego-to-allo or allo-to-ego), or combined (ego+allo) mechanisms according to procedure description of the paper or in the case of unclear definition by a blind assessment between two researchers (CT and SS) aided by research definitions and by a third researcher (CSB) in the case of discordant assessment; for unclear methodology, we used definitions outlined by previous studies to determine if an allocentric (i.e., boundary-based, survey-map knowledge), egocentric (i.e., landmark-based, route knowledge), or switch (i.e., route to survey-map or survey-map to route knowledge switch) was employed in the task (Chersi and Burgess, 2015; Klatzky, 1998; Zhong and Kozhevnikov, 2016); (3) reference standard parameters (classification, diagnostic criteria, neuropsychological assessment protocols); and (4) diagnostic performance metrics (accuracy, sensitivity, specificity, true positives, false positives, true negatives, false negatives). The comprehensive extracted dataset is presented in Table 1 (including spatial task details), reported in Supplementary Material 1.

2.4. Risk of bias assessment

Overall study quality was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-Comparative (QUADAS-2) framework (Whiting et al., 2011). Two blind researchers (CSB and GM) independently assessed each study for potential bias sources, categorizing them as 'high risk', 'low risk', or 'unclear risk' across four domains: (1) patient selection, (2) index test conduct and interpretation, (3) reference standard implementation and interpretation, and (4) patient flow procedures. A third researcher (CT) was consulted if consensus was not met. See

[1] AUC (Area Under the Curve) and ROC (Receiver Operating Characteristic) are commonly used metrics to evaluate the diagnostic accuracy of a test. The ROC curve plots the true positive rate (namely, sensitivity) against the false positive rate (1 - specificity) across different thresholds, while the AUC represents the ability of the test to discriminate between conditions (e.g., presence vs. absence of disease).

[2] Reasons are reported in detail in the Selection Criteria section. No paper was excluded due to Reason 6.

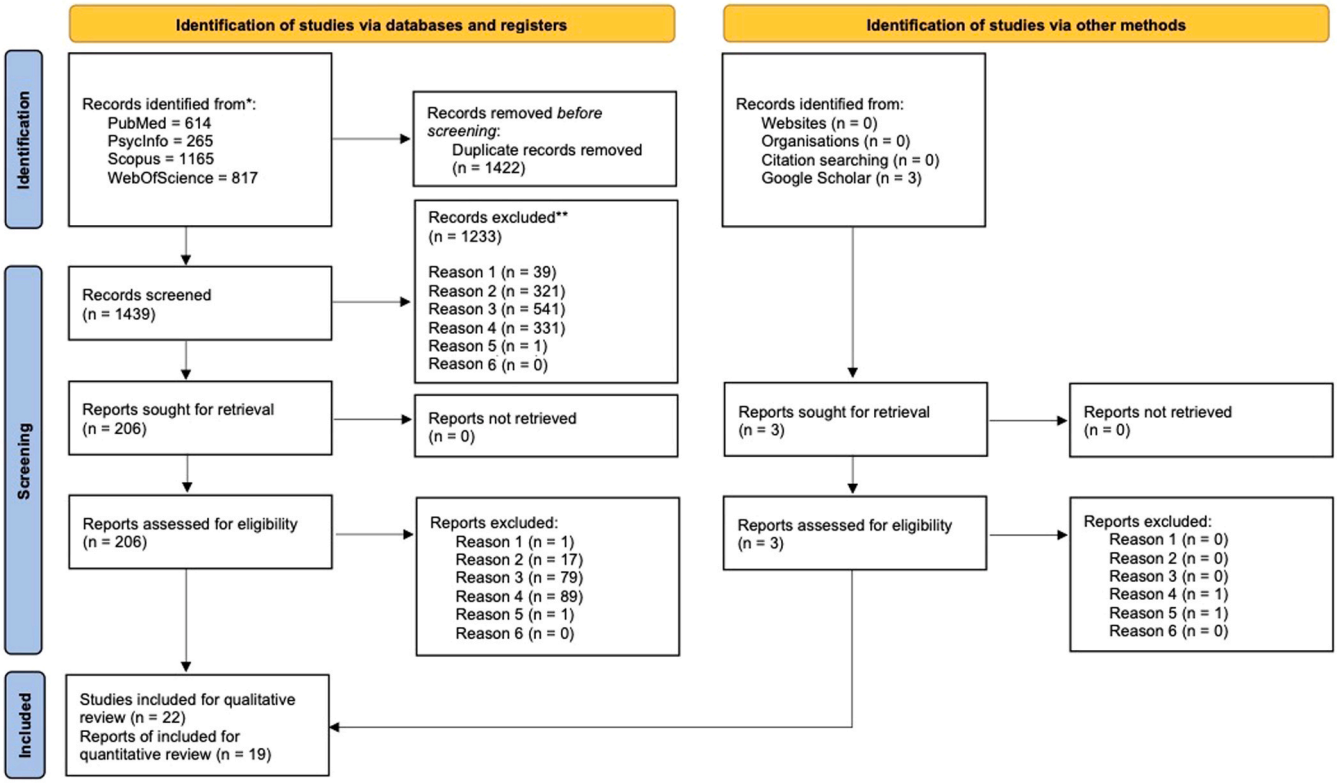

Fig. 1. *PRISMA Flow Chart.* Reason 1: English language publications; Reason 2: Original research articles; Reason 3: Human studies featuring participants within Alzheimer's disease continuum or other dementias; Reason 4: Inclusion of real-world, virtual reality, computer-based, or paper-pencil spatial navigation and spatial memory egocentric and allocentric tasks; Reason 5: Diagnostic or assessment studies; Reason 6: Utilization of a diagnostic reference standard for task outcome comparison. Reasons for inclusion/exclusion are reported in detail in Section 2.2.

Table 1
Specificity post-hoc comparisons. p-value is adjusted with the Bonferroni method.

Group1	Group2	Logit-transf. Diff.	SE Diff.	Z value	p-value	CI_lower	CI_upper	p-adjusted
allocentric	egocentric	0.20	0.40	0.50	0.617	−0.59	0.99	1.000
allocentric	ego+allo	−1.06	1.11	−0.96	0.338	−3.23	1.11	1.000
allocentric	switch	0.98	0.30	3.33	**0.001**	0.40	1.56	**0.005**
egocentric	ego+allo	−1.26	1.12	−1.13	0.258	−3.45	0.93	1.000
egocentric	switch	0.78	0.33	2.34	**0.019**	0.13	1.44	0.114
ego+allo	switch	2.04	1.08	1.89	0.059	−0.08	4.17	0.353

Figs. 1 and 2, Supplementary Material 2 for QUADAS-2.

2.5. Analyses

Articles reporting appropriate diagnostic data were included in the meta-analyses. The main outcomes of interest were raw data, namely TP, FP, TN, and FN. If absent, raw data were also calculated from reported sensitivity and specificity using an inverse formula (Whiting and Davenport, 2018), using the total of positive and negative cases and sensitivity and specificity values. If both sets of measures were not reported, the corresponding author was contacted to assess for availability to disclose this information. Three studies (Coughlan et al., 2019; Schoberl et al., 2020; Tu et al., 2015) were included only for qualitative analysis due to missing raw data. Three studies (Howett et al., 2019; Moodley et al., 2015; Pengas et al., 2010) had available only the diagnostic performance of some tasks. One study (Castegnaro et al., 2022) made available all the measures required. The raw data used in the analyses are available at https://osf.io/4guk9/?view_only=acdd2d7c5552467697b9ac086c0708ef.

