

Review

Visuospatial Perception: An Emerging Biomarker for Alzheimer's Disease

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Abstract. In recent years, the focus of research on Alzheimer's disease (AD) has shifted toward finding reliable diagnostic biomarkers that enable accurate detection of mild cognitive impairment (MCI) as well as AD. Functional magnetic resonance imaging (fMRI) has the potential to identify functional changes in the preclinical stages of AD. In addition to the cardinal deficits in memory, deficits in visuospatial cognition are pervasive in AD. Recent neurophysiological and imaging studies have revealed that changes in visuospatial perception (VSP) functions can be detected in the early stages of AD. This review highlights the scope of VSP functional alterations as a biomarker for AD. We describe the neuroanatomical regions involved in the processing of various VSP tasks, and discuss the effect of AD on these regions from a pathological as well as a functional point of view. A comprehensive synopsis of the existing fMRI literature that has assessed VSP in patients with MCI and AD has been provided. The diagnostic scope of monitoring the brain activation correlates of VSP processing in AD is discussed in terms of the key advantages of utilizing VSP-related deficits in AD for early detection and longitudinal tracking of AD.

Keywords: Alzheimer's disease, biomarker, functional magnetic resonance imaging, mild cognitive impairment, visuospatial perception

INTRODUCTION

The past decade has seen tremendous advances in Alzheimer's disease (AD) research and provided much insight into the molecular mechanisms governing AD pathology. However, the clinical criteria to diagnose AD have continued to primarily rely on neuropsychological tests. Existing literature reports cases where clinical manifestation and cognitive assessment batteries have been unable to diagnose AD even several years from its onset [1–3]. Even when AD is successfully diagnosed with the help of neuropsychological

tests, substantial neuronal loss has already occurred in numerous brain regions [4, 5]. It is thus imperative to develop biomarkers that can identify AD in its pre-clinical stage, so as to initiate early neuroprotective treatment and thereby maximize treatment efficacy. Researchers are therefore utilizing *in vivo* imaging modalities for identifying biomarkers that can aid in early and accurate diagnosis of AD [1]. Functional magnetic resonance imaging (fMRI) is increasingly being used to detect early functional brain changes, which may precede acute structural atrophy and the consequent cognitive impairment typically seen in AD [5–8].

In addition to prominent memory problems, AD is hallmarked by dysfunctional visuospatial perception (VSP) [9, 10]. Several studies have reported the involvement of cerebral regions subserving VSP in

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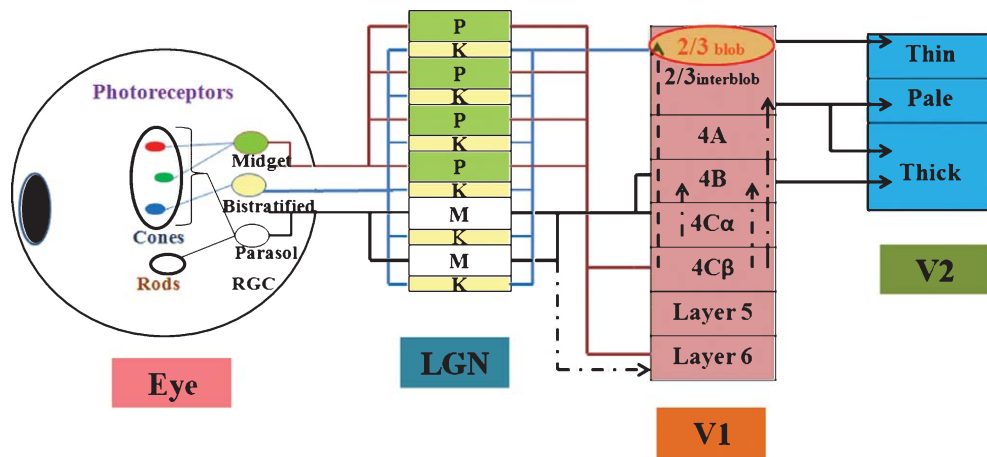


Fig. 1. Schematic of neuronal connections from retina to primary visual cortex (Figure adapted from two earlier works [19, 39]). The schematic represents the flow of visual information from the retina to the sub-cortical LGN, and further onto the primary visual cortical areas V1 and V2. Visual information is first sensed by the rod (contrast-sensitive) and cone (color-sensitive) photoreceptor cells in the retina. It is then received by the retinal RGCs, namely midget (green), bistratified (yellow), and parasol (white), which are arranged in distinct patterns to aid in the segregation of visual information. These RGCs then project through distinct pathways (P, M, and K) to the sub-cortical LGN, and further onto V1. The P pathway (green) receives color and form information from the midget cells, the K pathway (yellow) receives blue-on/yellow-off color-opponent information from bistratified cells and the M pathway (white) carries luminance and motion information from parasol cells. Visual information that has been thus segregated in V1 is projected to the V2 processing region. The V2 region comprises of thick stripes, which are direction- and disparity-selective; thin stripes, which are hue-selective; and pale stripes, which are orientation-selective.

the early stages of AD [11–15]. VSP abilities are essential for translating visual signals into a correct mental impression of where objects are in 3D space. Therefore, impairment of visuospatial function in AD patients profoundly affects their performance in everyday activities [10, 16, 17]. A study demonstrated that the functional ability of AD patients correlates significantly with measures of visuospatial functions and attention [18]. Further, their multiple regression analyses revealed visuospatial function to be the ‘sole cognitive predictor’ of functional abilities in patients with AD [18].

Monitoring VSP functional networks in AD using fMRI can aid in the identification of the activation changes within these networks due to AD pathology. Characterization of such functional alterations in the VSP brain networks can not only provide insight into the neural basis of visuospatial dysfunction in AD, but also provide valuable clues for AD diagnosis. This review examines the key advantages of monitoring the functional brain activation correlates of VSP processing in AD and proposes functional VSP deficits in AD as an early predictor of AD onset and an indicator of disease progression.

In the following section, we provide a brief introduction of the neuroanatomy involved in VSP processes and also discuss the different VSP paradigms from a functional point of view.

