

**Neurocognition of spatial memory:  
Studies in patients with acquired brain damage and  
healthy participants**

Neurocognitie van het ruimtelijk geheugen  
Studies bij patiënten met niet-aangeboren hersenletsel en gezonde proefpersonen.

(met een samenvatting in het Nederlands)

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*Voor Corrie en Otto*



## **Chapter 1**

### **Introduction**

## **Introduction**

Spatial memory is an essential cognitive process that is used to encode the space around us, for example when traveling to our job or when trying to find our car keys. The enormous amount and the variety of spatial information we rely on to find our way through the world suggests it is a complex function which can be subdivided into a number of different components (cf Nadel & Hardt, 2004; Postma, 2005). This variety of processes makes it likely that it is not one single brain area that is crucially involved in spatial memory, but that several brain areas work together entailing an extended neural network for spatial information processing. In the first part of this Introduction I will discuss the different ways of encoding spatial information and the brain areas that are involved in these processes. From a purely functional perspective it has been argued that throughout evolution spatial memory might have developed into a function that works largely automatic. That is, spatial memory is used on a daily basis when trying to find our belongings or move around in the environment, but we are rarely aware of this process. We usually start thinking about it at the moment that something goes wrong and we get hopelessly lost. The underlying mechanisms of automatic encoding of spatial information will be discussed in the second part of the introduction.

### **General issues in spatial memory**

Over the past years, neuroimaging, animal and patient studies have been aimed at disentangling the different processes involved in spatial memory. A common distinction is that between spatial working memory, route learning, and object-location memory. In working memory, information is maintained online in order to be processed or manipulated. It is generally seen as a multi-component system, including two subsidiary slave systems, the ‘phonological loop’ and the ‘visuospatial sketchpad’, which hold limited amounts of information, respectively of verbal and visuospatial nature, active in working memory (Baddeley, 2002). These slave systems are under attentional control of the ‘central executive system’, which is responsible for efficient planning and organizing. In general, working memory is associated with the prefrontal cortex (Fletcher & Henson, 2001). Also, different parts of the prefrontal cortex are specialized in specific working memory processes, e.g. keeping object information active in working memory would rely on ventral areas of the lateral prefrontal cortex, whereas spatial information would depend on

dorsal areas of the lateral prefrontal cortex (Nelson, Monk, Lin, Carver, Thomas & Truwit, 2000; Smith & Jonides, 1999; Wilson, Scalaidhe & Goldman-Rakic, 1993).

In order to keep spatial information in memory over a longer time period it has to be encoded into long-term memory. Encoding spatial information from working memory into long-term memory seems to depend largely on the hippocampus (Feigenbaum, Polkey & Morris, 1996; Abrahams, Pickering, Polkey & Morris, 1997; Abrahams, Morris, Polkey, Jarosz, Cox, Graves & Pickering, 1999) and the parahippocampal gyrus (Hayes, Ryan, Schnyer & Nadel, 2004). The parahippocampal gyrus was originally associated with processing different types of contextual features, including spatial and nonspatial information (Bar & Aminoff, 2003; Eichenbaum, 2001). However, a recent study in rats has shown that processing spatial information and other types of context information are processed by distinct neural pathways (Burwell, Saddoris, Bucci & Wiig, 2004). Similarly, an fMRI study in human participants has shown that the right parahippocampal gyrus is specifically activated during the retrieval of spatial-location information, while retrieval of spatial and temporal contextual information was associated with activation of prefrontal cortical areas (Hayes, Ryan, Shnyer & Nadel, 2004).

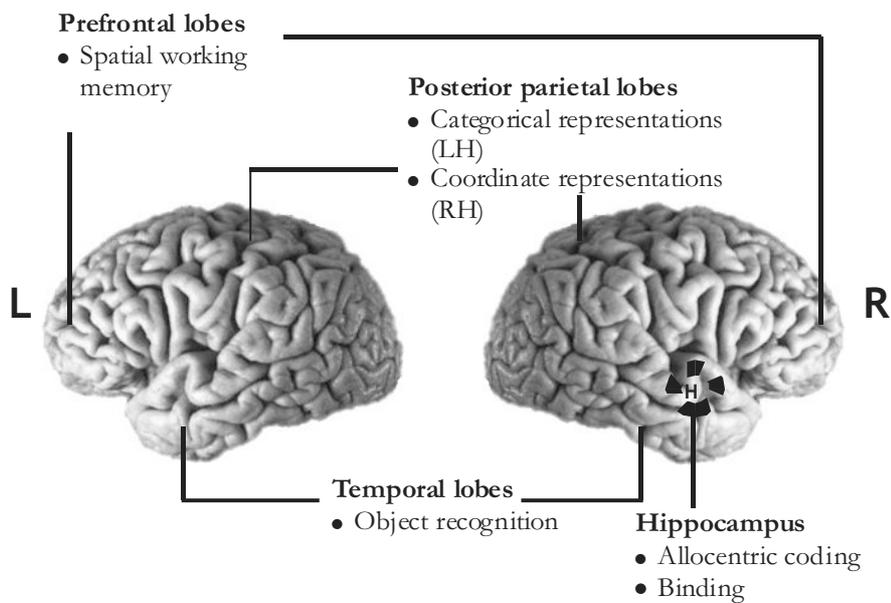


Figure 1.1: Brain areas involved in different spatial memory processes.

In addition to spatial working memory, another dynamic aspect of spatial memory is route learning, which is used for wayfinding and navigation, such as traveling from A to B. In order to find your way in the environment and go from one location to another, you continuously have to update the knowledge of the environment. In order to do this, different cognitive strategies can be used. One way is to learn the relationship between multiple environmental landmarks, also known as spatial learning. For example, you know the position of the bakery in relation to the supermarket and your own house. This implies that a cognitive map of the environment is represented in memory. Another way is to learn the environment through the repetition of rewarded responses to stimuli, i.e. response learning (e.g. Bohbot, Iaria & Petrides, 2004). That is, in order to go to the bakery, you know you have to turn right at the end of the street, pass the pharmacy and you will find the bakery on your right-hand. Interestingly, these two learning strategies seem to rely on different brain areas. Neuroimaging studies using computer-generated virtual environments found that a spatial strategy was related to specific activation of the hippocampus, while using a nonspatial strategy was related to activation of the caudate nucleus (Bohbot et al., 2004; Hartley, Maguire, Spiers & Burgess, 2003; Iaria, Petrides, Dagher, Pike & Bohbot, 2003).

Accordingly, O'Keefe and Nadel (1979) hypothesized that the hippocampus is an area that is essential for processing information from an allocentric perspective. Allocentric information contains the positions of objects in relation to other objects in the environment, independent of the position of the viewer. In contrast, egocentric memory represents positions of locations that are related to the position of the viewer. Whereas allocentric information is used to create a representation of the environment, egocentric information can be used to guide goal-directed action, such as reaching for a specific object. Encoding egocentric and allocentric information is thought to depend on different processing streams. The ventral pathway, including the occipitotemporal cortex, processes visual information from an allocentric perspective, while the dorsal pathway, including the parietal cortex, does so from an egocentric perspective (Milner & Goodale, 1995). Although this distinction was originally applied to perception, it was later shown that it also accounts for memory processes (cf. Feigenbaum & Morris, 2004).

Object-location memory is a static aspect of spatial memory, involving the ability to remember fixed positions of objects in the environment. A distinction can be made between remembering the identity of objects and the positions of these objects (Moscovitch, Kapur, Kohler & Houle, 1995), while a third process enables these two features to be integrated in memory. Importantly, Kosslyn (1989) proposed that there are two ways of describing relations between objects in the

environment, i.e. coordinate and categorical spatial representations. Categorical representations refer to relative spatial relations, such as remembering that your cup is to the right of the computer. This type of information ignores the exact spatial position of an object, and categorizes objects according to a certain relation (above/below, left/right, inside/outside). In contrast, coordinate representations contain fine-grained, metric information, which can be used to guide actions, for example when visual information is not at hand or insufficient, such as when walking around in the dark (Kosslyn, 1989). Supposedly, encoding coordinate and categorical spatial information relies on specialized systems within the brain (Kosslyn, 1989). Since categorical relations partly dependent on language processes, this type of information would be better processed by brain areas in the left hemisphere, while the more purely spatial/metric nature of coordinate representations suggests that they are more effectively encoded by brain areas in the right hemisphere (Kosslyn, 1989; Laeng, 1994). In a recent review including cognitive, neuroimaging and patient studies moderate support was found for a functional dissociation between categorical and coordinate spatial relations. Additionally, the support for a right-hemisphere advantage concerning coordinate spatial relations was stronger than for a left-hemisphere advantage concerning categorical spatial relations (Jager & Postma, 2003).

Recently, Postma, Kessels and Van Asselen (2003) proposed that object-location memory does not involve three functionally different processes (i.e. remembering objects, positions and integrating these features), but rather five, thus making a distinction between categorical and coordinate position information. These five components are: 1) encoding object information; 2a) encoding categorical position information; 2b) encoding coordinate position information; 3a) binding object and categorical position information; 3b) binding object and coordinate position information (Figure 1.2). Encoding categorical and coordinate position information would rely on the left and right posterior parietal cortex respectively (Kosslyn, 1994). Although the importance of the right posterior parietal cortex for coordinate position memory has been shown, evidence was less convincing for the involvement of the left posterior parietal cortex in categorical position memory (e.g. De Renzi, 1982). Additionally, binding object and spatial information in memory is thought to rely on the hippocampus, which is involved in integrating different types of context information (Eichenbaum & Bunsey, 1995; Crane & Milner, 2004; Stepankova, Fenton, Pastalkova, Kalina & Bohbot, 2004). Object-location memory deficits have been found after lesions in the right (Kopelman, Stanhope & Kingley, 1997; Smith & Milner, 1981, 1989) and left hemisphere (Kessels, De Haan, Kappelle & Postma, 2000; Kessels, De Haan,

Kappelle & Postma, 2002, Kessels, Hendriks, Schouten, Van Asselen & Postma (2004). The exact role of brain areas such as the hippocampus in the left and right hemisphere in object-location memory remains unclear.

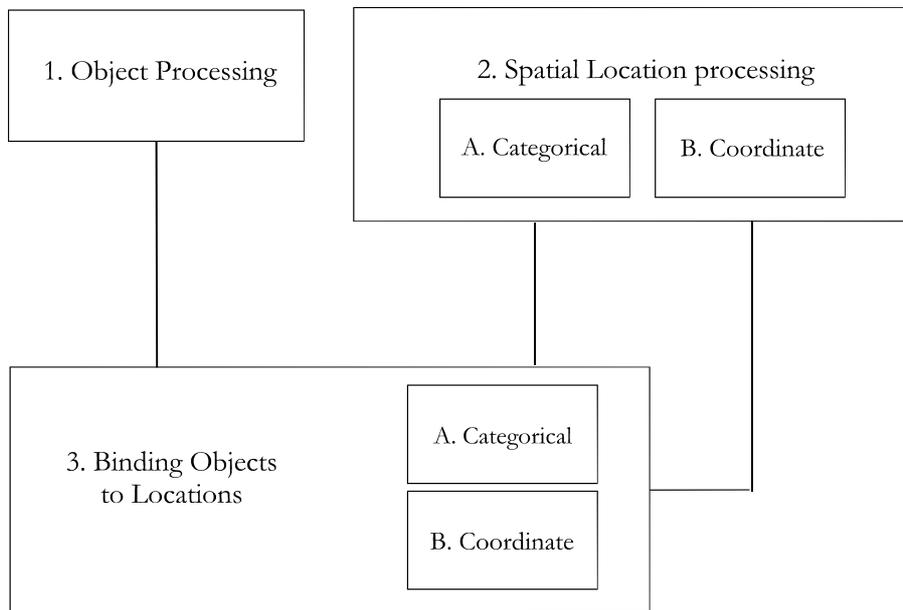


Figure 1.2: A functional analyses of object relocation memory as was proposed by Postma et al. (2004).

### **Automaticity of spatial memory**

The enormous amount of information in our environment indicates we cannot focus our attention to all information in order to be processed in memory. Therefore, it clearly is beneficial if some information would be automatically stored into memory. In contrast to effortful processes, automatic processes do not require focused attention or conscious awareness. Therefore, they are supposedly not influenced by intention to learn information, by practice and by simultaneous processing demands (Hasher & Zacks, 1979). Moreover, they would not be affected by age or other individual differences. These different characteristics can be used as criteria to test whether specific processes require effort. Automatic processing makes it possible to drive a car while talking to the person besides you at the same time. However, we also know that once we arrive in a new and

complex environment it is beneficial to stop talking for a while and focus our attention to where we are going.

The idea that spatial information is encoded automatically into memory (Hasher & Zacks, 1979) was supported by several studies demonstrating that performance on a spatial location task was not influenced by intention to learn (Ellis & Rickard, 1989; Ellis, 1990), practice (Ellis, 1990) and concurrent-processing demands (Ellis, 1990). Others, however, observed that these factors did affect the processing of spatial location information (Dayan & Thomas, 1995; Naveh-Benjamin, 1987, 1988; Perlmutter, Metzger, Nezworski & Miller, 1981). In general, it seems warranted to conclude that spatial information is not encoded fully automatically, since the criteria for automatic processes that were previously described are not met under all circumstances. However, the mixed results underline the notion that the difference between automatic and effortful processes may not be strictly dichotomous, but rather can be seen as continuous. Accordingly, memory processes could operate to some extent automatically and would benefit only in a restricted sense from focused attention. Since various processes are involved in encoding the different spatial characteristics of our environment, some of these processes might be more automatic than others. The extent to which processes are more automatic or effortful might depend on variables such as the complexity, importance or amount of information.

Additionally, a natural consequence of an automatically operating memory system would be that certain types of information are automatically integrated with others. Besides spatial information, temporal information is an important feature, providing information about when an event occurred. Spatial and temporal-order information seem to be naturally linked, since in our daily life events take place in a certain place at a specific moment. Accordingly, spatial and temporal-order information might not be encoded by separate processes, but rather depend on one single process in which both features are encoded together in memory. This would mean that when you process the temporal order of a number of ongoing events in memory you may automatically encode where these events took place, and vice versa (Hill & Moadab, 1995; Hill & Stuckey, 1993).

### **General outline**

The first part of this thesis focuses on the neural basis of different forms of spatial memory. Therefore, three main paradigms were used, covering three important aspects of spatial memory, i.e. object-location memory, spatial working memory,

and route learning. In chapter two, an object-location memory task is used to investigate the different processes that are necessary to remember the positions of fixed objects in our environment (Postma et al., 2004). Patients with focal lesions caused by cerebral stroke in either the left or right hemisphere are examined with a number of tasks assessing these different processes. This gives us important insight into a possible hemispheric specialisation for processing categorical and coordinate representations when position information has to be encoded alone, and when it has to be integrated with object information.

Whereas chapter two deals with static aspects of spatial memory (remembering the fixed positions of spatial memory), chapter three and four will examine a more dynamic spatial memory process, i.e. spatial working memory. Therefore, a spatial search task is used, in which participants have to search for objects hidden in boxes on a computer screen and remember the locations of previously located objects. Thus, participants have to keep spatial information active in working memory, and continuously 'update' this knowledge with new information.

In chapter three a group of patients with Korsakoff amnesia is studied. Although long-term memory is clearly impaired in these patients, it remains unclear whether working memory is affected as well. Additionally, the effect of contextual cueing is studied in this patient group. Chapter four is aimed at defining the exact brain areas that are involved in spatial working memory. Animal and neuroimaging studies have revealed the importance of the prefrontal and parietal cortices in spatial working memory. However, these studies have some limitations. Although studying cognitive processes in animals is a very important way of defining the mechanisms of the brain, animal and human brains are not the same. Particularly when studying higher order cognitive functions, it is important to examine human participants as well. Therefore, neuroimaging techniques such as functional Magnetic Resonance Imaging (fMRI) have proven to be essential by showing the areas of the brain that are activated during a working memory task (e.g. Smith & Jonides, 1999). However, this does not give information about whether a brain area is merely involved in a specific process, or whether it is essential. In order to overcome these limitations, a newly developed lesion-overlap technique is used to unravel the importance of specific brain areas in spatial working memory, such as the hippocampal formation, the posterior parietal and dorsolateral prefrontal cortex.

The same lesion-overlap technique is used in chapter five to define the brain areas involved in another dynamic aspect of spatial memory, i.e. route learning. When navigating through space, we continuously have to update our knowledge of

the environment. In contrast to working memory, route learning involves storing information over a longer time period and on a larger scale. The effect of focal lesions in the brain on different aspects of route learning, such as landmark recognition (objects or scenes that characterize a certain location along the route), the order of the landmarks, map drawing and route retracing are investigated. Importantly, by assessing different types of route knowledge, a distinction can be made between information that is stored as an egocentric (viewer-dependent) and allocentric representation (viewer-independent).

The extensive neural network subserving spatial memory and the importance of this function in our daily lives, suggests that it might have evolved into a process requiring little attention. This automaticity of spatial memory is studied in the second part of this thesis. In chapter six automaticity of spatial memory is studied under the most natural circumstances, namely when learning a route. As was argued before, we can use different aspects of the environment to orient ourselves when going from one place to another, such as landmarks, direction and sensorimotor information. The different nature and complexity of these aspects of route learning suggests that some require more attention than others.

Finally, spatial information might be automatically integrated with other context features, in particular temporal order information, considering they usually co-occur. This relationship between spatial and temporal-order information is the focus of the final two chapters. Two of the criteria as were defined by Hashers and Zacks (1979) to study automaticity are used, i.e. intention to learn and aging. In chapter seven the automaticity of spatial and temporal-order memory is examined by presenting objects one by one on a display, using intentional and incidental learning conditions, while chapter eight focuses on the effect of aging on encoding temporal-order and spatial information.

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**BRAIN AREAS INVOLVED IN  
SPATIAL MEMORY**



## Chapter 2

# Categorical and coordinate spatial representations within object-location memory

Van Asselen, M., Kessels, R.P.C., Kappelle, L.J., & Postma, A. *Manuscript submitted for publication.*

**Abstract**

An important aspect of spatial memory is the ability to remember the positions of objects around us. There is evidence that spatial information can be represented in different ways, involving a coordinate representation (fine-grained, metric information) and a categorical representation (above/below, right/left relations). The current study is aimed at investigating possible lateralization effects for categorical and coordinate information when encoding position information alone and when integrating position information and object information in memory. Twenty-five patients who had suffered from a stroke and 36 healthy controls were tested with different tasks assessing categorical and coordinate position memory, and categorical and coordinate object-to-position memory. The identity task that was used by Laeng (1994) was included as well as a control task for measuring lateralisation effects for categorical and coordinate information processing. Moreover, object recognition and visuospatial perception was assessed. The results showed that processing categorical and coordinate spatial information was impaired by a lesion in the left and right hemisphere respectively. No lateralization effects were found when spatial information had to be integrated with object information. These results bear on the functional components of object-location memory and their underlying hemispheric basis.

## Introduction

Object-location memory is an important aspect of spatial memory, enabling us to remember the positions of objects in our environment. Smith and Milner (1981, 1989) showed that object-location memory is impaired by damage to the right medial temporal lobe (Kopelman, Stanhope & Kingley, 1997). In particular, the right parahippocampal gyrus (Milner, Johnsrude & Crane, 1997) and the right hippocampus (Crane & Milner, 2004; Stepankova, Fenton, Pastalkova, Kalina, & Bohbot, 2004) seem to be involved in processing object-location information in memory. Importantly, however, object-location memory is not a unitary construct, but can be subdivided into a number of components. Processing object information and position information clearly deal with distinct aspects (Moscovitch, Kapur, Kohler & Houle, 1995), whereas a third process is responsible for the integration of these two features. These components can be selectively impaired, as was shown by examining patients with focal lesions with different tasks assessing the ability to encode object or position information or both features (Kessels, De Haan, Kappelle & Postma, 2000a; Kessels, De Haan, Kappelle & Postma, 2002b). Interestingly, lesions in the right hemisphere resulted in impaired position memory, whereas lesions in the left hemisphere disrupted object-location binding, indicating that object-location memory does not simply rely upon a right sided circuitry (Kessels, Postma, De Haan & Kappelle, 2002b).

This lateralization effect might be the result of the coordinate and categorical nature of these two memory tasks. Categorical representations refer to relative spatial relations, such as remembering that your cup is to the right of the computer. This type of information ignores the exact spatial position of an object, and categorizes objects according to a certain relation (above/below, left/right, inside/outside). In contrast, coordinate representations contain fine-grained, metric information, which can be used to guide actions, particularly when visual information is not at hand or insufficient, such as when walking around in the dark (Kosslyn, 1989). Supposedly, encoding coordinate and categorical spatial information relies on distinct subsystems. Since categorical relations partly dependent on language processes, this type of information would be primarily subserved by brain areas in the left hemisphere. The more “purely” spatial nature of coordinate representations suggests that they are possibly more effectively encoded by the right hemisphere. Kosslyn (1989) showed that healthy participants could evaluate categorical representations better when they were initially presented to the left hemisphere, whereas coordinate representations were evaluated better when information was initially presented to the right hemisphere (Kosslyn, 1989).

Similar effects were found when examining categorical and coordinate memory processing in patients with focal lesions in either the left or right hemisphere (Laeng, 1994). The “identity task” was used in which a drawing of one or more objects was shown during a short period of time. Subsequently, two drawings were presented, one of which being the same as the initially presented drawing, whereas the other was altered by changing either the categorical or coordinate spatial relation. Participants were instructed to judge which of these two drawings was the same as the initially presented drawing. Results showed that patients who had suffered from a stroke with a lesion in the right hemisphere made more errors when the coordinate spatial relation was changed, whereas patients with a lesion in the left hemisphere made more errors when the categorical spatial relation was changed. A recent review including cognitive, neuroimaging and patient studies showed moderate support for a functional and neuroanatomical dissociation between categorical and coordinate spatial relations. Importantly, it was emphasized that finding lateralisation effects seem to be highly dependent of methodological aspects of the individual experiments (Jager & Postma, 2003; Wilkinson & Donnelly, 1999).

In a recent paper, Postma, Kessels and Van Asselen (2003) further applied the categorical/coordinate distinction to memory processes in more detail. They suggested that object-location memory entails five different processing components: 1) encoding object information, 2a) encoding categorical position information; 2b) encoding coordinate position information, 3a) binding object and categorical position information; 3b) binding object and coordinate position information (Figure 1.2). Kessels, Hendriks, Schouten, Van Asselen & Postma (2004) demonstrated that right amygdalahippocampectomy patients were impaired on a task assessing coordinate position information, whereas left amygdalahippocampectomy patients were impaired on a task assessing binding of object and coordinate location information. However, processing categorical position information in isolation was not impaired. This might have been due to the fact that patients that were included in this study had specific damage to the hippocampus, which is thought to be particularly involved in integrating different types of information in memory, including object and spatial information (Eichenbaum & Bunsey, 1995). In contrast, encoding position information in isolation seems to rely predominantly on the posterior parietal cortex, in particular in the right hemisphere (e.g. Smith & Jonides, 1999; Wilson, Scalaidhe, & Goldman-Rakic, 1993). Additionally, it remains unclear whether a similar hemispheric specialization for categorical and coordinate information processing is found when spatial information is integrated with object information. That is,

Kessels et al. (2004) reported that patients with a lesion in the left hemisphere were impaired on a task assessing the ability to integrate object and coordinate location information, but not object and categorical location information, suggesting they rely on different processes.

The current study was aimed at systematically exploring hemispheric specialization for categorical and coordinate representations when processing spatial information in isolation or when integrating or 'binding together' spatial and object information. Patients with focal cerebral lesions due to stroke were tested with an object-location memory task, in which separate conditions were included to assess memory for objects, categorical and coordinate position information, and integrating this information. Since Laeng (1994) found clear lateralization effects for categorical and coordinate spatial information, the identity task was included as a control task. It was hypothesized that encoding coordinate spatial positions would relate to the right hemisphere, whereas encoding categorical spatial positions was impaired by damage to the left hemisphere. Additionally, the same lateralization effects were expected when integrating categorical and coordinate position information with object information.

