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Spatial Navigation Impairment in Healthy Aging and Alzheimer's Disease

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1. Introduction

The prevailing number of studies dealing with spatial navigation in animals and also in human have been connecting it to the function of the medial-temporal lobe (MTL), hypothesized to serve as the neuronal basis for the spatial cognitive map. Changes in the MTL are characteristic for both healthy aging and Alzheimer's disease (AD), with markedly more severe changes in AD. The level of hippocampal dysfunction therefore counts among the boundaries between healthy aging and development of AD. Furthermore, the decline in the spatial navigation abilities has been described for healthy aging and is among the diagnostics marks of early AD. While the impact of this decline on the life of elderly seems to be minor, subjects suffering AD become lost in new environments and later in the course of the disease even inside their homes. The spatial navigation is however a complex process using a number of brain regions besides MTL. The regions discussed in this review also include prefrontal cortex (PFC), whose changes in healthy aging are often considered more typical than changes in MTL, and parietal cortex documented to deteriorate from the very early stages of AD. Due to its complexity, spatial navigation is a promising cognitive ability to be investigated in the phases of development from healthy aged to AD.

The aim of this review is to investigate the complexity of the spatial navigation and its neural basis in healthy aging and in AD, including several available studies concerning the boundary between these two. We will focus on the differences in the spatial navigation abilities between healthy aging and AD and on the potential of spatial navigation to differentiate between them. The current review follows up two papers on similar topic (Iachini et al., 2009; Moffat, 2009) and in contrast to them focuses just on wayfinding and navigation, its underlying neural structures and the distinction between healthy aging and Alzheimer's disease.

2. Neural basis of spatial navigation

Functional neuroimaging and lesion studies have identified a complex network of structures that are involved in spatial navigation. The proposed network includes the hippocampus, parahippocampal gyrus, medial and right inferior parietal cortex, regions within prefrontal cortex, cerebellum, parts of the basal ganglia, posterior cingulate cortex and retrosplenial cortex (Aguirre et al., 1996; Barrash, 1998; Ekstrom et al., 2003; Hartley et al., 2003; Maguire

et al., 1998a). Here we will shortly review the role of some of those areas whose changes in elderly and Alzheimer's subjects have been documented in relation to spatial navigation.

The concept of hippocampus as a neural basis for cognitive map (O'Keefe & Nadel, 1978) stems from the discovery of place cells responding when an animal is in a particular location as defined by the spatial configuration of objects in the environment (O'Keefe & Dostrovsky, 1971) and from the effect of hippocampal lesions impairing navigation to an invisible goal in a water maze from variable start positions (Morris et al., 1982). The cognitive map theory dissociated the navigation based on a configuration of distal landmarks from the navigation to and from landmarks. This concept has evolved into the dissociation between allocentric and egocentric navigation. The allocentric navigation uses flexible representation (Eichenbaum et al., 1999) of an ensemble of distal landmarks and independent of actual subject positions. On contrary, the egocentric navigation uses distances and angles to or from individual landmarks. In humans, the allocentric mode of navigation was shown to be connected with the hippocampal function in analogues of the Morris water maze (Astur et al., 2002; Feigenbaum & Morris, 2004), in place navigation inside a virtual town (Maguire et al., 1998a), and also in remembering the location of objects on a table (Abrahams et al., 1997). The hippocampal function have often been confused with the function of parahippocampal gyrus, but there is evidence that parahippocampal cortical areas are required for iconic representations of scenes, with hippocampus being required in addition when memory for locations in three-dimensional space is required. Functional neuroimaging of recognition memory for object location within a two-dimensional array (Johnsrude et al., 1999) and the perception of spatial scenes (Epstein & Kanwisher, 1998) and buildings (Aguirre et al., 1998) consistently activates the posterior right parahippocampal gyrus, but not the hippocampus.

While allocentric representation of space has been connected with the MTL, the egocentric representations were documented within the parietal cortex (Hyvarinen & Poranen, 1974; Mountcastle et al., 1975). Posterior parietal areas appear to support the necessary translation of spatial information between allocentric and body-centred reference frames (Snyder et al., 1998) and between the various egocentric reference frames (Andersen et al., 1985). Lesions of the right posterior parietal cortex are characteristic by an egocentric orientation deficit presenting as the inability to represent the spatial relationship between the subject and other objects (Kase et al., 1977; Levine et al., 1985; Stark et al., 1996).

Evidence of PFC involvement in spatial navigation is based mainly on animal research, however its functional activation associated with navigation in human was described several times including activation during successful relative to unsuccessful navigation (Maguire et al., 1998a) or activation associated with navigational goals and conjunction of goals and places (Ekstrom et al., 2003). Ablating or inactivating part of the rat orbitofrontal cortex impairs performance of an allocentric foraging task (Corwin et al., 1994), escape in the Morris water maze and conditioned place avoidance (Vafaei & Rashidy-Pour, 2004). Several studies have reported double dissociation with hippocampal and/or fimbria fornix lesions impairing place learning in the place version of the Morris water maze and PFC lesions impairing response learning (de Bruin et al., 1997; de Bruin et al., 2001).

3. Healthy aging

The decline of cognitive function in elderly people have been thoroughly studied, the role of spatial navigation impairments in the difficulties experienced in daily life is however probably underestimated. During driving elderly individuals have self-perceived deficits in

navigation and develop behavioural patterns to avoid unfamiliar routes and places (Burns, 1999). These deficits can have negative implications for peoples' well-being and independence. In addition, several studies in elderly describe objective route learning and navigational deficits that can affect daily life not only during driving.