NEUROANATOMY OF VSP

VSP is a cognitive process that entails the extraction and interpretation of spatial information from visual stimuli. It involves the integration of several neuronal mechanisms, beginning from the segregation of visual information at the retina to the systematic, hierarchical, and modular integration in the primary and associative visual cortical areas. This spatial information processing occurs in the striate and extrastriate regions, as well as the higher associative brain areas [19–22]. Detailed schematic of the anatomy and mechanism of visual information processing, from the retinal photoreceptors to the layers of primary (V1) and secondary (V2) visual areas, is shown in Fig. 1. Visual information sensed by photoreceptors (contrast-sensitive rod and color-sensitive cone cells), passes through the inner plexiform layer of retina (bipolar, horizontal, and amacrine cells), and onto the retinal ganglion cells (RGCs) (midget, parasols, and bistratified) [19]. The arrangement of these three distinct types of RGCs forms different receptive fields, which help in the segregation and encoding of visual information [19, 23–25]. Midget ganglions receive excitatory inputs from the long-wavelength sensitive L-cones and the medium-wavelength sensitive M-cones, and project red/green color-opponent signal to the parvocellular (P) layers in the lateral geniculate nucleus (LGN) [23].

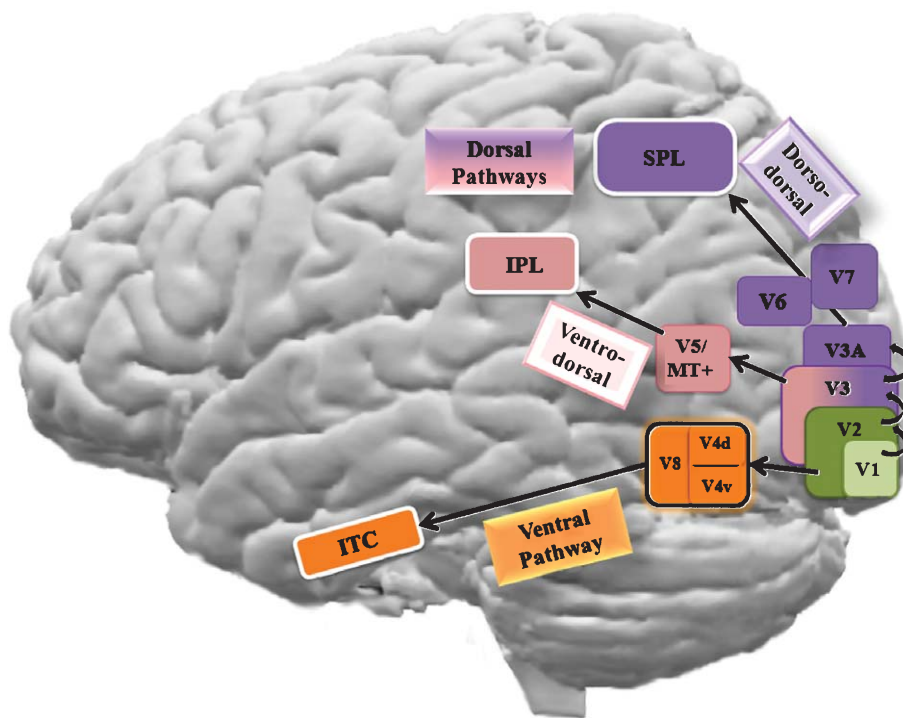


Fig. 2. Visual processing: Dorsal (where) and ventral (what) cortical pathways. This schematic represents the two major pathways engaged in visual perception: the dorsal ('where') pathway responsible for motion and spatial perception, and the ventral ('what') pathway responsible for form, color, and object perception. The dorsal pathway segregates from V3 into two streams, i.e., the ventro-dorsal stream (shown in pink) containing the V5/MT+ and IPL; and the dorso-dorsal stream (shown in purple) that contains V3A, V6, V7, and SPL. On the other hand, the ventral pathway (shown in orange) projects from V2 to V4 (dorsal: V4d, ventral: V4v), V8, and ITC. Abbreviations: IPL, Inferior parietal lobe; ITC, Inferior temporal cortex; MT+, Middle temporal and medial superior temporal cortex; SPL, Superior parietal lobe.

This constitutes the P-pathway, which traverses from layers 4C β and 6 of V1, to the blob and inter-blob regions in layer 2/3 of V1, and then to the thin and pale stripes of V2, respectively. This pathway carries information selective to color and high spatial frequencies [21, 26]. Parasol ganglions are large in size and receive signals from many rods and cones. They are highly sensitive to contrast changes as well as temporal frequencies. Projection of the parasol ganglions into the magnocellular (M) layers in the LGN represents the M-pathway, which traverses predominantly from layer 4C α to layer 4B of V1, and then to the thick stripe layer of V2 [19]. This pathway facilitates the transmission of motion and luminance information [19, 21, 27, 28]. Bistratified ganglions receive blue-on/yellow-off color-opponent excitation signals from the short-wavelength sensitive S cones, and project this information to the koniocellular (K) layers in the LGN [25]. These signals are further carried by the K-pathway through layer 1 and cytochrome oxidase blobs in layer 2/3 of V1, to the thin stripe layer of V2 [19]. Some of the K-cells possess direction selectivity and

are responsible for encoding the motion information [27]. Visual information that has thus been selectively divided by the P, M, and K parallel pathways in V1 is further differentiated in V2. Thick stripes located in the V2 region contain direction- and disparity-selective neurons, while the thin and pale stripe neurons in V2 are respectively hue- and orientation-selective [19, 29]. This segregated visual information is then projected to higher visual cortical and associative areas through a hierarchical and modular processing scheme [19, 30, 31].

VSP processing in higher cortical areas

Visual processing is segregated into dorsal 'where' and ventral 'what' streams (Fig. 2) [32, 33]. The dorsal ('where') stream originates from V1 (Brodmann Area (BA) 17); traverses through visual areas V3, V3A (part of BA 19), V5/MT+ (MT+ comprises of middle temporal and medial superior temporal regions), V6 and V7; and further extends to the posterior parietal cortex [21, 34–37]. The extensions of this pathway include

the dorso-dorsal stream, which connects to V6 and V7, and further to the superior parietal lobe (SPL); and the ventro-dorsal stream, which extends from V5/MT+ to the inferior parietal lobe (IPL) [35]. Both the dorsal streams are together responsible for perception of space and motion, as well as action organization and interpretation [35, 38]. The ventral stream originates from V1 (BA 17), passes through the thin and pale stripes of V2 (BA18), projects to V4 and V8 (which are the color centers in humans), and further extends to the inferior temporal cortex (BA20) [19, 39]. It is involved in the perception and identification of objects along with storage of visual memory in the medial temporal lobe [32, 39].