## Methods

### *Participants*

Twenty-five patients who had suffered from a stroke and were admitted to the University Medical Center Utrecht (UMCU) were tested. Thirteen patients had a lesion in the left hemisphere, 12 patients had a lesion in the right hemisphere. All patients were examined at least six months after the stroke and were mobile at the time of testing. Patients were all between 21 and 75 years of age and did not suffer from other neurological or psychiatric diseases. The study was approved by the medical ethics committee of the UMCU and written informed consent was obtained according to the declaration of Helsinki. We also examined 36 age- and education matched, healthy control participants who were recruited through an advertisement in the local newspaper and were paid for their participation. Characteristics of the patients and comparison group are shown in Table 2.1. Handedness was assessed with a Dutch version of the Annett Handedness Inventory (Briggs & Nebbs, 1975). Education level was measured using seven categories (1 being the lowest and 7 the highest; Hochstenbach et al., 2003). No difference was found between the three groups for education level [ $F(2, 62) = 2.1$ ], age [ $F(2, 63) = 0.1$ ], or gender distribution [ $\chi^2(2) = 4.4$ ].

Standard neuropsychological tests were used to assess overall intelligence and memory performance. Verbal intelligence was assessed with the Dutch version of the National Adult Reading Task (Schmand, Bakker, Saan, & Louman, 1992); non-verbal intelligence with the 12-item short form of the Raven Advanced Progressive Matrices (Raven, Raven, & Court, 1993). Verbal memory was assessed with the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT, Rey, 1964; Taylor, 1959). The Letter Number Sequencing task (WAIS-III) was used as an index of verbal working memory (Wechsler, 1997).

Table 2.1: Characteristics and neuropsychological test results of patients with a lesion in the right hemisphere (RH), patients with a lesion in the left hemisphere (LH) and control participants separately.

	RH n = 12	LH n = 13	Controls n = 36
Age	56.8 (3.2)	58.2 (3.0)	56.4 (1.8)
Education level (1-7)	4.8 (0.4)	4.9 (0.3)	5.5 (0.2)
Annett Handedness Inventory (-24/ 24)	14.5 (4.4)	18.6 (3.3)	15.3 (2.2)
Sex (m:f)	10:2	8:5	20:16
NLV-IQ	106.4 (3.0)	101.6 (4.0)	107.3 (4.7)
RAVLT: immediate recall	37.2 (3.0)*	34.0 (4.3)*	47.6 (1.7)
RAVLT: delayed recall	8.9 (1.1)	6.2 (1.6)	9.8 (0.6)
Raven APM (short form)	7.2 (0.9)	7.3 (0.8)	12.2 (2.9)
Letter Number Sequencing task	9.8 (0.9)	7.6 (0.7)	9.9 (0.3)
Corsi Block-Tapping Task	46.8 (4.9)	39.8 (2.7)	43.1 (2.4)

\* = significant difference with the controls ( $p < 0.05$ )

Note. NLV = National Adult Reading Task, RAVLT = Rey Auditory Verbal Learning Test, Raven APM = Raven Advanced Progressive Matrices.

### *Material and Procedure*

#### *Identity task*

This computerized version of the Identity test used by Laeng (1994) included the same 20 stimulus pairs as the original experiments with cards. Black- and-white drawings of animals (e.g. rabbit) and objects (e.g. football) were shown on a 15 inch computer-screen during five seconds. Participant received the instruction to pay attention to the drawing and to try to remember it. Then, after an interval of another five seconds in which an empty screen was seen, two drawings were

shown. One of these drawings was the same as the original drawing, whereas the other was slightly different. Drawings could be changed according a coordinate relation (distance on the horizontal, vertical or both axes, distance relative to a frame, position of body parts, orientation in angle, object size) or a categorical relation (laterality, verticality, confrontation, inclusion and contact). Participants had to indicate which of the two pictures was the same as the drawing that was initially shown, by pressing either one of two buttons on the keyboard.

#### *Object-relocation task*

The Object Relocation program was used (Kessels, Postma & De Haan, 1999), in which everyday objects (e.g. ball, frog) were shown within a frame of 19 by 19 cm on a computer-screen (15 inch LCD touch-screen). After a presentation time of 30 seconds, the objects disappeared from the display and were placed above the frame. Participants could replace them by touching the objects and touching the location they wanted to place the object. Two control conditions were used. First, the *object-recognition condition*, in which 10 objects were shown in a 2 x 5 grid. During the relocation phase 20 objects were shown and participants were instructed to place the 10 correct objects in the matrix, disregarding the correct location. Second, in the *visuo-spatial construction condition* two frames of 10 by 10 cm were shown, one of which contains 10 objects, the other was empty but had the 10 objects placed above the frame. Then, participants were instructed to copy the frame. Subsequently, four experimental conditions were used (see Figure 2.2). In the *categorical positions-only condition* 10 equal objects were shown in a 7 x 7 grid. During the relocation phase the objects were placed above the same grid, and participants were instructed to place the objects on the correct location. In the *coordinate positions-only condition* 10 equal objects were shown within an empty frame, and during the relocation phase participants had to replace these objects to the correct location within the same empty frame. In the *categorical object-to-position condition*, 10 different objects were shown within a frame. During the relocation phase the locations of the objects were marked with dots. Participants were instructed to replace the objects to their correct locations. In the *coordinate object-to-position condition* again 10 different objects were shown within a square, but now participants had to replace the objects within an empty frame. Each condition contained two different trials and was preceded by a practice condition of four trials. A different set of objects and locations was used for each trial.

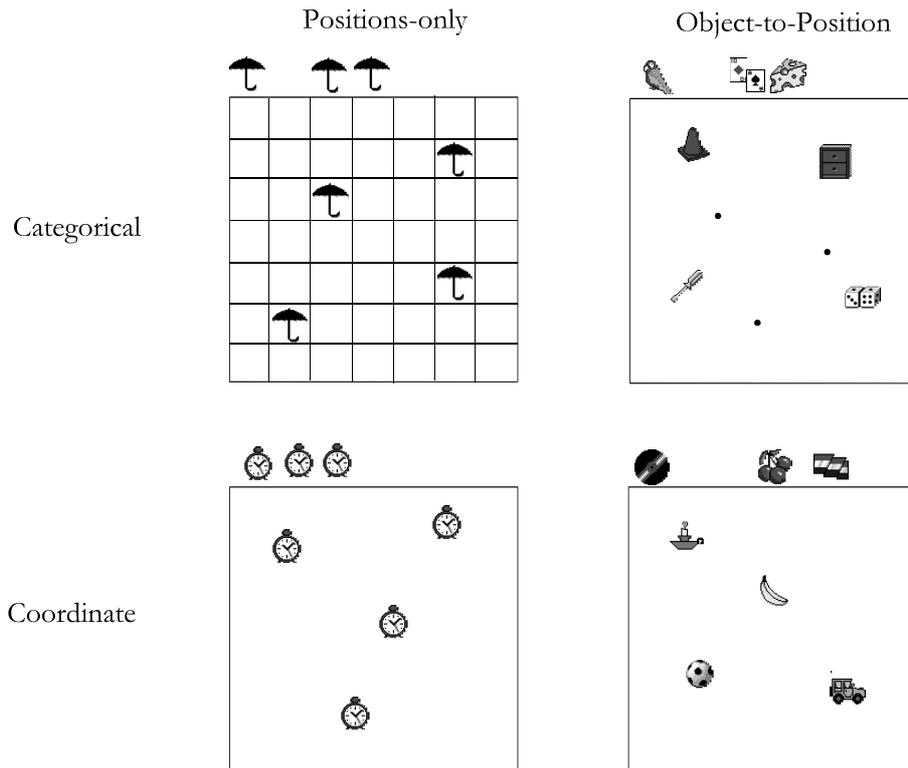


Figure 2.2: Example of a display of the four task conditions that were used.

## Results

### *Neuropsychological tests*

Independent-samples t-tests revealed no differences on any of the standard neuropsychological tests between the patients and controls, except on immediate reproduction of the RAVLT [ $F(2, 58) < 7.1, p < 0.01$ ]. Patients with a lesion in the right or left hemisphere performed worse than the control participants [ $t(48) = 3.2, p < 0.01, t(48) = 2.8, p < 0.01$ , respectively]; no difference was found between performance of the patients with damage to the left or to the right hemisphere [ $t(24) = 0.2$ ].

*Identity task*

Performance on the Identity task was analysed by means of a 2 x 3 ANOVA with within-subject variable Type of error (coordinate, categorical) and between-subject variable Group (patients with a lesion in the left hemisphere, patients with a lesion in the right hemisphere, controls). No main effect was found for Type of error [ $F(1, 63) = 2.4$ ] or Group [ $F(1, 63) = 1.1$ ], nor an interaction effect [ $F(2, 63) = 1.1$ ].

*Object Relocation task*

Z-scores were computed based on the performances of the patients and control participants taken together (Figure 2.3). A 2 x 2 x 3 Repeated measures GLM analyses with within-subject variable Feature (categorical, coordinate), Binding (single feature, binding) and Group (patients with a lesion in the left hemisphere, patients with a lesion in the right hemisphere, controls) was conducted. Performance on the object recognition task and the visuospatial perception task were used as covariates. A significant effect between Feature x Binding x Group was found [ $F(2, 56) = 5.2, p < 0.01$ ], but no main effects were found [ $F(1, 56) = 0.1$ ], nor other interaction effects [ $F(1, 56) = 0.2$ ].

To study hemispheric specialization for categorical/coordinate representations in position information, a 2 x 3 Repeated Measures GLM analyses was performed, with within-subject variable Feature (categorical positions-only task, coordinate positions-only task) and Group (patients with a lesion in the left hemisphere, patients with a lesion in the right hemisphere, controls). Performance on the perception task was taken as a covariate. This indicated a significant Feature x Group effect [ $F(2, 57) = 4.3, p < 0.05$ ], but no main effects [ $F(1, 57) < 0.6$ ]. Subsequently, Independent-samples t-tests indicated that patients with a lesion in the right hemisphere performed worse than the controls on the coordinate task [ $t(47) = 2.8, p < 0.01$ ], but not the categorical task [ $t(47) = 0.2$ ], also after using performance on the visuospatial task as a covariate [ $F(1, 46) = 5.0, p < 0.05$ ]. Patients with a lesion in the left hemisphere performed worse on the categorical task [ $t(47) = 2.1, p < 0.05$ ], but not the coordinate task [ $t(46) = 1.0$ ].

To define hemispheric specialization for categorical/coordinate representations when position information has to be integrated with object information, a 2 x 3 Repeated Measures GLM analyses was conducted with within-subject variable Feature (coordinate object-to-position task, categorical object-to-position task) and between-subject variable Group (patients with a lesion in the left hemisphere, patients with a lesion in the right hemisphere, controls). No main effects were found [ $F(1, 56) = 0.2$ ], nor an interaction effect [ $F(2, 56) = 1.4$ ].

### Correlations

A two-tailed Pearson's correlation was performed using the performances of patients with a lesion in either the right or left hemisphere. This revealed a significant correlation between performance on the categorical and coordinate object-to-position task ( $r = 0.52$ ,  $p < 0.01$ ), but not between the categorical and coordinate positions-only task ( $r = 0.39$ ).

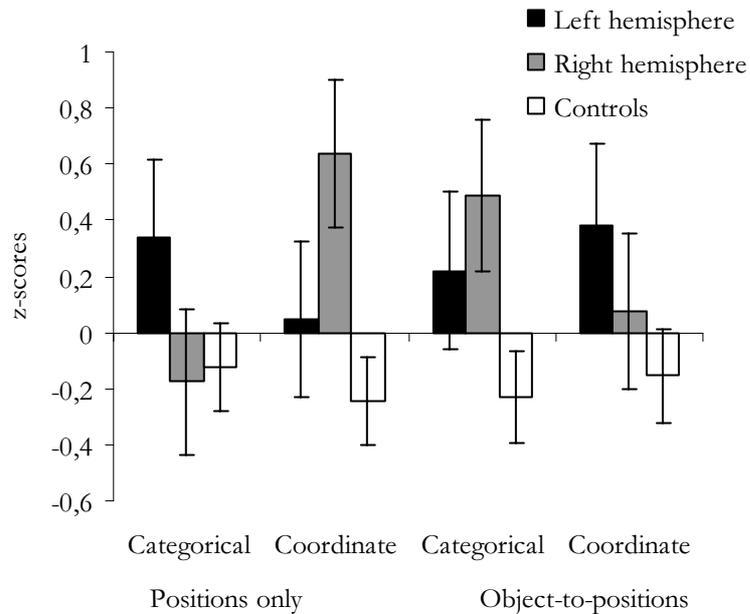


Figure 2.3: Mean z-scores of the categorical and coordinate positions-only task and the categorical and coordinate object-to-position task.

### Discussion

The current study was aimed at investigating memory for categorical and coordinate spatial representations when position information is encoded in isolation, and when it is integrated with object information (i.e. binding). Interestingly, lateralization effects were found when only position information had to be encoded, but not when this information had to be integrated with object information in memory. That is, patients with a lesion in the left hemisphere

performed worse on the categorical positions-only task, but were unimpaired on the coordinate positions-only task, whereas the reverse effect was found for patients with a lesion in the right hemisphere. Importantly, this is not the result of differences in general cognitive ability and memory function as was assessed with standard neuropsychological tests. Although impaired memory for coordinate position information due to damage to the right hemisphere was previously found (Kessels et al., 2002a), this is the first time that a deficit for categorical position memory is demonstrated after damage to the left hemisphere. These results are in line with the idea that categorical spatial representations are processed by the left hemisphere and coordinate spatial representations are processed by the right hemisphere (Kosslyn, 1989; Laeng, 1994; Laeng & Peters, 1995).

Importantly, as already mentioned, this lateralization effect for categorical and coordinate spatial information was not found when position information had to be integrated with object information. Moreover, performance on the categorical and coordinate object-to-position task was highly correlated, whereas no correlation was found between performance on the categorical and coordinate positions-only task. This suggests that the former conditions to some extent reflect one underlying functional process. Possibly, to remember the locations of multiple objects, the objects serve as 'landmarks' characterizing the positions. Subsequently, the relative (categorical) relations between the objects are remembered (e.g. 'the ball and lizard are in the right upper corner, whereas the calculator and orange are in the left upper corner'). Accordingly, Alexander, Packard and Peterson (2002) indicated that the exact coordinate location might only be remembered when objects are presented individually, whereas multiple simultaneously presented objects are encoded categorically. This notion is partly in line with the finding of Kessels et al. (2002b), who showed that patients with a lesion in the left hemisphere are impaired on both a categorical and coordinate object-to-position task including multiple objects, whereas no deficit was found in the right hemisphere group with respect to object-to-position memory. A similar dissociation between position information and object-to-position information was found by Mitchell, Johnson, Raye and D'Esposito (2000), who used fMRI to demonstrate that the left anterior hippocampal area was activated during a task requiring binding of object-to-location. This activation was not found when only object information or spatial information had to be remembered.

However, although as was previously suggested, Kessels et al. (2002b) demonstrated an impairment on the categorical and coordinate object-to-position task after damage to the left hemisphere, it should be noted that no such impairment was found on these tasks in the current study. Additionally, no overall

lateralization effects were found for the identity task assessing memory for categorical and coordinate spatial representations. This might be the result of the patient group that was tested in the current study, which might have different lesion characteristics than previous studies. Additionally, the data of the identity task show that in absolute terms both patients and controls make only few errors, indicating that the task might not be sensitive enough to reveal differences in the present patient group, in contrast to the categorical and coordinate positions-only task. Another important difference is that the identity task of Laeng (1994) contains manipulations related to both within-object and between-object spatial relations.

The results of the current study have important implications for the object-location memory model (Figure 1.2). As was hypothesized by Postma et al. (2003), two distinct processes are involved in remembering categorical and coordinate position information, which clearly rely on brain areas in the left and right hemisphere respectively. However, no evidence was found supporting the hypothesis that a similar hemispheric specialization for categorical and coordinate information processing is found when spatial information is integrated with object information. Although previous case studies offered indications for dissociations between categorical and coordinate object-to-position memory (Kessels et al., 2002a), the current results point more towards a shared, single mechanism responsible for integrating object and location information.

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## Chapter 3

# Spatial working memory and contextual cueing in patients with Korsakoff amnesia

Van Asselen, M., Kessels, R.P.C., Wester, A. & Postma, A. (in press). Journal of Clinical and Experimental Neuropsychology.

**Abstract**

The current study investigated the effect of Korsakoff syndrome on memory for spatial information and, in particular, the effect of contextual cueing on spatial memory retention. Twenty Korsakoff patients and a comparison group of 22 age- and education matched participants were tested with a newly developed spatial search task (the Box task). Participants were asked to search through a number of boxes shown at different locations on a touch-sensitive computer screen to find a target object. In subsequent trials, new objects were hidden in boxes that were previously empty. Two conditions were used; the boxes were either completely identical or had different colors serving as a cue. Within-search errors were made if a participant returned to an already searched box; between-search errors occurred if a participant returned to a box that already contained a target item. Moreover, the use of a strategy to remember the locations of the target objects was calculated. The results show that Korsakoff patients make more within- and between-search errors than the comparison group, and although they were able to apply a search strategy, it did not help them to remember the locations of the targets. Interestingly, whereas the comparison group benefited from color cues that were given to the boxes, Korsakoff patients failed to do so.

## Introduction

Korsakoff syndrome is a seriously disabling chronic disorder, usually caused by severe alcoholism in combination with malnutrition. This can lead to a thiamine (vitamin B<sub>1</sub>) deficiency, causing a degeneration of neurons in the thalamic, mammillary bodies and paraventricular grey matter. Neuroimaging data have shown atrophy of the hippocampi and prefrontal cortex, but not in all patients (Reed et al., 2003). Dysfunction of these brain areas is suspected to underlie the serious memory problems that are found in these patients, including both anterograde and retrograde amnesia.

According to the context-deficit hypothesis, amnesia in Korsakoff patients is the result of the inability to encode contextual information, such as the moment and place that an event occurs (Mayes, Meudell & Pickering, 1985). This inability to encode contextual information in episodic memory has been found for features such as temporal order information (Kopelman, Stanhope & Kingsley, 1997; Postma, Van Asselen, Keuper, Kessels & Wester, in revision), and recency information (Huppert & Piercy, 1978; Meudell, Mayes, Ostergaard & Pickering, 1985). Moreover, one of the most important contextual features, that is, spatial information, is clearly affected. This impairment includes memory for exact, metric spatial information and object-to-location binding (Kessels, Postma, Westers & De Haan, 2000; Shoquierat & Mayes, 1991), the exact position of words (Mayes, Meudell & MacDonald, 1991), top or bottom positions of words (Kopelman, Stanhope & Kingsley, 1997) and both allocentric (object-to-object relation) and egocentric (self-to-object relation) spatial information (Holdstock, Mayes, Cezayirli, Aggleton & Roberts, 1999).

Although amnesia is the main characteristic of Korsakoff syndrome, not all memory components seem to be impaired to the same extent. In particular, it is unclear whether working memory is affected by Korsakoff syndrome. Working memory is generally seen as a multi-component system, including two subsidiary slave systems, the 'phonological loop' and the 'visuospatial sketchpad', which hold limited amounts of information, respectively of verbal and visuospatial nature, active in working memory (Baddeley, 2002). These slave systems are under attentional control of the 'central executive system', which is responsible for efficient planning and organizing. Recently, a third limited-capacity storage system has been added to the multi-component model, called the 'episodic buffer', in which information from the slave systems and long-term memory can be integrated (Baddeley, 2000). At this moment, the exact nature of the episodic buffer and its relation with long-term episodic memory remain unclear. In Korsakoff patients the

central executive system seems to be impaired, as was measured with the Wisconsin Card Sorting test (Janowsky, Shimamura, Krichevsky & Squire, 1989; Mayes, Daum, Markowisch, and Sauter, 1997) and the Tower of London task (Joyce & Robbins, 1991). In contrast, Korsakoff patients commonly have a normal immediate memory span for both verbal and visual information, indicating that the storage capacities of the 'visuospatial sketchpad', and the 'phonological loop' are intact, as was studied with the standard and computerized version of the Corsi Block Tapping task and the Digit Span task (Haxby, Lundren & Morley, 1983; Joyce & Robbins, 1991). Kopelman (1991) found no impairment on the Block span task, while a moderate impairment was found on a non-verbal, short-term forgetting task. However, recently it was shown that Korsakoff patients do have a working memory impairment as was measured with the n-back task (Brokate, Hildebrandt, Eling, Fichtner, Runge & Timm, 2003). Accordingly, Mayes, Daum, Markowisch, and Sauter (1997) showed a reduced performance in Korsakoff patients on the Digit Span test of the Wechsler Adult Intelligence Scale - III. These mixed results indicate that it is not yet clear whether working memory is impaired in Korsakoff patients and, if so, what the exact nature of this impairment is.

The current study set out to further investigate working memory in Korsakoff patients, in particular spatial working memory. A spatial search task (the Box task) was used, which is similar to the Executive Golf task (Feigenbaum, Polkey & Morris, 1996) and the working memory task of the Cambridge Neuropsychological Testing Automated Battery (CANTAB) (Morris, Evenden, Sahakian & Robbins, 1987). This spatial search task requires participants to search for target objects that are hidden in different boxes that are shown on a computer screen. This requires participants to keep spatial information in memory both over a very short time period (i.e. keeping it 'on-line') and a more extended time range (possibly marking the transfer from working memory into long term memory). Moreover, a strategy can be used to relieve the memory load, for example by starting each search with the same box. The spatial memory deficit that was found in previous studies suggests that Korsakoff patients would perform worse than the comparison group when longer term spatial memory is tested (Holdstock, Mayes, Cezayirli, Aggleton & Roberts, 1999; Kessels, Postma, Wester & De Haan, 2000; Kopelman, Stanhope & Kingsley, 1997; Mayes, Meudell & MacDonald, 1991; Shoquierat & Mayes, 1991). Since strategy use is thought to be part of executive functioning, this aspect of the task would be expected to be impaired as well (Janowsky, Shimamura, Krichevsky & Squire, 1989; Mayes, Daum, Markowisch, & Sauter, 1997). However, it remains unclear how Korsakoff patients will perform on an index of the visuospatial sketchpad.

Apart from working memory, the current study focused on another aspect of memory functioning in Korsakoff patients, that is, the effect of contextual cueing. Although Korsakoff patients show profound memory deficits for contextual information, the effect of contextual cueing has rarely been studied in this patient group. Winocur and Weiskrantz (1976) showed that Korsakoff patients are unable to learn a paired-associate list of semantically-related items when the stimulus words have previously been associated with similar, competing response words. They argued that this was due to the amnesic patients' inability to keep distinct learning episodes separately in memory. This deficit was significantly reduced when learning strategies were made sufficiently distinct, by using both intrinsic (Winocur & Weiskrantz, 1976) and extrinsic task cues (Winocur & Kinsbourne, 1978), especially when these cues were presented during the learning phase (Winocur, Moscovitch & Witherspoon, 1987). Moreover, Parkin, Montaldi, Leng and Hunkin (1990) showed that Korsakoff patients performed worse than the comparison group when asked to name personalities who became famous in each of the decades beginning 1935. Performance of the comparison group and the Korsakoff patients improved with clear extraneous cues, although Korsakoff patients' improvement declined when more recent decades were assessed.

To our knowledge, the effect of contextual cueing in Korsakoff patients has not yet been studied with a spatial search task or any other spatial memory task. Hence, contextual cues were added to the currently used spatial search task. Two conditions were created. In one condition the boxes were completely identical, while in the other condition the boxes were given different colours. Since these colours make the locations more distinct they would be easier to remember.

## Method

### *Participants*

Twenty Korsakoff patients who had been administered to the Korsakoff Clinic of the Vincent Van Gogh Institute in Venray, The Netherlands, were compared with 22 age- and education-matched healthy participants. Korsakoff syndrome was the result of chronic alcohol abuse in combination with malnutrition, and was determined according to the criteria of the DSM-IV (APA, 1994).

Characteristics of the patients and comparison group are shown in Table 3.1. Handedness was assessed with a Dutch version of the Annett Handedness Inventory (Briggs & Nebbs, 1975). Education level was measured using seven categories; 1 being the lowest and 7 the highest. The Corsi Block-Tapping Task

(both forward and backward) was used as a standardized measure of spatial working memory (Berch, Krikorian, & Huha, 1998; Kessels, Van Zandvoort, Postma, Kappelle, & De Haan, 2000), revealing no significant difference between the Korsakoff patients and controls on both the forward and backward score (all  $t$ s  $< 1.5$ ). Informed consents were obtained from all participants and the comparison group was paid for their participation.