3.1 Cognition and neural changes

Before reviewing literature concerning changing spatial abilities during aging we will review shortly general cognitive changes. The prevailing concept explains most of the cognitive effects of aging by changes in prefrontal cortical function. This viewpoint is evidenced by both neuropsychological and functional brain imaging data and related decrements are typically found in tasks as working memory, episodic free recall or recollection of the source of the learned information (Johnson et al., 1993). Working memory tasks require to manipulate in some way the material held in memory, in contrast to short-term memory tasks, requiring only holding the presented material in memory for several seconds. One example is repeating a sequence of presented digits in a reversed order. Working memory is dependent on the prefrontal regions (Courtney et al., 1998; D'Esposito et al., 2000; Smith & Jonides, 1999) and deteriorates with aging (Salthouse & Meinz, 1995). Also free recall of episodic information without contextual or any other cues activates prefrontal brain areas (Petrides, 2002) and there is considerable evidence that age differences in memory performance diminish when retrieval is facilitated by providing additional cues at the time of memory test (Craik & McDowd, 1987; Rabinowitz, 1984).

Another source of evidence concerning age dependent changes in prefrontal function comes from functional imaging experiments. Aging is generally connected with reduced activation of the left PFC during encoding (Cabeza et al., 1997; Grady & Craik, 2000) and a pattern of reduced activation in those prefrontal regions that are most activated in younger subjects together with an increased activation in the contra-lateral regions. This pattern, referred to as reduced hemispheric asymmetry (Cabeza et al., 2002), is often interpreted as a sign of compensatory function, as those older individuals who have the most successful task performance tend to display the largest bilateral PFC activations (Reuter-Lorenz & Lustig, 2005). Several studies document another pattern of age dependent changes in brain activation with decreased activity of hippocampal region and simultaneously increased prefrontal activation during encoding (Gutchess et al., 2005; Park et al., 2003), interpreted as compensatory mechanism for the decrease of hippocampal function. Structures of the PFC also exhibit age-related volumetric changes that are larger than in any other cortical region (Raz et al., 2004; Raz et al., 2005; Resnick et al., 2003; West, 1996).

The age dependent changes in the MTL are less clear. Results of the volumetric studies are somewhat ambiguous: while numerous both cross-sectional and longitudinal studies show an effect of age on the hippocampal volume (Golomb et al., 1993; Jernigan et al., 1991; Persson et al., 2006) with the rate of decline in the range of 0.79–1.5% per year (Jack, Jr. et al., 1998; Pruessner et al., 2001; Raz et al., 2004; Raz et al., 2005), some studies did not find any age dependent hippocampal volume decline (Sullivan et al., 1995; Van et al., 2004). The finding of decreased medial-temporal involvement for older adults compared to young adults during encoding is robust however and has been reported in a number of studies, including encoding of faces (Grady et al., 1995), natural scenes (Park et al., 2003), verbal materials (Daselaar et al., 2003; Grady et al., 1999) and line drawings (Grady et al., 1999). The neuropsychological evidence of age related changes in MTL is scarce and confined mainly to the domain of spatial navigation.

3.2 Spatial memory and navigation

Results from various types of spatial memory tasks have been explained by limits in cognitive capacity connected to the PFC. Age dependent deficit in the memory for location of several object was shown in a number of studies (Light & Zelinski, 1983; Naveh-Benjamin, 1987; Naveh-Benjamin, 1988; Park et al., 1983; Sharps, 1991), but not when using specific experimental conditions (Sharps & Gollin, 1987; Waddell & Rogoff, 1981; Waddell & Rogoff, 1987). The factors influencing similar performance of elderly to young subjects seem to include intentional versus incidental learning and distinctiveness of the object locations (Uttl & Graf, 1993). In experiments focusing on this distinctiveness theory, Sharp and Gollin (1987) showed that the age dependent deficit is absent when the objects are presented in a real space or are in different colors or are three-dimensional blocks of wood. Similar effect of the form of the objects these authors described even for the free recall of identity of objects located on a table-top map (Sharps & Gollin, 1988). They suggested that visually distinctive context facilitates object memory because it provides a rich associative base for elaboration of memory traces. It seems that elderly participants spontaneously engage in less elaboration than do younger respondents. This interpretation is in agreement with reports showing less efficient encoding in elderly adults (Grady et al., 1995; Stebbins et al., 2002), was however not confirmed in a control study on a different group of subjects (Park et al., 1990). Interestingly, object location memory was shown to be dependent on the MTL region (Nunn et al., 1999; Pillon et al., 1999; Stepankova et al., 2004) or more specifically on the parahippocampal gyrus (Maguire et al., 1998b; Owen et al., 1996). Thus another interpretation of this age dependent object location memory deficit may attribute it to the decline in MTL activity. The incidental learning and distinctiveness may then facilitate compensational strategies supported by the PFC.

3.2.1 Large-scale real spaces

Other authors studying spatial memory in large-scale environments proposed explanation of age related deficits by working memory demands. In one of these studies, subjects should remember spatial position of building pictures standing in a large room either in a spatial configuration corresponding to the real position in the subject's hometown or in a novel spatial configuration. Most of the pictures were hidden and the subjects should learn their position by replacing them several times until they could do all items accurately. Then, at several points in the room, they should estimate direction and distance to the current position from these hidden pictures. They were instructed to do so either by mental rotation of their current position or by taking perspective from the picture. Mental rotation and perspective taking was more difficult for elderly subjects in the novel but not in the known environment (Kirasic, 1989). Because all subjects learned the object positions before testing, the understanding of the experiment was based on working memory demands larger in novel configuration than in known configuration. Similar effect of increased deficit associated with aging in a novel relative to a familiar environment was documented in a navigational task in supermarket (Kirasic, 1991) and explained also by working memory demands.