2.6. Meta-analysis

A diagnostic test accuracy (DTA) meta-analysis was conducted to evaluate the discriminatory performance of spatial navigation tests in distinguishing AD patients from healthy controls (HC). The analysis synthesized sensitivity, specificity, and diagnostic odds ratio (DOR) across studies through both univariate and bivariate approaches. All analyses were conducted with R (version 3.6.3) according to the code and method for DTA suggested by Shim and colleagues (R packages *mada*, *meta*, *metafor*, *rmeta*) (Shim et al., 2019).

For sensitivity, specificity, and DOR, studies were stratified based on spatial strategies assessments to examine potential differences in diagnostic performance between these approach types using a univariate approach. If there were two or more studies available for each specific spatial strategy, then we performed a meta-analysis using the methods recommended by the Cochrane Diagnostic Test Accuracy Working Group (Macaskill et al., 2010). Forest plots were generated to visualize individual and pooled estimates. If the group Q test was significant, the difference among subgroups spatial tasks estimates was calculated on the logit scale. Statistical significance was assessed using Z-tests, with

Z-values calculated as the ratio of the difference to its standard error. Two-tailed p-values were derived from the standard normal distribution. Ninety-five percent confidence intervals for the differences were constructed using the normal approximation. To account for multiple comparisons, p-values were also adjusted using the Bonferroni correction method. Crucially, the suggested acceptable sensitivity/specificity cut-off for AD studies is 0.80.(Davies et al., 1998).

For sensitivity calculations, the proportion of TP among patients with the condition (TP + FN) was computed. Similarly, specificity was calculated as the proportion of TN among subjects without the condition (TN + FP). These proportion data were logit-transformed to normalize their distribution and meet statistical model assumptions (Littenberg and Moses, 1993). The Clopper-Pearson method was employed to compute 95 % confidence intervals for both metrics. The DOR, which represents the ratio of the odds of positivity in individuals with disease to the odds of positivity in individuals without disease, was calculated to provide a single indicator of test accuracy. This was computed using the formula (TPxTN)/(FPxFN) and analyzed using a random-effects model with the inverse variance method. A meta-regression analysis was conducted on DOR models to investigate whether key variables were significant moderators of the observed heterogeneity in diagnostic accuracy and effect size. The restricted maximum-likelihood estimator was used to calculate between-study variance.

All meta-analyses employed inverse-variance weighting, where individual studies were weighted according to the inverse of their variance ($1/SE^2$). For sensitivity and specificity analyses using *metaprop*() function, study weights were determined by the precision of logit-transformed proportions, with studies reporting more events receiving greater weight due to smaller standard errors. For DOR analysis using *metabin*() function, weights were calculated based on the precision of the log odds ratio estimates. This weighting scheme ensures that studies with larger sample sizes and more diagnostic events contribute proportionally more to the pooled estimates, reflecting their greater statistical power and precision. Random-effects models were used throughout to account for between-study heterogeneity while maintaining the inverse-variance weighting structure.

A hierarchical bivariate random-effects model was employed to simultaneously account for both sensitivity and specificity, as these measures are inherently correlated (Reitsma et al., 2005). This approach allows for both within-study and between-study variation while accommodating the trade-off relationship between sensitivity and specificity due to threshold effects. Bivariate random-effects models based on sensitivity and specificity pairs were used to calculate the pooled estimates of sensitivity, specificity, and the area under the curve (AUC) of summary receiver operating characteristic (SROC), along with the 95 % confidence intervals (CI). AUC is a global measure of test performance and was classified as low (AUC < 0.7), moderate ($0.7 \leq$ AUC < 0.9), or high (AUC ≥ 0.9) (Okeh and Okoro, 2012). A partial AUC (restricted to observed false positive rates and normalized) was also reported. Statistical significance was set at $p < 0.05$ in all the analyses.

2.7. Investigation of heterogeneity

Random-effects models were used to account for the anticipated heterogeneity between studies for sensitivity, specificity, and DOR. P-value and I^2 were used to quantitatively judge the heterogeneity, which indicated significant heterogeneity if p-value < 0.1 or $I^2 \geq 50$ % and considered insignificant if p-value > 0.1 and $I^2 < 50$ % (Higgins et al., 2003). The potential sources of variance might include study populations, diagnostic criteria, task procedures (e.g., immediate vs. delayed recall), and methods (e.g., VR vs. paper-and-pencil) to assess the spatial strategy, and conceptualization within each task strategy to assess egocentric, allocentric, combined (ego+allo), and frame-switching processes.

2.8. Publication bias

Potential publication bias was evaluated using the trim-and-fill method (Duval and Tweedie, 2000). This technique examines the symmetry of funnel plots and estimates the number of potentially missing studies; it imputes potentially missing studies and recalculates adjusted effect estimates, providing both visual and quantitative assessments of possible bias. Contour-enhanced funnel plots were generated to visualize publication bias (Peters et al., 2008). Note that the funnel is centered not at the model estimate (as is usually done when drawing funnel plots), but at 0 (i.e., at the value under the null hypothesis of no effect). Various levels of statistical significance of the points/studies are indicated by the shaded regions. In particular, the unshaded (i.e., white) region in the middle corresponds to p-values greater than 0.10, the dark, gray-shaded region corresponds to p-values between 0.10 and 0.05, the medium gray-shaded region corresponds to p-values between 0.05 and 0.01, and the region outside of the funnel corresponds to p-values below 0.01. Funnel plots drawn in this way are more useful for detecting publication bias due to the suppression of non-significant findings. See Peters et al. (2008) for more details.

3. Results

3.1. Participants

The current diagnostic meta-analysis included 19 studies (one study was a multicenter study; (Moodley et al., 2015) with a total of 1884 participants. Most of the studies were cross-sectional (N = 15). 321 participants were classified as HC, of whom 27 were classified as having positive AD biomarkers and 15 converted to dementia during the study follow-up. 599 were diagnosed as MCI, of whom 22 were also profiled with positive AD biomarkers and 79 converted to dementia during the studies follow-up. 64 patients had a diagnosis of AD dementia. A mixed sample of AD dementia and aMCI (N = 63) was used in two studies (Moodley et al., 2015; Ruggiero et al., 2020). In addition, 42 participants were diagnosed with non-AD dementia (vascular and frontotemporal lobar degeneration). In one study, participants with AD dementia were compared with a mixed sample of participants with frontotemporal lobar degeneration (N = 11) and HC (N = 24). Four studies followed participants (377; no AD biomarker) longitudinally to track the progression to dementia diagnosis, of whom 135 received a dementia diagnosis (total participants with dementia = 239). See Figs. 2, 4, and 6 for the exact number of participants included in each model.

HC groups consisted of cognitively healthy individuals, as assessed by neuropsychological, functional, and neurological examination. aMCI was the principal diagnostic phenotype according to standard guidelines (Albert et al., 2011; Petersen, 2004; Petersen et al., 1999; Portet et al., 2006). Single (aMCIsd) and multi-domain (aMCImd) aMCI was determined in one study (Caffò et al., 2012). In two studies (Bažadona et al., 2020; Howett et al., 2019), MCI individuals were recruited, with no clear statement concerning neuropsychological phenotype. Individuals were diagnosed with AD dementia, according to clinical guidelines (McKhann et al., 1984; McKhann et al., 2011). Specific biomarker guidelines were followed to profile AD neuropathology (Fagan et al., 2006; Mulder et al., 2010; Shaw et al., 2009).