Table 3.1: Characteristics of the Korsakoff patients and the comparison group.

	Korsakoff patients		Comparison group	
	n = 20		n = 22	
Sex (m:f)	12: 8		15: 7	
Handedness (R:L:Mixed)	16: 1: 2 <sub>1</sub>		19:2:1	
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>
Age	52.2	8.6	56.3	12.5
Education level <sub>2</sub>	4.2	1.6	4.4	1.6
Corsi's block span:				
Forward	4.8	0.6	5.0	1.2
Backward	5.1	1.2	4.73	1.2
California Verbal Learning test <sub>3</sub>	-5.4	2.0		
Tower of London Task <sub>4</sub>	26.3	5.4		

*Note.* 1) Handedness was unknown for one patient; 2) Education rate indicated on a scale of 1 (less than primary school) to 7 (university degree); 3) Mean score of a reference group is 0 (range -7, 7 (SD 2); 4) Mean score of a reference group is 30.6 (SD 2.7).

#### *Material and procedure*

Pictures of closed boxes were displayed on different locations within a square of 19 by 19 cm on a 15" touch-sensitive LCD computer monitor. At the bottom of the square an easy-to-name, colored target object (e.g. ball, tomato) was presented in icon-format (approximately 1 x 1 cm). Participants were instructed to find the target object, which was hidden in one of the boxes. The boxes could be opened by touching them, after which either an empty box or the target object was shown. An empty box remained open for two seconds, while the target object was shown until

the participant initiated a new search. After successfully locating a target object, a new target appeared below the square. Importantly, the target object that was found before remained in the box where it was found and no second object could be added to this box. Thus, the participant not only had to remember which box was searched, but also in which box a previous target object was found. After locating the second target object, a third target appeared below the square. This would continue until all boxes contained a target object. When a certain box was filled with an object it was randomly determined and not dependent on the participants' response. The experiment included two conditions, one condition in which all boxes were given the same color and one condition in which all boxes were given different colors. Each condition began with two practice trials of three boxes, after which two trials of four, six and eight boxes were used. No time limit was set. A single search through the boxes in order to locate a target object took approximately 5 – 11 seconds and a trial (either 4, 6 or 8 searches together) 20 – 88 seconds, depending on the Set size and number of errors. Figure 3.1 shows an example of the layout of the Box task when making a search through six boxes.

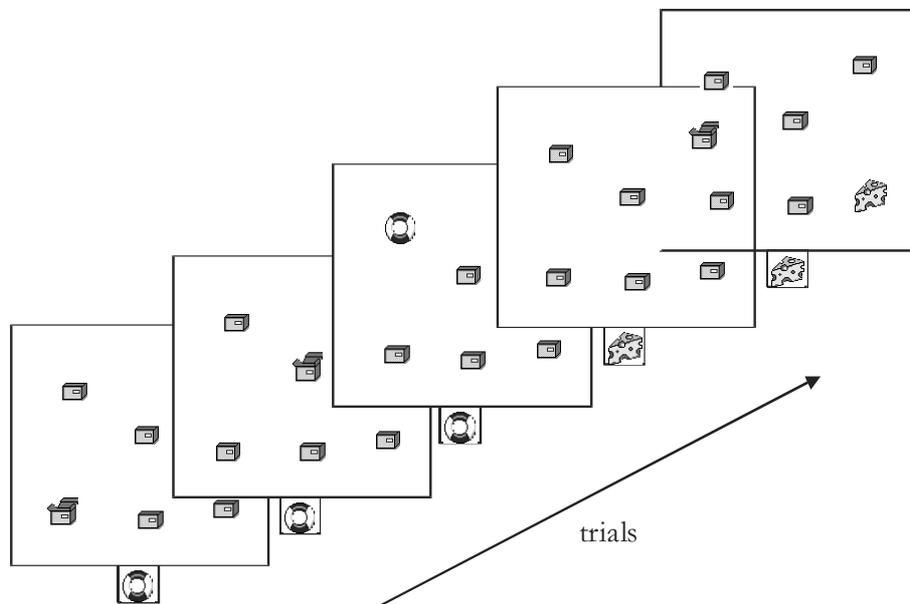


Figure 3.1: Example of the display of a search through six boxes, including presentation of two different target objects.

## Results

### Analyses

Two types of dependent measures were defined: 1) *within-search errors* were made when a participant returned to an already opened box within a search; 2) *between-search errors* were made when a participant returned to a box where a target object was found in one of the previous searches; 3) efficient use of *strategy* was defined by counting the number of times a participant started a search with a different box within one trial. Since strategy use would be more efficient if a participant would follow a predetermined search sequence, a low score on the strategy index would indicate efficient use of strategy (see also Feigenbaum, Polkey & Morris, 1996).

The two types of errors were analyzed separately by means of a 2 x 2 x 3 Repeated Measures analyses, including within-subjects factor Cueing (identical and colored boxes) and Set size (4, 6, 8 boxes), and a between-subject factor Group (Korsakoff and control participants). As an index of the magnitude of the post hoc effects, the effect size was computed. Strategy use was analyzed by looking at the correlation between the strategy index and the between-search errors of the conditions with six and eight boxes.

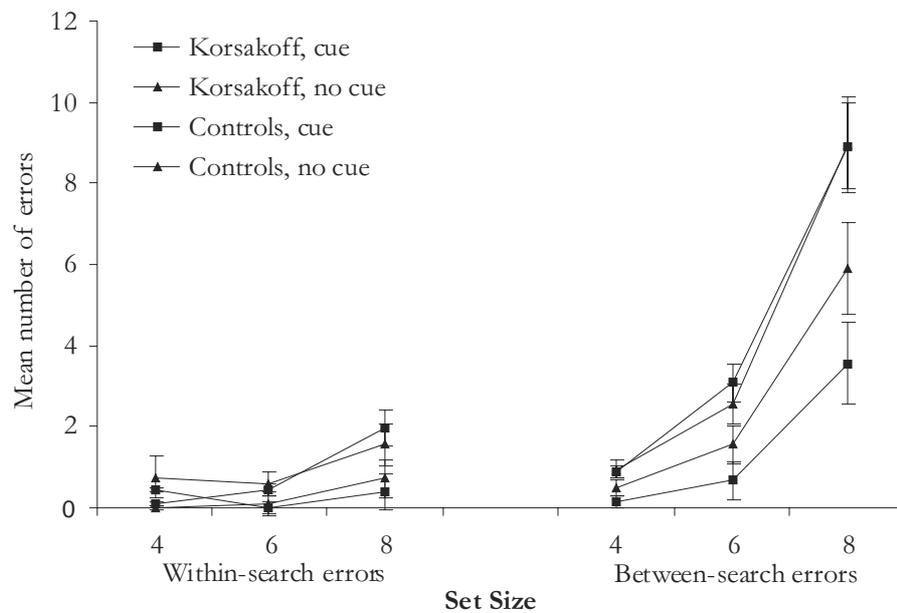


Figure 3.2: Within-search and between-search errors (Set sizes 4, 6, 8) of Korsakoff patients and control participants for the cueing and no-cueing condition separately.

*Within-search errors*

As can be seen from the error scores in Figure 3.2, relatively few within-search errors were made by both the comparison group and the Korsakoff patients, although in absolute terms the patients make significantly more within-search errors than control participants, [ $F(1, 40) = 5.00, p < 0.05$ ]. Furthermore, a main effect was found for Set size [ $F(2, 80) = 13.29, p < 0.001$ ]. A test of within-subject contrasts showed that more errors were made in the condition with eight boxes than six boxes [ $F(1, 40) = 13.14, p < 0.001$ ], but no difference was found between the conditions with four and six boxes [ $F(1, 40) = 2.95$ ]. Moreover, Korsakoff patients deteriorated more than the comparison group with increasing Set size [ $F(2, 80) = 3.27, p < 0.05$ ]. However, no significant interaction effect was found for the four and six boxes ( $F = 2.1$ ) and the six and eight boxes ( $F = 2.4$ ) separately. Neither a main Cueing effect, nor other interaction effects were found (all  $F_s < 2.6$ ).

*Between-search errors*

It was found that Korsakoff patients made significantly more between-search errors than control participants did [ $F(1, 40) = 10.8, p < 0.005$ ]. A significant main effect was found for Set size [ $F(2, 80) = 89.9, p < 0.001$ ]. More errors were made in the condition with six boxes than four boxes [ $F(1, 40) = 88.1, p < 0.005$ ], and in the condition with eight than six boxes [ $F(1, 40) = 29.1, p < 0.005$ ]. Moreover, an interaction effect for Group x Set size [ $F(2, 80) = 7.2, p < 0.005$ ] indicated that Korsakoff patients were more impaired by increasing set size than the comparison group. Tests of within-subjects contrasts showed a significant Group x Set size effect for the four and six boxes [ $F(1, 40) = 5.9, p < 0.05$ ] and six and eight boxes [ $F(1, 49) = 4.7, p < 0.05$ ]. Although no main effect for Cueing was found ( $F = 2.8$ ), a Group x Cueing effect [ $F(1, 40) = 4.5, p < 0.05$ ] indicated that control participants improved when color cues were added while Korsakoff patients did not.

Table 3.2: The total score of the Korsakoff patients and healthy participants of the six and eight box conditions together on the strategy index for the no-cueing and cueing condition separately.

	Korsakoff patients (n = 20)		Comparison group (n = 22)	
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>
No-cueing condition	17.3	2.2	16.9	3.0
Cueing condition	17.3	2.9	16.4	3.0

### *Strategy*

A mixed-factor ANOVA analyzes was used to analyze the total scores of the strategy-index (Table 3.2), with between-subject factor Group (Korsakoff patients and comparison group) and within-subject factor Cueing (identical and colored boxes). No main effect was found for Cueing ( $F(1, 40) = 0.007$ ) nor for Group ( $F(1, 40) = 1.4$ ). To analyze whether applying a strategy indeed results in fewer between-search errors we looked at the correlation between the strategy index and the within- and between-search errors for the six and eight box conditions, using a one-tailed Pearson's correlation coefficient. For the comparison group a significant correlation between the strategy index and the between-search errors [ $r = 0.77$ ,  $p < 0.005$ ] and strategy index and the within-search errors [ $r = 0.66$ ,  $p < 0.005$ ] was found. For the Korsakoff patients no correlation was found between the strategy index and the between [ $r = 0.13$ ] and within-search errors [ $r = 0.13$ ].

### **Discussion**

This research set out to study different aspects of spatial working memory in Korsakoff patients using a spatial search task in which a target object had to be found in a number of boxes located on a display. It was found that both the comparison group and Korsakoff patients made very few within-search errors, although the comparison group was slightly more accurate than the Korsakoff patients. Korsakoff patients' performance also deteriorated more than the comparison group with increasing set sizes. Within-search errors can be seen as a measurement of the visuo-spatial sketchpad of working memory (Feigenbaum et al., 1996), which is a temporary workspace in which visual and spatial information can be stored and manipulated (Baddeley, 2002). Apparently, this aspect of working memory is impaired in Korsakoff patients, possibly due to damage to the prefrontal

cortex that often accompanies this type of amnesia and has been found important for spatial working memory in previous studies (Fletcher & Henson, 2001).

Spatial working memory span was also measured with the Corsi Block Tapping task, indicating no difference between the Korsakoff patients and the comparison group, supporting previous results of Haxby, Lundgren and Morley (1983) and Joyce and Robbins (1991). In contrast to the Corsi Block Tapping task, the working memory span measurement of the Box task includes an active search through a number of boxes instead of only passively remembering a sequence of locations. The latter requirement might have resulted in the numerically small, but consistent and statistically significant, difference in within-search errors between the Korsakoff patients and the control participants.

Concerning the between-search errors it was found that Korsakoff patients made significantly more errors than the control participants. Performance of both groups decreased with increasing set sizes, but this was more so for the Korsakoff patients. To avoid between-search errors, information has to be held in memory over a longer time period. Impairments in this function have also been reported by Holdstock, Mayes, Cezayirli, Aggleton and Roberts (1999), Kessels, Postma, Wester and De Haan (2000), Kopelman, Stanhope and Kingsley (1997), Mayes, Meudell and MacDonald (1991), Shoquierat and Mayes (1991).

Furthermore, previous studies have indicated that Korsakoff patients generally show an impaired planning ability and an inability to organize efficient response sequences (Janowsky, Shimamura, Krichevsky & Squire, 1989; Joyce & Robbins, 1992). In the current study no difference between the strategy index of the Korsakoff patients and the comparison group was found, indicating that they applied a search strategy to the same extent. However, for the comparison group a correlation between the use of a strategy and the number of within and between-search errors was found, indicating that performance improved when a strategy was used, whereas no such correlation was found for the Korsakoff patients. Thus, although the latter group tried to apply a search strategy, they were still unable to remember which boxes had been searched and in which boxes a target-object had been found in previous searches. The inability of Korsakoff patients to successfully apply a search strategy was confirmed by previous studies suggesting impaired executive function in Korsakoff patients (Janowsky, Shimamura, Krichevsky & Squire, 1989; Joyce & Robbins, 1991; Mayes, Daum, Markowisch, and Sauter, 1997).

Finally, the current study examined the effect of contextual cueing on memory in Korsakoff patients by presenting the boxes of the spatial search task in different colors, which could help to remember the locations of searched and empty boxes.

This was then compared to a condition in which all boxes were given the same color. This comparison revealed no effect of contextual cueing on the within-search errors for both the comparison group and the Korsakoff patients. Possibly, contextual cues are not processed when spatial information has to be encoded for a very short period of time when making a spatial search. Alternatively, the inability of the comparison group to benefit from contextual cueing in the current study might be the result of the relative ease of this task regarding the within-search errors. An effect of contextual cueing might be found when this aspect of the spatial search task would be more difficult. Korsakoff patients, however, did make more within-search errors than the comparison group, as was previously described, but showed no effect of contextual cueing on this type of errors.

Regarding the between-search errors, control participants were found to improve their performance when color cues were added. Apparently, they were able to use the different colors of the boxes to remember where a target-object was located. This might have been the result of combining location and color information in order to use both cues to successfully search the boxes. Alternatively, participants could have switched from using location information to using color information, since the latter feature might be a more salient cue than location information. Korsakoff patients, however, failed to benefit from the color cues in order to remember the locations of the filled boxes, further supporting the context-deficit hypothesis. Apparently, Korsakoff patients not only failed to encode spatial information, which is one of the most important contextual cues, but were also unable to benefit from color information. Since both spatial and color information have to be held in memory for a longer time period it is likely that this impairment is due to damage to the (memory) circuit involving the thalamus, mammillary bodies and possibly also the hippocampi.

Spatial search tasks, similar to the Box Task, have been used to study the effect of localized lesions in the temporal and frontal lobes on spatial memory performance. A comparison between these patients and the Korsakoff patients might give better insight in the neural correlates of spatial search behavior. Concerning the involvement of the prefrontal cortex mixed results have been found. Owen, Downes, Sahakian, Polkey and Robbins (1990) used the CANTAB spatial working memory task to show that frontal-lobe patients make significantly more within- and between-search errors than the comparison group. Moreover, the frontal-lobe group was less likely to adopt an effective search strategy than the healthy comparison group, and no lateralization effects were found. Miotto, Bullock, Polkey and Morris (1996) used the Executive Golf task (Feigenbaum, Polkey & Morris 1996) and found no difference in within-search errors between

the comparison group and patients with both left and right frontal lobe excisions. In contrast, both patient groups made more between-search errors than the comparison group, but this was more so for the right frontal lobe patients. Furthermore, right-hemisphere patients were less likely to use an effective search strategy than both the left-hemisphere patients and the comparison group.

The latter findings are highly similar to the deficits shown by medial temporal lobectomy (MTL) patients (Feigenbaum, Polkey & Morris, 1996). Right MTL patients showed more between-search errors than the comparison group and left MTL patients, while the within-search errors and use of strategy were not impaired. Thus, these studies have shown the importance of both the frontal lobes and the right temporal lobe in spatial memory. The current study reveals that Korsakoff patients show similar spatial memory impairments as patients with right temporal and frontal lobe damage. This supports the existence of a neural network involving these regions of the brain, as was previously suggested by Feigenbaum et al. (1996). Similarly, by studying non-human primates, Goldman-Rakic (1990) proposed a neural network involved in spatial memory, which includes the prefrontal cortex and hippocampus.

Another patient group to which our current sample can be compared are chronic alcoholics. It has been suggested that the memory deficits in Korsakoff patients are not necessarily the result of brain damage found in Korsakoff patients, but rather due to cerebral dysfunction following chronic alcohol abuse. However, recently Brokate, Hildebrandt, Eling, Fichtner, Runge and Timm (2003) showed that, while Korsakoff patients have clear memory impairments and performed worse on tasks testing executive functioning, chronic alcoholics showed no memory impairments and were unimpaired on most of the executive tasks. Therefore, the impairments that are found in the current study are most likely specific for Korsakoff syndrome and related to the brain damage found in these patients.

In sum, the current study used a spatial search task to show Korsakoff patients inability to keep spatial information in working memory and encode it into long-term memory. The inability of Korsakoff patients to remember spatial information could not be ameliorated by adding contextual color cues to the boxes. To our knowledge, this is the first time that contextual cueing has been studied in Korsakoff patients within a spatial search paradigm. Together these results indicate a major impairment in Korsakoff patients in handling spatial information over short periods of time and to integrate this with nonspatial cues. This further supports and extends the context deficit hypothesis.

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## Chapter 4

# Brain areas involved in spatial working memory

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**Abstract**

Spatial working memory entails the ability to keep spatial information active in working memory over a short period of time. To study the areas in the brain that are involved in spatial working memory, a group of stroke patients was tested with a spatial search task. Patients and healthy controls were asked to search through a number of boxes shown at different locations on a touch-sensitive computer screen in order to find a target object. In subsequent trials, new target objects were hidden in boxes that were previously empty. Within-search errors were made if a participant returned to an already searched box; between-search errors occurred if a participant returned to a box that was already known to contain a target item. The use of a strategy to remember the locations of the target objects was calculated as well. Damage to the right posterior parietal and right dorsolateral prefrontal cortex impaired the ability to keep spatial information ‘on-line’, as was indicated by performance on the Corsi Block-Tapping task and the within-search errors. Moreover, patients with damage to the right posterior parietal cortex, the right dorsolateral prefrontal cortex and the hippocampal formation bilaterally made more between-search errors, indicating the importance of these areas in maintaining spatial information in working memory over an extended time period.

## Introduction

Spatial working memory, also known as the visuospatial sketchpad (Baddeley, 2002), serves to manipulate and keep spatial information active during a short period of time. Much attention has been paid to the areas in the brain that are involved in spatial working memory, specifically the prefrontal cortex (Fletcher & Henson, 2001). Different parts of the prefrontal cortex are thought to be involved in specific working memory processes. For example, keeping object information active in working memory would rely on ventral areas of the lateral prefrontal cortex, whereas processing spatial information is thought to depend on dorsal areas of the lateral prefrontal cortex, as has been shown in animal studies (e.g. Wilson, Scalaidhe, & Goldman-Rakic, 1993), functional Magnetic Resonance Imaging (fMRI) studies in children (Nelson, Monk, Lin, Carver, Thomas, & Truwit, 2000) and fMRI studies in adults (Smith & Jonides, 1999).

Furthermore, neuroimaging studies have shown that in addition to the dorsolateral prefrontal cortex, the posterior parietal cortex may play a role in spatial working memory as well (Jonides, Smith, Koeppe, Awh, Minohsima, & Mintun, 1993; Nelson et al., 2000; Walter et al., 2003). Over the past years, different theories have been developed to scrutinize the role of the posterior parietal lobe in spatial memory. Ungerleider and Mishkin (1982), for example, have proposed that two information processing streams can be distinguished, i.e. a dorsal pathway including the posterior parietal cortex, which is important for spatial information processing (“where” pathway), and a ventral pathway, which is important for processing object information (“what” pathway). Later, however, Milner and Goodale (1995) have argued that the ventral pathway encodes spatial information from an allocentric perspective (i.e., viewpoint-independent), which is used to create a representation of the environment. In contrast, the dorsal pathway is thought to encode information from an egocentric perspective (i.e., viewpoint-dependent), which can be used to guide goal-directed action, such as reaching for a specific object. Accordingly, both the dorsal and the ventral pathway process object and spatial information. In monkeys performing a spatial working memory task, concurrent metabolic activation of the parietal and prefrontal cortex has been observed (Friedman & Goldman-Rakic, 1994), suggesting these are important areas of the previously hypothesized network mediating spatial working memory (Goldman-Rakic, 1988). In humans, several studies have shown concurrent activation of the prefrontal and parietal cortices in working memory as well (e.g. Jonides et al., 1993; Constantinidis & Wang, 2004; Glabus et al., 2003; Owen, Stern, Look, Tracey, Rosen, & Petrides, 1998).

Patient studies have provided further information about brain areas involved in spatial working memory. These studies have not only given further support to the involvement of the left and right prefrontal cortex in spatial working memory (Owen, Downes, Saahakian, Polkey, & Robbins; Miotto, Bullock, Polkey, & Morris, 1996), but have also implicated a role for the medial temporal lobe, in particular the hippocampus. Presumably, this brain area is involved in the transition of information from working memory into long-term memory. Patients with a lesion in the right medial temporal lobe have been shown to be impaired on a spatial search task (Feigenbaum, Polkey, & Morris, 1996; Abrahams, Pickering, Polkey, & Morris, 1997), which appeared predominantly the result of damage to the right hippocampal region (Abrahams et al., 1999). However, Kessels, Hendriks, Schouten, Van Asselen and Postma (2004) showed that patients with left or right amygdalohippocampectomy were not impaired on any aspects of spatial working memory as measured with a search task, indicating a limited role for the hippocampal formation in spatial working memory (see also Bohbot et al., 2002).

Thus, although neuroimaging and patient studies have shown the importance of brain areas such as the dorsolateral prefrontal cortex, the posterior parietal cortex and possibly the hippocampal formation, the exact role of these areas in humans remains unclear. Therefore, the goal of the present study was to further examine the neural correlates of different aspects of spatial working memory by examining patients with focal lesions caused by cerebral stroke. Patient studies have some clear benefits compared to animal and neuroimaging studies. That is, although the cerebral organization of animals and humans might be comparable to some extent, there are apparent differences as well, which are particularly important when studying higher cognitive functions such as memory. In turn, fMRI makes it possible to demonstrate which brain areas are involved in spatial working memory in humans, but cannot indicate whether a brain area is crucial (i.e. damage to this function leads to an impairment) or whether it is merely involved in a specific process. In the current study, a spatial search task (Van Asselen, Kessels, Wester, & Postma., in press) was used, requiring subjects to search for target objects that are hidden in a number of boxes shown on a computer screen. Importantly, this task enables us to distinguish between processes that are related to keeping spatial information 'online' in memory over a very short time period and the transfer from working memory into long-term memory. Moreover, the use of a strategy that can be applied to relieve the memory load could be determined. In addition to the spatial search task a commonly used spatial working memory task was administered as well, i.e., the Corsi Block-Tapping Task. To study the effect of damage to the dorsolateral prefrontal cortex, the posterior parietal cortex and the hippocampal

formation on these different processes, the spatial extent of the lesions was defined by transforming individual CT or MR images of the patients to a standard brain template, using lesion cost function masking (Brett, Leff, Rorden, & Ashburner, 2001). Mapping the patients' brains with marked lesions to standard brain coordinates enables the comparison of lesions across patients and the correlation with the amount of damaged tissue in a brain area of interest with the observed behaviour in standard neuropsychological tests.

We hypothesized that damage to the posterior parietal and dorsolateral prefrontal cortex impairs the ability to keep spatial information in working memory over a short time period, whereas damage to the hippocampal formation might hamper the ability to keep spatial information in working memory over a more extended time period. These effects were hypothesised to be more profound for the right hemisphere than for the left hemisphere. Moreover, strategy use might be related to general "central-executive" aspects of working memory (Baddeley, 2002), possibly related to the dorsolateral prefrontal cortex.