CLASSIFICATION OF VSP PARADIGMS

Over the years, several visuospatial paradigms have been developed in order to elucidate the various facets of VSP. The chronological evolution of VSP research, with respect to the key VSP paradigms and the corresponding brain activation maps, is presented in Fig. 3. These various paradigms provide an understanding of the brain regions involved in processing specific aspects of VSP. Different VSP paradigms activate a different combination of the VSP network, based on the different visuospatial capacities required to execute a given task (Fig. 3). VSP may be broadly classified on the basis of these functionally specialized neural mechanisms for different types of perception into: A) Stereopsis (perception of depth); B) Motion perception; C) Clock processing and angle discrimination; and D) Spatial localization and navigation (Fig. 4). However, this classification is not exclusive as the modular neural processing of visual signals is intermixed at various hierarchical levels; this allows sharing of appropriate perception cues with the involved brain regions, thereby integrating various VSP functions. These varied perception types are briefly described below, with specific mention of the brain regions involved in each of the VSP activities.

Stereopsis

Depth perception is one of the fundamental cognitive tasks of the visual system. It enables us to perceive the environment and objects in three dimensions (3D), a requisite for making judgments about accurate body/limb movements with respect to the environment. The neural process of reconstructing a 3D scene, which enables the basic perception of depth, is based on binocular disparity — the disparity present

in the information entering through the two eyes due to their different positions [40–42]. Apart from this binocular disparity, the visual system also uses other cues for stereopsis, such as linear perspective, texture gradient, and motion parallax [43]. Neuroanatomically, interactions between V1, specifically layers 4, 3B and 2/3A, and V2 are reported to contribute to stereopsis [44].

Stereopsis can be studied in its purest form when the visual stimulus contains only binocular disparity, in the absence of monocular or familiarity cues [45]. This is accomplished by using a specifically generated random dot stereogram (RDS) (Fig. 4A1) [45]. Two independent fMRI studies have used the RDS paradigm to show that stereoscopic processing occurs in the occipitoparietal cortex [46, 47]. The first study showed predominant right hemispheric activation in the V2, V3, V3A, V7, and SPL [46], while the other reported activation of dorsal V4, V3A, V7, and the caudal parietal disparity region [47].

Stereovision can be assessed by utilizing an interplanar disparity paradigm (Fig. 4A2) [48]. In this paradigm, absolute disparity can be studied by moving planes symmetrically in relation to a central fixation point, while relative disparity can be examined with asymmetrical movement of planes relative to the central fixation point [48]. In this context, an fMRI study on stereopsis indicated the involvement of cortical regions that are specialized in processing absolute and relative disparity [48]. Stereoscopic processing for absolute disparity induced activation in V3A, V5/MT+, and V7; while a combination of absolute and relative disparity activated the V4 and V8/V4 α regions [48]. Another fMRI study using dynamic RDS with interplanar disparities revealed the specific involvement of V3A in processing stereoscopic stimuli [49].

Motion perception

Visual motion processing infers the speed and direction of elements oriented in the spatiotemporal frame [50]. Motion perception serves the following functions: 1) Encoding 3D shapes; 2) Estimation of time to collision; 3) Ability to distinguish objects from background (segmentation); 4) Perception of self-motion; 5) Control of saccadic eye movements; 6) Perception of pattern vision; and 7) Perception of moving objects [51]. To understand these diverse functions of motion perception, various paradigms have been designed. Some key paradigms pertaining to the spatial aspect of motion perception, including radial motion and stereo motion, are highlighted in the Fig. 4 (Fig. 4B1, B2).



Fig. 3. Chronological evolution of VSP research using functional neuroimaging. This flow diagram provides a timeline depicting the chronological development of key VSP paradigms (shown on the left side), together with the corresponding brain regions activated during those paradigms (shown on the right side). 1) Spatial location matching [68], 2) Local and global processing of visuospatial patterns [167], 3) Object discrimination based on spatial properties [168], 4) Rigid and non rigid motion of 3D structures [53], 5) Visuospatial navigation in 3D virtual-reality maze [79], 6) Dynamic RDS with varying inter-planer disparity [49], 7) Coherent motion versus noise [55], 8) Binocular disparity stereopsis [46], 9) Clock drawing test [63], 10) Disparity defined checkerboard [47], 11) High level (saliency-based) and low level (luminance-based) motion [52], 12) Virtual city navigation tasks using spatial memory and non-spatial strategies [77], 13) Simultaneous form discrimination and spatial localization [70], 14) Absolute and relative disparity-based stereopsis [48], 15) Spatial location matching [169], 16) Angle discrimination [66], 17) Visuospatial attention [94], 18) Drifting edges, radial rings and radial optic flow [57]. Abbreviations: CPDR, Caudal parietal disparity region; FEF, Frontal eye field; IPS, Intraparietal sulcus; ITG, Inferior temporal gyrus; LO, Lateral occipital; MOG, Medial occipital gyrus; OT, Occipitotemporal; SFS, Superior frontal sulcus; SOG, Superior occipital gyrus; SPL, Superior parietal lobe; STS, Superior temporal sulcus; VO, Ventral occipital.

Different electrophysiological and imaging studies have reported stimulus-specific involvement of the subcortical, primary, and higher cortical areas. In an fMRI study, luminance-based motion perception was shown to activate the contralateral lower level motion processing system, involving

projections from V5/MT+ to dorsal intraparietal sulcus (IPS) and superior temporal sulcus; while saliency-dependent motion perception, based on chromatic grating, activated the bilateral higher level motion processing system in IPL [52]. An electrophysiology study showed that the tritan motion