3.2. Egocentric and allocentric spatial measures

Metrics extracted from VR tasks were used in the logistic model in most of the comparisons considered for this meta-analysis (35 comparisons[3]). Mixed (VR plus paper-and-pencil) metrics were used in three

[3] This is not the number of studies but the number of comparisons, which can be multiple within one study and are reported in sensitivity, specificity, and DOR figures. Therefore, comparison and study are not used interchangeably.

classifications (Bellassen et al., 2012; Lowry et al., 2020). Nine comparisons used scores from standard paper-and-pencil procedures. Intriguingly, six comparisons (Ruggiero et al., 2020; Tangen et al., 2022) used real-world task metrics. Most of the comparisons (N = 24) assessed allocentric performance, 14 assessed egocentric performance, and mixed (ego+allo) performance was evaluated in seven comparisons. Intriguingly, ego-to-allo was used in eight diagnostic performance comparisons, whereas allo-to-ego was used in only two comparisons (Da Costa et al., 2022). The most used assessment tools and methods were the '4 Mountains Test' (Castegnaro et al., 2022; Moodley et al., 2015; Wood et al., 2016) and the 'cognitive mapping task' (Allison et al., 2016; Levine et al., 2020).

Crucially, heterogeneity in the procedures of tasks and methods was observed by qualitative inspections of descriptions reported in the papers included.

3.3. Univariate approach: overall diagnostic accuracy for Alzheimer's continuum vs. HC

We performed diagnostic accuracy (sensitivity, specificity, and DOR) by comparing participants classified as HC vs. participants having AD, regardless of the staging of the clinical syndrome (e.g., dementia, MCI) or biomarker profile (+ and -). Overall, we summarized 46 sample comparisons (e.g., AD vs. HC, HC + vs. HC-, aMCI vs HC) extracted from 16 studies (one multicenter) for the diagnostic accuracy of detecting AD vs. HC. We gathered 20 sample comparisons from 10 studies for the allocentric strategy, 12 comparisons from seven studies for the egocentric strategy, five from four studies for the mixed (ego+allo) strategy, and nine from four studies for the switch strategy.

3.3.1. Sensitivity

Analysis of comparisons (k = 46) revealed that spatial cognition tests demonstrated strong overall sensitivity for detecting AD dementia, MCI, and individuals with positive AD biomarkers (random effects model: 79.82 %, 95 % CI [75.55 %, 83.51 %]). Significant heterogeneity was observed (I^2 = 59.6 %, Q = 68.16, df = 45, p = 0.0145). Fig. 2 shows these results.

Subgroup analysis by spatial frame of reference type showed non-significant differences in sensitivity (Q = 7.47, df = 3, p = 0.058). In terms of clinical significance, only the allocentric and switch tasks passed the desired cut-off of 0.80; consequently, these two tasks should be used to rule out AD.

Heterogeneity varied across subgroups (see Fig. 2), with allocentric and combined strategies showing significant heterogeneity; egocentric and switching strategy tasks, on the other hand, showed lower heterogeneity.

A trim-and-fill method was used to adjust for publication bias. The analysis combined 57 comparisons, with 11 added through the trim-and-fill procedure to correct funnel plot asymmetry (see Fig. 3). The random effects model yielded a pooled sensitivity proportion of 0.73 (95 % CI [0.69, 0.77]), which is lower than the overall sensitivity without the trim-and-fill method. Again, significant heterogeneity was observed (I^2= 52.2 %, Q = 117.12, p < 0.001).

A meta-regression with sample age and percentage of males was conducted on logit sensitivity, which did not reveal significant effects (see Supplementary Material 2).

We also performed AD vs. non-AD dementia sensitivity analysis, which is reported in Supplementary Material 2.

3.3.2. Specificity

Analysis of comparisons (k = 46) revealed that spatial cognition tests demonstrated a promising overall specificity for detecting AD dementia, MCI, and individuals with positive AD biomarkers (81.59 %, 95 % CI [76.13 %, 86.02 %]). Significant heterogeneity was observed (I^2 = 84.6 %, Q = 140.93, df = 45, p < 0.001).

Subgroup analysis by spatial strategy type revealed highly significant differences in specificity among groups (Q = 16.77, df = 3, p < 0.001). Table 1 shows the significant post-hoc differences among the tasks; crucially, allocentric tasks were significantly superior to switch tasks. In terms of clinical significance, only the switch tasks did not pass the desired cut-off of 0.80; consequently, this type of task should be avoided to rule in AD, and combined, allocentric, or egocentric tasks should be preferred.

Heterogeneity varied considerably across subgroups (see Fig. 4). In particular, it is possible to note that combined egocentric-allocentric, allocentric, and egocentric strategies showed significant heterogeneity. On the other hand, switching-based tests demonstrated no observed heterogeneity (I^2 = 0.0 %), suggesting consistent specificity findings across comparisons employing this strategy type.

Again, we used a trim-and-fill method to adjust for publication bias (see Fig. 5). The analysis combined 61 comparisons, with 15 added through the trim-and-fill procedure to correct for funnel plot asymmetry. The random effects model revealed a pooled proportion of 0.70 (95 % CI [0.62, 0.76]), which is lower than the unadjusted specificity. Significant heterogeneity was observed across comparisons (I^2 = 76.7 %, Q = 257.49, p < 0.001).

A meta-regression with sample age and percentage of males was conducted on logit specificity, which did not reveal significant effects (see Supplementary Material 3). We also performed AD vs. non-AD dementia specificity analysis, which is reported in Supplementary Material 3.

3.3.3. Overall diagnostic performance for Alzheimer's continuum detection

A random-effects meta-analysis across 46 comparisons revealed a strong overall diagnostic performance (DOR = 15.57, 95 % CI [11.12, 21.78], z = 16.01, p < 0.001). Significant heterogeneity was observed (I^2 = 52.1 %, 95 % CI [32.9 %, 65.8 %], Q = 94.02, df = 45, p < 0.001). Fig. 6 shows the findings.

Subgroup analysis by spatial strategy type showed non-significant differences in diagnostic performance (Q = 6.76, df = 3, p = 0.080). These findings suggest that allocentric spatial cognition tests offer the strongest diagnostic performance for distinguishing between AD syndrome or pathology and HC; nevertheless, all spatial cognition task types demonstrate clinically meaningful diagnostic utility.

Also in this case, a trim-and-fill method was carried out to adjust for publication bias see Fig. 7). The analysis included 63 comparisons, with 17 added through the trim-and-fill procedure to correct for funnel plot asymmetry. The random effects model revealed a significant pooled odds ratio of 8.71 (95 % CI [6.01, 12.62], p < 0.001), which is lower than the DOR observed without this method. Substantial heterogeneity was observed across comparisons (I^2 = 66.4 %, Q = 184.75, p < 0.001).

A meta-regression with sample age and percentage of males was conducted on DOR, which revealed a significant effect of percentage of males, the greater the number of male participants the greater the DOR (see Supplementary Material 3). We also performed AD vs. non-AD dementia DOR analysis, which is reported in Supplementary Material 3.

3.3.3.1. The role of assessment method, memory process, and sample size on DOR. A mixed-effects meta-regression was conducted to examine the potential moderating effects of assessment method (VR, paper-and-pencil, real-world, combined VR+paper-and-pencil), memory process (immediate recall, delayed recall, composite immediate and delayed recall, visuospatial reasoning), and total sample size on DOR. The analysis included 46 comparisons and employed the restricted maximum likelihood (REML) method.