## Methods

### *Participants*

Thirty stroke patients who were admitted to the University Medical Center Utrecht (UMCU) were examined. Sixteen patients had a lesion in the left hemisphere, 13 patients had a lesion in the right hemisphere and one patient had a large lesion in the right hemisphere accompanied by a small lesion in the left hemisphere. All patients were examined at least six months after the stroke and were mobile at the time of testing. Patients were all between 21 and 75 years of age and did not suffer from other neurological or psychiatric diseases. The study was approved by the medical ethics committee of the UMCU and written informed consent was obtained according to the declaration of Helsinki. We also examined 36 age- and education matched, healthy control participants who were recruited through an advertisement in the local newspaper and were paid for their participation. Characteristics of the patients and comparison group are shown in Table 4.1. Handedness was assessed with a Dutch version of the Annett Handedness Inventory (Briggs & Nebbs, 1975). Education level was measured using seven categories (1 being the lowest and 7 the highest; Hochstenbach, den Otter, & Mulder, 2003). No differences were found between the three groups for education level [ $F(2,62) = 2.1$ ], age [ $F(2,63) = 0.1$ ], or gender distribution [ $\chi^2(2) = 4.4$ ].

Standard neuropsychological tests were used to assess overall intelligence and memory performance. Verbal intelligence was assessed with the Dutch version of the National Adult Reading Task (Schmand, Bakker, Saan, & Louman, 1992); non-verbal intelligence with the 12-item short form of the Raven Advanced Progressive Matrices (Raven, Raven, & Court, 1993). Verbal memory was assessed with the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT, Rey, 1964). The Letter Number Sequencing task (WAIS-III) was used as an index of verbal working memory (Wechsler, 1997). No differences were found on any of the standard neuropsychological tests between the patients and controls, except on immediate reproduction of the RAVLT [ $F(2, 58) < 7.1, p < 0.01$ ]. Patients with a lesion in the right or left hemisphere performed worse than the control participants [ $t(48) = 3.2, p < 0.01, t(48) = 2.8, p < 0.01$ , respectively]; no difference was found between performance of the patients with damage to the left or to the right hemisphere [ $t(24) = 0.2$ ].

Table 4.1: Characteristics and neuropsychological test results of patients with a lesion in the right (RH) or in the left hemisphere (LH) and of control participants.

	RH n = 14	LH n = 16	Controls n = 36
Age (yrs)	57.8 (3.1)	58.3 (2.9)	56.9 (1.8)
Education level (1-7)	4.7 (0.4)	5.3 (0.3)	5.5 (0.2)
Annett Handedness Inventory (-24/ 24)	15.2 (4.2)	17.7 (3.1)	15.3 (2.2)
Sex (m:f)	12:2	11:5	20:16
NLV-IQ	107.5 (3.2)	105.5 (3.7)	107.0 (4.7)
RAVLT: immediate recall	36.5 (2.8)*	36.5 (3.2)*	46.9 (1.8)
RAVLT: delayed recall	8.5 (1.1)	7.5 (1.6)	9.6 (0.6)
Raven APM (short form)	7.0 (0.9)	8.0 (0.8)	12.0 (2.8)
Letter Number Sequencing task	9.5 (0.8)	8.4 (0.8)	9.8 (0.3)
Corsi Block-Tapping Task	45.8 (4.6)	43.8 (3.8)	42.6 (2.5)

\* = significant difference with the controls ( $p < 0.05$ )

Note. NLV = Dutch version of the National Adult Reading Task, RAVLT = Rey Auditory Verbal Learning Test, Raven APM = Raven Advanced Progressive Matrices.

### *Material and procedure*

#### *Corsi Block-Tapping Task*

The Corsi Block-Tapping Task is a widely used neuropsychological test of spatial working memory (Berch, Krikorian, & Huha, 1998; Kessels, Van Zandvoort, Postma, Kappelle, & De Haan, 2000). It consists of 9 blocks mounted on a black board in a random pattern. The experimenter taps a sequence of blocks at a rate of about one block per second. Then, the participant has to tap the same sequence immediately after the experimenter has finished. The length of the sequences ranges from two to nine blocks and each sequence contains two different trials. When an error is made in both trials of the same sequence, the task is stopped. A recently introduced sensitive measure of the Corsi task is used in the current experiment, which is the product of the total number of correct trials and the length of the largest sequence (Kessels et al., 2000).

#### *Box Task*

In this spatial working memory task (Kessels, Hendriks, Schouten, Van Asselen, & Postma, 2004; Van Asselen, Kessels, Wester, & Postma, in press), pictures of closed boxes were randomly displayed on different locations within a square of 19 by 19 cm on a 15" touch-sensitive LCD computer monitor. An easy-to-name, colored target object (e.g. ball, tomato) was presented (approximately 1 x 1 cm) at the bottom of the square. Participants were instructed to find the target object, which was hidden in one of the boxes and could not be seen when the boxes were closed. The boxes could be opened by touching them, after which either an empty box or the target object was shown at the same location. An empty box remained open for two seconds, whereas the target object was shown until the participant initiated a new search. After successfully locating a target object, a new target appeared below the square. Importantly, the target object that was found before remained in the box where it was found until the end of the trial and no second object could be added to this box. Thus, the participant not only had to remember which box was searched, but also in which box a previous target object was found. After locating the second target object, a third target appeared below the square. This would continue until all boxes contained a target object. Which box was filled with an object was randomly determined and not dependent on the participants' response. The experiment began with two practice trials of three boxes, after which two trials of four, six and eight boxes were used. No time limit was set. A single search through the boxes in order to locate a target object took approximately 5 – 11 seconds and a trial (4, 6 or 8 searches together) 20 – 88 seconds, depending on

the set size and number of errors. Figure 3.1 shows an example of the layout of the Box task when making a search through six boxes.

Three dependent variables were included: 1) *within-search errors* were scored when a participant returned to an already opened box within a search; 2) *between-search errors* were scored when a participant returned to a box where a target object was found in one of the previous searches; 3) efficient use of *strategy* was defined by counting the number of times a participant started searching for a target object with a different box (within one trial). Strategy use is considered more efficient if a participant follows a predetermined search sequence, since this relieves memory load. Thus, a low score on the strategy index would indicate efficient use of strategy (see also Feigenbaum et al., 1996; Van Asselen et al., in press).

#### *Lesion location*

CT or T1-weighted MR images were available for 26 patients (12 patients with a lesion in the right hemisphere, 13 patients with a lesion in the left hemisphere and one patient with a lesion in both hemispheres). For five patients no digital scans were available, who were excluded from further lesion analyses. The Corsi Block-Tapping Task was not performed by one patient, and in another patient the Box task was not administered. In order to define the locations of the lesions, an experienced neurologist who was unaware of the clinical status of the patients, manually delineated for all patients the regions of interest (ROI) covering the lesion in all slices, using the MRIcro software (<http://www.psychology.nottingham.ac.uk/staff/cr1/micro.html>). ROIs were saved as image volumes containing 1 for voxels inside the lesion area and 0 for voxels outside the lesion area. CT images were skull stripped by only including voxels with a CT-intensity value between 0 and 100. All images were then normalized to standard brain coordinates (MNI) according to the method described by Brett et al. (2001) using the software package Statistical Parametric Mapping (SPM2) (<http://www.fil.ion.ucl.ac.uk/spm/software/spm2/>). CT or T1-weighted MRI-scans were normalized to a T1-weighted template, using cost function masking with smoothed masks (FWHM = 8 mm) based on the ROI (Figure 4.2). By doing so, voxels in the lesioned tissue do not contribute to the calculation of the spatial transformation from the patients brain to MNI (standard brain) coordinates, which results in a standardized map of the pathological brain images (Brett et al., 2001). Finally, the ROI images and CT/MRI scans were resliced with a  $1 \times 1 \times 1 \text{mm}^3$  voxel size. The lesion size of each patient was calculated as defined by the number of voxels that were above threshold (threshold = 0.5), since due to interpolation artefacts at the reslicing stage voxels in the normalized images could have values between 0 and 1. Importantly, no difference was found

between the lesion sizes of the group of patients with a lesion in the right hemisphere and those with a lesion in the left hemisphere [ $t(24) = 1.3$ ]. Normalized brain scans including the lesions are shown in Figure 4.3 for each patient separately.

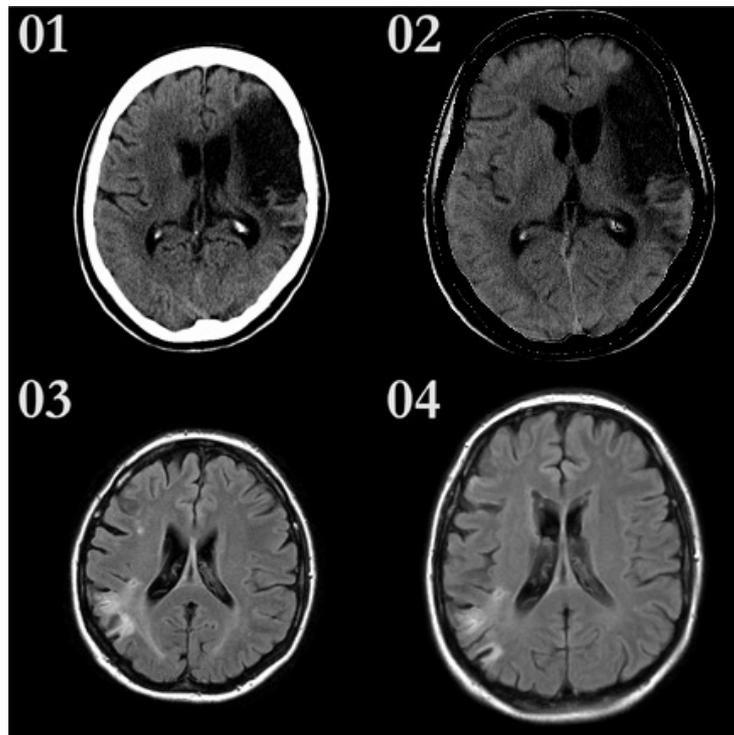


Figure 4.2: An example of a CT scan before (1) and after (2) transforming it to standard brain template and an example of an MRI scan before (3) and after (4) transforming it to standard brain template.

Volumes of interest (dorsolateral prefrontal cortex, posterior parietal cortex and hippocampal formation) were used that were established by probability density estimates of locations from the BrainMap database (Nielsen & Hansen, 2002). For each patient it was determined whether the lesion included one or more of these areas and subsequently the size of the lesion in the target area was calculated as defined by the number of voxels of the lesion that were above threshold and located within the target region divided by the total number of voxels in the target region (lesion overlap ratio). Twelve patients had a lesion in the dorsolateral prefrontal cortex (Figure 4.3: no 2, 6, 7, 8, 9, 12, 13, 14, 18, 20, 24, 26), 16 patients

had a lesion in the hippocampal formation (Figure 4.3: no 1, 4, 5, 6, 7, 10, 11, 12, 13, 15, 17, 18, 22, 23, 24, 25) and six patients had a lesion in the posterior parietal cortex (Figure 4.3: no 5, 6, 7, 10, 11, 12).

#### *Analyses*

First, to examine general lateralization effects, performances of patients with a lesion in the left and patients with a lesion in the right hemisphere were compared with the performances of control participants (*overall hemispheric differences*). Lateralization effects for the Corsi task were analysed by means of one-way ANOVA (patients with damage to the left hemisphere, patients with damage to the right hemisphere, control participants). To determine lateralisation effects for the within-search errors and the between-search errors a  $3 \times 3$  Repeated Measures general-linear model analysis of variance (GLM) with between-subject variable Group (patients with a lesion in the right hemisphere, patients with a lesion in the left hemisphere, controls) and within-subject variable Set size (4, 6, 8 boxes) was used. For the strategy-index of the Box task lateralisation effects were analysed by means of a  $2 \times 3$  Repeated Measures analysis with within-subject variable Set size (6 and 8 boxes) and between-subject variable Group (patients with a lesion in the right hemisphere, patients with a lesion in the left hemisphere, controls).

Second, to study the effect of damage to a specific target area (e.g. hippocampal formation, dorsolateral prefrontal cortex) in either the left or right hemisphere on the within- and between-search errors,  $3 \times 3$  Repeated Measures analyses were performed with between-subject variable Group (patients with damage to the target region in the right hemisphere, patients with damage to the same target region in the left hemisphere and control participants) and within-subject variable Set size (condition with 4, 6 and 8 boxes). ANOVA was performed to study the effect of damage to a specific target area (patients with damage to the left hemisphere, patients with damage to the right hemisphere, control participants) on the Corsi Block-Tapping task (*analyses of specific brain areas*). Patients with limited damage to the target region were included in the first or second group.

Third, to study the influence of the extent of damage within a particular area on the different spatial memory tasks, one-tailed Pearson correlations were performed between the lesion overlap ratio of a target area and performance on the working memory tasks (*correlations*). No correlations were calculated between the lesion overlap ratio of the left posterior parietal cortex and performance on the spatial working memory tasks, since there was only one patient with a lesion that included this area.

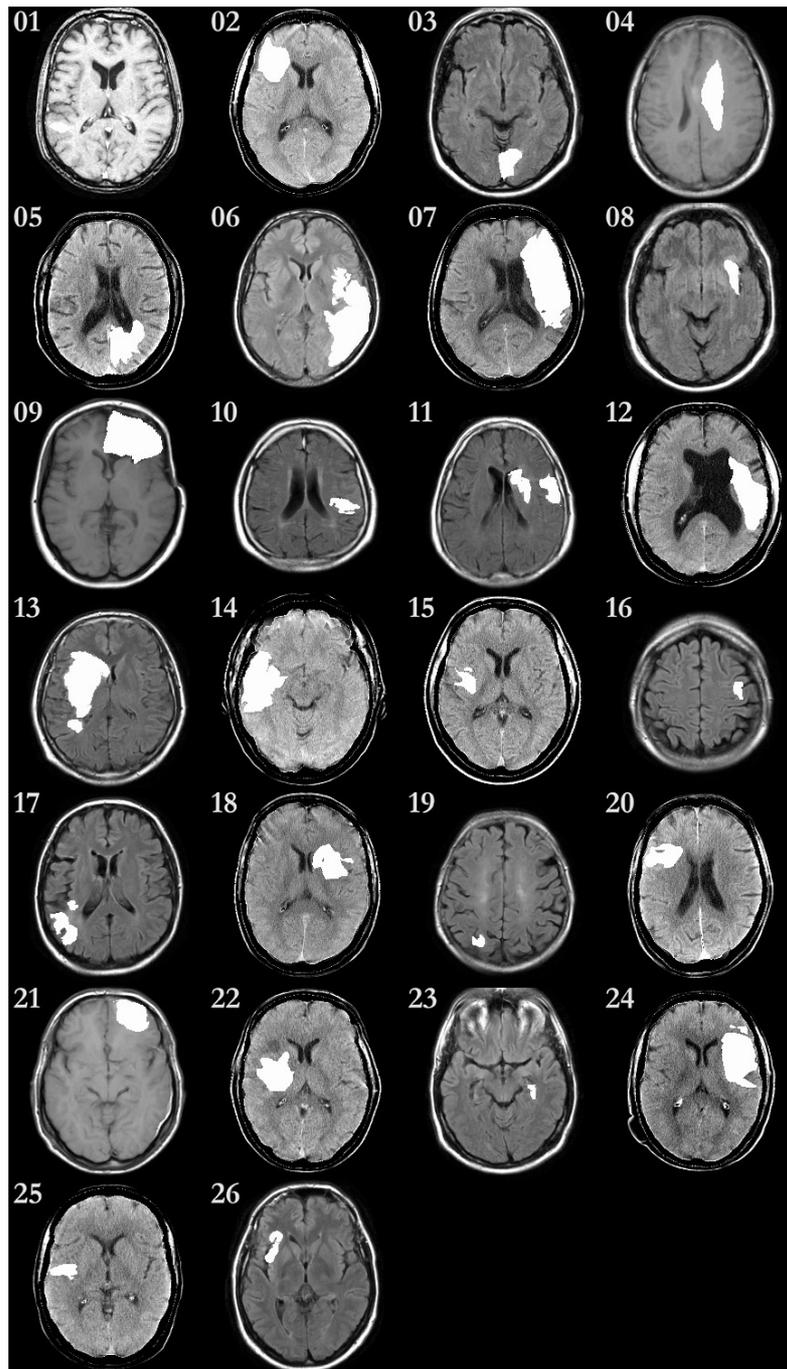


Figure 4.3: CT and MRI scans of the 26 patients after transformation to standard brain template.

## Results

### *Corsi Block-Tapping task*

#### a) Overall hemispheric differences

One-way ANOVA showed no difference in the total score between patients with a lesion in the right hemisphere, patients with a lesion in the left hemisphere and the control group [ $F(2, 65) = 0.26$ ].

#### b) Analyses of specific brain areas

ANOVA did not show differences between patients with a lesion in the right dorsolateral prefrontal cortex, patients with a lesion in the left dorsolateral prefrontal cortex, and controls [ $F(2, 46) = 0.1$ ]. Similarly, no differences in performance were found between patients with a lesion in the right *posterior parietal cortex*, patients with a lesion in the left posterior parietal cortex, and controls [ $F(2, 39) = 0.1$ ]. Finally, no differences were found between patients with a lesion in the right *hippocampal formation*, patients with a lesion in the left hippocampal formation, and control participants [ $F(2, 49) = 1.0$ ].

#### c) Correlations

Significant negative correlations were found between performance on the Corsi Block-tapping task and the lesion overlap ratio of the right dorsolateral prefrontal cortex [ $r = -0.43, p < 0.05$ ] and the right posterior parietal cortex [ $r = -0.42, p < 0.05$ ]. No significant correlations were found between performance on the Corsi Block-Tapping task and the left dorsolateral prefrontal cortex ( $r = 0.05$ ), or the hippocampal formation ( $r = 0.25$ ). It should be noted, that of the six patients with damage to the right dorsolateral prefrontal cortex, two patients had severe damage (Figure 4.3, no. 7 + 24), and four patients had only minor damage. Importantly, the patients with large lesions were severely impaired, whereas the others were not. Since the patients with minor damage to the right dorsolateral prefrontal cortex were unimpaired on the Corsi test, no difference was found in a group comparison. Similarly, of the five patients with damage to the right posterior parietal cortex, only one patient had a large lesion (Figure 4.3, no. 7) and this patient was clearly impaired.

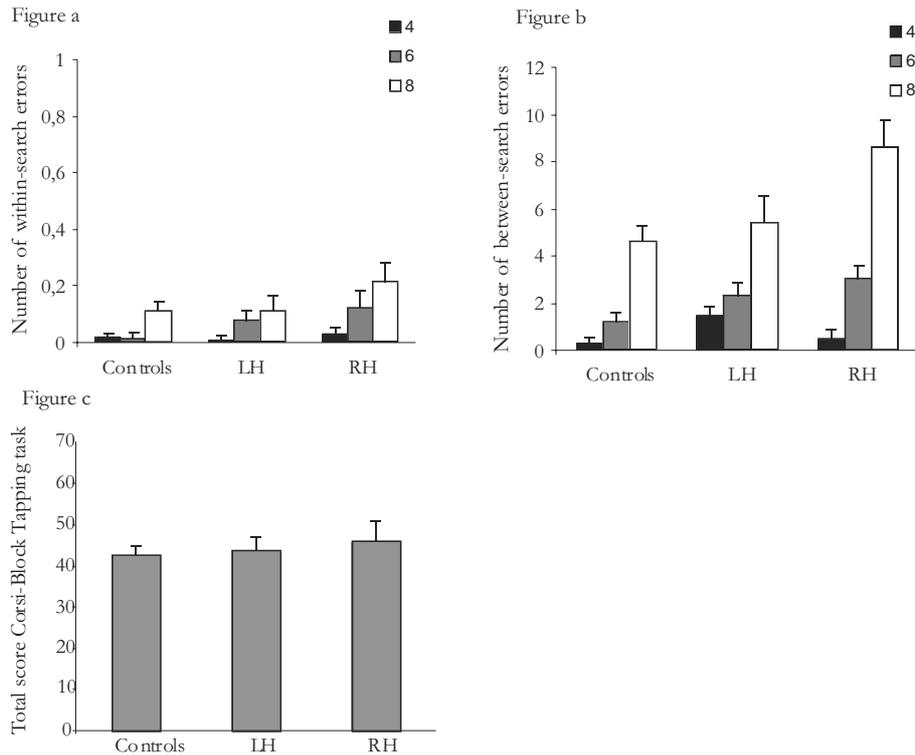


Figure 4.4a): The average number of within-search errors (Set sizes 4, 6, 8) of the patients with a lesion in the right (RH) or left hemisphere (LH) and control participants; b) Average number of between-search errors (Set sizes 4, 6, 8) of the patients with a lesion in the right or left hemisphere and control participant; c) Total score on the Corsi Block Tapping task of the patients with a lesion in the right hemisphere or left hemisphere and control participants.

*Box task: Within-search errors*

a) Overall hemispheric differences

A  $3 \times 3$  Repeated Measures GLM with between-subject variable Group (patients with a lesion in the right hemisphere, patients with a lesion in the left hemisphere and controls) and within-subject variable Set Size (4, 6, 8 boxes) revealed that more within-search errors (Figure 4.4) were made with increasing Set Size [ $F(2, 126) = 13.6, p < 0.001$ ]. A test of within-subject contrasts showed that more errors were made in the condition with six than with four boxes [ $F(1, 63) = 7.3, p < 0.01$ ] and in the condition with eight boxes than with six boxes [ $F(1, 63) = 5.7, p < 0.05$ ]. Moreover, a main effect for group was found [ $F(2, 63) = 3.7, p < 0.05$ ]. Contrast analysis showed that patients with a lesion in the right hemisphere made

significantly more errors than the control participants [ $p < 0.01$ ], whereas no difference was found between patients with a lesion in the left hemisphere and the control group. No interaction effect between Group and Set Size was found [ $F(4, 126) = 1.1$ ].

b) Analyses of specific brain areas

Repeated measures analyses including patients with damage to the dorsolateral prefrontal cortex revealed a significant effect for Set size [ $F(2, 90) = 4.4, p < 0.015$ ], indicating that more within-search errors were made in the condition with six boxes than the condition with four boxes [ $F(1,46) = 11.3, p < 0.005$ ], whereas no difference was found between the condition with eight boxes and the condition with six boxes [ $F(1,45) = 0.8$ ]. Moreover, a trend was found for the variable Group [ $F(2,45) = 2.6, p = 0.087$ ]. Contrast analyses indicated that patients with a lesion in the right dorsolateral prefrontal cortex performed worse than the controls ( $p < 0.05$ ), whereas no difference was found between patients with a lesion in the left dorsolateral prefrontal cortex. A trend was also found for the interaction effect between Set size x Group [ $F(4, 90) = 2.6, p = 0.087$ ]. Separate 2 x 3 Repeated Measures analyses indicated that patients with a lesion in the right dorsolateral prefrontal cortex deteriorated more with increasing set size [ $F(2, 80) = 4.0, p < 0.05$ ], but not the patients with a lesion in the left dorsolateral prefrontal cortex [ $F(2, 80) = 0.6$ ].

Repeated Measures analyses including the patients with damage to the right hippocampal formation, patients with damage to the left hippocampal formation and controls demonstrated a significant effect for Set Size [ $F(2, 96) = 14.2, p < 0.001$ ], indicating that more errors were made in the condition with six boxes than in the condition with four boxes [ $F(1,50) = 4.4, p < 0.05$ ], and more errors were made in the condition with eight boxes than in the condition with six boxes [ $F(1,48) = 11.6, p < 0.001$ ]. However, no effect for Group [ $F(2, 48) = 1.2$ ] was found, nor an interaction effect between Group x Set size [ $F(4, 96) = 0.8$ ].

Similarly, Repeated Measures analyses including patients with damage to the right posterior parietal cortex, patients with damage to the left posterior parietal cortex and controls revealed no significant effect for Set size [ $F(2, 78) = 2.1$ ] or Group [ $F(2, 39) = 2.54$ ], nor an interaction effect between Group x Set size [ $F(2,78) = 1.74$ ].

## c) Correlations

No correlations were found between the lesion overlap ratio of the left and right dorsolateral prefrontal cortex ( $r = 0.29$ ), the right posterior parietal cortex ( $r = 0.10$ ), or the left and right hippocampal formation ( $r = 0.17$ ) and the mean number of within-search errors of the four, six and eight boxes.