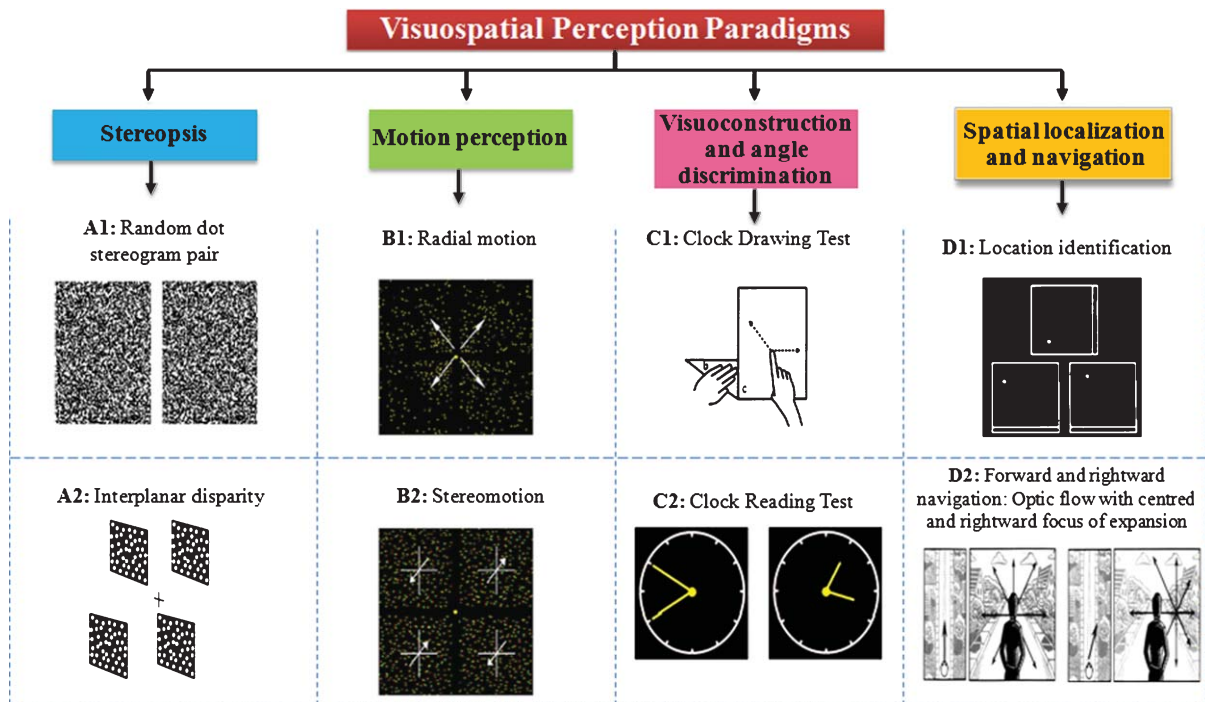


Fig. 4. VSP paradigms. This schematic showcases few of the key VSP paradigms. For each of the four main aspects of VSP, two prominently used paradigms are presented with due permissions. Stereopsis: A1. Random dot stereogram pair [47], A2. Interplanar disparity [48]; Motion perception: B1. Radial motion [116], B2. Stereo-motion [116]; Visuoconstruction and angle discrimination: C1. Clock drawing test (for visuoconstruction) [63], C2. Clock reading test (for angle discrimination) [128]; Spatial localization and navigation: D1. Location identification [68], D2. Forward and rightward navigation [74].

stimulus selectively engages the K-pathway, while luminance-based motion is processed by the M-pathway [27]. Extraction of depth information from a stimulus with geometric structures (2D/3D) undergoing rigid and non-rigid motion has been shown to activate the V5, IPS, and the lateral and ventral occipital regions, with right hemispheric dominance [53].

Disparity-selective neurons in MT+, which are involved in stereopsis and integration of motion cues, have been shown to process disparity- and velocity-based cues for 3D motion perception [47, 54]. In an fMRI study using an optic flow task, randomly moving dots led to the activation of area V1, while coherently moving dots prominently activated the V5/MT+, V3A, ventral occipital, IPS, and superior temporal sulcus areas [55]. In an attempt to study the role of V1 and V5 in optic flow perception, repetitive transcranial magnetic stimulation (applied at a low frequency of 0.9 Hz for 10 min) was used as a virtual brain lesion on healthy young subjects [56]. The study indicated a prolonged inhibition of optic flow perception up to 40 minutes after stimulation [56]. Further, recent fMRI studies have shown that while unidirectional motion

stimuli activate V3, V3A, V6, and V5/MT+; optic flow tasks, including coherent movement patterns and stimuli resembling self-motion, activate V6 [34, 57].

Clock processing: Visuoconstruction and angle discrimination

The clock processing paradigm includes the clock drawing test (CDT) and the clock reading test (CRT) [58]. In CDT, subjects are verbally commanded to draw a clock with a specific time ('command' condition) or are asked to copy the presented clock ('copy' condition) (Fig. 4C1) [58]. CDT requires visuospatial processing and visuoconstructional skills as well as executive abilities; the 'command' condition of CDT also requires semantic memory in addition to the above cognitive processes [59–62]. An fMRI study using the CDT in healthy young subjects showed activation predominantly in the posterior parietal cortex, including the SPL, IPS, bilateral dorsal premotor area, left pre-supplementary motor area, left ventral prefrontal cortex, and left precentral gyrus [63].

In contrast to CDT, CRT requires no executive processing and strongly focuses on visuospatial processing of angle discrimination, i.e., the identification of a specific angle from a set of given angles (Fig. 4C2) [59, 64]. An event-related fMRI study with an angle discrimination task reported significant activation in the V2 and SPL, along with the activation of sensorimotor cortex [65]. A later rapid event-related fMRI study by the same authors performed a task demand dependent analysis to assess VSP task-related brain activation [66]. The study reported neural activity in the bilateral caudate nucleus, insula, right frontal gyrus, and left precentral gyrus, in addition to the aforementioned activation in V2, SPL, and sensorimotor cortex [66]. In an experimental study using a combination of repetitive transcranial magnetic stimulation and fMRI, the causal relationship between parietal cortex activation and visuospatial abilities was reported [67]. Specifically, the study showed enhanced activation in the SPL, IPS, and frontal eye fields (FEF) in response to an angle discrimination and conjunction task that tested for both angle and color discrimination [67]. Furthermore, inhibition of the SPL through repetitive transcranial magnetic stimulation led to significant impairment in performance of the angle discrimination task, indicating the functional role of SPL in processing visuospatial information [67].

Spatial localization and navigation

Location matching tasks have often been used to investigate the localization aspect of spatial vision (Fig. 4D1) [32, 68–70]. Studies with positron emission tomography (PET) have shown that the spatial location matching tasks selectively activate the lateral SPL in the dorsal pathway, along with prominent activation in the lateral occipital cortex [32, 68, 69]. To investigate interactions between the dorsal and ventral visual pathway, an fMRI and event-related potential study was conducted using a task that involved discrimination of shape as well as spatial localization [70]. The fMRI data of the above study showed activation in the precuneus and angular gyrus in the dorsal pathway, as well as the fusiform gyrus and inferior temporal gyrus in the ventral pathway [70]. In general, location processing requires mediation of the parietal and superior occipital lobes in the dorsal pathway [71].

