Spatial navigation—a unique window into physiological and pathological aging

Health & Medicine

Introduction

Spatial navigation is the ability to determine and maintain a route from one place to another (Gallistel, 1990). It consists of phylogenetically old cognitive functions allowing animals and humans to remember important locations and their mutual relations as well as their relation to the organism itself. Spatial navigation deficits are frequently observed in older population with a significant influence on the quality of life. Spatial navigation difficulties can represent the first sign of Alzheimer's disease (AD) development. The recent trend of spatial navigation research relies on tests translated from animal experiments, e. g., the human analog of the Morris Water Maze (MWM), used for clinical examination of people at risk of AD. In this article we summarize findings on spatial navigation changes in the physiological and pathological ageing and their practical significance for the early diagnosis of AD. As many neuropsychological tools still evoke controversies regarding the accuracy of detecting AD in its predementia stages, it is important to design a battery of tests, including spatial navigation testing for improving early diagnosis of AD.

Physiological and Pathological Ageing

Physiological ageing is associated with structural and functional changes, mainly in the prefrontal cortex (Cabeza et al., 1997 ; Resnick et al., 2003) and to a lesser extent in the hippocampus (Jack et al., 1998 ; Grady et al., 1999), these are mirrored by changes in cognitive functions. Age-related changes in cognition include mild decline in attention, executive functions, working memory, and free memory recall, while other functions such as

visuospatial functions, language, and semantic memory remain generally preserved for a long time (Park, 2000).

Pathological ageing is caused by underlying vascular or neurodegenerative diseases leading gradually to a dementia syndrome, where AD is the most common cause. The hallmark of AD is medial temporal lobe (MTL) atrophy including the hippocampus and the enthorinal cortex (Jack et al., 1997). Some recent studies on patients with AD suggested that atrophy is unequally distributed even within the hippocampus being most pronounced in the CA1 subfield compared to hippocampal atrophy pattern in normal ageing, where the CA1 subfield is relatively spared (Frisoni et al., 2008 ; Mueller and Weiner, 2009). The CA1 atrophy in patients with mild cognitive impairment (MCI) can even predict conversion to dementia due to AD (Chételat et al., 2008 ; Devanand et al., 2012). Besides the MTL structures, the precuneus was shown to be impaired very early even in presymptomatic AD (Scahill et al., 2002). With the disease progression, structures beyond MTL including lateral temporal, parietal and frontal cortices become affected (Braak and Braak, 1991). The first clinical sign of AD is usually the insidious onset of episodic memory impairment caused by neuropathological changes in MTL. Early in the course of the disease, memory impairment is followed by executive dysfunction together with impairment of working memory and attention. Later on, other cognitive domains including praxis, visuo-constructive skills, and language become affected, which reflects the spreading of the pathology further to the neocortex (Kertesz et al., 1986 ; Baudic et al., 2006). Proceeding cognitive impairment leads to a decline in

every day functional abilities, which constitutes an important criterion for the diagnosis of the dementia syndrome.

In recent years, increasing attention has been paid to the mild end of the cognitive spectrum encompassing a transient zone between the normal ageing and dementia, caused most frequently by AD. This transitional zone has been described by the term MCI (Petersen et al., 1999). The concept of MCI refers to a group of individuals who have some cognitive impairment yet of insufficient severity to constitute dementia due to a very slight degree of functional impairment. The individuals with MCI form a heterogeneous group. Those with memory impairment (amnesia) present amnestic MCI (aMCI), those with the non-memory domain impairment (i. e., executive functions, language, and visuo-spatial skills) present non-amnestic MCI (naMCI) (Petersen et al., 2001). Further sub-classification of both MCI subtypes is based on the number of affected cognitive domains. Isolated memory impairment represents aMCI single domain (aMCIsd), similarly, single non-memory domain impairment represents naMCI single domain (naMCIsd). Impairment in additional domains to these two subtypes assigns to aMCI multiple domain (aMCImd), or naMCI multiple domain (naMCImd). Individuals with aMCI subtype have a high risk of AD development; while those with naMCI subtype have a higher probability of progressing to non-AD dementias such as dementia with Lewy bodies, frontotemporal or vascular dementia. The risk of progression from MCI to dementia, particularly to AD, is not uniform and varies across epidemiological studies (Tierney et al., 1996 ; Petersen et al., 1999 ; Morris et al., 2001). The average rate of conversion is estimated to 12% per year (Petersen and Morris, 2003). In contrast, in

healthy elderly subjects the rate of conversion to dementia is about 1–2% per year (Petersen et al., 1999).