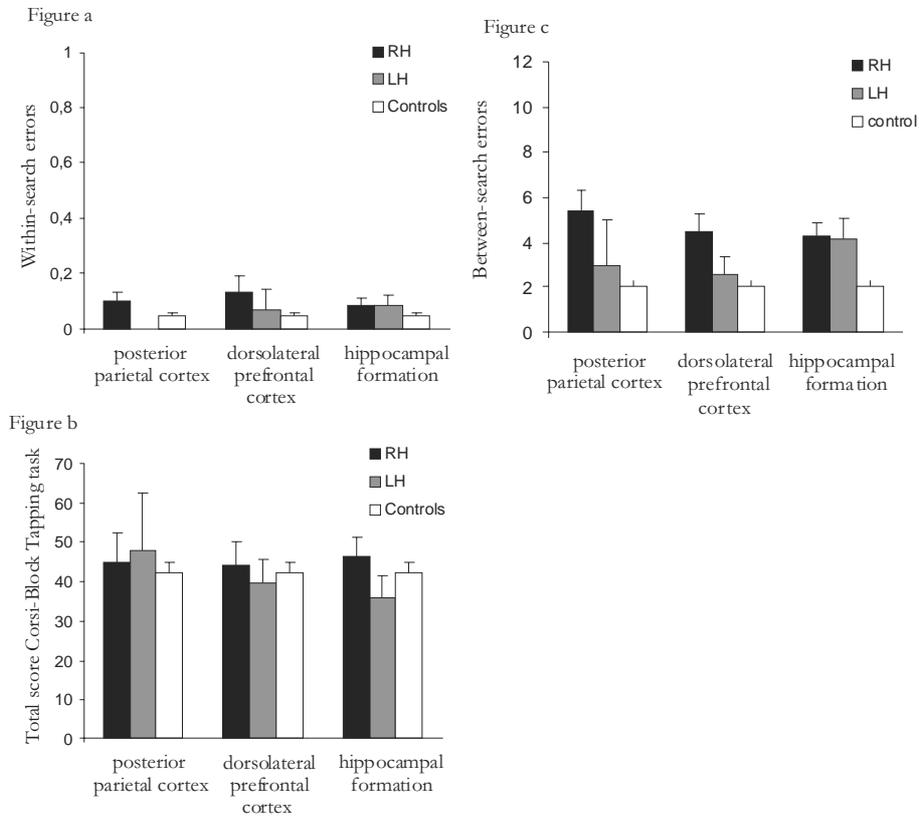


Figure 4.5 a) Average number of within-search errors (Set sizes 4, 6, 8) of the patients with a lesion in the dorsolateral prefrontal cortex, posterior parietal cortex and hippocampal formation (left and right hemisphere lesions separately) and control participants; b) Average number of between-search errors (Set sizes 4, 6, 8) of the patients with a lesion in the dorsolateral prefrontal cortex, posterior parietal cortex and hippocampal formation (left and right hemisphere lesions separately) and control participants; c) Total score on the Corsi-Block Tapping task of the patients with a lesion in the dorsolateral prefrontal cortex, posterior parietal cortex and hippocampal formation (left and right hemisphere lesions separately) and control participants.

*Box task: Between-search errors*

## a) Overall hemispheric differences

For the between-search errors (Figure 4.4) a  $3 \times 3$  repeated measures GLM with between-subject variable Group (patients with a lesion in the right hemisphere, patients with a lesion in the left hemisphere and controls) and within-subject variable Set size (4, 6, 8 boxes) revealed a significant main effect for Set size [ $F(2, 126) = 74.2, p < 0.001$ ]. A test of within-subject contrasts showed that the errors increased as a result of increasing set size (4-6 boxes [ $F(1, 63) = 44.2, p < 0.001$ ] and 6-8 boxes [ $F(1, 63) = 64.4, p < 0.001$ ]). Additionally, a significant effect for Group was found [ $F(2, 63) = 5.1, p < 0.01$ ]. Contrast analysis showed that patients with a lesion in the right hemisphere made more between-search errors than control participants ( $p < 0.01$ ), whereas no difference was found between the patients with a lesion in the left hemisphere and control participants. Moreover, an interaction effect for Group  $\times$  Set size [ $F(4, 126) = 3.6, p < 0.01$ ] was found. Tests of within-subjects contrasts showed a significant Group  $\times$  Set size effect for the four and six boxes [ $F(2, 63) = 5.6, p < 0.01$ ], but not the six and eight boxes [ $F(2, 63) = 2.1$ ].  $2 \times 3$  repeated measures GLM with between-subject variable Group (patients with a lesion in the right hemisphere and controls) and within-subject variable Set size (4, 6, 8, boxes) showed that patients with a lesion in the right hemisphere were more impaired by increasing set size than the comparison group [ $F(2, 96) = 7.6, p < 0.01$ ]. The same analysis comparing patients with a lesion in the left hemisphere with controls did not reveal a significant interaction effect [ $F(2, 100) = 0.04$ ].

## b) Analyses of specific brain areas

Figure 4.5 shows the between-search errors of the patient groups with damage to the posterior parietal cortex, the dorsolateral prefrontal cortex and the hippocampal formation (left and right separately). A significant effect was found for Group, revealing a difference between patients with a lesion in the right dorsolateral prefrontal cortex, patients within a lesion in the left dorsolateral prefrontal cortex and controls [ $F(2, 45) = 3.9, p < 0.05$ ]. Contrast analysis indicated that patients with a lesion in the right dorsolateral prefrontal cortex performed worse than the controls ( $p < 0.01$ ), whereas no difference was found between patients with a lesion in the left dorsolateral prefrontal cortex and controls. A significant effect for Set size was found [ $F(2, 90) = 25.8, p < 0.001$ ], indicating that the errors increased as a result of increasing set size (4-6 boxes [ $F(1, 46) = 26.3, p < 0.001$ ] and 6-8

boxes [ $F(1, 46) = 18.9, p < 0.001$ ]. Additionally, a significant interaction effect between Group x Set size was found [ $F(4, 90) = 3.5, p < 0.05$ ]. Separate 2 x 3 Repeated Measures analyses indicated that patients with a lesion in the right dorsolateral prefrontal cortex deteriorated more than the controls with increasing set size [ $F(2, 80) = 3.3, p < 0.05$ ], as well as the patients with a lesion in the left posterior parietal cortex [ $F(2, 80) = 3.1, p < 0.05$ ].

To study the importance of the posterior parietal cortex, Repeated measured analyses demonstrated that patients with a lesion in the right posterior parietal cortex performed worse than controls [ $F(1, 39) = 15.6, p < 0.001$ ]. A significant effect for Set size was found [ $F(2, 78) = 69.0, p < 0.001$ ], indicating that the errors increased as a result of increasing set size (4-6 boxes [ $F(1, 59) = 19.1, p < 0.001$ ] and 6-8 boxes [ $F(1, 57) = 15.7, p < 0.001$ ]). Additionally, a Group x Set size effect was found, revealing that patient with a lesion in the right posterior parietal cortex deteriorated more with increasing set size than the healthy controls [ $F(2, 46) = 26.3, p < 0.001$ ].

A group effect was found between patients with a lesion in the right hippocampal formation, patients with a lesion in the left hippocampal formation, and controls [ $F(2, 48) = 7.4, p < 0.005$ ]. Contrast analysis showed that patients with a lesion in the right hippocampal formation performed worse than controls ( $p < 0.005$ ), as well as patients with a lesion in the left hippocampal formation ( $p < 0.05$ ). Additionally, a significant effect for Set size was found [ $F(2, 96) = 94.2, p < 0.001$ ], indicating that the errors increased as a result of increasing set size (4-6 boxes [ $F(1, 50) = 37.0, p < 0.001$ ] and 6-8 boxes [ $F(1, 48) = 83.4, p < 0.001$ ]). Finally, a Group x Set size effect was found [ $F(4, 96) = 6.8, p < 0.001$ ]. Performance of patients with a lesion in the right hemisphere deteriorated more with increasing set size [ $F(2, 88) = 8.1, p < 0.005$ ], as well as performance of patients with a lesion in the left hemisphere [ $F(2, 78) = 8.2, p < 0.005$ ].

### c) Correlations

A significant correlation was found between the mean number of between-search errors of the three conditions (set size 4, 6, 8,) and the lesion overlap ratio of the right dorsolateral prefrontal cortex [ $r = 0.56, p < 0.005$ ] and the right posterior parietal cortex [ $r = 0.42, p < 0.05$ ]. No correlations were found between the right and left hippocampal formation ( $r = 0.16$ ) and the mean number of between-search errors over the conditions with four, six and eight boxes. A negative correlation was found with the left dorsolateral prefrontal cortex [ $r = -0.34, p < 0.05$ ].

Table 4.2: The mean total scores of the patients with a lesion in the right (RH) and left hemisphere (LH) and the controls of the six and eight box conditions separately on the strategy index.

	6 boxes		8 boxes	
	Mean	SE	Mean	SE
RH n = 14	3.9	0.2	4.6	0.2
LH n = 16	3.7	0.2	4.7	0.2
Controls n = 36	3.4	0.1	4.7	0.2

### *Strategy use*

#### a) Overall hemispheric differences

A  $2 \times 3$  Repeated Measures analysis with within-subject variable Set size (6 and 8 boxes) and between-subject variable Group (patients with a lesion in the left hemisphere, patients with a lesion in the right hemisphere, controls) was used for the strategy index (Table 4.2). No difference in performance was found between the three groups [ $F(1,62) = 0.7$ ]. However, a significant effect was found for Set Size [ $F(1,62) = 43.8, p < 0.001$ ], indicating that strategy index increased with more boxes.

#### b) Analyses of specific brain areas

ANOVA revealed no significant difference with respect to the involvement of the dorsolateral prefrontal cortex in the use of a strategy between patients with damage to the right dorsolateral prefrontal cortex, patients with damage to the left dorsolateral prefrontal cortex, and control participants [ $F(2, 44) = 2.0$ ].

#### c) Correlations

No correlation was found between the extent of damage to either the left or the right dorsolateral prefrontal cortex and the strategy index ( $r < 0.31$ ). Moreover, to analyze whether applying a strategy indeed resulted in fewer between-search errors the correlation between the strategy index and the within- and between-search errors for the six and eight box conditions was calculated based on the group as a whole (patients and control participants). A significant correlation was found for the between-search errors ( $r = 0.28, p = 0.01$ ), but not the within-search errors ( $r = 0.15$ ). However, when performance of the patients and controls were analyzed separately no correlation was found with both within- ( $r < 0.16$ ) and between-search errors ( $r < 0.25$ ).

## Discussion

The aim of the current study was to examine in more detail the neural correlates of spatial working memory in a group of stroke patients. The Corsi Block-Tapping task is a commonly used test of spatial working memory, which requires participants to passively keep spatial information in working memory over a very short period of time without any kind of manipulation. The current study revealed no difference in performance on this task between patients with a lesion in either the left or the right hemisphere and control participants. However, when performance was correlated with damage to the right dorsolateral prefrontal cortex and the right posterior parietal cortex, a significant correlation was found, indicating that these areas serve to keep a sequence of locations in working memory. Damage to the left dorsolateral prefrontal cortex, the left posterior parietal cortex or the hippocampal formation did not impair this aspect of spatial working memory.

The spatial search task enabled us to examine various aspects of spatial working memory, that is, within-search errors, between-search errors and use of strategy. Patients with damage to the right hemisphere made more within-search errors than controls, whereas no difference was found between patients with a lesion in the left hemisphere and controls. Similar to the Corsi-Block Tapping Task, within-search errors reflect the ability to keep a sequence of locations in spatial working memory over a very short time period. Although previous studies have shown mixed results concerning lateralization effects for within-search errors (Owen, et al., 1990; Miotto et al., 1996), the current study provides evidence that the right hemisphere is more specialised in this aspect of working memory. Importantly, this is not a result of a difference in the size of the lesions in the left and right hemisphere or a difference in general cognitive ability and memory function as was assessed with standard neuropsychological tests. Looking at the relation between the number of within-search errors and damage to specific brain areas, we found that patients with damage to the right dorsolateral prefrontal cortex made more within-search errors, but not the patients with damage to the left dorsolateral prefrontal cortex, posterior parietal cortex or hippocampal formation. These results give further support for the importance of the right dorsolateral prefrontal cortex in keeping spatial information active in working memory during a short time period. In contrast to the Corsi Block-Tapping task, damage to the right posterior parietal cortex did not lead to more within-search errors. It should be noted, however, that only few within-search errors were made by both the patients and the healthy controls, indicating that this aspect of the search task might not

have been very sensitive. However, the fact that damage to the posterior parietal cortex did not lead to more within-search errors might also suggest that this area is of less importance to spatial working memory than the right dorsolateral prefrontal cortex.

With respect to the between-search errors we found that patients with damage to the right hemisphere, but not those with lesions in the left hemisphere, were impaired in comparison to the controls. This lateralization effect supports previous findings of right hemisphere-specialisation for spatial aspects of working memory (Feigenbaum et al., 1996, Miotto et al., 1996; Nelson et al., 2000). Moreover, as expected, overall performance deteriorates with increasing set size. This deterioration, however, was stronger in the case of right-hemisphere lesions than of left hemisphere lesions. Furthermore, it was found that patients with damage specifically to the right dorsolateral prefrontal cortex, the right posterior parietal cortex, or the left or right hippocampal formations made more between-search errors than control participants. Moreover, a significant correlation of the between-search errors with lesion size in both the right dorsolateral prefrontal cortex and the right posterior parietal cortex was found, but not with lesion size in the left dorsolateral prefrontal cortex or the hippocampal formation. This can be explained by the fact that the hippocampal formation is less crucial for spatial working memory than the right posterior parietal cortex and the right dorsolateral prefrontal cortex. It should, however, be noted that although several patients had a lesion in the right posterior parietal cortex, only one patient had a larger lesion and this patient's lesion extended to the dorsolateral prefrontal cortex.

When interpreting these results it is important to consider that in order to avoid between-search errors, spatial information has to be kept in memory over a longer time period (possibly reflecting transfer into long-term memory), whereas the Corsi Block-Tapping Task requires spatial information to be kept in memory over a short time period. Interestingly, this would suggest that the dorsolateral prefrontal cortex and the posterior parietal cortex are essential for keeping spatial information in memory over a short time period, whereas the hippocampal formation is involved in the transfer from working memory into long-term memory. However, the current study cannot exclude the possibility that the hippocampal formation is also involved in the reverse process, i.e. transferring spatial information from long-term memory into working memory, in order to use this information during a search. The current results are in line with observations from neuroimaging and animal studies suggesting that brain areas that are active in spatial working memory; including the dorsolateral prefrontal cortex, posterior parietal cortex and hippocampal formation, serve different roles (Constantinidis, &

Wang, 2004; Friedman, & Goldman-Rakic, 1994; Glabus et al., 2003; Inoue, Mikami, Ando, & Hideo, 2004).

Finally, an index was calculated assessing the use of an efficient strategy to remember the target locations and the previously opened empty boxes. Using a strategy could therefore help to overcome memory problems, and thus would be especially important with larger set sizes. No difference in the use of a strategy was found between the entire patient group and the control participants. However, the strategy-index may not be a very sensitive measure, since a correlation between the strategy index and the within- and between-search errors was only found when both the patients and controls were taken together.

The Corsi Block-Tapping Task revealed no lateralization effects, whereas impairments were found when specific brain areas were studied. This underlines the disadvantage of studying heterogenic groups of patients. By defining the exact locations of the lesions of our patients, we were able to study the effect of damage to specific areas in the brain on spatial working memory. Moreover, defining the sizes of the lesions in specific areas of the brain enabled us to calculate correlations between the extent of damage and performance on the working memory tasks. This is an even more accurate measure, since impairments are expected to be larger when more tissue is damaged. A possible limitation of the current study, however, is that MRI and CT scans were not made at the moment of testing. Therefore, the size of the lesions may have changed in the period between making the scan and testing the patient or new lesions could have developed. Further research should also focus on testing more patients, particularly with damage to the posterior parietal cortex, to define more specifically this brain areas' role in spatial working memory.

In conclusion, the current study demonstrated that in particular the right dorsolateral prefrontal cortex and to a lesser extent the right posterior parietal cortex, are involved in keeping spatial information in memory over a short time period, as was assessed with the Corsi Block-Tapping task and the within-search errors. Moreover, both right and left hippocampal formation seem to have a fundamental role in maintaining spatial information in working memory over an extended time period, as was assessed with the between-search errors. The role of the left posterior parietal and left dorsolateral prefrontal cortex in spatial working memory seems to be limited.

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## Chapter 5

# Neuroanatomical correlates of route learning in stroke patients

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**Abstract**

Route learning is a complex cognitive function involving different types of information, such as knowledge about landmarks and direction information. This variety of processes suggest that multiple neural mechanisms are involved, e.g. the hippocampal system, the posterior parietal and temporal cortical areas. Although patient studies and imaging studies have given important insights in the exact neural circuitry underlying route learning, many controversies remain. Therefore, the current study set out to further examine the neuroanatomical correlates of route learning in a sample of 31 stroke patients with unilateral lesions, tested with a series of different route learning tasks, including landmark recognition, landmark ordering, route reversal and map drawing. For all patients the exact location of their lesion was determined using CT or MRI scans. Based on existing literature a number of relevant brain areas were demarcated, after which the extent of damage to these areas was determined for each patient separately. Performance on the landmark recognition task was impaired by damage to the right hippocampal formation, whereas a weak correlation was found between damage to the dorsolateral prefrontal cortex and processing the order of the landmarks. Memory for allocentric spatial information was impaired by damage to the right hippocampal formation, dorsolateral prefrontal cortex and the right posterior parietal cortex, as was assessed with the route-retracing task and the right temporal lobe, as was assessed with the route-retracing and map-drawing task.

## Introduction

Successful navigation involves remembering the spatial layout of an environment and using this information in order to find one's way around. Brain damage can seriously affect people's ability to find their way in the environment, as was shown by several case studies that report impaired route learning in patients suffering from topographical disorientation (Bottoni, Cappa, Geminiani, & Sterzi, 1990; Suzuki, Yamadori, Hayakawa & Fujii, 1998). Topographical disorientation is generally divided into two main syndromes, i.e. landmark amnesia (the inability to remember specific landmarks) and topographical amnesia (the failure to create a spatial map of an environment). Bottini et al. (1990) describe a patient with a glioma of the splenium of corpus callosum, who was unable to recognize or recall previously known itineraries and to learn new ones (i.e. topographical amnesia). However, this patient was still able to recognize visual information that is essential for topographical orientation, such as landmarks and scenes. Suzuki et al. (1998) report a patient with similar symptoms following haemorrhage in the right medial parietal lobe, who was unable to navigate through the world, whereas she was still able to recognize familiar landscapes or buildings. Moreover, this patient was able to draw a map of the environment. In contrast, a patient with landmark amnesia after a stroke in the right medial occipito-temporal region was unable to recognize and learn scenes lacking salient landmarks, although he was able to read and draw maps, describe familiar routes and provide correct directions (Mendez & Cherrier, 2003).

The double dissociation that is shown by these case reports underlines the notion that route learning is not a unitary process, but involves different cognitive processes that can be selectively impaired due to brain damage. A distinction can be made between different types of information that are involved in route learning, for example metric (i.e. information about exact distances), landmark (i.e. visual information that characterizes a certain point along the route), sensorimotor and direction information. This notion obviously raises the question whether specific neural correlates of these different processes can be distinguished. The existing literature suggests that especially the hippocampal formations as part of the medial temporal lobes, the parietal and temporal cortex and the caudate nucleus are important (Barrash, Damasio, Adolphs & Tranel, 2000; Maguire, Burgess, Donnett, Frackowiak, Frith & O'Keefe, 1998; Worlsey, Recce, Spiers, Marley, Polkey & Morris, 2001; Spiers, Burgess, Maguire, Baxendale, Hartley, Thompson & O'Keefe, 2001).

The importance of the temporal lobes, including the hippocampus was shown by Maguire who examined patients with damage to either the left or right temporal

lobes after viewing a videotaped route. Both patients with right and left hemisphere lesions were impaired on topographical orientation tasks, including landmark recognition, tasks entailing route knowledge and drawing a sketch map. Patients with lesions in the right hemisphere were also impaired on making proximity judgments, whereas the patients with lesions in the left hemisphere were unimpaired. Similarly, Spiers et al. (2001) found that patients who underwent a right temporal lobectomy performed worse than healthy controls when asked to navigate or recognize scenes from a virtual town and draw a map of this town. In contrast, patients with a left sided temporal lobectomy were only impaired when asked to draw a map of the virtual town, although to a smaller extent than the right temporal lobe group. Path integration, the process required for wayfinding that infers position information from information about distance and travelled direction derived from self-motion cues, is also seriously affected by damage to the right temporal lobe (Worsley et al., 2001). A neuroimaging study using positron emission tomography (PET) showed that navigating in both direct and detour way activates the right hippocampus in particular (Maguire et al., 1998). This study suggests that this structure is particularly important for route learning, since it provides an allocentric (viewer-independent) representation of space. This is in line with the theory of O'Keefe and Nadel (1978) who proposed that the hippocampus is particularly responsible for processing allocentric spatial information.

Although many studies have found the medial temporal lobes (specifically the hippocampus) to be involved in route learning (e.g. Kessels, De Haan, Kappelle & Postma 2001), other areas of the brain seem to be important as well. In a study of Aguirre and D'Esposito (1997), in which functional Magnetic Resonance Imaging (fMRI) was used, participants learned a route in a virtual "town" after which they were asked to make judgments regarding the appearance and position of familiar locations. A functional dissociation was then found between processing landmark (appearance of locations) and survey information (position of locations). Landmark information seemed to be processed by the lingual and fusiform gyri in the occipital cortex, whereas position information was processed by posterior parietal (and premotor) areas. Moreover, in a large patient study, Barrash et al. (2000) showed that bilateral damage to the medial occipital cortices and damage to the right inferior temporal region resulted in impaired navigation behavior. They suggested that these areas play an important role in the ability to quickly process and learn topographical scenes. These findings are in concordance with the distinction that is made by Ungerleider and Mishkin (1982) between the ventral ("what") and dorsal ("where" and "how") processing routes. According to this model, the ventral visual processing stream is important for processing object information and complex

visual arrays, whereas the dorsal processing stream is responsible for processing spatial information. Later, however, Milner and Goodale (1995) suggested that both ventral and dorsal pathways process object and spatial information. The ventral system would encode spatial information from an allocentric (viewer-independent) perspective, whereas the dorsal pathway would do so from an egocentric (viewpoint-dependent) perspective.

Finally, the caudate nucleus might play a role in route learning as well. Iaria Petrides, Dagher, Pike and Bohbot (2003) suggested that two different strategies could be used to find your way in a computer-generated virtual environment, i.e. a nonspatial and a spatial strategy. A nonspatial strategy would include counting the arms of a radial maze, whereas a spatial strategy relies on remembering the relationship between landmarks in the environment. By using fMRI it was shown that the hippocampus is specifically involved in spatial strategies during navigation, whereas the caudate nucleus is predominantly involved in nonspatial strategies (Bohbot, Iaria & Petrides, 2004).

Although the foregoing patient reports and neuroimaging studies have provided important insights into the neural circuitry underlying spatial memory, thus far most studies have investigated either one specific patient group (e.g. patients with damage to the temporal lobes) or applied a single route-learning task (e.g. a navigation task). Additional knowledge can be obtained by systematically comparing all relevant task dimensions together across multiple patient groups. Hence, the goal of the present study was to examine a series of sensitive spatial memory tasks, including a landmark recognition task, placing landmarks in the correct temporal order, drawing a map of the route and retracing the route (Van Asselen, Fritschy & Postma, in press), in stroke patients with predominantly unilateral lesions and to relate the performance to the lesion locations. First, performance of the patients was compared to a group of control participants to examine possible lateralization effects. Based on the previously discussed literature a number of relevant brain areas were demarcated, including the temporal cortex, hippocampal system and the caudate nucleus. For all patients the extent of damage to these regions was determined, which was then used to study the relation between these regions and performance on the spatial tasks.