The limits in cognitive capacity in temporospatial processing were assessed by another study presenting to the subjects a set of colour slides of two routes through unfamiliar neighbourhood. The two routes shared a common section. In a series of tests following the presentation, older adults were less likely to recall the landmarks sequentially, more likely to recall non-spatial associations to the routes and more likely to regard salient landmarks,

rather than turns, as critical route-maintaining events (Lipman, 1991). The older adult's landmark memory was organized according to the distinctiveness of landmarks rather than their spatial order. The authors hypothesized that with the advancing age sequential processing of route information is curtailed or precluded by the cognitive capacity limits. Preferred mode of spatial processing used by older people, which captures distinctive but not critical route events, may require less cognitive effort.

Similar age related deficits were found in an experiment by Wilkniss et al. (1997), where subjects were guided along a complicated route through a university building. After the tour they were asked to lead the experimenter along the same route and their errors were recorded. Then they completed landmark recognition and ordering tasks, followed by another test on navigation in the same building using a just learned map of a new route. The elderly adults recognized well the landmarks, but were impaired in their temporal ordering, in recalling the route, and in using the learned map to navigate successfully. Although the older adults encoded visual information and recognized landmarks, they were less likely than younger adults to select or effectively use critical cues. This was interpreted as consistent with the studies by Kirasic (1991) and Lipman (1991) (see above) by an age-related deficit in selection of information most useful in route maintenance. The impairment of navigation using a learned map in the second part of the test offers additional explanation, mentioned by the authors, by deficit in using a configural spatial representation to navigate a route.

Real space route learning ability in a hospital lobby was the subject of another study (Barrash, 1994). The participants in the age of 18 to 78 were lead by the experimenter through a long route containing 28 intersections and 16 turns and at the end they were asked to lead the experimenter back to the route origin. The complete test consisted of three trials. Although all groups showed significant learning between the trials, the participants 60 and older made significantly more errors than the youngest group and the oldest participant in their 8th decade committed almost 4 times more errors than the youngest group. There was a tendency even for the participants in their 6th decade to be impaired. The impairment seems to be explicable by cognitive capacity limits in the elderly subjects, because the retracing test was performed in an opposite direction than the learning and there were only three trials to learn the route.

3.2.2 Virtual maze environments

Other studies employed virtual reality design to assess navigation in highly controlled environment. In a simple virtual maze composed of richly textured alleys connected by four intersections, participants were required to find a trophy at the goal point as fast as possible and to learn the correct route in five learning trials (Moffat et al., 2001). The time, distance and number of errors to reach the goal increased with age, with the groups of 45-65 and 66-91 years old participants impaired relative to younger subjects. The impairment resulted from incorrect entrances to dead ends or already visited alleys. The authors found significant correlations between the performance in the maze and measures of working, non-verbal and verbal memory and mental rotation.

Spatial relational learning was investigated in a virtual reality study using a treadmill to simulate locomotion (Lovden et al., 2005). The subjects were assessed in a virtual museum using combination of two conditions: city-block topography with straight corridors vs. variable topography with winding corridors and with vs. without walking support. Variable topography was expected to be more difficult than city-block topography when using

spatial strategy, but not when using non-spatial cued navigation strategy. Elderly subjects were impaired under all conditions, and their performance was slightly better using walking support and not influenced by variable topography. This contrasted with the increase in travelled distance with variable topography in younger subjects and no effect of walking support. The elderly subjects were also less successful in locating landmarks from the museum on its map. Findings of this study suggest that elderly subjects do not use spatial relations between parts of the maze. In analogy, animal research showed that aged organisms more often adopt stimulus-response learning and cue guidance strategies to locate places in space, whereas younger organisms rely more on spatial relational learning in tasks where both activities could be used (Rapp et al., 1987; Tanila et al., 1997). In addition, the finding of walking support helping elderly subjects in navigation indicates that walking per se is an attention demanding activity for elderly subjects.

Results distinct from the real space study by Wilkniss et al. (1997, see above) were described in an experiment using immersive virtual reality with head mounted display in simple city model (Zakzanis et al., 2009). The elderly subjects were impaired in retracing a short route with four intersections after passively viewing it, but made also more false alarm errors in the landmark recognition test, contradicting the above mentioned study. It is questionable whether the landmark recognition error could result from small angle of view (40°) or the passive way of learning the route.

In an interesting recent study using virtual reality, subjects were trained thoroughly to acquire the spatial relationships of the environment and tested in this knowledge by locating six landmarks on a schematic map (Iaria et al., 2009). Elderly subjects not only spent longer time learning the environment, but even after meeting the criterion of knowing it, they were slower and made more errors in the navigational tasks. The authors interpret this finding as impairment both in the formation of a cognitive map and in using the acquired cognitive map for navigation, similarly to the above mentioned study by Wilkniss et al. (1997). It may be questionable however if during the training the elderly subjects really learned a map of the environment containing spatial relations or if they learned rather a visual view of the schematic map with landmarks. This visual view would then be naturally more difficult to use for navigation. Anyway, this approach should be a fruitful one and deserves further elaboration.