Spatial navigation is the vital cognitive ability of finding a way through the environment using spatial information processing [72, 73]. Spatial navigation, including self-movement, requires the maintenance of spatial orientation in a 3D environment and

has been shown to rely on optic flow perception (Fig. 4D2) [74, 75]. For navigation tasks, visuospatial information is required to be updated at regular intervals. In a virtual navigation task during free navigation, it has been shown that the anterior hippocampus and bilateral retrosplenial cortex (RSC), which play an important role in encoding of visuospatial information, are prominently activated [76]. Further, fMRI studies have shown that while in a navigation task in a known environment, the retrieval of encoded information leads to activation of the right hippocampus, parahippocampus, and bilateral RSC; spatial navigation task using non-spatial information cues leads to activation of the caudate nucleus [76, 77]. It has been demonstrated that during encoding of spatial information about the layout of the local surroundings, activity in the parahippocampal place area is predominant [78]. An fMRI study using a visuospatial navigation task in a virtual 3D maze, reported activation in the right hippocampus, bilateral medial occipital region, parahippocampus, and lingual gyrus, along with the posterior cingulate and superior colliculus areas [79]. The study also reported gender-specific differences in activation patterns, with significantly increased activity in the left hippocampus of males, in contrast to increased activation of the left SPL, fusiform gyrus, and medial frontal gyrus in females [79]. Finally, the perception of space around us constructs multiple spatial representations, with each individual representation playing an integral role in spatial navigation tasks [80]. While, the lateral intraparietal area has been shown to be responsible for spatial information updates for egocentric representations (representations in relation to self), spatial information updates of allocentric representations (representations in relation to environment) have been shown to be governed by the medial temporal areas [80–82].

Involvement of attention in VSP

Attention is the ability to exert voluntarily control over the automatic brain functions [83]. Neuronal mechanisms play an important role in controlling the attention and are basically understood in the top-down and bottom-up processing scheme of visual information [84]. While top-down processing is goal-oriented and relies on knowledge from previous experience and expectations about a given display, bottom-up processing is stimulus-driven and based on the saliency of a visual scene [84]. Various types of attention have been investigated extensively for their neuroanatomical and functional substrates, with consistent findings on the

mediation of executing, orienting, and alerting attention by the anterior cingulate cortex, the parietal cortex, and the thalamic regions, respectively [85, 86].

A PET study on visuospatial attention indicated the differential contribution of the parietal and frontal cortex in the control of spatial selection [87]. Superior parietal region was reported active during the shifting of attention to locations based on sensory cues, while frontal region showed activity when stimuli appeared at expected locations [87]. It has been demonstrated that due to the limited processing capacity of the brain for processing multiple stimuli simultaneously, presentation of multiple stimuli leads to sensory suppressive interactions, which alter the receptive field size of neurons in the extrastriate cortex by either bottom-up or top-down mechanisms [88].

Existing literature has indicated the role of the frontoparietal network for sustained attention, whereas selective attention has been shown to activate different brain regions in both ventral and dorsal streams, based on the specific attribute attended to in the given stimulus [88–92]. The prefrontal cortex plays a specific role in modulating activity in the distributed network of cortical and cerebral structures sensitive to sensory signals and responsible for motor outputs [88]. Specifically, for spatial shifting of attention (both overt and covert), the brain areas involved in modulating the activity of visual cortex include the SPL, frontal eye field, supplementary eye field, IPL, middle frontal gyrus, and anterior cingulate cortex [88, 93]. Furthermore, a study with Granger causality measures on blood-oxygen-level-dependent (BOLD) signal for visuospatial attention indicated that activation in the FEF and IPS modulates the visual occipital cortex; and the direction of causality was shown to be from FEF to IPS, suggesting a top-down mechanism of attention network [94].

AD PATHOLOGY IN RETINA AND SUBCORTICAL REGIONS

Within the visual brain regions, the initial pathology of AD has been thought to originate in the visual association area [95, 96]. An analysis of autopsied brains in an AD study revealed the presence of neuritic plaques and neurofibrillary tangles (NFTs) in the visual association cortex (BA 19) in more than half of cognitively intact subjects, and all subjects with mild cognitive impairment (MCI) or AD [95]. Further, some brains exhibited AD pathology in the visual association area but not in the hippocampus area, suggesting that in a subset population, AD pathology might first

manifest in the visual association areas instead of the hippocampal regions.

The primary visual cortex has been considered to be relatively spared in AD; while some studies have shown presence of NFTs in this region, these pathological changes were observed only in a subset of AD population that presents with a visual variant of the disease [97]. On the other hand, several studies have reported thinning of retinal nerve fiber layer (RNFL) in MCI and early AD patients, with the help of optical coherence tomography [98–102]. Further, a study used laser Doppler to show a significant decrease in blood flow to the RNFL in AD [103]. The effect of AD on RGCs has been contentious. While earlier studies reported no histopathologic differences in the RGCs of individuals with AD and those of age-matched normal individuals [104, 105], several groups have since reported degeneration of RGCs and optic nerve axons in patients with AD [98, 106–108].

A pathological study investigated the subcortical visual centers of AD patients for evidence of AD pathology [109]. They reported the presence of amyloid deposits, neuritic plaques, NFTs, and neuritic threads in the superficial and deeper layers of superior colliculus, while the inferior pulvinar, pregeniculate nucleus, and LGN showed only amyloid deposits.

Subsets of pyramidal neurons belonging to the M-pathway are significantly decreased in AD individuals [110]. The M layers in the LGN have also been shown to develop plaques [109]. Dysfunction in the M-pathway in AD was reported by a study using chromatic and luminance grating, which found significance differences in the latency of luminance-evoked pattern electroretinograms between AD and control subjects [111].

VSP TASK-RELATED DEFICITS IN AD

VSP functions are primarily mediated by the dorsal pathway [96, 112, 113]. Several studies on AD patients have shown impairment of dorsal stream functions, such as angle discrimination [11, 114], motion perception [74, 115–117], and spatial location matching [118]. A multimodal imaging study examined the structural evidence for the functional alterations in MCI using fMRI and diffusion tensor imaging [113]. Loss of connectivity between the dorsal and ventral streams in the cingulum was indicated, with a decrease in diffusion explaining the functional reorganization in the mediolateral parietal and orbitofrontal regions, and an increase in activation and diffusion in the

precuneus, IPL, middle cingulum, and middle temporal gyrus, suggesting compensatory mechanisms in MCI [113]. Neuropsychological, electrophysiological, and fMRI studies have used the radial optic flow perception paradigm to show the selective impairment of dorsal stream function in MCI and AD patients [74, 96, 112, 119]. These studies have shown that cognitive decline in MCI and AD significantly correlates with radial optic flow perception deficits, as indicated by neuropsychological measures, observed prolongation of P200 latency in visual event-related potential studies and reduced fMRI-BOLD responses [96, 112, 119]. Furthermore, while MCI patients showed impairments specific to the ventro-dorsal stream (IPL), in AD patients both streams of the dorsal pathway were found impaired (IPL and SPL) [96, 112].