We hypothesized that lesions in the temporal cortex and/or the hippocampal formation may disrupt landmark recognition, in particular in the right hemisphere. Performance on the landmark ordering task could be affected by damage to the dorsolateral prefrontal cortex (Konishi, Uchida, Okuaki, Machida, Shirouzu & Miyashita, 2002) and/or the caudate nucleus. Moreover, damage to the temporal cortex and/or the hippocampal system, in particular in the right hemisphere, may

impair performance on the map drawing task and the route retracing task, considering that these areas are important for processing allocentric information in memory. Since retracing the route might require working memory in order to manipulate information that was previously seen from a different perspective, damage to the (right) dorsolateral prefrontal cortex might result in impaired route retracing as well.

## Methods

### *Participants*

Thirty-one patients with a stroke that occurred between 1999 and 2003 who had been treated in the University Medical Center Utrecht (UMCU) were included. The group consisted of 17 patients with a lesion in the left hemisphere, 13 patients with a lesion in the right hemisphere and one patient with a large lesion in the right hemisphere and a small lesion in the left hemisphere. The patients participated in a larger study that was aimed at investigating the effect of focal brain damage on different aspects of spatial memory and perception. Patients were between 21 and 75 years of age, did not suffer from other neurological or psychiatric diseases, were examined at least six months after the stroke and were mobile at the time of testing. The study was approved by the medical ethics committee of the UMCU and written informed consents were obtained according to the declaration of Helsinki. Moreover, the study included 36 age- and education matched, healthy control participants who were recruited through an advertisement in the local newspaper and were paid for their participation. Characteristics of the patients and comparison group are shown in Table 5.1. Handedness was assessed with a Dutch version of the Annett Handedness Inventory (Briggs & Nebbs, 1975). Education level was measured using seven categories (1 being the lowest and 7 the highest) (Hochstenbach, Den Otter & Mulder, 2003). No differences were found between the three groups for education level [ $F(2, 63) = 2.0$ ], age [ $F(2, 64) = 0.0$ ], or gender distribution [ $\chi^2(2) = 4.7$ ].

Standard neuropsychological tests were used to assess overall intelligence and memory performance. Verbal intelligence was assessed with the Dutch version of the National Adult Reading Task (Schmand, Bakker, Saan & Louman, 1991); non-verbal intelligence with the 12-item short form of the Raven Advanced Progressive Matrices (Raven, Raven & Court, 1993). Verbal memory was assessed with Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964; Taylor, 1959). The Letter Number Sequencing task (WAIS-III) was used as an index of

verbal working memory (Wechsler, 1987). No differences were found on any of the standard neuropsychological tests between the patients and controls, except on immediate reproduction of the RAVLT [ $F(2, 58) < 7.1, p < 0.01$ ]. Patients with a lesion in the right or left hemisphere performed worse than the control participants [ $t(48) = 3.2, p < 0.01, t(48) = 2.8, p < 0.01$ , respectively]; no difference was found between performance of the patients with damage to the left or right hemisphere [ $t(24) = 0.2$ ].

Table 5.1: Characteristics and neuropsychological test results of the patients with a lesion in the right (RH) or left hemisphere (LH) and control participants (SE).

	RH n=14	LH n=17	Controls n=36
Age (yrs.)	57.8 (3.1)	57.8 (2.8)	56.9 (1.8)
Education level (1-7)	4.7 (0.4)	5.3 (0.3)	5.4 (0.2)
Annett Handedness Inventory (-24/ 24)	15.2 (4.2)	17.8 (2.9)	15.4 (2.2)
Sex (m:f)	12:2	11:5	20:16
NLV-IQ	105.7 (2.9)	105.6 (3.5)	107.2 (4.7)
RAVLT: immediate recall	36.5 (2.8)*	37.5 (3.1)*	47.6 (1.7)
RAVLT: delayed recall	8.5 (1.1)	7.8 (1.5)	9.7 (0.6)
Raven APM (short form)	7.0 (0.9)	8.0 (0.7)	12.0 (2.8)
Letter Number Sequencing task	9.5 (0.8)	8.5 (0.7)	9.9 (0.3)
Corsi Block-Tapping Task	45.9 (4.6)	43.6 (3.5)	42.6 (2.5)

\* = significant difference with the controls ( $p < 0.05$ )

*Note.* NLV = Dutch version of the National Adult Reading Task, RAVLT = Rey Auditory Verbal Learning Test, Raven APM = Raven Advanced Progressive Matrices.

#### *Materials and Procedure*

#### *Materials and Procedure*

An individual appointment was made with each participant to meet at the entrance of one of the buildings of the University of Utrecht, where the experiment took place. After informing the participant about what he or she was expected to do, the participant was taken to the beginning of the route. The participant was then told that he or she was going to walk a route, and the instruction was given in such a way to make sure that the participant should remember the route as accurately as possible. Conversation during walking was limited to responding briefly but politely to any questions that were asked or comments that were made by the participants. To secure that the walking speed was approximately equal for all participants the same experimenter examined all participants, explicitly focusing on keeping a

standard walking gait. When the participant arrived in the examination room, the subject was first engaged in another task during about 30 minutes. Subsequently, all participants performed four tasks that tested specific aspects of their route knowledge:

1. Landmark-recognition test: 20 pictures were presented on a computer screen, all of them including a landmark that characterizes either a path (e.g. pictures on the wall) or a decision point (e.g. computers at a corner). Ten pictures were taken from landmarks along the route (targets) and ten pictures of landmarks in another university building (distracters). The E-prime computer program was used to present the pictures of the landmarks on a computer screen. Participants were asked to indicate whether the landmarks on the pictures were along the route or not. The total number of correctly identified target landmarks and distracter landmarks were defined.
2. Landmark-ordering test: participants were given seven printed pictures of landmarks that were present along the route, which had to be placed in the correct temporal order. The total score on this task was defined by giving two points for a picture on its correct location, one for a picture in a position adjacent to its correct position and zero points for all others (maximum 14 points).
3. Route-reversal test: the participants had to navigate the route from the end to the beginning. The experimenter walked a few steps behind and corrected them when they made a wrong turn. The total score was defined by counting the total number of correct decisions at the sixteen decision points.
4. Map-drawing test: participants were given a map of the floor of the building where they had walked the route (see Figure 5.1). The experimenter indicated the starting point of the route on the map, after which participants were instructed to draw the route they had walked before. For this task a complex scoring method was used. One point was given for each correct decision point that was included and another one when the right direction was chosen at a decision point. Moreover, one point was deducted for each passed decision point that was not along the route. The maximum score on this task was 30.

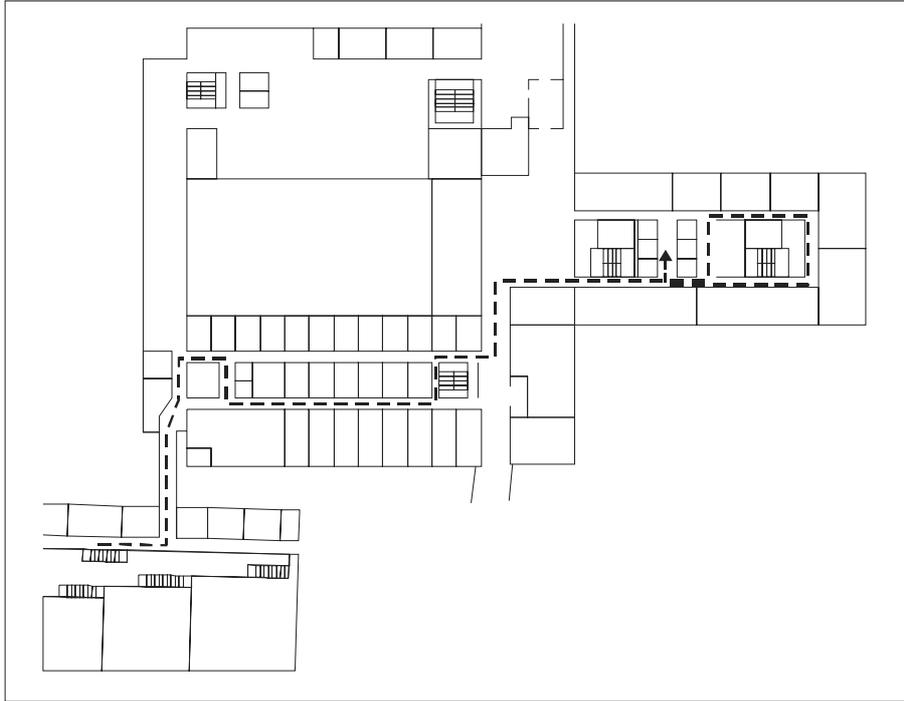


Figure 5.1: A map of the first floor of the university building showing the route that was walked during the learning phase.

#### *Lesion location*

CT- or T1-weighted MR images were available for 26 patients (12 patients with a lesion in the right hemisphere, 13 patients with a lesion in the left hemisphere and one patient with a lesion in both hemispheres). For five patients no digital scans were available, which excluded them from further lesion analyses. In order to define the locations of the lesions, an experienced neurologist who was unaware of the clinical status of the patients, manually delineated for all patients the regions of interest (ROI) covering the lesion in all slices, using the MRIcro software (<http://www.psychology.nottingham.ac.uk/staff/cr1/micro.html>). ROIs were saved as image volumes containing 1 for voxels inside the lesion area and 0 for voxels outside the lesion area. CT images were skull-stripped by only including voxels with a CT-intensity value between 0 and 100. All images were then normalized to standard brain coordinates (MNI) according to the method described by Brett et al. (2001) using the software package Statistical Parametric Mapping (SPM2) (<http://www.fil.ion.ucl.ac.uk/spm/software/spm2/>). CT- or T1-weighted MRI-scans were normalized to a T1-weighted template, using cost

function masking with smoothed masks (FWHM = 8 mm) based on the ROI (see Figure 4.2). By doing so, voxels in the lesioned tissue do not contribute to the calculation of the spatial transformation from the patients brain to MNI (standard brain) coordinates, which results in a standardized map of the pathological brain images (Brett, Leff, Rorden & Ashburner, 2001). Finally, the ROI images and CT/MRI scans were resliced with a  $1 \times 1 \times 1 \text{mm}^3$  voxel size. The lesion size of each patient was calculated as defined by the number of voxels that were above threshold (threshold = 0.5), since due to interpolation artefacts at the reslicing stage voxels in the normalized images could have values between 0 and 1. Importantly, no difference was found between the lesion sizes of the group of patients with a lesion in the right hemisphere and those with a lesion in the left hemisphere [ $t(24) = 1.3$ ]. Normalized brain scans including the lesions are shown in Figure 4.3 for each patient separately.

Volumes of interest (dorsolateral prefrontal cortex, posterior parietal cortex and hippocampal formation) were used that were established by probability density estimates of locations from the BrainMap database (Nielsen & Hansen, 2002). For each patient it was determined whether the lesion included one or more of these areas and subsequently the size of the lesion in the target area was calculated as defined by the number of voxels of the lesion that were above threshold and located within the target region divided by the total number of voxels in the target region (lesion overlap ratio).

### *Analyses*

Three different analyses were used to analyse the data. First, to examine overall lateralization effects of the different aspects of route learning, performance of patients with a lesion in the left or right hemisphere was compared with performance of the control patients for each task separately by means of an ANOVA ('overall group analyses'). All 31 patients were included in this analysis.

Second, to study the effect of damage to specific areas within a hemisphere on the different dependent variables ANOVA was performed for each task with three groups: 1) patients with damage to the target region in the right hemisphere; 2) patients with damage to the same target region in the left hemisphere; 3) control participants ('specific group effects'). These analyses included the 26 patients of whom a digital scan was available.

Third, the influence of the extent of damage on the different spatial memory tasks was studied by means of one-tailed Pearson correlation between the lesion overlap ratio with a target area and performance on the dependent variables

(‘correlations’). No correlations were calculated between the lesion overlap ratio with the left posterior parietal cortex and performance on the spatial working memory tasks, since there was only one patient with a lesion that included this area.

## Results

### *Landmark recognition task*

a) Overall hemispheric differences:

ANOVA showed no difference in performance between patients with a lesion in the right hemisphere, patients with a lesion in the left hemisphere and controls [ $F(2, 64) = 1.1$ ].

b) Analyses of specific brain areas:

No difference in performance was found on the landmark recognition task between patients with a lesion in the right temporal cortex, patients with a lesion in the left temporal cortex, and control participants [ $F(2, 50) = 2.3$ ]. Moreover, no difference in performance was found between the patients with damage of the right hippocampal formation, the left hippocampal formation and the healthy control subjects [ $F(2, 49) = 1.4$ ].

c) Correlations:

A significant correlation was found between performance on the landmark-recognition task and the lesion overlap ratio with the right hippocampal formation [ $r = -0.37, p < 0.05$ ], but not with the left hippocampal formation, nor with the right or left temporal cortex. A more detailed look at the data shows that the six patients with minor damage of the right hippocampal formation were not impaired, whereas the four patients with more extensive damage to this area (Figure 4.3; 5 + 6 + 11 + 18) were clearly impaired. Since the patients with minor damage were included in the patient group with damage to the right hippocampal area, no difference was found when the groups were compared, although the correlation revealed that patients perform worse with more extensive damage to the right hippocampal formation.

### *Landmark-ordering task*

a) Overall hemispheric differences:

No difference was found between patients with a lesion in the right hemisphere, the left hemisphere and controls [ $F(2, 64) = 0.4$ ].

## b) Analyses of specific brain areas:

ANOVA revealed no difference between patients with a lesion in the right caudate nucleus, patients with a lesion in the left caudate nucleus, and control participants [ $F(2,47) = 0.1$ ]. Moreover, no difference was found between patients with a lesion in the right dorsolateral prefrontal cortex, patients with a lesion in the left dorsolateral prefrontal cortex, and control participants [ $F(2,45) = 0.1$ ].

## c) Correlations:

No positive correlations were found between performance on the landmark-ordering task and the lesion overlap ratio with the caudate nucleus or the dorsolateral prefrontal cortex when the right and left hemisphere patients were tested separately. However, when patients with damage to the left and right dorsolateral prefrontal cortex were taken together, a correlation between the extent of damage to these areas and performance on the landmark ordering task ( $r = -0.34, r < 0.05$ ) was found.

*Route reversal task*

## a) Overall hemispheric differences:

A significant difference was found between patients with a lesion in the right hemisphere, patients with a lesion in the left hemisphere and control participants [ $F(2, 64) = 5.6, p < 0.01$ ]. Contrast analysis showed a significant difference between patients with a lesion in the right hemisphere and control participants ( $p \leq 0.001$ ), whereas no difference was found between patients with a lesion in the left hemisphere and control participants.

## b) Analyses of specific brain areas:

A significant difference was found between patients with a lesion in the right temporal cortex, patients with a lesion in the left temporal cortex and control participants [ $F(2, 50) = 5.6, p < 0.01$ ]. Contrast analysis revealed that patients with a lesion in the right temporal cortex performed worse than control participants ( $p \leq 0.01$ ). No difference was found between patients with a lesion in the left temporal cortex and the control participants. A group effect was also found for damage to the hippocampal formation [ $F(2, 48) = 4.6, p < 0.05$ ]. Contrast analysis showed that patients with a lesion including the right hippocampal formation ( $p \leq 0.05$ ) performed worse than control participants. No difference was found between patients with a lesion in the left hippocampal formation and controls. Moreover, a group effect was found between the patients with a lesion in the right dorsolateral

prefrontal cortex, the left dorsolateral prefrontal cortex and the controls [ $F(2,45) = 3.5, p < 0.05$ ]. Contrast analysis indicated that patients with a lesion in the right dorsolateral prefrontal cortex ( $p < 0.05$ ) performed worse than control participants ( $p < 0.01$ ). No difference was found between the patients with damage to the left dorsolateral prefrontal cortex and the control participants. Finally, a significant effect was found for the posterior parietal cortex [ $F(2, 39) = 6.9, p < 0.05$ ]. Contrast analyses indicated that the patients with a lesion in the right or left posterior parietal cortex performed worse than the controls ( $p < 0.05$ ). Importantly, however, there was only one patient with a lesion in the left posterior parietal cortex, and this patient also had a large lesion in the right hemisphere.

c) Correlations:

A significant correlation was found between the performance on the route reversal task and the lesion overlap ratio with both the right temporal cortex [ $r = -0.34, p < 0.05$ ] and the right hippocampal formation [ $r = -0.42, p < 0.05$ ], but not with the left hippocampal formation, the right posterior parietal cortex, the left temporal cortex or the dorsolateral prefrontal cortex.

*Map-drawing task*

a) Overall hemispheric differences:

No difference in performance was found between patients with a lesion in the right hemisphere, the left hemisphere and control participants [ $F(2, 63) = 1.1$ ].

b) Analyses of specific brain areas:

No group effects were found for damage to either the left or right temporal cortex [ $F(2,49) = 0.7$ ] or the left or right hippocampal formation [ $F(2,48) = 0.0$ ].

c) Correlations:

A significant correlation was found between performance on the map-drawing task and the extent of damage to the right temporal cortex [ $r = -0.42, p < 0.05$ ], but not with the size of the lesion in the left temporal cortex or the hippocampal formation.

Table 5.2: Mean scores (SE) on the four navigation tasks of patients with a lesion in the target area of the right (RH) or of the left hemisphere (LH). Mean scores are only reported when they were used in the analyses.

		Landmark Recognition task	Landmark- ordering task	Route- retracing task	Map- drawing task
HF	RH (n= 10)	13.5 (0.8)	--	10.4 (0.6)	11.8 (2.1)
	LH (n= 6)	12.8 (0.6)	--	10.5 (0.7)	12.2 (1.7)
TC	RH (n= 9)	13.0 (0.7)	4.7 (0.7)	9.9 (0.5)	9.7 (1.3)
	LH (n= 8)	13.0 (0.5)	4.6 (0.8)	11.1 (0.7)	11.9 (1.3)
DLPFC	RH (n= 6)	--	5.2 (0.9)	10.2 (0.7)	--
	LH (n= 6)	--	4.7 (0.9)	12.7 (0.8)	--
PPC	RH (n= 5)	--	--	9.8 (0.6)	--
NC	RH (n= 7)	--	4.4 (0.9)	--	--
	LH (n= 7)	--	4.4 (0.8)	--	--
Controls =36		14.1 (0.3)	4.8 (0.4)	12.2 (0.3)	12.3 (1.2)

*Note.* HF = *hippocampal formation*, TC = *temporal cortex*, DLPFC = *dorsolateral prefrontal cortex*, PPC = *posterior parietal cortex*, CN = *Caudate nucleus*.

## Discussion

The current study set out to investigate multiple aspects of route learning in patients with focal damage in different areas of the brain. Stroke patients with cortical and subcortical lesions were examined using different route learning tasks, including a landmark recognition task, a landmark ordering task, a route retracing task and a map drawing task. With respect to the landmark recognition task, no differences were found between patients with a lesion in the right hemisphere, patients with a lesion in the left hemisphere and control participants. However, when the effect of lesions in specific brain areas was studied, we found that patients with damage to the right hippocampal formation performed worse than healthy control participants, whereas patients with damage to the left hippocampal formation and the temporal cortex were unimpaired. These results confirm previous findings of Spiers et al. (2001) who showed that patients with a lesion in the right medial temporal lobe were impaired on a landmark recognition task. In accordance with this observation, it was suggested that the temporal cortex (excluding the hippocampal formation) was important in landmark recognition,

considering its role in processing object information (Ungerleider & Mishkin, 1982). However, in our study damage to either the left or the right temporal cortex did not result in impaired landmark recognition. Importantly, Janzen and Turenhout (2004) recently found that processing navigationally relevant decision points or landmarks activates the parahippocampal gyrus in particular, which is closely connected to the hippocampus, when contrasted with non-decision point objects. Thus, objects or scenes that are relevant for route learning seem to be processed by the right hippocampal formation or parahippocampal gyrus, whereas other types of object information might depend on the temporal cortical areas.

The landmark ordering task required participants to remember the order of the landmarks from the beginning to the end of the route, which is considered to be the minimal information that is required to find your way (Siegen & White, 1975). The current study revealed no differences in performance between patients with a lesion in the right hemisphere, patients with a lesion in the left hemisphere or control participants. An fMRI study in which participants were required to navigate through a computer-generated virtual maze showed that using a nonspatial strategy was associated with activation of the caudate nucleus, whereas using a spatial strategy was associated with activation of the hippocampus (Iaria et al., 2003; Bohbot et al., 2004). We have speculated that temporal ordering might be a part of this nonspatial navigation strategy and thus, would engage the caudate nucleus. However, although 14 of the 26 patients had a lesion affecting either the left or the right caudate nucleus, patients with caudate lesions were not impaired on the landmark-ordering task in the present study. Possibly, using a task that depends more on a nonspatial strategy, such as remembering the turns (right/left) would reveal the involvement of the caudate nucleus. Alternatively, recent findings in patients with caudate dysfunction following Huntington's disease have suggested that other brain areas, such as the hippocampus, might compensate defective route recognition in case of caudate dysfunction, resulting in normal performance (Voermans et al. 2004). Finally, the present results indicate that the dorsolateral prefrontal cortex is involved in processing the order of the landmarks, although the effects were very small. These findings are in line with the idea that the prefrontal cortex is involved in encoding temporal information (Konishi et al., 2002; Wolbers, Weiller & Buchel, 2004).

The current study also examined the distinction between egocentric and allocentric route representations. The route reversal task required participants to retrace the route from the end to the beginning. Whereas egocentric knowledge of a route, i.e. remembering when to make a left/right turn or recognizing landmarks, might suffice when retracing a route in the direction it was originally learned,

allocentric knowledge is required when the route is walked from a different perspective. As was expected, patients with a lesion in the right hemisphere performed worse on the route-reversal task than control participants or patients with a lesion in the left hemisphere. More specifically, patients with damage to the right hippocampal formation, the right temporal cortex, the right posterior parietal cortex and the right dorsolateral prefrontal cortex performed worse than the control group. No difference was found between the control participants and patients with a lesion in the left hemisphere. These findings are in line with previous studies suggesting the involvement of the right hippocampus in navigating a familiar complex virtual reality town (Maguire et al., 1996), as well as the importance of the posterior parietal cortex in navigation (Suzuki et al., 1998) and remembering positional information (Aguirre & D'Esposito, 1997). Further support was found for the theory of Milner and Goodale (1995), suggesting that the ventral pathway (including the temporal cortex) is particularly involved in processing allocentric spatial information. Importantly, damage to the right dorsolateral prefrontal cortex also was found to impair performance on the route-retracing task. The right dorsolateral prefrontal cortex is thought to be particularly important for spatial working memory (Nelson, Monk, Lin, Carver, Thomas & Truwit, 2000; Smith & Jonides, 1997). Arguably, spatial working memory might be an important process for navigation as well, since spatial information has to be manipulated and held active when walking.

Finally, although no overall lateralisation effects were found for the map-drawing task, patients with damage to the right temporal cortex were impaired on this task requiring allocentric knowledge of the route. In contrast, patients with damage to the left temporal cortex or the hippocampal formation were unimpaired. Previously, map drawing has been studied by investigating patients after hippocampectomy. Spiers et al. (2001) found right hippocampectomy patients to be impaired especially when asked to draw a map of a route. Since hippocampectomy usually involves partial removal of other structures than the hippocampus itself, such as the parahippocampal gyrus and the amygdala, the exact areas that are critical for map drawing remained unclear. The current study enables us to make a distinction between the temporal cortex and the hippocampal system, which showed that it is the temporal cortex in particular that is involved in creating an allocentric representation of a route. Spiers et al. (2001) also showed that patients with damage to the left medial temporal lobe were impaired on a map drawing task, although to a smaller extent. It was suggested that the left hemisphere deficit might be due to involvement of verbal processes. That is, a task was used in which pictures of common objects had to be placed on the correct position within a grid

on a computer screen. Possibly, using objects that can be remembered by means of a verbal strategy might have resulted in patients with lesions in the left hemisphere to be impaired as well. The current study, however, used a map of the floor in which participants had to draw the route, thus not requiring any verbal information processing. The purely spatial nature of the current task hence only tapped on right-hemisphere areas.