3.2.3 Analogies of the Morris water maze

The theory explaining spatial navigation deficit in elderly by changes in using of the cognitive map was directly tested using human analogues of the Morris water maze (MWM) (Morris, 1981). The cognitive map, as introduced by Tolman (1948) and later by O'Keefe and Nadel (1978), contains flexible representation of the environment, which can be used in novel circumstances independently on actual subject's position. Navigation using this flexible representation should not be affected by rotation or deletion of individual landmarks (Markus et al., 1994; O'Keefe & Speakman, 1987). In the experiment using a real space analogue of the Morris water maze (Newman & Kaszniak, 2000), subjects were required to learn to find an invisible target position in an octagonal arena 7.3 m in diameter. Then they were assessed in three testing conditions: after arena rotation, cues deletion and delay. The elderly subjects were impaired under all of these conditions but not in the control trials allowing non-spatial strategy, confirming the assumption of impaired acquisition or use of their cognitive map of the maze.

In navigational experiments using virtual analogue of the MWM with variable start position, strong association was found between age and time to find the invisible platform and also between age and time spent in the correct quadrant during the probe trial with the platform removed (Driscoll et al., 2005; Driscoll et al., 2003; Moffat & Resnick, 2002). In the latter of these experiments (Moffat & Resnick, 2002), older participants were able to use proximal objects but not room-geometry cues to locate the goal on overhead diagrams of the environment. This difference in strategy in aged subjects is similar to the effect of hippocampal lesions in rats, which results in impaired use of distal but not proximal landmarks (Save & Poucet, 2000). This similarity suggests that the age dependent atrophy in the human hippocampus (Jack, Jr. et al., 1998) underlies the age related shift to cue-use strategies observed in the present study. In a strong relation to these views are the findings from another report using virtual MWM analogue in elderly subjects (Laurance et al., 2002). The elderly participants were impaired in learning the goal position and also in locating it on a diagram of the maze, but on the same diagram they were able to arrange correctly the patterned walls and objects on the walls. It seems therefore that they acquired cognitive map of the maze structure but not of the goal position. Two dissociable cognitive processes could be responsible for these two abilities, according to authors' suggestion. The possibility should be excluded however, that the elderly subjects used pure visual memory to reconstruct the maze, but could not use it to estimate the goal location that was never shown.

Important observation from the Moffat and Resnick (2002) study was that elderly subjects were impaired even in the first trial of the test, following only practice trials with different goal location. Elderly individuals probably continued to search in locations that have been already adequately explored, suggesting a preservative component to their behaviour, the working memory deficit, or more generally, the selection of inefficient spatial search strategy. Thus, besides relational spatial memory, executive and strategic functions probably play a significant role in spatial skill acquisition in the MWM.

3.2.4 Brain imaging

From the above results we can hypothesize about the underlying neural structures, primarily the PFC and MTL. More direct evidence about the connection between neural function changes during aging and navigational performance was provided however by several brain imaging studies. Two approaches used in the aging research include correlating brain volumes with spatial navigation performance and functional imaging. The first approach was used in three studies with surprisingly contrasting results. The hippocampal volume was significantly correlated with navigational performance in the virtual MWM in the first study (Driscoll et al., 2003); more specifically the positive correlation was found with the time in the target quadrant in the probe trial in all subjects together, younger and older. In contrast, another study using also virtual MWM (Moffat et al., 2006b) described correlation of the hippocampal volume with the distance travelled only in the first learning trial (with not yet known goal position) and only in the younger subjects group. Finally, in a report describing navigation in a maze consisting of several alleys and seven intersections (Head & Isom, 2010) significant correlation was found between the wayfinding performance and hippocampal volume in only elderly subjects. Spatial strategy selection could account for these discrepancies. The brain areas correlating with the navigational performance was shown to depend on the strategy selection (Bohbot et al.,

2007). In addition, the virtual MWM performance depends on extrahippocampal brain areas, namely PFC and caudate nucleus (Moffat et al., 2006b). The link between hippocampal volume and navigational performance probably depends on the specifics of the virtual maze and successfulness of individual spatial strategies.

The second approach to assess changes in brain function in spatial navigation accompanying aging is to use functional imaging. In the first route encoding and recognition study in a virtual reality building (Meulenbroek et al., 2004) subjects should remember a set of turns marked by arrows on the walls and then, during the recognition phase, on the same places choose the correct one of two arrows to follow the route. The elderly subjects reached slightly lower scores than young subjects, and compared to the young they showed diminished posterior fusiform-parahippocampal and parietal activity during route encoding, corresponding to the role of these brain areas in navigation. In addition, the elderly subjects exhibited increased anterior parahippocampal activity relative to the young subjects during the route recognition, which might indicate decreased familiarity with the route. Finally, the elderly subject activated more the anterior cingulate and perisylvian cortices during encoding, interpreted as a failure to suppress irrelevant information. In a related paper by Moffat et al. (2006a) subjects learned a virtual environment consisting of several rooms and hallways by navigating between various objects. Compared to their younger counterparts, elderly adults showed reduced activation in several regions of the MTL and of the parietal lobe. They also showed greater anterior cingulate gyrus and medial frontal lobe activation during encoding than younger subjects. The findings were interpreted as aging dependent compensatory shift from more posterior and medial temporal systems supporting navigation to more anterior frontal systems. Contrasting activation pattern was found in the only fMRI study in virtual MWM in elderly subjects (Antonova et al., 2009). Differently from younger group, the elderly adults did not activate hippocampal-parahippocampal region either during encoding or retrieval and also lacked activation of the frontal pole and dorsolateral prefrontal cortex. The compensatory shift to frontal system seems therefore to be limited to several structures, some of which may be related to inhibitory processes.

In summary, many descriptions of spatial navigation impairment in aging are compatible with the lower cognitive resources theory of aging and weaker prefrontal function. Evidence for mediotemporal function decline in aging comes mainly from studies using analogies of Morris water maze and brain imaging.