Below, we present the various VSP functions affected by AD, with special focus on the related functional alterations in the brain activation patterns as detected by fMRI using different VSP paradigms.

Stereopsis

Stereopsis interpretation of both monocular and binocular depth cues has been shown to be impaired in mild AD patients, due to disordered local stereopsis and decreased sensitivity to perspective [120]. On the other hand, a study focusing on age-related changes in stereopsis found that while stereovision involving stationary 3D shapes was largely preserved, there is an age-related decline in the ability to discriminate the depth and shape of moving 3D surfaces [121]. To the best of our knowledge, no study has reported stereopsis-related impairments in MCI.

Motion perception

An fMRI study characterized and compared the brain activation patterns of AD patients and healthy elderly subjects with respect to visuospatial tasks involving stereomotion and radial (optic flow) motion [116]. The study showed that during radial motion tasks, cognitively normal elderly subjects showed activation in the left paracentral lobule (BA 24/7), left inferior and middle temporal gyrus (BA 19/37), left occipitoparietal cortex (BA 19/39), left SPL (BA 7), right MFG (BA6), and right precentral gyrus. On the contrary, brains of AD patients showed no significant activation in the above mentioned regions, indicating marked functional deficits in AD [116]. Interestingly, in AD patients subjected to the stereomotion task, regions normally activated in healthy elderly

subjects, i.e., V5, bilateral SPL, occipitoparietal regions, and premotor regions, showed hypoactivation; instead, activation was observed in the bilateral IPL, caudate, and cingulate cortices. These data not only provide the pathophysiological basis for visuospatial disorientation in AD patients, but also highlight the neuroanatomical compensatory mechanisms observed in early stages of AD.

Spatial localization and navigation

To investigate deficits in guiding self-movement and maintaining spatial orientation in AD, a study used visual patterns with horizontal motion and radial optic flow [74]. By varying the number of dots moving coherently in a particular direction, the coherency thresholds for detection of the motion pattern (horizontal or radial) were identified for control and AD subjects [74, 122]. In comparison to healthy controls, AD patients performed poorly on spatial navigation tests and showed a relatively higher threshold for detecting horizontal motion as well as a dramatically impaired ability for detecting radial optic flow patterns [74, 122]. Visuospatial orientation abilities among young normal, elderly normal, MCI patients, and AD patients have also been investigated by utilizing a motion perception test with horizontal motion and radial optic flow, along with other neuropsychological tests, including the Money Road Map test to compare the spatial navigation abilities, as well as other visual and verbal memory tests [119]. The study showed that one fifth of elderly normal, one third of MCI, and half of the AD patients showed deficits in visual motion processing. Interestingly, these deficits only showed significant correlation with performances on the Money Road Map test, indicating the possibility of independent existence of VSP impairment in the preclinical stages of AD [119]. In a later study, which delineated the cognitive mechanisms contributing to visual self-movement processing impairment in the normal elderly and AD patients, it was shown that while in normal elderly these deficits were largely due to attention deficits, impairment of visual self-movement processing in AD patients could be primarily attributed to deficits in visual motion processing [115]. Dysfunctional integration of multisensory cues related to self-motion at the posterior parietal cortex has been suggested to lead to impairment in path integration and visuospatial disorientation in AD [123].

fMRI studies involving location matching tasks have reported increased brain activation in MCI and AD patients in comparison to the healthy elderly [118,

124]. In healthy elderly controls, location matching tasks have been shown to activate the middle occipital gyrus, precuneus, IPL, and MFG. In MCI, all of the above mentioned regions, except IPL, showed activation along with additional activation in the SPL, MFG, superior frontal gyrus fusiform, and hippocampal gyrus [118, 124]. In AD, increased activation compared to healthy controls was found in the left superior temporal gyrus, precuneus, inferior frontal gyrus, right insula, precentral gyrus, bilateral post central gyrus, and posterior cingulate [118, 124].

Clock-drawing test/visuoconstruction

CDT has been widely used as a screening tool for various visuospatial dysfunctions and dementias, particularly AD [59, 125]. A CDT study analyzed the performance of AD and cerebral vascular dementia (CVD) patients in comparison to cognitively normal controls, on both the 'command' and 'copy' conditions of CDT [126]. In both conditions, AD as well as CVD patients performed significantly worse than controls. In the command condition of CDT, which requires semantic memory along with constructive abilities, there was no difference between AD patients and patients with CVD. However, in the copy condition of CDT, the performance of the AD group was significantly better than the CVD group, indicating relatively preserved visuospatial constructive abilities in AD compared to CVD [126].

Furthermore, a recent neuroanatomical study of AD subjects with MRI reported a significant correlation between poor performance in a figure copying task and reduced gray matter volume in the right parietal cortex [127]. However, no such correlation was observed between performance on the task and reduced gray matter volume in the right dorsolateral prefrontal cortex, signifying bottom-up aspects of VSP deficits in AD [127]. A region-of-interest-based study showed significant correlation between CDT performance and reduced gray matter volume in the right anterior and posterior superior temporal lobe in AD [60], while whole brain voxel-based morphometry revealed significant correlation between CDT performance and reduced gray matter density in the left temporal lobe region [62]. A PET study indicated that CDT performance is mediated by the left posterior temporal region (fusiform area) in AD [61]. Another fMRI study reported a positive correlation between CDT performance and activation in the left SPL during a radial motion task, implying that reduced activation is

responsible for the poor performance of AD patients in CDT [117].

Angle discrimination

Two independent fMRI studies have tested the angle discrimination paradigm with MCI and AD patients [64, 128]. Both studies utilized two different analysis, i.e., the conventional task demand independent boxcar function and the task demand dependent BOLD response predictor function [64, 128]. In progressing MCI, task demand independent analysis revealed increased activation in the left precuneus, while task demand dependent analysis showed increased activation in the left SPL region [64]. The authors suggest that the increased activation in the parietal region of brains with progressing MCI reflects compensatory neuronal activity [64]. In AD, task demand independent analysis showed reduced activation in the SPL and increased activation in the occipitotemporal cortex and right MTG as compared to healthy elderly controls [11, 128]. Task demand dependent analysis reported significantly weaker to no BOLD response in the precuneus, middle occipital gyrus, and IPL in AD, as compared to elderly controls [128]. Decreased SPL activation in AD patients was also demonstrated in an angle discrimination task-related fMRI study [11]. The study further showed that the decrease in SPL activation led to compensatory recruitment of occipitotemporal cortex [11].