Results revealed significant residual heterogeneity (QE(38) = 70.37, p = 0.001), with an I^2 value of 48.32 %, indicating that approximately 48 % of the total variability was attributable to between-study heterogeneity. The model explained 14.33 % of the heterogeneity (R^2 = 14.33 %). The omnibus test of moderators was not statistically significant (QM(7) = 10.39, p = 0.167), suggesting that the combined effect of

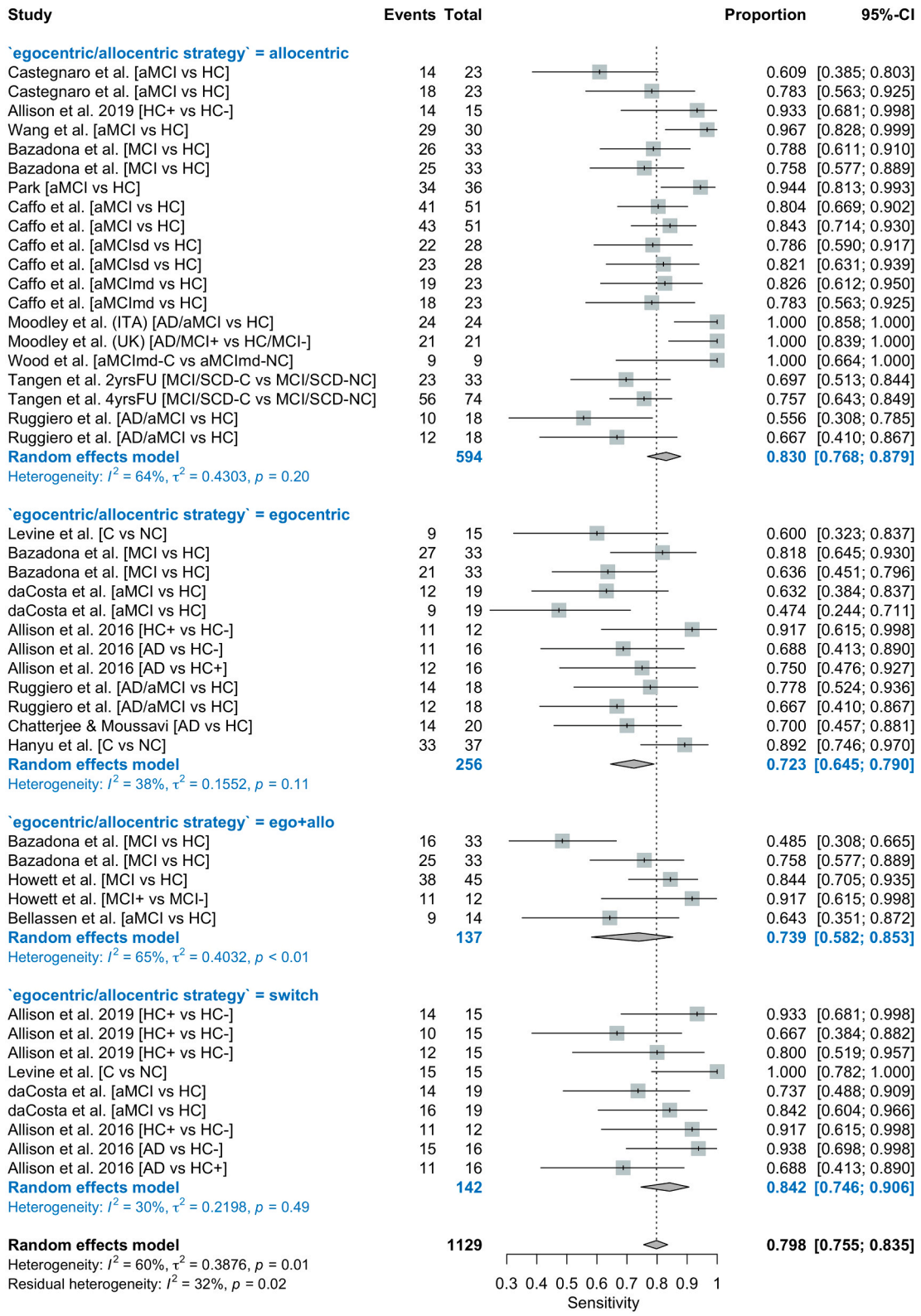

Fig. 2. Task sensitivity for Alzheimer's continuum. Forest plot of sensitivity values from diagnostic accuracy studies grouped by egocentric/allocentric strategy. The plot displays individual study results showing events (correct classifications) out of total cases, proportions (represented by squares with size proportional to study weight), and 95 % confidence intervals (horizontal lines). Diamond shapes represent the pooled estimates using random effects models for each subgroup, and the vertical dotted line serves as a reference for comparing studies to the overall effect. P-value and I^2 were used to quantitatively judge the heterogeneity, which indicated significant heterogeneity if $P < 0.1$ or $I^2 \geq 50$ % and considered insignificant if $P > 0.1$ and $I^2 < 50$ %. AD: Alzheimer's disease dementia; aMCI: amnestic mild cognitive impairment; HC: healthy controls; + : positive Alzheimer's disease biomarkers; - negative Alzheimer's disease biomarkers; aMCIsd: aMCI single domain; aMCImd: aMCI multi-domain; MCI: mild cognitive impairment; C: converter to dementia; NC: non-converter to dementia; FU: follow-up; yrs: years; /: mixed sample (e.g., AD/aMCI).

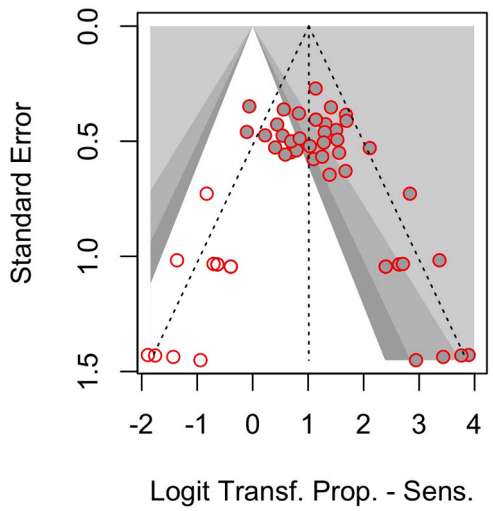

Fig. 3. Sensitivity publication bias. Contour-enhanced funnel plot with trim-and-fill adjustment for publication bias. The plot displays the relationship between logit-transformed proportion (x-axis) and their corresponding standard errors (y-axis) for included studies. Red open circles represent observed studies (gray-filled actual studies, unfilled imputed studies). The gray-shaded regions represent 90 % ($0.05 < p \leq 0.10$), 95 % ($0.01 < p \leq 0.05$), and 99 % ($p < 0.01$) confidence contours. The white areas represent non-significant regions ($p > 0.10$). The dotted vertical line indicates the model estimates without imputed observations, and the dotted diagonal lines represent the expected 95 % confidence limits assuming no heterogeneity.

all moderators did not significantly affect the effect size.

3.4. Bivariate approach: overall diagnostic accuracy for Alzheimer's continuum detection

The diagnostic accuracy for differentiating AD from HC was assessed using a hierarchical bivariate random-effects meta-analysis.

The egocentric strategy model revealed a pooled sensitivity of 0.72 (95 % CI [0.64, 0.79]) and a false positive rate of 0.23 (95 % CI [0.16, 0.33]), which corresponds to a specificity of 0.77 (95 % CI [0.67, 0.84]). The AUC was 0.80, indicating moderate diagnostic accuracy. The partial AUC (restricted to observed false positive rates and normalized) was 0.72. Between-study heterogeneity was minimal, with I^2 estimates ranging from 0 % (Zhou and Dendukuri, 2014) to 8.5 % (Holling sample size unadjusted approach). Both the sensitivity logit intercept ($\beta = 0.94$, $SE = 0.20$, $p < 0.001$) and false positive rate logit intercept ($\beta = -1.19$, $SE = 0.25$, $p < 0.001$) were statistically significant. This consistency strengthens confidence in these tests as reliable diagnostic tools for AD, as the results appear stable regardless of specific study conditions or samples.