Although aMCI patients represent at-risk population for AD development, this population is somewhat heterogeneous as it encompasses also individuals who will never progress to dementia. Lately, much effort is spent to identify the high risk patients with underlying AD pathology already in this prodromal (predementia) stage of the disease. For identification of prodromal AD patients, a combination of neuropsychological tests with various biomarkers is used. These include structural and functional neuroimaging, focused on the hippocampus and related structures (Small et al., 1999 ; Visser et al., 1999 ; Desikan et al., 2010), magnetic resonance spectroscopy (Modrego et al., 2011), cerebrospinal fluid assessment of amyloid-β peptide, tau and phosphorylated tau proteins (Hulstaert et al., 1999 ; Shaw et al., 2009), and amyloid labeling PET ligands (Resnick et al., 2010). Among neuropsychological tools, specific memory tests play an important role for identification of memory profile characteristic for AD that is present already in the predementia stages (Sarazin et al., 2007)—“ amnestic syndrome of the hippocampal type” (Dubois and Albert, 2004). This syndrome forms a clinical core of the revised research diagnostic criteria for AD (Dubois et al., 2007) and is characterized by decreased memory recall despite controlled encoding and using of facilitation retrieval techniques (cueing or recognition) (Dubois, 2000). The MCI individuals with amnestic syndrome of the hippocampal type (HaMCI), compared to those with the amnestic syndrome of the non-hippocampal type (NHaMCI), form the major at-risk subgroup of MCI population (Sarazin et al., 2007) for the development of dementia due

to AD. Although the tests designed to detect hippocampal amnestic syndrome (Grober et al., 1988) were shown to reflect atrophy of the hippocampus, especially its CA1 subfield (Sarazin et al., 2010), it still remains controversial, whether these tests are superior to other tests for the detection of early stage dementia (de Jager et al., 2010 ; Carlesimo et al., 2011). The uncertainty about the usefulness of cued recall as a diagnostic tool for MCI and AD is expressed also in the National Institute on Aging and the Alzheimer's Association guidelines (Albert et al., 2011 ; McKhann et al., 2011), which take into account symptoms of patients with predominant parietal atrophy.

Recent studies indicate that there is a promising chance that, spatial navigation tests reflecting MTL damage may identify patients with AD already in the prodromal stages (Laczó et al., 2009).

Spatial Navigation Strategies and its Morphological Correlates

While navigating through the environment, people can use two basic navigation strategies associated with distinct internal representations of space. The egocentric navigation is body-centered strategy that utilizes distances and directions to or from individual landmarks with respect to the subject's body position. The allocentric navigation is a world-centered strategy using information about distances and angles between different locations in the environment independent of the position of the subject.

Animal research yielded valuable information about the role of MTL in the processes of spatial navigation (O'Keefe and Dostrovsky, 1971 ; O'Keefe and

Nadel, 1978 ; Morris et al., 1982). A key structure of the allocentric navigation is the hippocampus, especially its CA1 subfield (Brun et al., 2008). In 1971 O'Keefe and Dostrovsky discovered specific place-firing cells in the hippocampus of the rat (O'Keefe and Dostrovsky, 1971). These findings supported the theory of a cognitive map (Tolman, 1948) and the dissociation between the egocentric and allocentric navigation strategies. Experiments in the MWM demonstrated spatial navigation impairment in the rats after hippocampal lesion (Morris et al., 1982). Hippocampus is crucial for consolidation, encoding, and long term storage of spatial information (Squire, 1992). The association of hippocampus with allocentric navigation in humans has been demonstrated in various studies in real-space and virtual environments (Maguire et al., 1998 ; Astur et al., 2002). In one study, Holdstock et al. (2000) tested patient (YR) with selective bilateral hippocampal lesion for recall of visuospatial information and found that YR was more impaired at recalling allocentric than egocentric information. More specifically, right CA1 hippocampal subfield seems to be involved in encoding of allocentric spatial information in humans (Suthana et al., 2009). There is evidence that egocentric information is processed outside of the hippocampal system (O'Keefe and Nadel, 1978), in the parietal cortex including precuneus and the caudate nucleus (Mountcastle et al., 1975 ; Maguire et al., 1998). Lesions of the right posterior parietal cortex are characterized by an egocentric orientation deficit (Kase et al., 1977 ; Levine et al., 1985 ; Stark et al., 1996).