4. Alzheimer's disease

4.1 Progression of Alzheimer's disease

AD is a neurodegenerative disorder, which predominantly and initially affects mediotemporal structures, especially hippocampus and parahippocampal gyrus. Its early symptom is the impairment in episodic memory. Patients have difficulty with learning of new information and retaining it for more than a few minutes. As the disease advances, the ability to learn is increasingly impaired and the access to older, more distant memories is lost. With the development of the disease also other cognitive domains than memory are impaired, like judgment and executive functioning, together with aphasia, apraxia, disorientation and visuospatial functioning. Important diagnostic criterion for dementia is that these cognitive deficits affect daily life of the patients.

Due to its neurodegenerative nature, the development of AD from normal ageing is gradual and long. Increasing attention is now being paid to the mild end of the cognitive spectrum from normal ageing to AD. There is probably a transitional period between normal ageing and the clinical diagnosis of probable very early AD and this transitional zone is now mostly described using term mild cognitive impairment (MCI) (Petersen et al., 2001). Originally, the concept of MCI was limited to memory deficits with relative preservation of other cognitive domains (Petersen et al., 1999). As the research on MCI has advanced, it has become apparent that several clinical subtypes of MCI exist, covering all cognitive domains (Petersen et al., 2001; for review see Petersen, 2004). Besides memory, the impaired cognitive domains can be language, executive function or visuospatial skills. Based on this pattern of impairment, the MCI subtypes comprise amnesic and non-amnesic forms, both possibly single or multi domain. This distinction is particularly relevant when considering the outcomes of subjects with MCI, which can be also non-AD forms of dementia such as vascular dementia or dementia with Lewi bodies. All of these clinical subtypes of MCI have minimal impairments in functional activities and do not meet criteria for dementia. Although amnesic MCI presents a high risk of developing AD, this category includes patients who will develop AD together with others who will never convert. The conversion rates from MCI to dementia reported by different authors range from 7.2% per year (Morris et al., 2001; Rubin et al., 1998) to 12% (Bowen et al., 1997; Petersen et al., 1999) or 13.5 % (Tierney et al., 1996). This is in contrast to conversion rate from healthy elderly subjects to dementia which is between one and two percent per year (Petersen et al., 1999).

4.2 Cognition and neural changes

The MTL atrophy is the hallmark of AD. In individuals at risk of autosomal dominant familial AD it can even precede the onset of cognitive changes (Fox et al., 1996). Neuropathological investigations (Braak & Braak, 1991; Hyman et al., 1984) suggest that AD-related changes may begin in the entorhinal cortex and subsequently spread to the hippocampus. Entorhinal volume was found to be the most useful metric for discriminating healthy from MCI individuals, whereas hippocampal volume was best for classifying MCI and Alzheimer's disease patients (Pennanen et al., 2004). Volumetric studies in AD subjects consistently reveal both volume reductions in the hippocampus relative to age-matched controls (e.g. Jack, Jr. et al., 1992; Jack, Jr. et al., 1997; Killiany et al., 1993) and higher rate of hippocampal decline (Fox et al., 1996; Jack, Jr. et al., 1998; Jobst et al., 1994). The brain pathology in AD shows also in functional brain imaging studies. A pattern of bilateral temporoparietal hypoperfusion or hypometabolism well discriminates AD patients not only from age-matched healthy controls but also from patients with vascular or frontotemporal dementia (Silverman, 2004).

This MTL atrophy is closely related to the episodic delayed recall impairment from the onset of the disease (Greene et al., 1996; Small et al., 2003). Memory for both verbal and visual material is affected in the majority of cases (Greene et al., 1996; Hodges & Patterson, 1995; Small et al., 2003). AD patients seem incapable of learning due to deficient encoding rather than due to impaired retrieval since their free recall performance is as poor as their recognition performance (Greene et al., 1996).

In addition to the MTL, other brain regions degenerate as the disease spreads beyond the hippocampus. Parietal lobe atrophy is well documented from moderate stages (Braak & Braak, 1991; Brun & Gustafson, 1976; Foundas et al., 1996), but medial parietal atrophy

could be detectable even from presymptomatic AD (Scahill et al., 2002) and even in MCI patients converting to AD (Chetelat et al., 2005). Also frontal lobe atrophy was shown from moderate stages (Haxby et al., 1988; Scahill et al., 2002). This extrahippocampal brain affection is related to deficits of other non-memory domains, manifesting as impairment of executive functions with later involvement in constructional praxis, language and sustained attention (Baudic et al., 2006).

Distinguishing evolving from stable amnesic MCI in order to prescribe appropriate treatment as quickly as possible in the evolution of AD is a primary objective of majority of the MCI research. The available biological markers predicting the disease development are not reliable, a combination of several markers increases however the discrimination power. Markers in use include biochemical measures, like amyloid β -protein and tau levels in the cerebrospinal fluid (Hulstaert et al., 1999), brain imaging of hippocampal (Jack, Jr. et al., 1999) or parahippocampal (Visser et al., 1999) atrophy and hippocampal hypoactivation (Johnson et al., 1998; Small et al., 1999), and cognitive neuropsychological evaluation. Episodic memory deficits occur very early in the course of the disease and decreased performance in delayed recall of words, sentences, or series of objects is the most reliable predictor of AD in preclinical individuals (Masur et al., 1994; Tierney et al., 1996). Memory deficit may be a more efficient indicator than MTL atrophy on MRI (Laakso et al., 2000; Visser et al., 1999).