For allocentric strategy, the bivariate random-effects meta-analysis revealed a pooled sensitivity of 0.78 (95 % CI [0.74, 0.82]) and a false positive rate of 0.18 (95 % CI [0.12, 0.26]), which corresponds to a specificity of 0.82 (95 % CI [0.74, 0.88]). The AUC was 0.79, indicating moderate diagnostic accuracy, with a partial AUC of 0.78. Between-study heterogeneity varied by estimation method, with I^2 estimates ranging from 0 % (Zhou and Dendukuri, 2014) to 62.2 % (Holling sample size unadjusted approach). Both sensitivity ($\beta = 1.27$, $SE = 0.11$, $p < 0.001$) and false positive rate ($\beta = -1.54$, $SE = 0.25$, $p < 0.001$) logit intercepts were highly significant.

For mixed egocentric-allocentric tasks, the analysis yielded a sensitivity of 0.71 (95 % CI [0.54, 0.83]) and a false positive rate of 0.11 (95 % CI [0.03, 0.33]), corresponding to a specificity of 0.89 (95 % CI [0.67, 0.97]). The AUC was 0.83, which is considered moderate, with a partial AUC of 0.71. Heterogeneity was minimal ($I^2 = 0$ % across all estimation approaches). Both the sensitivity ($\beta = 0.88$, $SE = 0.36$, $p = 0.015$) and false positive rate ($\beta = -2.06$, $SE = 0.70$, $p = 0.003$) logit intercepts were statistically significant.

For strategy switching tasks, the model showed a sensitivity of 0.80 (95 % CI [0.71, 0.86]) and a false positive rate of 0.35 (95 % CI [0.29, 0.41]), corresponding to a specificity of 0.65 (95 % CI [0.59, 0.71]). The overall performance was moderate (AUC = 0.74), with a partial AUC of 0.51. Heterogeneity was minimal (I^2 estimates ranged from 0 % to 8.5 %, depending on the estimation method). Both sensitivity ($\beta = 1.35$, $SE = 0.23$, $p < 0.001$) and false positive rate ($\beta = -0.64$, $SE = 0.14$, $p < 0.001$) logit intercepts were highly significant. Fig. 8 shows the SROC plot.

We also performed AD vs. non-AD dementia bivariate analysis, which is reported in Supplementary Material 3.

4. Discussion

This meta-analysis aimed to evaluate the diagnostic performance of egocentric, allocentric, and frame-switching navigation tasks for detecting AD across its continuum, from preclinical to clinical stages. Based on a substantial amount of evidence, we predicted differential diagnostic performance across spatial strategies. For allocentric tasks, we expected a balanced diagnostic profile with comparable levels of sensitivity and specificity, making them effective diagnostic tools for the early detection of AD. As regards egocentric tasks, we predicted high specificity but limited sensitivity. For frame-switching tasks, we expected high sensitivity but relatively lower specificity, successfully detecting most AD cases but potentially misclassifying some cognitively healthy older adults experiencing typical age-related declines in the ability to translate between reference frames. We also included in our analysis "combined tasks" that involve multiple spatial reference frames simultaneously, as both baseline conditions and ecologically valid approaches to comprehensively assess spatial cognition. Overall, our prediction was that spatial navigation assessments would emerge to be promising diagnostic tools for detecting AD across its continuum.

Our meta-analysis in large part confirms our predictions (see Fig. 9 for findings summary). Concerning sensitivity (namely, the ability to correctly identify individuals with AD given low false negatives; i.e., used to rule out AD), surprisingly, no statistically significant difference was found. This finding was unexpected, as the literature did not suggest that egocentric tasks would perform similarly to allocentric and reference-switch tasks. However, from a clinical perspective, only the allocentric and reference-switch tasks achieved the desired sensitivity cut-off of 0.80 (Ronald and Group, 1998). Regarding specificity (namely, the ability to correctly identify individuals without AD, given low false positives; i.e., used to rule in AD), allocentric tasks demonstrated significantly higher specificity than reference-switch tasks. Reference-switch tasks fell below the desired specificity cut-off of 0.80, whereas all other spatial tasks exceeded this threshold. Crucially, any effects of gender or age affected sensitivity and specificity estimates. Analysis confirmed promising sensitivity-specificity performance, with all AUC values exceeding 0.70 (indicating moderate performance).

DOR analysis revealed that, overall, all spatial navigation tasks demonstrated statistically comparable diagnostic performance, with allocentric tasks showing slightly higher DOR values. Importantly, regardless of the spatial strategy, the greater the percentage of male participants included in the overall sample, the greater the DOR, whereas age did not influence the result. This might indicate that spatial navigation is particularly effective for AD diagnosis in males, possibly due to known gender differences in spatial cognition abilities (Yuan et al., 2019), which may hamper the validity of spatial tasks.

Crucially, it is important to note that publication and QUADAS-2 bias were detected, and the accuracy performances were reduced when we adjusted the estimates with the trim-and-fill method.

Our findings confirm that deficits in egocentric and allocentric spatial processing, along with impairments in the ability to switch between these reference frames, collectively emerge as promising