Spatial Navigation Impairment in Physiological and Pathological Ageing

Spatial navigation has been thoroughly studied in animal models. Navigational tasks based on the models of MWM (Morris, 1981) were used in testing rats of different age (Ingram, 1988 ; McLay et al., 1999 ; Begega et al., 2001). Results of these studies suggested age-related deficit of navigational abilities in aged rodents and inspired translational research of spatial navigation in humans. Studies in different environments compared healthy elderly persons with younger adults. Significant deficits in learning a route through a hospital lobby was described in participants 60 years and older, with a tendency to be impaired even in participants in their 50s (Barrash, 1994). Several studies suggested that elderly people have lower cognitive capacity limits in temporospatial processing. In one experiment using series of slides of unfamiliar neighborhood, elderly adults recalled landmarks by their saliency and non-spatial associations rather than by their spatial relationships (Lipman, 1991). However, many other studies emphasized deficits specifically in spatial configuration memory and in place navigation in aged population. Wilkniss et al. (1997) let participants undergo navigational tasks in university building and found that older persons made more errors than their younger counterparts in temporal ordering of landmarks, in recalling the learned route, and in using the learned map in navigation. These deficits suggest a lower ability to use a configural spatial representation to navigate. Another study showed navigational difficulties of healthy elderly while driving a car leading to avoidance of unfamiliar places and routes and thus limiting their mobility (Burns, 1999). Human analog of the MWM was developed in an effort to transform navigational tasks into

laboratory conditions. It was employed in a study that demonstrated impairment in acquisition and use of the cognitive map of the maze in the group of elderly participants (Newman and Kaszniak, 2000). Moffat and Resnick (2002) were among the first authors implementing the use of virtual reality in testing of spatial navigation. They compared performance of elderly and younger individuals in the virtual analog of MWM and found deficit of place learning using room-geometry cues in the group of older participants. Furthermore, they suggested that allocentric impairment may contribute to age-related deficit of spatial navigation. This hypothesis was later supported by the study of Iaria and colleagues, according to which the older participants are less effective in forming and using the cognitive maps of an environment (Iaria et al., 2009). A recent study examined age-related differences in strategy preference and found a shift toward egocentric navigation strategy in older participants, which may reflect an adaptation mechanism for the hippocampal dysfunction (Rodgers et al., 2012). Studies correlating hippocampal volume with spatial navigation performance in cognitively healthy elderly provided however contradicting results, with some of them documenting positive correlation (Driscoll et al., 2003 ; Head and Isom, 2010) and other reporting no association (Moffat et al., 2006 ; Nedelska et al., 2012).

Spatial navigation impairment occurs early in AD (Monacelli et al., 2003 ; Pai and Jacobs, 2004); reports about spatial deficits such as getting lost in familiar places and other can in many cases lead to diagnosis of dementia (Klein et al., 1999). The combination of visual perception and memory deficits is probably the mostly defining factor of spatial disorientation in