4.3 Spatial navigation impairment in AD

Deficit in the spatial domain is well documented in Alzheimer's disease. Clinically-relevant impairments in navigational skills are often apparent in the early stages and reports of impaired spatial behaviour, like getting lost in familiar places, can in many cases lead to the recognition of cognitive impairment and diagnosis of dementia (Klein et al., 1999). Disorientation and episodes of getting lost were documented both in outpatients (McShane et al., 1998) and patients residing in a community (Pai & Jacobs, 2004). According to global deterioration scale of Reisberg (Reisberg et al., 1982) the first orientation difficulties at the early stage of the disease (stage three) may affect journeys in unfamiliar and macro-scale environments, while at stage six patients only can move in very familiar home settings. Patients with AD have a tendency to become lost and then wander even in familiar surroundings. This "wandering" seems to be associated with an increased tendency to walk (Hope et al., 2001), parietal dysfunction (de Leon et al., 1984) and general confusion.

Many Alzheimer's disease patients suffer from higher visual motion processing deficits (Rizzo & Nawrot, 1998), including selective impairments in perceiving the optic flow (Tetewsky & Duffy, 1999). Optic flow is the patterned visual motion seen by a moving observer (Gibson, 1950). It provides cues about heading direction and the three-dimensional structure of the visual environment (Royden et al., 1992; Warren & Hannon, 1988) and its perception activates right posterior parietal cortex (Morrone et al., 2000). An atypical form of AD with higher visuospatial impairment was described (Kiyosawa et al., 1989), based also on deficits in judging spatial relations (Cogan, 1985) and atrophy (Benson et al., 1988), hypometabolism (Pietrini et al., 1996) and neuropathology (Hof et al., 1989) of the posterior cortical regions.

4.3.1 Perceptual deficits

Most studies on spatial disorientation in AD focus on its connection with optic flow discrimination deficit. This theory was documented several times by a significant correlation

of optic flow discrimination thresholds with several measures of spatial navigation. In a test of navigation in a hospital lobby (Tetewsky & Duffy, 1999) poor performance was associated with an elevated optic flow threshold. In contrast, there was no significant correlation between the MMSE score and spatial navigation score and adding MMSE scores to optic flow threshold in a regression model did not explain more variance in the spatial navigation scores. Another study found significant correlation of the optic flow thresholds also with a score in the table-top left-right orientation Money Road Map test and the ability to respect lane boundaries during sustained driving in On-the-Road Driving test (O'Brien et al., 2001). Rather convincing evidence of the importance of visual perception deficit in spatial disorientation in AD was recently provided in a study by Kavcic et al. (2006). The authors required elderly and AD subjects to attend to a 300 m path through a hospital lobby being pushed on a wheelchair, retrace it and complete a set of tests. Then they correlated navigational to neuropsychological, perceptual and neurophysiological measures. The AD subjects were impaired in all navigational tests, with best results in route and location knowledge and worst results in identifying photo and video location along the route. In a multiple linear regression model, the total score of navigation in AD subjects correlated significantly with optic flow discrimination thresholds, amplitude of the evoked occipital EEG responses N200 and with contrast sensitivity, but with none of the memory tests. The authors concluded that navigational impairment in Alzheimer's disease is linked to a disorder of visual cortical motion processing reflected in specific perceptual and neurophysiological measures.

Consistent with this perceptual deficit theory of spatial disorientation in AD are also two other experiments using route learning in a hospital lobby. The perceptual nature of disorientation was inferred either from correct recognition of landmarks mentioned during the walk in contrast to impaired recognition of incidental not-mentioned landmarks in AD patients (Cherrier et al., 2001) or a lack of relationship between disorientation and memory tests and a failure to use spatial architectural information (Monacelli et al., 2003). The discrepancy between memory impairment, being the defining characteristics of AD, and perceptual nature of disorientation in these patients have been explained by the memory deficits limiting the usage of spatial navigation strategies to these based on visual perceptual analyses (Monacelli et al., 2003), unfortunately without specifying these strategies.

4.3.2 Complex cognitive deficits

While the series of just reviewed studies consistently propose that the factor defining mostly the spatial disorientation in the AD is the perceptual deficit, other articles describe also the role of other cognitive processes. In a study using Memory and Behavior Problems Checklist (Zarit et al., 1985), which contains four items dealing specifically with spatial disorientation (wandering, getting lost indoors, getting lost on familiar streets, being unable to recognize familiar surroundings), Henderson et al. (1989) compared the sum score of these four items with a set of neuropsychological measures. Stepwise regression analysis showed scores from delayed recall memory test and clock drawing and house copying visuoconstructive test as the significant predictors of the disorientation score, but not disease severity, attention or language impairment. As wandering or getting lost is unusual among focal-lesion patients with constructional deficits and is also not reported in association with discrete disturbance in long-term memory, the authors propose that it is the combination of the visuoconstructive and memory deficits that is crucial.

The importance of perceptual and higher cognitive spatial skills for navigation in AD was examined in another study comparing these skills in AD and healthy control subjects with

the functional spatial skills in the subject's own home and in an unknown building (Liu et al., 1991). The AD group was worse than elderly healthy subjects in navigation inside the unknown building but not in their homes. The AD group was also impaired in all cognitive spatial orientation tests and a subset of perceptual spatial orientation tests requiring to mentally represent shapes. Some of the basic orientation skills were intact: visual object recognition of shape, visual and tactual discrimination of size and left-right discrimination. The visuospatial deficit seen in early AD, such as getting lost or misplacing objects, are probably due to the impairment of the mental shape representation or other higher order processes, rather than to visual-perceptual skills.