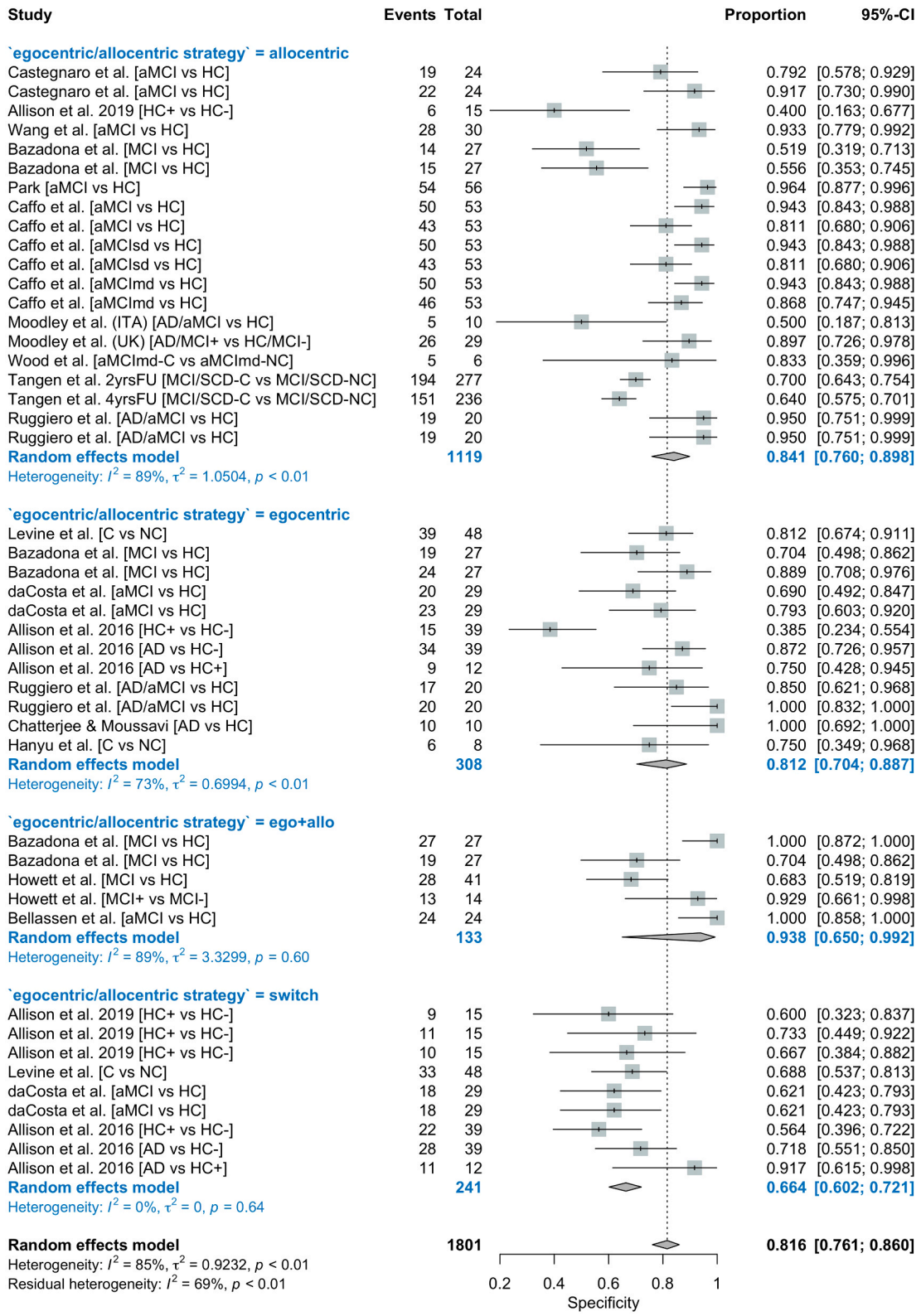

Fig. 4. Task specificity for Alzheimer's continuum. Forest plot of specificity values from diagnostic accuracy studies grouped by egocentric/allocentric strategy. The plot displays individual study results showing events (correct classifications) out of total cases, proportions (represented by squares with size proportional to study weight), and 95 % confidence intervals (horizontal lines). Diamond shapes represent the pooled estimates using random effects models for each subgroup, and the vertical dotted line serves as a reference for comparing studies to the overall effect. P-value and I^2 were used to quantitatively judge the heterogeneity, which indicated significant heterogeneity if $P < 0.1$ or $I^2 \geq 50$ % and considered insignificant if $P > 0.1$ and $I^2 < 50$ %. AD: Alzheimer's disease dementia; aMCI: amnestic mild cognitive impairment; HC: healthy controls; +: positive Alzheimer's disease biomarkers; - negative Alzheimer's disease biomarkers; aMCIsd: aMCI single domain; aMCImd: aMCI multi-domain; MCI: mild cognitive impairment; C: converter to dementia; NC: non-converter to dementia; FU: follow-up; yrs: years; /: mixed sample (e.g., AD/aMCI).

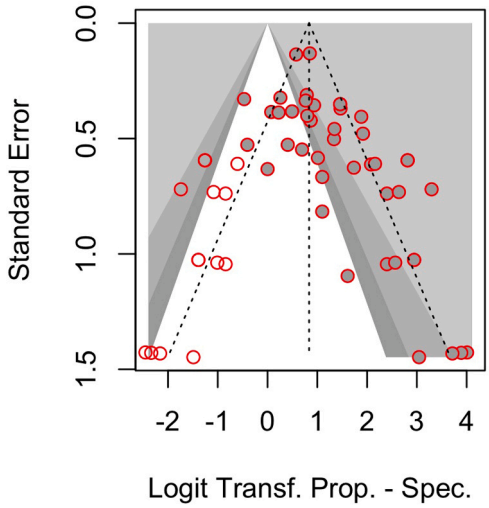

Fig. 5. Specificity publication bias. Contour-enhanced funnel plot with trim-and-fill adjustment for publication bias. The plot displays the relationship between logit-transformed proportion (x-axis) and their corresponding standard errors (y-axis) for included studies. Red open circles represent observed studies (gray-filled actual studies, unfilled imputed studies). The gray-shaded regions represent 90 % ($0.05 < p \leq 0.10$), 95 % ($0.01 < p \leq 0.05$), and 99 % ($p < 0.01$) confidence contours. The white areas represent non-significant regions ($p > 0.10$). The dotted vertical line indicates the model estimates without imputed observations, and the dotted diagonal lines represent the expected 95 % confidence limits assuming no heterogeneity.

cognitive markers for AD diagnosis (Coughlan et al., 2018), a conclusion further supported by analyses comparing AD dementia versus non-AD dementias (see Supplementary Material 3). However, it is crucial to underline that clinicians and researchers should implement these assessment approaches strategically and in combination to optimize both sensitivity and specificity in AD detection. Specifically, tasks based on allocentric and frame-switching strategies demonstrate superior sensitivity for ruling out the disease, whereas egocentric, allocentric, and combined tasks offer enhanced specificity for ruling in the disease.

Among these tasks, as predicted, allocentric tasks emerge as the most effective diagnostic tool, showing well-balanced diagnostic properties (both sensitivity and specificity above 0.80) and a high DOR for AD detection. This aligns with robust evidence that AD, from its preclinical to clinical stages, produces more profound impairments in allocentric navigation (Serino et al., 2014; Tuena et al., 2021; Weintraub et al., 2012) that are compatible with neuropathological changes mainly occurring in the hippocampus and medial temporal lobe structures that support allocentric spatial processing (Zhang and Ekstrom, 2013).

On the other hand, it is interesting to further underline that combined spatial navigation tasks demonstrate enhanced specificity (0.94) for AD identification, which likely derives from the ecological validity of comprehensive assessments that involve multiple spatial cognition mechanisms simultaneously. In real-world scenarios, indeed, navigation typically involves a dynamic interplay between egocentric and allocentric strategies, with individuals continuously translating between these reference frames to successfully orient themselves and reach their goal destinations. This integration depends critically on the retrosplenial cortex, which functions as a hub for converting between egocentric and allocentric representations (Byrne et al., 2007; Vann et al., 2009). The retrosplenial cortex performs functions beyond coordinate transformation, including perspective shifting and predicting current sensory input with internal environmental representation, processes essential for effective navigation (Alexander et al., 2023). As suggested by Bicanski and Burgess (2018), this multifaceted role provides a theoretical basis for understanding why AD patients struggle with tasks requiring flexible navigation strategies: damage to the neural circuit that integrates egocentric and allocentric information would fundamentally impair one's ability to reorient or form a cognitive map from a new viewpoint. These integrative networks are compromised even in early AD (see, for example, Terstege et al., 2024), potentially explaining why ecological combined tasks requiring coordination across multiple spatial reference frames demonstrate particularly high specificity for detecting the disease.

Frame-switching tasks show high sensitivity (0.84) but lower specificity (0.66), making them valuable for excluding AD but less reliable for confirming it. This pattern suggests that while intact switching ability effectively rules out AD, deficits in switching cannot reliably confirm it, as such impairments may also occur in normal cognitive aging (Harris and Wolbers, 2014; Serino & Riva, 2013). Notably, many age-related navigation difficulties derive directly from difficulties in translating between reference frames. For instance, Zhong et al. (2017) assessed spatial abilities in healthy young and older adults using a virtual Morris water maze. Their results suggested that while high-performing older adults maintained spatial abilities comparable to younger participants, spatial difficulties in poor-performing older adults could not be attributed to differences in age, education, or general cognitive abilities, pointing instead to specific deficits in frame-switching flexibility. Finally, egocentric tasks demonstrate good specificity (0.81) but lower sensitivity (0.72), indicating they are better suited for confirming AD than for excluding it, consistent with findings that egocentric navigation remains relatively preserved until later disease stages (Bianchini et al., 2014; Hashimoto et al., 2020).

Taken together, these results suggest that a strategic, complementary approach to spatial navigation assessment is crucial for optimal AD detection. Coherently, the choice of assessment tool should be guided by specific research and clinical questions: when ruling out AD is the priority, allocentric and frame-switching tasks are most appropriate; when confirming AD is the goal, allocentric, egocentric, and combined tasks offer superior performance.