SCOPE AND ADVANTAGES OF VSP AS A BIOMARKER FOR AD

Tracking VSP deficits with fMRI

Detection of changes in visuospatial function can be achieved with fMRI by monitoring activation patterns during visuospatial tasks. The use of fMRI for monitoring functional activation changes associated with the various VSP deficits in AD can allow for detection of AD at its earliest preclinical stages; it therefore has tremendous potential as a biomarker for AD diagnosis and monitoring [6, 96]. Of recent, this potential is being investigated and several studies have looked at the changes in functional activation patterns with respect to VSP deficits in MCI and AD [64, 116, 129]. Table 1 summarizes the findings of VSP task-related fMRI studies in MCI as well as AD brains with respect to the changes in activation of the key brain regions involved in VSP functions. The table provides a comparison between these fMRI studies, and the PET

Table 1
Functional neuroimaging of VSP in AD

Brain regions		Clinical Status			
		fMRI		PET/SPECT	
		MCI	AD	MCI	AD
Parietal	Precuneus	↑[64, 113]	↓[128]		↓[114, 173, 174] ↓[175] [#]
	IPL	↑[113, 176]	↓[128] ↑[116]	↓[170] ↓[171, 172] [#]	↓[114, 174] ↓[177] [#]
	SPL	↑[64]	↓[11, 116]		↓[114, 173, 174] ↓[177] [#]
Temporoparietal	-	-	-	↓[144, 175]	-
Temporal	ITG	-	↓[116, 128]	-	↓[177] [#]
	MTG	↑[113]	↑↓[128] ↓[116]	-	↓[173] ↓[177] [#]
	STG	-	↑[118]	-	↓[174] ↓[177] [#]
Frontal	IFG	↑[124]	↓[128] ↑[118]	↑[172] [#]	-
	MFG		↓[116, 128]	-	-
Posterior cingulate	-	-	↓[116]	-	↓[175, 177] [#]

Existing literature with VSP studies on MCI and AD using fMRI and PET/SPECT has been summarized. For fMRI studies, only VSP task-related studies that report significant functional activation changes during performance of the task are reported. For PET/SPECT studies, only the studies that show significant correlation between functional metabolic findings and VSP task performance are included (except for the studies marked with [#]. Please see below). The hyper (↑) or hypo (↓) activation in respective brain areas are compared to age-matched cognitively normal control subjects. (↓↑) refers to inconclusive results from different laboratories; (–) refers to no available data. [#]These studies showed significant changes in both PET/SPECT metabolic data and VSP task performance, but did not run correlational analysis between them.

and Single Photon Emission Computed Tomography (SPECT) studies in MCI and AD brains that correlated brain metabolism with performance in VSP tasks.

An evaluation of the data from these PET/SPECT studies (Table 1) revealed that the visuospatial processing brain regions exhibit decreased glucose metabolism in both MCI and AD patients. A similar

evaluation of the data from the fMRI studies suggests an interesting trend. All reviewed fMRI studies demonstrate increased functional activation during VSP tasks in MCI. On the other hand, a majority of fMRI studies show decreased functional activation during VSP tasks in AD (Table 1). While some literature does not follow this trend, these conflicting findings might be due to

variation in the progression stage of AD, e.g., mild versus moderate AD. The AD subjects used in the Bokde et al. [118] study, which showed increased activation in AD, had a mean Mini Mental Status Examination (MMSE) score of 25.3, while other studies have followed the canonical classification and categorized patients with MMSE score of 24 and above as MCI [130].

However, most fMRI studies show hyperactivation in MCI and hypoactivation in AD. For instance, a location matching task-based fMRI study showed increased activation in the SPL of MCI patients in comparison to healthy elderly controls [124]. An angle discrimination task-dependent fMRI study in MCI patients also showed increased activation in the SPL [64]. On the other hand, another fMRI study revealed that in mild-to-moderate AD patients, SPL exhibits decreased activation in response to an angle discrimination task [11]. Similar pattern of increased activation in MCI and decreased activation in AD has been observed for other brain regions involved in VSP processing, including the precuneus [64, 113, 128] and the MFG [116, 124, 128]. It is important to note the significant diagnostic relevance of these findings. While PET/SPECT studies showed metabolic decrease in affected brain regions for both MCI and AD, they cannot be used to distinguish between MCI and AD patients. On the other hand, fMRI can be used to monitor the changes in activation levels between MCI and AD, thereby not only facilitating the distinction between MCI and AD, but also assisting in the detection of the MCI-to-AD converting population.

It has been hypothesized that the increased activation in MCI is reflective of compensatory mechanisms [11, 64, 113, 124]. A study examined the correlation between the functional activation in MCI and AD patients performing a CRT task, and the decline in their cognitive state, as measured by the MMSE score [131]. Their correlational analysis revealed a quadratic rather than a linear relationship between brain activation changes and cognitive state, with hyper-activation in MCI and in the early stages of AD, followed by a decline in activation in later stages of AD [131]. These studies suggest that in the early stages of AD, there is functional compensation for AD-related neuronal loss, through increased activity of remaining neural resources in the region.

Further, several fMRI studies have also revealed compensatory recruitment of 'additional' brain regions, including regions from the ventral pathway, during VSP task performance in MCI and AD patients [11, 113]. A recent study used fMRI to compare the

activation patterns of healthy control and amnesic MCI patients during performance of a recognition task with canonically and non-canonically oriented objects [113]. The study showed that during recognition of non-canonically placed objects, MCI patients showed increased activation of the dorsal pathway as well as activation in additional ventral pathway regions.

Taken together, these studies indicate that onset of neuronal loss in the brain leads to functional compensation in VSP task-related brain networks. These compensatory changes include increased activation response in the brain regions associated with a VSP task, as well as recruitment of additional brain regions that are generally not involved in performing the given VSP task. fMRI-based monitoring of these activation changes can allow for early diagnosis of AD in at-risk individuals, prior to the onset of detectable cognitive deficits.

Further, comparing the VSP task-related functional activation maps in AD and other dementias can also effectively discriminate between various dementias. An fMRI study investigated the differences in VSP task-related activation patterns among patients with AD and dementia with Lewy bodies [132]. Using a motion task, the study showed that while AD patients had significantly higher activation in the V5 region, dementia with Lewy bodies patients showed greater activation in the superior temporal sulcus [132].

In addition to aiding in early and accurate diagnosis of AD, monitoring the response of VSP task-dependent activation patterns to drug treatments in MCI and AD patients can provide an invaluable tool for examining the functional therapeutic effects of potential AD treatments. A longitudinal fMRI study on AD patients that tested the treatment effects of cholinesterase inhibitors on visuospatial processing indicated functional improvement in their brain activation maps during VSP tasks as well as an improvement in the Activities of Daily Living scale [133].