Another approach was chosen in an experiment by Passini et al. (1995). Spatial navigation was considered as a problem solving task demanding development of a decision plan containing a hierarchy of sub-problems. Subjects diagnosed with AD were told to take the experimenter to the dental clinic in an unknown hospital and were asked to express verbally everything that went through their mind. By interventions from the experimenter the subject were reminded about the task to minimize the effect of memory and attentional deficit. It was observed that irrelevant stimuli affected behavior of the subjects. Some patients acted impulsively without analyzing the constituent elements, e.g. they tended to read uncritically almost all of the written information that they encountered on the trip. The behaviour of many DAT patients was seemingly more driven by external stimuli than by the goal of the wayfinding task. The major difficulty for DAT patients was probably to distinguish relevant from irrelevant information and to structure their decision plan.

Virtual analogue of hospital lobby can probably substitute the real space environment in estimating the navigational deficits of MCI and AD patients, as implied by similar group differences and a strong correlation across all subjects in a recent study (Cushman et al., 2008). The subjects were taken passively (in the real space they were pushed on a wheelchair) along a 300 m path through a hospital lobby, and then should retrace it and complete a set of tests. Stepwise discriminant analysis was then used to find which scores of the follow-up tests distinguished best between the groups. The MCI and AD subjects were best differentiated by tests assessing the ability to locate of scenes from the lobby on its map and the free recall of the landmarks along the route. The cognitive deficit of MCI and AD was interpreted as a dual one consisting of visuospatial and verbal memory deficits. Slight gender differences in performance in a similar task in a hospital lobby were described in AD and MCI patients, with only women performing better in recognition of photographs from the lobby and in free landmark recall (Cushman & Duffy, 2007). Using multiple regression, their general navigational performance was however explained by scores in different neuropsychological tests: mostly radial optic flow perceptual thresholds in men and category naming and figural memory in women. The impairment found in AD and MCI patients can therefore results from different grounds in men and women.

An interesting study used positions of home locations and two familiar landmarks individual for each subject to compare the knowledge of their spatial relations with learning a new environment (Jheng & Pai, 2009). Early AD patients were similarly successful to healthy elderly subjects in drawing simple diagrams of the home and two landmarks positions. The two groups were also similar in learning new goal position in an virtual reality water maze analogue; the elderly subjects were only more successful in learning to navigate to home location in the same water maze analogue using positions of the two familiar landmarks. It is difficult to estimate however if the similarity between the two groups could results from difficulty of the tests even for the healthy subjects.

4.4 Spatial navigation in MCI

The question not sufficiently answered yet concerns with the spatial navigation impairment in a MCI, a diagnosis with a high progression rate to AD. Optic flow perception, the visuoperceptual ability compromised in AD, can be impaired already in amnesic MCI subjects, as documented by Mapstone et al. (2003). In this study, approximately half of the amnesic MCI patients were impaired in radial motion perception, suggesting a visuospatial subtype of MCI based on spatial perception. The motion perception thresholds correlated significantly with the results of the Money Road Map test, requiring subjects to follow a path through a city on a map and indicate left and right turns, but not with figural and verbal memory. However, the MCI subjects were not impaired in the Money Road Map test. The study, therefore, does not document any spatial navigation deficit.

Results of another study using two types of virtual environments might also be interpreted in the context of deficits in parietal lobe function (Weniger et al., 2010). The MCI patients and elderly control subjects should learn in five trials a route through a maze, without any landmarks and containing six intersections, and through a virtual park, a model of a village with many landmarks, both near and distant. The MCI patients performed worse than the control group in both environments, more impaired were however in the maze environment without any learning evident during the five trials. In addition, the performance in this environment was correlated with right precuneus volume. The MCI seem therefore to be connected to both egocentric navigation deficits in the maze and allocentric navigation deficits in the park, with more evident egocentric deficits. This is consistent with the following studies documenting general spatial navigation impairment in multi-domain MCI subjects.

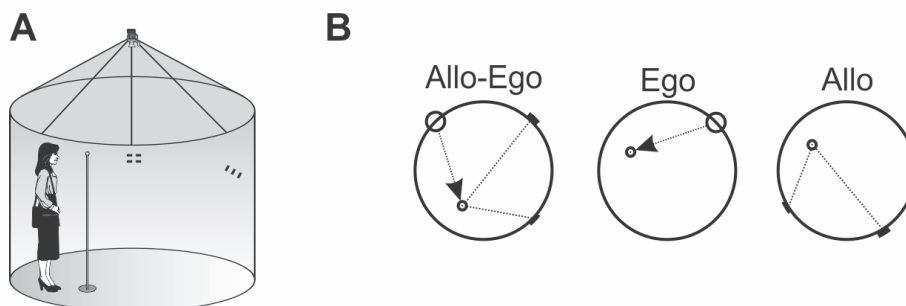


Fig. 1. Experimental environment and the scheme of the test from Hort et al. (2007)

That spatial navigation deficits could be detected even in amnesic single-domain MCI patients and that the memory deficit is the determining factor in this deficit was suggested by our recent experiment (Hort et al., 2007). In a real space analogue of the Morris water maze, we found navigational impairment in single-domain amnesic MCI subjects only in allocentric but not in egocentric configuration. To locate an invisible goal, the subjects were required to use two landmarks in the allocentric configuration or their own position in the egocentric configuration. The specificity of their impairment only to the allocentric part suggests that spatial configuration memory was the critical factor affecting the results of the amnesic MCI group in our experiment, in contrast to visuospatial perceptual functions which were required probably throughout the whole test. This interpretation is consistent with the MTL atrophy found in MCI (Du et al., 2001) and with the progression rate to AD from amnesic MCI higher than from non-amnesic subtypes of MCI (Yaffe et al., 2006). In

contrast to the results in single-domain amnesic MCI subjects, the group of multi-domain amnesic MCI patients was impaired in all subtests including both egocentric and allocentric configuration. This suggests that together with the decline in other domains, but before progression to AD, the impairment includes even simpler forms of navigation, presumably not dependent on the MTL. Similar pattern of impairment mainly in allocentric navigation was described in our previous studies in the AD group, which was broadly defined mainly by severe memory problems (Kalova et al., 2005; Laczo et al., 2010).