4.1. *Limitations*

Some limitations deserve to be taken into consideration when interpreting our results. First, the spatial strategy screening process, despite being conducted by two blinded researchers using literature-based definitions, may have introduced classification bias, particularly given the considerable variability in operational definitions of spatial concepts across the literature (Németh et al., 2025). Second, we found qualitative and quantitative heterogeneity in terms of methods, procedures, and sample comparisons included in the studies, which might have biased the findings; however, our results are consistent with theoretical and clinical evidence gathered so far. Third, our meta-analysis was also constrained by the predominance of cross-sectional designs (15/19 studies), limiting insights into the prognostic value of spatial navigation deficits across disease progression. Longitudinal studies represent the most effective approach to evaluate cognitive changes across the AD continuum, as they can fully capture the evolution of cognitive decline, and they might help in establishing causal relationships between early spatial deficits and subsequent disease progression. The uneven distribution of spatial strategy assessments and the small number of studies for certain comparisons (particularly the AD vs. non-AD dementia analysis, with only 3 studies) reduced the reliability of subgroup comparisons. Lastly, we found evidence of publication bias, confirmed through trim-and-fill analyses that consistently reduced effect estimates. More importantly, this issue also highlights the urgent need for a more transparent and objective publication process that ensures the possibility of disseminating both null and significant results supported by rigorous research design.

Future research should address these limitations through several approaches. First, implementing systematic strategies to handle publication bias, including mandatory preregistration of studies and more systematic reporting of null results, would enhance the reliability of

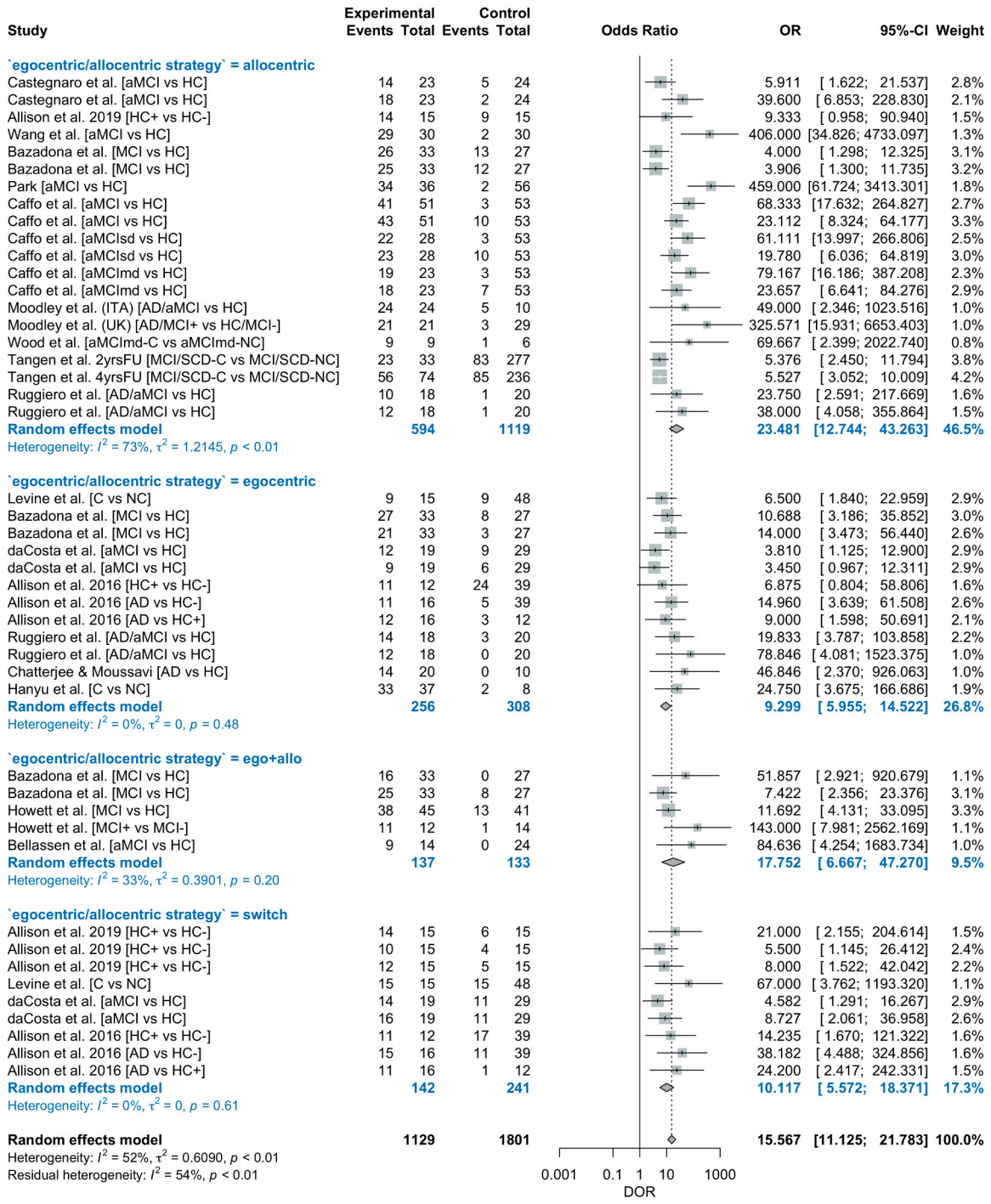

Fig. 6. Tasks DOR for Alzheimer's continuum. Forest plot of diagnostic odd ratio (DOR) values from diagnostic accuracy studies grouped by egocentric/allocentric strategy. The plot displays individual study results showing events (correct classifications) out of total cases, proportions (represented by squares with size proportional to study weight), and 95 % confidence intervals (horizontal lines). Diamond shapes represent the pooled estimates using random effects models for each subgroup, and the vertical dotted line serves as a reference for comparing studies to the overall effect. P-value and I^2 were used to quantitatively judge the heterogeneity, which indicated significant heterogeneity if $P < 0.1$ or $I^2 \geq 50$ % and considered insignificant if $P > 0.1$ and $I^2 < 50$ %. The weight column represents the statistical weight on the pooled DOR (i.e., larger weight means greater statistical power and more influence on the final estimate). AD: Alzheimer's disease dementia; aMCI: amnestic mild cognitive impairment; HC: healthy controls; + : positive Alzheimer's disease biomarkers; - negative Alzheimer's disease biomarkers; aMCIsd: aMCI single domain; aMCImd: aMCI multi-domain; MCI: mild cognitive impairment; C: converter to dementia; NC: non-converter to dementia; FU: follow-up; yrs: years; /: mixed sample (e.g., AD/aMCI); TP: true positive; FP: false positive.

future meta-analyses. Second, standardization of spatial cognition assessment protocols would reduce methodological heterogeneity and facilitate more direct comparisons across studies. Third, longitudinal designs with consistent biomarker profiling are essential to establish the prognostic value of spatial navigation tasks across the AD continuum and determine their utility for early detection. Parallel to this, we found that spatial navigation assessment could be a promising approach to aid the differential diagnosis between AD dementia and non-AD dementias; although based on only three studies, the metrics are encouraging (sensitivity = 0.86, specificity = 0.85, DOR = 31.32). Future studies