These studies elucidate the scope of *in vivo* fMRI monitoring of visuospatial processing as an investigative and therapeutic tool in AD research. In the next section, we further discuss the necessary advantages of monitoring VSP abilities in AD.

ADVANTAGES FOR MONITORING VSP DEFICITS IN AD

Canonically, fMRI biomarkers have focused on monitoring the activation patterns of 'memory networks'. Given the early emergence of episodic memory

deficits in AD, fMRI has been extensively used with episodic memory tasks to detect brain activation pattern changes in medial temporal lobe structures in MCI and AD brains [134–138]. In addition to episodic memory, changes in other forms of memory function, such as semantic, procedural, declarative, and even visuospatial, have also been detected using fMRI [8, 139–141].

While memory impairment is an indicator of AD, deficits in VSP are also a hallmark of AD [74, 96, 120, 142, 143]. Several studies have indicated that VSP deficits can be monitored in MCI and the early clinical stages of AD [144–146]. Objective psychological measurement of visuospatial ability exhibited high specificity and sensitivity in distinguishing between cognitive decline in MCI and healthy elderly subjects [147]. A longitudinal study monitored global cognitive capacity as well as specific cognitive domains, i.e., verbal memory, working memory, and visuospatial ability, of cognitively normal elderly subjects over time and compared individuals who developed dementia to those who remained cognitively healthy [146]. This study showed that visuospatial deficits could be detected earlier than deficits in other cognitive domains in preclinical AD subjects [146]. Further, a recent large-scale longitudinal study examined the course of functional cognitive decline during the prodromal phase of AD, prior to the onset of MCI, with respect to five cognitive domains: orientation, attention, memory, language, and visuospatial ability [145]. The study showed that deficits in VSP could be detected in the prodromal stages of AD (65 months prior to clinical onset). Further, occurrence of VSP deficits was synchronous with the global cognitive decline marking the prodromal stages of AD (65 months prior to clinical onset) [145]. These findings are significant given the urgent need for biomarkers that can diagnose AD prior to the onset of clinical symptoms. Furthermore, several key studies over the past decade have suggested that VSP deficits are not only detectable in the early preclinical stages of AD, but also might precede other memory deficits [119, 143, 148]. Additionally, certain aspects of VSP have been shown to deteriorate as AD progresses, providing a reliable means of tracking the progress of AD in a given patient. It has been demonstrated that visuo-perceptual organizational skills, which allow the mental assembly of an image from its parts, gradually deteriorate with disease progression and can be useful for tracking disease course [149].

It is also crucial to note the link between age of AD onset and pattern of neurophysiological profile. Early-onset AD patients present with a different pathological

and cognitive profile from late-onset AD patients [150, 151]. A recent study demonstrated that early-onset AD patients perform worse than late-onset patients on visuospatial functioning tasks [152]. The above study also demonstrated that in early stages of early-onset AD, the memory function was well preserved. These findings highlight the need to adequately test cognitive domains other than memory for reliable AD diagnosis and tracking; and the validity of VSP as a biomarker for early-onset AD. Posterior cortical atrophy (PCA) is a clinical syndrome hallmarked by higher visual processing dysfunction [153, 154]. While PCA can be associated with various neurodegenerative disorders, it most frequently presents as a visual variant of AD [119, 155–158]. These AD patients with PCA have relatively preserved memory functions, intact language, and preserved judgment and insight; and instead, exhibit prominent bottom-up VSP deficits, such as visual agnosia, constructional apraxia, optic ataxia, gaze apraxia, simultanagnosia, avisual field defect, decreased visual attention, impaired color perception, and decreased contrast sensitivity [153, 154]. VSP biomarkers are imperative for diagnosis and monitoring of such focal visuospatial variants of AD.

Furthermore, while the canonical clinical criteria that focus on memory impairment have certain diagnostic value for AD, various other dementia syndromes also exhibit memory impairments leading to diagnostic challenges. The use of VSP deficits as a biomarker in conjunction with biomarkers for limbic dysfunction can enhance the specificity of AD diagnosis [159]. For instance, retrospective studies have shown that in comparison to frontotemporal lobar dementia patients, AD patients are less sensitive to tests implicating frontal lobe dysfunction, such as word generation tasks and letter fluency, but more impaired on tests of memory (i.e., Mattis Dementia Rating Scale Memory subscale) and visuospatial abilities (i.e., WAIS Block Design and CDT) [160, 161]. The severity of VSP deficit has been suggested as the most salient feature demarcating dementia with Lewy bodies from AD, with visuo-perceptual and visuospatial impairment being far more pronounced in the former [132, 162–165]. Furthermore, while visuospatial deficits are characteristic of both AD and Huntington's disease, the specific components of visuospatial processing are differentially affected in the two disorders. A study on visuo-constructional abilities found that while AD patients were impaired on visuo-constructional tests requiring extrapersonal orientation (e.g., copying a complex figure), patients with Huntington's performed poorly on visuospatial tasks requiring personal orientation (e.g., the

Money Road Map Test requiring egocentric mental rotation in space). As such, a combinatorial test for VSP function and other cognitive domains can serve to differentiate between dementias with similar symptoms and diagnose AD accurately. In line with this, the Swedish council of Technology Assessment in Health Care demonstrated that CDT had a high positive likelihood ratio (12.4), indicating the capacity of this test to significantly enhance the diagnostic certainty [166].

To summarize, VSP deficits are prominent in AD and can be detected at the earliest prodromal stages. Monitoring of VSP function in addition to the other cognitive domains affected in AD, such as episodic and semantic memory, can allow for earlier detection of AD as well as enhance the accuracy of AD diagnosis through differentiating between AD and other dementias.

CONCLUSION

In conclusion, functional mapping of visuospatial processing in AD has tremendous scope as a biomarker for AD. Screening for functional changes related to decline in VSP abilities, in addition to other cognitive deficits in preclinical AD, will improve our ability to reliably detect AD prior to disease onset. Longitudinal follow-up examination of functional activation maps of VSP can reflect pathologically induced changes across various stages of preclinical and clinical progression in AD. Monitoring VSP functional networks of MCI and AD patients also opens new avenues for examining the functional efficacy of novel disease-modifying drugs and can be used as a reliable tool in clinical trials. As such, investigating the functional reorganization of VSP networks in association with AD pathology is likely to have significant impact on AD diagnostics and is an active ongoing research focus in our laboratory. We propose that *in vivo* functional mapping of VSP network alterations in addition to the utilization of other fMRI biomarkers can significantly enhance the specificity and accuracy of AD diagnosis.

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