The view of multiple domain based disorientation in MCI patients was supported by several other reports. MCI patients reporting problems with navigation in a structured interview had lower volumes in temporo-parietal brain regions, including hippocampus and parahippocampal gyrus, than patients without navigation problems (Lim et al., 2010). Another study correlated navigational impairment in AD and MCI patients to standard neuropsychology tests and regional neural atrophy (deIpoli et al., 2007). The key finding was that the patients who made at least one error in retracing a route through a hospital lobby did not differ from other patients in any memory or executive neuropsychological tests but had lower right posterior hippocampus and right posterior parietal cortex volumes. The fact that both medial temporal and parietal volumes corresponded to errors in navigation supports the view of visuoconstructive and memory deficits are in the basis of spatial navigation impairment in AD and MCI.

In the last published study focusing on spatial navigation in MCI, a small virtual city was used (Tippett et al., 2009). The subjects passively watched movement along a path though the virtual city comprising four intersections and should reproduce it in five trials. The group of MCI subjects differed only in the speed of movement from the control subjects, but was similar in the number of errors. This similarity was probably due to the ceiling effect in the very simple maze.

In summary, both visual perception changes and deficits in spatial memory seem to predict navigational performance of Alzheimer's disease patients. While the severe memory deficits in AD may emphasize the role of visual perception efficiency, both cognitive abilities apparently contribute to navigational capacity of MCI patients.

	Brain changes	Cognitive abilities linked to spatial navigation impairment
Healthy Aging	Prefrontal areas Medial temporal lobe	Working memory Cognitive capacity limits Temporal ordering Relevant information selection Formation and usage of cognitive map Place recognition by room geometry
Mild cognitive impairment and Alzheimer's Disease	Medial temporal lobe Parietal lobe	Optic flow perception Long-term memory Relevant information selection Egocentric navigation

Table 1. Summary of the brain and cognitive changes linked to spatial navigation impairment in healthy aging and Alzheimer's disease

5. Conclusion

From the reviewed literature some important points can be made. During aging, the most affected brain regions are in the PFC and most neuropsychological studies on episodic memory and also spatial memory explain the deficit in elderly subject by this prefrontal decline. Some navigational experiments in a real space or in a virtual reality points however to the hippocampal and MTL affection in aging and several object location memory experiments allow similar interpretation. More experiments are needed to compare these explanations, but in any case the spatial navigation is a promising choice of hippocampal function assessment in elderly.

Spatial navigation impairment in AD is probably closely related to its multi-domain nature. The necessary condition for navigation in a novel environment is a contribution of higher visual perceptual functions which are impaired in AD. Due to this impairment, the perception seems to be the more important factor in the documented navigational impairment than memory. In a known environment however, like in a familiar building or in familiar streets, the perceptual requirements may become smaller and the spatial memory seems to become another important factor of navigational impairment in AD.

The boundary between the healthy aging and AD in the domain of spatial navigation presumably lies in the cognitive changes connected to parietal lobe atrophy during the dementia development. Optic flow perception deficits and egocentric navigation impairment appear to be detectable in some MCI patients and are profound in AD patients. This hypothesis, implied by the current review, deserves however further examination. Future studies should focus on connection between these abilities and spatial disorientation also in other types of environments, as in water maze analogues and virtual mazes, and on the possibilities of outcome prediction of MCI patients. MCI subtypes differentiation based on individual cognitive domains could be essential for these predictions. Another area worth more experimentation is the navigation of AD patients in familiar environments. The knowledge of the strategies and orientation abilities these patients have in their homes should help with their well-being.

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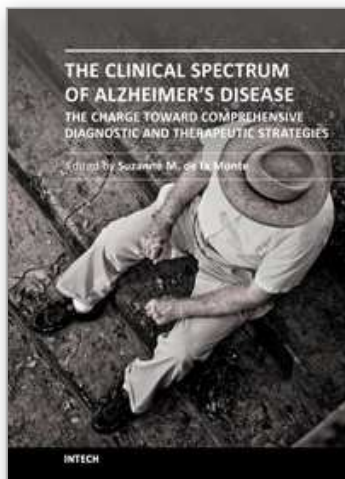
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The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies

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The Clinical Spectrum of Alzheimer's Disease: The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies is highly informative and current. Acknowledged experts in the field critically review both standard and under-appreciated clinical, behavioral, epidemiological, genetic, and neuroimaging attributes of Alzheimer's disease. The collection covers diverse topics of interest to clinicians and researchers alike. Experienced professionals and newcomers to the field will benefit from the read. The strengths and weaknesses of current clinical, non-invasive, neuro-imaging, and biomarker diagnostic approaches are explained. The perspectives give fresh insights into the process of neurodegeneration. Readers will be enlightened by the evidence that the neural circuits damaged by neurodegeneration are much broader than conventionally taught, suggesting that Alzheimer's could be detected at earlier stages of disease by utilizing multi-pronged diagnostic approaches. This book inspires renewed hope that more effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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