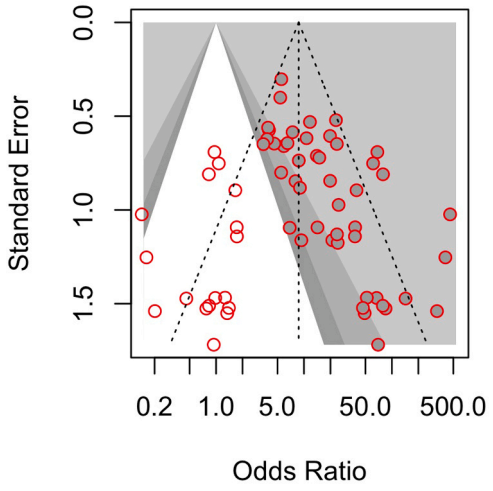

Fig. 7. DOR publication bias. Contour-enhanced funnel plot with trim-and-fill adjustment for publication bias. The plot displays the relationship between the odds ratio (x-axis) and its corresponding standard error (y-axis) for included studies. Red open circles represent observed studies (gray-filled actual studies, unfilled imputed studies). The gray-shaded regions represent 90 % ($0.05 < p \leq 0.10$), 95 % ($0.01 < p \leq 0.05$), and 99 % ($p < 0.01$) confidence contours. The white areas represent non-significant regions ($p > 0.10$). The dotted vertical line indicates the model estimates without imputed observations, and the dotted diagonal lines represent the expected 95 % confidence limits assuming no heterogeneity.

should enhance the ecological validity of spatial navigation assessments (Vigliocco et al., 2024). This could be achieved by incorporating multisensory body-based cues (e.g., vestibular and proprioceptive signals) into VR-based tasks following recent methodological advances (McAvan et al., 2021), and by implementing large-scale real-world navigation assessments such as mobile app-based paradigms (e.g., Sea Hero Quest; (Coutrot et al., 2019) that capture naturalistic spatial behavior in everyday environments. These naturalistic assessments could be particularly relevant for early AD detection; recent studies have indeed demonstrated that spatial navigation big data from the Sea Hero Quest mobile game can reliably distinguish high-risk from low-risk individuals based on genetic (APOE ε4) and demographic factors, even when traditional neuropsychological episodic memory tests fail to detect differences (Coughlan et al., 2019).

Fifth, future research must prioritize demographic diversity to

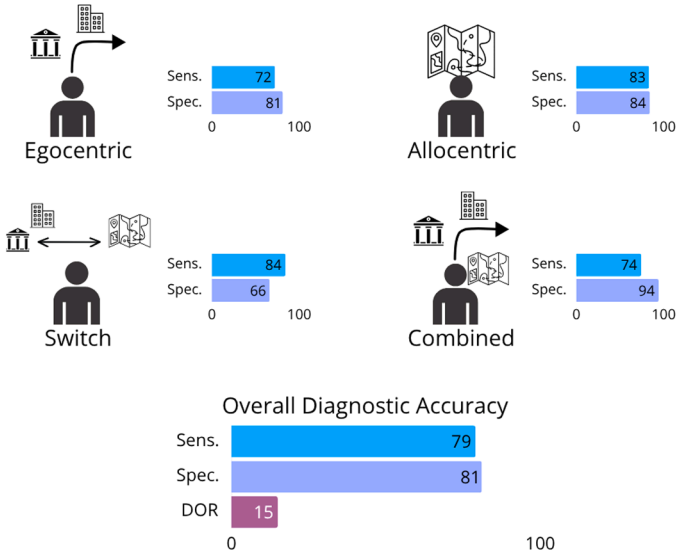

Fig. 9. Summary of the diagnostic meta-analysis.

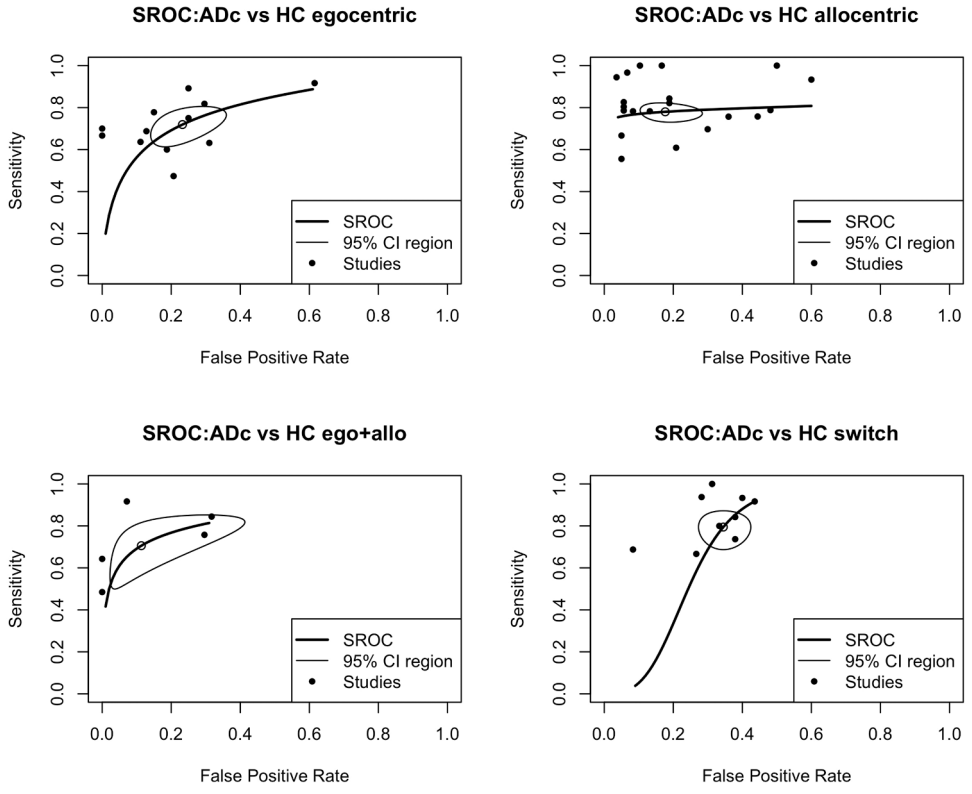

Fig. 8. Bivariate accuracy for Alzheimer's continuum diagnosis. Summary receiver-operator characteristic (SROC) curve for ADc vs HC for each spatial strategy. ADc: Alzheimer's disease continuum.

ensure findings are applicable across different populations and cultural contexts. Building on the personalized diagnostic approaches demonstrated with mobile-based assessments, additional promising directions include investigating combined cognitive batteries that integrate spatial tasks with established memory measures to enhance diagnostic accuracy, and further exploring how the interplay between demographic factors (age, sex, education) and genetic markers influences spatial navigation performance across diverse populations. Finally, exploring potential interventions targeting spatial navigation abilities may assess whether enhancing these skills affects disease progression or functional outcomes in early-stage AD.

5. Conclusion

Our meta-analysis provides compelling evidence supporting the value of spatial navigation assessment as a cognitive marker for AD across its spectrum. The differential diagnostic performance of egocentric, allocentric, and frame-switching tasks highlights the importance of a strategic approach to spatial navigation assessment, with task selection guided by specific clinical and research needs. Each task strategy provides unique and complementary insights into the nature of spatial navigation deficits in the AD continuum. As emphasized by Coughlan and colleagues in their seminal review, "*spatial navigation is emerging as a potential cost-effective cognitive biomarker to detect AD in the preclinical stages, which has important implications for future diagnostics and treatment approaches.*" (Coughlan et al., 2018). This represents a further step in the search for effective cognitive markers of incipient AD, potentially enabling earlier and more accurate diagnosis.

CRediT authorship contribution statement

Conceptualization: S.S., C.T.; Methodology: S.S., C.T., C.S.-B., G.M., A.C., G.R.; Data collection: C.S.-B., G.M., C.T.; Statistical analysis: C.T.; Writing—original draft: S.S., C.T.; Writing—review and editing: C.S.-B., G.M., A.C., G.R.; Supervision: S.S., C.T.; All authors have read and agreed to the published version of the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2025.106379.

Data availability

The raw data used in the analyses is available at https://osf.io/4guk9/?view_only=acdd2d7c5552467697b9ac086c0708ef

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