Interestingly, overall lateralization effects were only found for one task (i.e. the route-retracing task), whereas for the other tasks deficits were revealed only when specific brain areas were studied. This lack of overall lateralization effects is most likely due to the heterogeneity of the patient group that was tested, and underlines the importance of developing methods that make it possible to study the relation between damage to specific neural structures and cognitive tasks. By defining the sizes of the lesions in specific areas of the brain using image volumes that were converted to a standard neurological space (MNI), we were able to compare performance of patients with lesions in different brain areas and to calculate correlations between the extent of damage and performance on the memory tasks. Studying correlations might even be more insightful than studying differences in performance between patient groups, since impairments are expected to be larger when more tissue is damaged. It should be mentioned, however, that in order to reveal weak correlations (e.g. the relation between damage to the dorsolateral prefrontal cortex and performance on the landmark ordering task) larger sample sizes including more patients with prefrontal lesions and left posterior parietal lesions are required. Another shortcoming of the correlation analysis was the difference in the timing of the brain scans with respect to the timing of the psychological examinations. Since the size of a lesion may change in the time period between scanning and testing a patient, future research should aim at scanning a patient at the moment of testing (Van Asselen, Kessels, Neggers, Kappelle, Frijns, & Postma, in revision).

In conclusion, route learning is not a unitary cognitive function, but clearly involves a variety of processes, which rely on distinct brain areas. The right hippocampal formation is important for the basic aspects of route learning, such as processing landmark information, but also for processing allocentric spatial information. In addition to the hippocampal formation, the right temporal and the posterior parietal cortex seem to be involved in allocentric spatial memory as well, as measured with a map-drawing and route retracing task respectively. Interestingly, dorsolateral prefrontal cortical areas are important for route learning as well, especially in the encoding of the order of landmarks. Moreover, spatial working memory seems to be an important process when navigating through space, since

patients with damage to the dorsolateral prefrontal cortex were impaired on retracing a route, but not on any of the other route-learning tasks. As such, our findings provide more insight in the neural substrates of the multifaceted tasks of finding one's way in the world.

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**AUTOMATICITY OF SPATIAL  
MEMORY**



## Chapter 6

# The influence of intentional and incidental learning on acquiring spatial knowledge during navigation

Van Asselen, M., Fritschy, E. & Postma, A. (in press). *Psychological Research*.

**Abstract**

In order to study the influence of intentional and incidental learning conditions on route learning, young adults walked a route through a university building. Half of the participants focused their attention on the route (intentional learning condition), while the other half did not (incidental learning condition). Five tests of spatial knowledge were employed: a route-length-estimation, landmark recognition, landmark ordering, map drawing and navigation task. The intentional group performed better than the incidental group on the map-drawing and navigation task. No difference between the intentional and incidental group was found on the landmark-recognition and landmark-ordering task. Moreover, the intentional group overestimated the walking distance, while the incidental group underestimated it. These results suggest that route knowledge (landmark recognition and landmark ordering) requires less effortful processing than survey knowledge (developing a map-like representation and actual navigation).

## Introduction

An important aspect of our daily life is to navigate from one place to the other. During navigation we can use different types of spatial information to find our way, such as landmarks that characterize relevant locations along the route (e.g. billboard, tree, painting), metric information (after 400 meters to the right) and sensorimotor information (kinesthetic and vestibular inputs). These different types of information can be used to create a cognitive spatial representation of this environment and keep it in memory.

Siegel and White (1975) proposed a sequential development of spatial representations including three 'stages', which are hierarchically ordered. First, landmark information is encoded, which is the minimal requirement for successful wayfinding. Second, route knowledge is processed, including the order of the landmarks from one place to another and direction information. Finally, survey knowledge is stored, including configural information. The three 'stages' of spatial representation acquisition were originally applied to describe the development of spatial representation acquisition in children. Very young children were assumed to be only able to recognize landmarks. With age they learn to encode route knowledge, and finally they become able to process survey knowledge.

More recently, however, it was shown that participants who learned a route from a map performed better on tasks measuring survey knowledge, while participants who learned by navigation performed better on route perspective tasks (Taylor, Naylor & Chechile, 1999). This suggests that two functionally distinct spatial representations can coexist in memory, i.e. a route representation and a survey representation. The route representation includes information about landmarks and scenes along the route, i.e. taken from a perspective within the route, while a survey representation includes information about the configural Euclidean layout of the route, i.e. taken from a perspective above the route (e.g. Berthoz, 1999; Noordzij & Postma, in press).

Since wayfinding is an essential part of our daily life and is frequently combined with other cognitive processes (e.g. driving, talking), it would be advantageous if some of the spatial information were processed automatically. Automatic processes can be established either through abundant practice, or they are essentially innate. The frequent use of navigation and the relevance of remembering the environment around us might have biased the human information processing system to encode at least some spatial information automatically. Therefore, it is clearly relevant to study whether and to what extent spatial knowledge of a route is acquired automatically.

In order to determine whether a process is automatic or effortful, Hasher and Zacks (1979) proposed a number of criteria that distinguish these processes. According to their theory automatic processes require limited mental effort to encode information, and they do not interfere with other cognitive processes. Thus, automatic processes would not be influenced by practice, concurrent processing demands, aging or intention to learn information. In contrast to automatic processes, effortful processes require considerable cognitive resources and therefore are affected by these variables. Most importantly, Hasher and Zacks (1979) further hypothesized that spatial memory works automatically.

Concerning the effect of the first criterion of Hasher and Zacks on route learning, it was found that practice improves acquisition of locational information during navigation, including direction and distance information (Lindberg and Gärling, 1983). This implies that effort is required to process route information. Similar results were obtained when the second criterion, the influence of concurrent processing demands, was tested. When performing a concurrent task while viewing sequentially presented color slides of a route, performance on a landmark recognition, distance estimation and map verification task deteriorated (Allen & Willenborg, 1998). Accordingly, Albert, Reinitz, Beusmans and Gopal (1999) studied the effect of a concurrent task on different aspects of route learning during simulated route navigation. They showed that participants performance deteriorated when trying to remember the sequence of landmarks and landmark–turn associations, binding landmarks and routes into a single context and acquiring survey knowledge when performing a concurrent task. However, some caution is necessary when interpreting these results, since encoding route information from slides might not be the same as navigating through the real physical world and thus could require more attentional processing. However, similar results were found when the influence of a concurrent task on acquisition of route knowledge was studied during actual locomotion. That is, performing a concurrent task affected estimates of spatial relations between reference points along the route negatively, suggesting that acquisition of information about directions and distances requires central information processing capacity (Lindberg & Gärling, 1981; 1982).

The effect of practice and concurrent task procedures on the different aspects of route learning suggests that effort is required to process both route and survey information. However, aging seems to have a more selective effect on route learning. Lipman (1991) showed that older adults were less likely than younger adults to remember landmarks in their sequential order or in an integrated fashion, while memory for landmarks was relatively unimpaired. Similarly, Wilkniss, Jones, Karol, Gold and Manning (1997) found that older adults perform as well as

younger adults on a task of landmark recognition, but are impaired on a landmark ordering and navigation task. Moreover, by comparing a large group of participants between 18 and 78 years of age, it was shown that performance declined with age when participants were asked to learn a complex real-life route (Barrash, 1994). Thus, the aging literature suggests that for landmark recognition automatic processes might suffice, while for other aspects of route learning effortful processes are required.

The last criterion, the influence of intention on route learning, has been studied through various methods. Anoshian and Seibert (1996) used the process dissociation task to study different processes within place recognition. In this task participants were shown a number of video frames from a route that they previously walked and frames that were changed through computer editing. By employing inclusion and exclusion conditions they were able to estimate the proportion of implicit and explicit retrieval. The results showed that place recognition can involve both implicit, unconscious retrieval as well as explicit, conscious retrieval. Magliano, Cohen, Allen and Rodrigue (1995) studied the mechanisms of acquiring spatial information by having subjects attend to different types of spatial information, i.e. remembering landmarks, routes or configurations, when viewing a series of slides depicting a walk through a small town. Landmark and route knowledge was not influenced by the instructions that were given. In contrast, tasks pending on configurational knowledge improved when participants were instructed to attend to this type of information. Thus, it was concluded that wayfinders are capable of learning a new environment according to a goal. However, the data also suggested that learning is constrained by stage-based processes such as proposed by Siegel and White (1975).

A particular important way to study the role of intention in acquisition of spatial information during navigation is to contrast incidental and intentional learning conditions. Incidental learning refers to a highly natural learning condition, encountered frequently in daily life. For example, when walking with someone who knows the way you might not try to learn the route yourself. Herman, Kolker and Shaw (1982) studied route learning in children by letting them learn the locations of buildings in a large model town under intentional or incidental learning conditions. They found no difference in performance between the two groups, but argued that this could be due to the complexity of the task.

In line with the foregoing, the goal of the present study was to determine more systematically the influence of intention to learn on acquisition of spatial information during navigation. Therefore, an intentional learning condition (automatic and effortful learning processes) and an incidental learning condition

(automatic learning processes) was used to study route knowledge, i.e. landmark recognition, placing landmarks in the correct temporal order, and survey knowledge, i.e. map drawing and route reversal. When effortful processes are required to encode information, performance would improve under intentional learning conditions. In contrast, if automatic processes would suffice, no difference between the two conditions would be found. Based on the existing literature, it was expected that landmark recognition and remembering the order of the landmarks would be processed automatically. However, some effort might be required to process survey knowledge, taken into account that these processes are affected by aging and intention to learn. Since, to our knowledge, distance estimation has not been studied under the current or similar circumstances, it remains unclear how this process will be influenced by intention to learn. However, metric information can be seen as a part of survey knowledge, and thus it might be expected that distance estimation will be more accurate when processed under intentional learning conditions.

## Methods

### *Participants*

Forty-five students from the University of Utrecht participated in this research. At the end of the experiment participants were asked to indicate whether they had been in the building before on a scale of 1 to 8 (1: never been in the building before, 2 – 5: been in other parts of the building, which were closer (2) or further (5) away from where the experiment took place, but not on the same floor; 6: less than five times on the floor where the experiment took place; 7: between five and ten times on the same floor; 8: more than 10 times on the same floor). Six participants who had been once or more times on the floor where the experiment took place (6-8 points) were excluded from further analyses. Of the remaining participants 20 were randomly assigned to the incidental condition (12 women, 8 men; mean age 21 years) and 19 to the intentional condition (12 women, 7 men; mean age 23 years). Thirty-four participants were right-handed, four left-handed and one was bimanual.

### *Procedure*

An individual appointment was made with the participants to meet in a room on the first floor of one of the buildings of the University of Utrecht, where the experiment took place. The experimenter waited in front of the room and gave

instructions when the participant arrived. Participants in the intentional group were told that the aim of the experiment was to study route-learning behavior. They were asked to pay attention to the route they were going to walk, since they would be tested on their knowledge of this route. Participants in the incidental group were told that a mistake had been made with the reservation of the test room. They would have to walk to another room, where the experiment would take place. Both groups then walked the same route to the test room. Since participants in the incidental group should not become aware of the real purpose of the study, the experimenter attempted to limit talking without the participants becoming suspicious. However, in both groups, conversation was limited to responding shortly but politely to any questions that were asked or comments that were made by the participants. To secure that the walking speed was the same for all participants the same experimenter tested all participants, and explicitly focused on keeping a standard walking gait. However, since we did not want to give any cue to the participants in the incidental condition about the true aim of the study, we chose not to measure time or walking speed. When participants arrived in the test room, they were engaged in a distraction task for about 20 minutes. This task involved an irrelevant memory task that was intended to avoid active rehearsal of the spatial information by participants in the intentional condition. Next, participants in the incidental group were informed about the true aim of the study. Subsequently, all participants performed five tasks that tested selective aspects of their spatial knowledge. After performing all tasks participants were asked whether they were familiar with the building. In addition, the participants in the incidental group were asked whether they had any idea of the true aim of the experiment when they were walking the route.

### *Tasks*

Five tasks were used in the current experiment:

1. Landmark recognition task: 22 pictures were presented on a computer screen, all of them including a landmark that characterizes either a path (e.g. pictures on the wall) or a decision point (e.g. computers at a corner). Twelve pictures were taken from landmarks along the route (targets) and ten pictures of landmarks in another university building (distractors). E-prime software was used to present the pictures of the landmarks on a computer screen. Participants were asked to indicate whether the landmarks on the pictures were along the route or not. Sensitivity was calculated from z-scores for the intentional and incidental condition separately, as described by MacMillan & Creelman (1991). Sensitivity is expressed in  $d'$  and indicates the number of correctly identified targets, corrected for false alarms.

Moreover, the response bias  $c$  was calculated, which indicates the tendency of participants to identifying a landmark as a target or distractor.

2. Landmark ordering task: participants were given seven printed pictures of landmarks that were taken along the route, which then had to be placed in its correct temporal position. The total score on this task was defined by giving two points for a picture on its correct location, one for a picture in a position adjacent to its correct position and zero points for all others (maximum 14 points).

3. Map drawing task: participants were given a map of the floor of the building where they had walked the route (Figure 5.1). They were asked whether they knew the point on the map where the route started and ended. If they didn't, the experimenter marked the start and/or endpoint, after which they were instructed to draw the route they had walked before. For this task a complex scoring method was used. One point was given for the correct identification of the beginning and one point for the end of the route. Then, one point was given for each correct decision point that was included and another one when the right direction was chosen at a decision point. Moreover, one point was subtracted for each passed decision point that was not along the route. The maximum score on this task was 32.

4. Route reversal task: the participants had to navigate the route from the end to the beginning. The experimenter walked a few steps behind and corrected them when they made a wrong turn. The total score was defined by counting the total number of correct decision at the sixteen decision points.

5. Route length estimation task: participants had to estimate the length of the route from beginning to end in meters. The length of the route was 222 m.

## Results

A GLM Multivariate analyses was used with a within-subject variable Task (landmark recognition sensitivity, landmark recognition response bias, landmark ordering, map drawing and route reversal task) and a between-subject variable Group (intentional and incidental condition). An overall effect for Group was found, indicating that the intentional group performed better than the incidental group [ $F(5, 33) = 2.55, p < 0.05, \eta^2 = 0.279$ ]. Between subject effects for the different tasks separately showed that the intentional group performed better than the incidental group on the map drawing task [ $F(1, 37) = 5.83, p < 0.05, \eta^2 = 0.136$ ] and the route-reversal task [ $F(1, 37) = 10.31, p < 0.01, \eta^2 = 0.218$ ]. Concerning the landmark recognition task, no difference between the intentional and incidental

group was found for both the sensitivity [ $F(1,37) = 0.64$ , n.s.] and response bias [ $F(1,37) = 0.32$ , n.s.]. Moreover, no difference between the intentional and incidental group was found for the landmark-ordering task [ $F(1,37) = 2.07$ , n.s.]<sup>1</sup>.

Table 6.1: Mean scores (SE) of the intentional and incidental groups on the five spatial tasks.

	Intentional condition	Incidental conditional
Landmark recognition task: Sensitivity	1.2 (0.1)	1.3 (0.1)
Landmark recognition task: Response bias	0.5 (0.7)	0.5 (0.7)
Landmark ordering task (max. 14)	9.5 (0.9)	11.8 (0.9)
Route reversal task (max. 16)	14.0 (0.4)	12.1 (0.4)
Map drawing task (max. 32)	19.7 (2.9)	10.7 (2.9)
Route length estimation task (correct 222 m)	287.1 (35.0)	146.3 (31.4)

A separate t-test was done for the route length estimation task. A significant difference was found between the estimated route length of the intentional and incidental group [ $t(37) = 3.00$ ,  $p < 0.01$ ]. Participants in the intentional group overestimated the route length, while participants in the incidental group underestimated the route length. However, the size of the error, which was indicated by the absolute difference between the correct route length and the estimated route length, was not statistically different for both groups [ $t(37) = 0.21$ ].

## Discussion

The current experiment set out to study the effect of intentional and incidental learning on acquisition of spatial information during navigation. It was shown that participants in the intentional learning condition performed better on a route reversal and map drawing task than participants in the incidental learning condition. Retracing a route in the opposite direction and drawing a map of the route require

<sup>1</sup> Performance on the landmark recognition and landmark-ordering task seem to be naturally linked, since they both involve recognition of landmarks. Possibly, the non-significant effect that is found for the landmark-ordering task might result from the non-significant effect for the landmark recognition task. No attempt to solve this interdependence was made.

survey knowledge. In contrast, no difference was found between the two groups of participants in their ability to recognize landmarks or place landmarks in the correct temporal order. This could not be the result of a ceiling effect, since performance on both tasks was substantially below the maximum score, leaving enough room for improvement with intentional learning. Thus, the results of this study suggest that under the current circumstances acquisition of survey knowledge benefits from effortful processing. In contrast, the finding that landmark recognition and landmark ordering tasks were not influenced by intention to learn suggests that acquisition of route knowledge largely depends on automatic processing.

Possibly, this would indicate that we have an innate system that enables us to encode route knowledge to a substantial amount even without paying attention to it, providing the minimal information we need to orient ourselves. Performance can then be improved when we effortfully try to remember the route. When walking through a new environment, this might be exactly what we are doing. When not paying any attention to the new environment, we will most likely still be able to remember, or at least recognize some familiar landmarks (cf. Cornell, Heth & Alberts, 1994) and remember the temporal position of the landmarks along the route (beginning, middle, end). However, when we really employ effort to learn the route, we will remember where we have to turn left or right, and possibly can construct an adequate mental map of the route, which allows planning a detour when necessary.

These results are also in line with the idea proposed by Siegel and White (1975), according to which acquisition of a spatial representation includes a number of different knowledge types, which follow a predetermined developmental order (i.e. landmark, then route, then survey knowledge). Although the current results cannot determine whether this strict developmental order is necessary when acquiring a spatial representation, it does show that processes that are supposed to occur later in the developing sequence are more effortful than processes that occur earlier.

We like to point out that there is one characteristic of the current experiment, which might restrict the foregoing interpretation of the results. That is, the fact that the route was learned from a route perspective (i.e. navigation). Previous research has shown that participants who learned a route from a map performed better on tasks measuring survey knowledge, while participants who learned by navigation performed better on route perspective tasks (Taylor, Naylor & Chechile, 1999). Importantly, this advantage given by the route perspective might have accounted for relative performance differences between tasks (favoring tasks relying more on route knowledge above tasks measuring primarily survey knowledge) but not for

the absence of any differences between the two groups. Only if the participants achieved at ceiling for the route knowledge based tasks, this perspective aspect might have been the cause for the comparable performance in the landmark recognition and ordering tasks between the incidental and intentional group. As already discussed above, this was not the case. Still a worthwhile target for future research on the acquisition of environmental knowledge could be to manipulate the perspective taken, for example by letting subjects learn the environment and route from a map.

The extent to which metric knowledge is acquired accurately during navigation was determined by asking participants to estimate the length of the route they walked. Interestingly, the result of the route length estimation task showed that participants in the intentional group overestimated the route length, while the incidental group underestimated it. Thus, it seems that the length of a route is perceived as longer when one is focusing attention on the route, while it is perceived as shorter when no attention is given to where one is going. In a review of the literature, Montello (1997) suggested that knowledge of the distance of a route can be based on three sources of information: number of environmental features, travel time and travel effort. Since travel time and physical travel effort were constant factors in the current study environmental features might have indirectly influenced distance estimation under incidental and intentional learning conditions. Possibly, participants in the intentional learning condition have attended more to environmental features than participants in the incidental learning condition, since they knew they would be tested on their route knowledge. Montello (1997) suggested that these features could include any kind of object or element of structure of the route (turns, road signs, etc.) and would most likely be visually perceived, although other modalities could presumably be involved as well. In the current experiment, however, no difference was found between the intentional and incidental condition on the landmark recognition task, indicating that both groups encoded these environmental features to the same extent.

Then, what else could have caused the difference in estimated route length? We like to suggest here that the third source of information - travel effort - can be divided in physical effort and cognitive effort. Physical effort would be the amount of physical energy spent when walking a route. For example, hills appear steeper when people are carrying a heavy backpack, are fatigued, of low physical fitness, or are elderly and/or in declining health. (Bhalla & Proffitt, 1999). Moreover, walking distance is perceived as longer when carrying a heavy backpack (Proffitt, Stefanucci, Banton, Epstein, 2003). As noted above, physical effort can be presumed to be constant over the two learning conditions. In contrast, cognitive

effort, which is the amount of cognitive resources that are required during navigation, including attention and memory, might vary. At this point one could speculate that cognitive effort might involve the effortful elaboration of processing direction and sensorimotor information, or alternatively might result from a more general problem of cognitive workload, not specifically directed to spatial information processing. If the latter were true, overestimation of the route length would also be found when participants have to study information irrelevant to the route during navigation, such as a story told by the experimenter. Unfortunately, our study has to leave open of what exact nature the difference in cognitive effort is.

In sum, the current study indicates that during navigation, route knowledge (knowledge of landmarks and their temporal order) requires less effortful processing than survey knowledge (knowledge with which to reverse the route and draw a map of the route). Moreover, it was shown that intentional learning conditions lead to overestimation of the walking distance, while incidental learning conditions lead to underestimation. These results have important implications for the mechanisms people use to acquire spatial information during navigation.

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## Chapter 7

# **Are time and space automatically integrated in episodic memory?**

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**Abstract**

The aim of the present study was to determine to what extent spatial and temporal features are automatically integrated during encoding in episodic memory. Both nameable and non-nameable stimuli were presented sequentially at different locations on a computer screen. Mixed and pure blocks of trials were used. In the mixed blocks participants were instructed to focus either on the spatial or the temporal order of the objects, as on the majority of the trials recall of this feature was tested (expected trials). However, on a few trials participants had to reproduce the other feature (unexpected trials). In the pure blocks either the spatial or the temporal order of the objects was tested on all trials. More errors were made on unexpected than on expected trials of the mixed blocks. Moreover, no primacy or recency effects were found when performance on the spatial task was plotted as a function of the temporal position. These results suggest that spatial and temporal order information rely on separate encoding processes

## Introduction

In our daily life we need to remember a large amount of information, including contextual features such as the color and location of an object or the moment at which something happened. Part of this information seems to be remembered without actively encoding it into memory (we usually know how often we saw a good friend last month, even though we did not intend to remember this). Thus, as it is impossible to attend to all information around us, there would be a clear benefit if some encoding processes would be automatic. In contrast to effortful processes, automatic processes require no focused attention or conscious awareness. According to Hasher and Zacks (1979) automatic processes are not influenced by intention to learn information, practice and simultaneous processing demands. Moreover, they would not be affected by age and individual differences. Therefore, one of the hypothesized characteristics of the memory system is that some aspects of our environment are encoded in our memory no matter what is the age, education or motivation level of the subject, and that this process does not interfere with other ongoing cognitive processes. Hasher and Zacks (1979) proposed that information that is encoded automatically in episodic memory includes location information, temporal order and frequency of occurrence.

The hypothesis of Hasher and Zacks encountered controversial results. Some studies showed that intention to learn (Ellis & Rickard, 1989; Ellis, 1990), practice (Ellis, 1990) and concurrent-processing demands (Ellis, 1990) did not influence performance on a spatial location task, thus confirming the ideas of Hasher and Zacks (although these experiments have been commented upon for their methodological shortcomings). Others, however, observed that these factors did affect the processing of spatial location information (Dayan & Thomas, 1995; Naveh-Benjamin, 1987, 1988; Perlmutter, Metzger, Nezworski & Miller, 1981). Similar mixed results were found for temporal order memory. Some studies reported that performance on a temporal order memory task was not influenced by the previously discussed factors, thus supporting the automaticity of temporal order memory (Auday, Sullivan & Cross, 1988; Azari, Auday & Cross, 1989; Perlmutter et al., 1981). However, Naveh-Benjamin (1990) found substantial effects of intention to learn, competing task loads, encoding strategy and age, thus rejecting the automaticity claim. In general, it seems warranted to conclude that spatial and temporal order information are not encoded fully automatically, since the criteria for automatic processes are not met under all circumstances. However, the mixed results do underline the notion that the difference between automatic and effortful encoding processes may not be dichotomous, but rather can be seen

as continuous. Accordingly, some processes could operate to some extent automatically and would benefit only in a restricted sense from focused attention and are less affected by the specific factors.

In the previously described studies spatial and temporal order memory were tested separately. However, in real life features are usually not presented alone, but occur together with other features. Spatial features seem to be naturally integrated with temporal features, since in daily life events take place in a certain place at a specific moment. Moreover, events close in time typically are also close in space, underscoring the benefits of an integrated coding process. Therefore, the suggestion that spatial and temporal order information are not processed automatically does not exclude the possibility that these features are encoded in an integrated fashion in memory. That is, spatial and temporal order information might not be encoded by separate processes, but rather by a single process in which both features are encoded together in memory. This would mean that when you process the temporal order of a number of ongoing events in memory you may automatically encode where these events took place, and vice versa. In support of this view, Hill and Stuckey (1993) studied the effect of spatial cues to temporal serial position on a digit-span task and showed that temporal order judgment was superior when temporal and spatial cues were congruent. Moreover, a similar study of Hill and Moadab (1995) showed that memory for temporal order improved when spatial cues were added, again suggesting that temporal and spatial features are not independently encoded in memory.