patients with AD (Henderson et al., 1989), where both allocentric and egocentric navigation strategies are impaired (Hort et al., 2007 ; Weniger et al., 2011). According to several studies, these general spatial deficits in AD seem to be linked mainly to impairment of visual motion processing (Kavcic et al., 2006). Nevertheless, spatial navigation impairment can be detected even before the development of the full blown dementia syndrome, in the stage of MCI (Mapstone et al., 2003 ; delpolyi, 2007 ; Hort et al., 2007 ; Laczó et al., 2011). Given that aMCI is associated with a higher risk of progression to AD, the current research of spatial navigation has focused on this group of patients. A visuospatial subtype of aMCI with impaired radial motion perception indicating spatial perception deficit was identified in one of the first studies in this field (Mapstone et al., 2003). Spatial navigation impairment was documented in aMCI patients performing a route-learning task in the hospital lobby (delpolyi, 2007). In this study, the patients, who made at least one error on the road, did not differ in neuropsychological tests from those with no errors on the road, but they had lower right MTL and posterior parietal cortex volumes that probably underlie spatial navigation deficit. Temporal order spatial memory was recently suggested as another cognitive marker of AD and aMCI (Bellassen et al., 2012). Remembering a sequence of three turns in a simple maze distinguished well between AD, healthy older subjects, and group of patients with frontotemporal lobe degeneration. Spatial navigation impairment is present even in patients with isolated memory deficit aMCIsd (Hort et al., 2007). The patients with aMCIsd tested in the real-space human version of the MWM had an isolated impairment of allocentric navigation, suggesting spatial memory impairment

due to MTL dysfunction. On the other hand, the patients with aMCImd had more general spatial navigation impairment in both, allocentric and egocentric strategies, indicating that structures beyond MTL, presumably the parietal cortex, are affected in this group (Hort et al., 2007). Consistent with these findings patients with aMCI were impaired in both egocentric and allocentric strategies in a study using virtual reality environment, where right precuneus volume was associated with egocentric navigation performance (Weniger et al., 2011). Further study examined spatial navigation in a real-space human version of MWM and found more profound spatial navigation deficit in the HaMCI group in comparison to the NHaMCI group, especially in allocentric navigation, which corresponds with the probable hippocampal dysfunction (Laczó et al., 2009). In addition, the HaMCI group resembled the AD group in spatial navigation performance thus indicating that spatial navigation deficit in the HaMCI may be the first sign of incipient AD. In the same vein, in another study using real-space human analogy of MWM (Nedelska et al., 2012), right hippocampal volume in aMCI and AD patients was associated with an allocentric navigation performance. Thus testing of the allocentric navigation, targeting hippocampus and its CA1 subfield (Suthana et al., 2009), and egocentric navigation, focusing more on posterior parietal cortex and precuneus, could be a useful method of recognizing the aMCI patients at higher risk of AD.

Virtual analogs can probably substitute the real space environment in estimating the navigational deficits of MCI and AD patients, as implied by two recent studies. In an experiment consisting of learning a route through a hospital lobby and of a follow-up spatial tests series, strong correlation was

found across all subject groups between the total spatial score from the real hospital lobby and the total score from its virtual analog (Cushman et al., 2008). Similarly, high correlation was found in another study between scores in a real-space human version of MWM and its virtual 2D analog on a computer monitor representing the circular space as from above (Laczó et al., 2012). These results suggest that computer analogs of real space tests can yield measures of broad applicability to early detection of navigational impairment in MCI or AD.

Conclusion

In the course of physiological ageing, there is a selective mild decline of spatial navigation. Particularly allocentric navigation is impaired, which may be a consequence of the age-related deficits in mediotemporal functioning observed in the elderly. AD is associated with the development of characteristic pathological changes in the brain, especially in the hippocampus and its CA1 subfield, that further spread to parietal cortex, including precuneus, and other areas as the disease progresses. The severe spatial navigation deficits demonstrated in patients in early stage of AD are caused by both hippocampal and parietal dysfunction. Those spatial navigation deficits can be detected even in the stage of MCI patients with amnestic syndrome of hippocampal types, who are at the highest risk of AD development, and who manifest with the spatial navigation deficit similar to that in AD. Therefore, spatial navigation testing could become a reliable tool of identifying patients in the prodromal stages of AD, before the development of dementia syndrome (Vlcek, 2011). Adding spatial navigation tests to neuropsychological batteries will increase the diagnostic

accuracy and early detection of patients with AD in the predementia stages. Given that real-space testing is technically difficult, new methods of testing are being developed. 2D computer tests and virtual reality environments appear to be promising areas for extension of spatial navigation testing to the routine clinical use.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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