A related but slightly different notion is that encoding of spatial and temporal order information is hierarchical (Healy, 1975). In this case, encoding temporal information would be primary and spatial recall derivative. Accordingly, when spatial order information is encoded in memory, this feature must have been translated into a temporal sequence of events. Notice that the previously discussed results of Hill and Moadab (1995), which show that temporal order recall is enhanced when spatial information is added, are not in line with this option. If temporal order information was primary, spatial cues would not have improved memory for temporal order. Moreover, Nairne and Dutta (1992) found no correlation between temporal order and spatial retention, indicating that temporal order or spatial position provided little information about the position on the corresponding dimension. This would suggest that subjects do not use a temporally mediated code to process spatial information further refuting the hierarchical encoding of spatial and temporal order.

In contrast to the previously described options, another possibility is that both spatial and temporal order information engage independent memory processes.

This possibility is supported by a study showing that spatial and temporal order information are subject to selective interference, suggesting that they depend on distinct encoding processes (Hälbig, Mecklinger, Schriefers, Friederici, 1998). Moreover, aging studies have shown that older adults' memory for temporal information is impaired, while memory for spatial information is spared (Parkin, Walter & Hunking, 1995). Further support comes from patient studies indicating that temporal and spatial information are encoded by separate neuroanatomical systems. Spatial memory deficits were found to be due to temporal lobe deficits (Kopelman, Stanhope & Kingsley, 1997), while lesions in the frontal lobes caused an impairment in temporal context memory (Kopelman, Stanhope & Kingsley, 1997; Shimamura, Janowsky & Squire, 1990).

Köhler, Moscovitch and Melo (2001) proposed a distinction between general and domain-specific encoding and retrieval processes. Domain-specific processes are responsible for the processing of a single type of feature. In contrast, general processes underlie the encoding of a wide range of features, and therefore include integration of features within a single memory process. The distinction between general and domain-specific processes was supported by neuroimaging studies, which showed that functionally distinct general and domain-specific processes also recruit distinct cerebral structures (Köhler, Moscovitch, Winocur, Houle & McIntosh, 1998; Nyberg et al., 1996). Importantly, Köhler et al. (2001) showed that focusing on object identity information also led to coding of spatial locations. The reverse was not found, however. They thus reasoned that object identity processing involves a general process, while spatial location processing should be typified as domain specific. If we extend this conclusion to the spatiotemporal domain, we might deduce that spatial information is encoded separately from temporal order information. However, Köhler et al. (2001) based their conclusions on the finding that spatial information is not automatically integrated with object identity. This does not exclude the possibility that spatial information is integrated with other features, such as temporal order information. That is, we don't know yet whether domain specificity applies to all combinations of features, nor do we know in how far temporal order processing is domain specific.

The previously discussed literature clearly shows there is no general consensus about the relation between encoding of spatial and temporal order memory. Therefore, the current study was aimed at further establishing in how far these features are automatically integrated in memory or whether they are encoded by structurally independent processes. In order to do so stimuli were presented sequentially at different locations on a computer screen, so participants received both spatial and temporal order information. Pure and mixed blocks of trials were

used. In the mixed blocks participants were instructed to focus on either the spatial location or the temporal order of the stimuli, as on the majority of the trials recall of this feature was tested (expected trials). However, on some trials participants had to reproduce the other feature (unexpected trials). Moreover, a pure block was added, in which all trials included reproduction of the same feature. Inclusion of pure blocks enables us to control whether participants in the mixed block attended to the most likely feature. Although objects are commonly used in memory tasks, in the current experiment it could be argued that using nameable objects would lead to verbalization of the stimuli. This would benefit remembering the temporal order of the task more than remembering the location of the task. Therefore, two conditions were used, one in which colored pictures of daily life objects were used and one in which non-nameable characters were used.

If spatial and temporal order information are encoded in an integrated manner, then no difference should be found between performance on expected and unexpected trials. On the other hand, if temporal order information is used to encode spatial information, the difference between performance on expected and unexpected trials would be larger for the spatial task than for the temporal order task. Finally, if spatial and temporal order information are encoded separately in memory, a comparable difference between performance on expected and unexpected trials for both features would be found.

## **Methods**

### *Participants*

Nineteen young adults (5 males, 14 females), between ages 19 and 32 years, participated in this study. All participants were students from the Utrecht University. The Annett Handedness Inventory was used to assess the handedness of subjects, which showed that all participants were right handed. Participants were paid for their participation and all signed an informed consent form.

### *Material*

For this study the Object Relocation Task (Kessels, Postma & De Haan, 1999) was used. Within a frame of 19 by 19 cm, nameable objects or non-nameable characters were presented sequentially on different locations. The stimuli were presented three seconds each. After presentation, all seven stimuli appeared above the frame (Fig. 7.1). In the spatial task, the locations of the stimuli were marked by dots. Participants were instructed to replace the stimuli that were presented on the screen

to their correct location. In the temporal order task, the dots were arranged in a horizontal row. Participants were instructed to relocate the stimuli in the correct order from left to right by dragging them to one of the dots in the frame (Fig. 7.1). No time limit was used during the relocation phase.

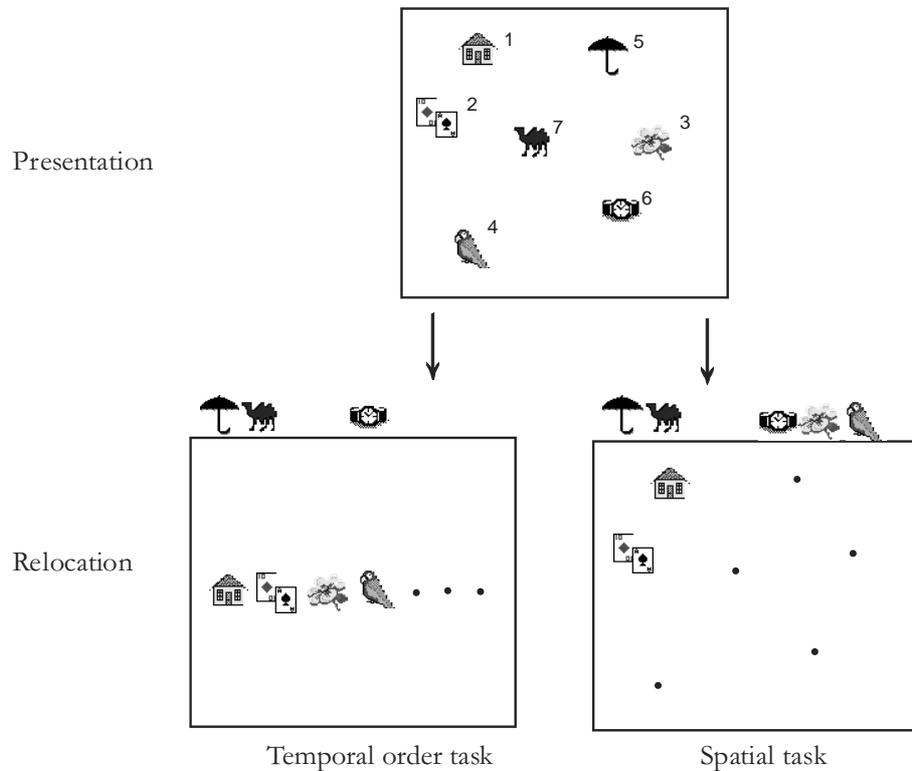


Figure 7.1: The display during the presentation phase and the display of the spatial and temporal order task in the relocation phase.

#### *Design and procedure*

Four blocks of trials were used; two 'pure' blocks of 10 trials (either the spatial or the temporal order task) and two 'mixed' blocks of 20 trials. Of these mixed blocks, 80% of the trials were 'expected trials', i.e. they were consistent with the instructions participants received. Twenty percent of the trials were 'unexpected trials', in which the other feature had to be recalled. A pure block was followed by its linked mixed block (e.g. the pure temporal order block, followed by the expected temporal order and unexpected spatial block). Half of the subjects started

with the pure spatial task, the other half with the pure temporal order task. These four blocks of trials were each done twice in different sessions, once with nameable stimuli and once with non-nameable stimuli.

### Results

Figure 7.2 and 7.3 present the percentages incorrect responses and the standard errors for the probability conditions and type of information. A  $2 \times 2 \times 3$  ANOVA with within-subject variables Stimulus type [nameable and non-nameable stimuli], Task [spatial and temporal order task] and Probability [100% (pure condition), 80% (mixed condition, expected trials) and 20% (mixed condition, unexpected trials)] was conducted. For post hoc testing, Bonferroni correction of the significance criterion  $\alpha$  was applied.

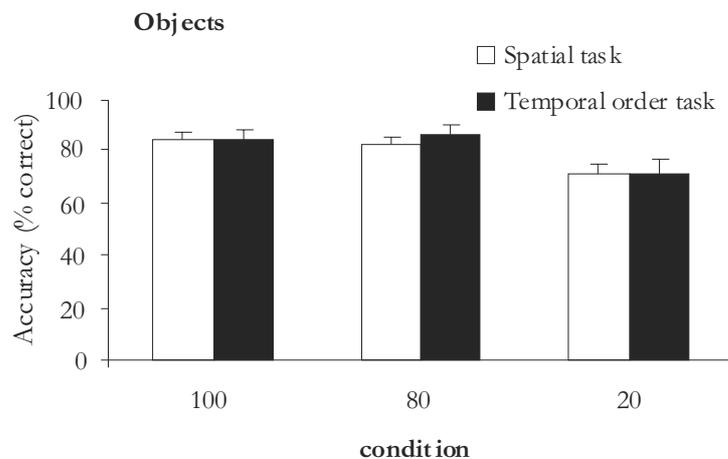


Figure 7.2: The mean correct responses and standard errors in percentages as a function of the type of feature to be recalled and probability of trials testing the feature for the nameable stimuli.

More errors were made when participants had to remember non-nameable stimuli than the nameable stimuli [ $F(1,18) = 15.56, p < 0.01$ ]. Overall, no difference in accuracy was found between the temporal order and spatial task [ $F(1,18) = 1.02, n.s.$ ]. A main effect was found for Probability [ $F(2,36) = 36.52, p < 0.01$ ]. Post-hoc testing was done for the nameable and non-nameable stimuli separately. For the nameable stimuli, a test of within-subject contrasts showed that more errors were made in the 20% condition than the 80% condition, [ $F(1,18) = 18.65, p < 0.01$ ], and the 100% condition, [ $F(1,18) = 17.48, p < 0.01$ ]. Importantly, the difference between the 80% and 100% conditions was not significant, [ $F(1,18)$

= 0.0, n.s.], nor was the interaction between Task x Probability, [ $F(2,36) = 0.37$ , n.s.]. The same effects were found for the non-nameable stimuli. Again, within-subject contrast showed that more errors were made in the 20% than the 80% probability conditions [ $F(1,18) = 32.6$ ,  $p < 0.01$ ], and more errors were made in the 20% probability condition than the 100% probability condition [ $F(1,18) = 40.8$ ,  $p < 0.01$ ]. No difference was found between the 80% and 100% probability condition [ $F(1,18) = 3.3$ , n.s.], nor was an interaction effect found between Task x Probability [ $F(1,18) = 0.3$ , n.s.].

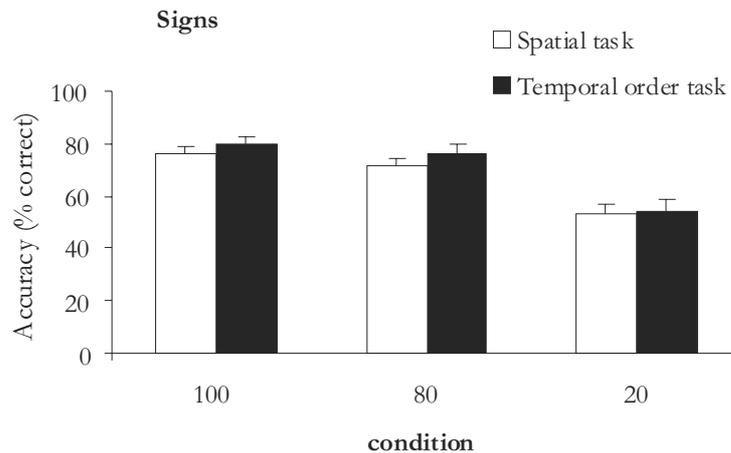


Figure 7.3: The correct responses and standard errors in percentages as a function of the type of feature to be recalled and probability of trials testing the feature for the non-nameable stimuli.

Moreover, an overall interaction effect was found between Stimulus type and Probability [ $F(2, 36) = 4.4$ ,  $p < 0.05$ ]. Post-hoc testing indicated that the difference between the 20% and 100% condition was greater for the non-nameable stimulus condition than for the nameable stimulus condition [ $F(1,18) = 9.9$ ,  $p < 0.01$ ], although the difference between the 20% and 80% conditions [ $F(1,18) = 2.3$ , n.s.] and the 80% and 100% conditions [ $F(1,18) = 1.7$ , n.s.] was not significant. No other significant interaction effects were found.

In order to study whether encoding spatial and temporal order memory rely on the same underlying encoding system, serial position (primacy and recency) effects were analysed by calculating the accuracy for the seven temporal positions separately (see Figure 7.4). ANOVA with within-subject variable Position indicated a serial position effect for the temporal task with the nameable [ $F(6,108) = 5.8$ ,  $p < 0.01$ ] and the non-nameable stimuli [ $F(6,108) = 17.2$ ,  $p < 0.01$ ]. As can be seen

from Figure 7.4, accuracy was higher in the first and last temporal positions than the middle positions. This effect was not found for the spatial task with the nameable [F (6,108) = 2.0, n.s.] and non-nameable stimuli [F (6,108) = 1.5, n.s.].

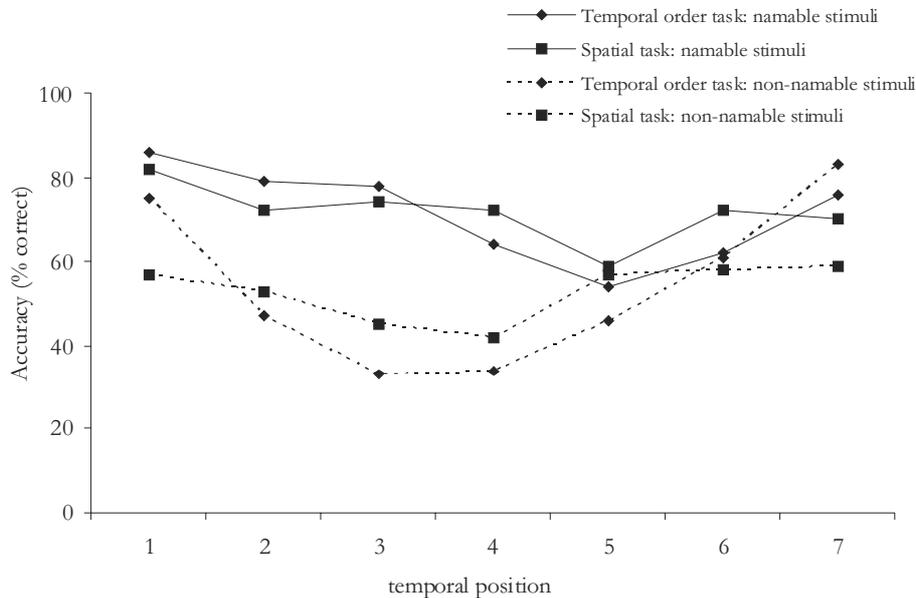


Figure 7.4: Serial position effects for the temporal order and spatial task, for the nameable and non-nameable stimuli separately.

In order to explore whether strategic shifts occurred across trials as the study progressed during a mixed block, the accuracy of the first and last two unexpected trials (see table 7.1) were compared. Our expectation was that participants might start with focusing on the relevant feature and shift to dividing attention between the two features in the last trials. For the nameable stimuli, no difference was found between the first and last two unexpected trials for the spatial, [ $t(18) = 1.6$ ], and the temporal task, [ $t(18) = 0.81$ ]. For the non-nameable stimuli, no difference between the first and last two unexpected trials was found for the temporal task [ $t(18) = 0.9$ ]. However, for the spatial task accuracy on the last two trials was higher than on the first two trials [ $t(18) = 2.9$ ,  $p < 0.01$ ].

Moreover, another possibility is that participants start dividing their attention after the first mixed block. For example, when participants perform the pure temporal, mixed temporal, pure spatial and mixed spatial condition subsequently, they might start to encode the temporal order of stimuli as well as the location after the mixed temporal task. If this is true, participants who started with the spatial

task would perform better on the unexpected temporal order trials, and the participants who started with the temporal order task would perform better on the unexpected spatial trials. However, when adding between-subject variable Task order (spatial task, than temporal order task and temporal order task, than spatial task) to the 2 x 2 x 3 ANOVA that was previously described, no effect of Task order was found, nor was an interaction effect with Task order found [all  $F_s < 2.7$ ].

A one-sample  $t$ -test showed that the accuracy of the 20 % probability condition of both the spatial and temporal order task was significantly higher than chance, [ $t(19) = 12.91, p < 0.001$ ] and [ $t(19) = 17.51, p < 0.001$ ] respectively, with chance in both cases 85.7% (one out of seven responses correct) incorrect responses.

Table 7.1: Mean percentages correct responses of the first and second two trials of the spatial and temporal order condition for the nameable and non-nameable stimuli separately.

	Nameable stimuli		Non-nameable stimuli	
	Mean	SE	Mean	SE
Spatial 1 <sup>st</sup>	69.2	7.0	55.6	4.7
Spatial 2 <sup>nd</sup>	73.3	4.6	52.6	5.5
Temporal 1 <sup>st</sup>	66.5	5.7	45.5	4.4
Temporal 2 <sup>nd</sup>	76.7	4.0	60.2	5.4

## Discussion

The aim of the current study was to determine whether spatial and temporal order information are automatically integrated in episodic memory or whether they rely on independent encoding processes. Therefore, stimuli were presented sequentially at different locations on a computer screen. Participants' expectations were manipulated by employing pure and mixed blocks of trials. In the pure blocks either the spatial or the temporal feature had to be recalled on all trials. In the mixed blocks participants were instructed to reproduce either the spatial or temporal order feature, as on 80% of the trials this feature was tested (expected trials). However, on 20% of the trials the other feature had to be reproduced (unexpected trials). Importantly, more errors were made on unexpected trials than on expected trials for temporal order and spatial information recall. A second important aspect of the current experiment was the inclusion of a condition with non-nameable stimuli. Although more errors were made in the condition with the non-nameable stimuli than the nameable stimuli, the previously described effects

were found in both conditions. This is an important finding since it excludes the possibility that verbalization influences performance on the temporal order task. That is, when verbalizing the objects, one might automatically encode the order of presentation. This would imply that temporal order information would be automatically encoded when attending spatial information, while spatial information would not be encoded when attending the temporal order of stimuli.

The foregoing findings support the notion that neither spatial nor temporal order information is encoded automatically in memory, nor does the automatic integration of these features take place. This is in line with the view that separate neuroanatomical systems underlie spatial and temporal order information processing in memory (Kopelman, Stanhope & Kingsley, 1997). The conclusion of Köhler et al. (2001) that spatial information is based on a domain-specific encoding process and not on a general process was also supported by these results. Moreover, the current data indicate that the same notion holds for temporal order memory. Spatial information processing seems to be domain specific, in the sense that at least two features, i.e. identity and temporal order, are not processed fully automatically concurrent with the spatial information. However, future studies will have to investigate the relation between temporal order information and other features, e.g. object identity information, to further examine the extent of exclusivity in domain specific processes.

Interestingly, no interaction effect between Task and Probability was found, indicating that attention elevates spatial and temporal order memory to the same extent. Thus, it seems that spatial information was not used to encode temporal information or vice versa. This notion is further supported when we look at the serial-position curves of the two tasks. When performance on the temporal order task is plotted as a function of the temporal position of the stimuli at presentation we see that accuracy is higher on the first (primacy effect) and last (recency effect) temporal positions than the middle temporal positions. In contrast, primacy and recency effects do not characterize the spatial task. Together this might be a further indication that processing spatial and temporal order information rely on independent encoding systems.

Notice that accuracy of the unexpected trials in both the temporal order and the spatial tasks was higher than would be expected when participants were simply guessing. This would indicate that subjects did encode some of the information that was not relevant for the anticipated response<sup>2</sup>. This does not seem to be the

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<sup>2</sup> It should be noted that we should be careful with drawing conclusions regarding automaticity of processes based on above chance performance. For example, Hyde and Jenkins (1969) indicated that even effortful processes might result in above chance performance, even under truly incidental instructions.

result of a gradual attention division, since no difference in accuracy between the expected trials of the mixed blocks and the trials of the pure blocks was found. Moreover, no difference in accuracy between the first and the last two trials of the unexpected condition was found for all of the conditions but one. This would indicate that participants didn't change their strategy (from focusing only on the relevant feature to dividing attention between the two features) during a mixed block. The above chance performance of the participants in the unexpected trials would indicate that some of the information that was not attended to was processed, although not as effectively as when attention is directed to a feature. Thus, it remains unclear what caused the above chance performance. Some information of the irrelevant feature might have been encoded, either automatically, or through divided attention that is present in all conditions (both pure and mixed condition).

No difference was found between performance on the temporal order and spatial task, indicating that encoding of both features is highly similar. However, there are some limitations in the design of the tasks, which do not fully warrant generalization of this conclusion to other situations. First, the two versions of the task are not completely symmetrical since temporal information could be used to relocate stimuli to the correct spatial location, while spatial information could not be used to relocate stimuli to the correct temporal order. Note, however, that no recency effects were found when performance on the spatial task was plotted as a function of the temporal position, indicating that temporal order information was not used to encode location information. Second, the stimuli of the temporal order task are uni-dimensional (left/right), while the stimuli of the spatial task are bi-dimensional (left/right, up/down). What is most important here is that the emphasis of this study concerned differences between the three probability conditions and possible interactions between Probability, type of Task and type of stimulus.

In conclusion, the current study showed that performance decreased when no attention was given to the location or temporal order of the stimuli. Moreover, no primacy or recency effects were found when performance on the spatial task was plotted as a function of the temporal position. These findings further support the notion that spatial and temporal order information is not automatically encoded in memory. Moreover, spatial and temporal order information are clearly not automatically integrated in memory by a single mechanism, even though they are naturally linked since events usually occur close in time and space.

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## Chapter 8

# The influence of aging on spatial and temporal order memory and binding

Van Asselen, M. & Postma, A. *Manuscript in revision.*

**Abstract**

Aging has a strong impact on cognitive processes such as memory. In particular, remembering contextual attributes may deteriorate. The aim of the current study was to determine whether aging selectively affects two different contextual attributes, namely spatial and temporal order memory. Moreover, the effect of aging on integration of these features was studied. Seven objects were presented within a frame on a computer screen. Two groups of younger and older subjects were instructed to relocate the objects to the correct spatial location, temporal order of appearance, or both. The older adults were impaired on both the temporal order and spatial task, but such to an equal extent. Moreover, older adults performed worse than the younger adults when both the spatial and temporal order feature had to be recalled, even when controlling for performance on the pure spatial and pure temporal order task. In conclusion, aging seems to influence encoding of spatial and temporal order information to the same extent. Additional impairments occur when both the location and temporal order have to be recalled.

## Introduction

One of the most important characteristics of normal aging is memory loss. Many older people report becoming progressively more forgetful as they get older. However, aging seems to have a stronger impact on some aspects of memory than others. In particular, context memory seems to be affected (e.g. Spencer & Raz, 1996), i.e. the ability to retrieve features that are associated with a target event, such as color, location and temporal order information. Besides this ability to retrieve individual features of an event, another process that is essential for human memory is the ability to integrate several different context features together in memory. By studying the effect of aging on these different memory processes, we can gain important insights in the memory function of older people. Moreover, studying the effect of normal aging on context memory will enable us to recognize abnormal patterns of aging, such as found in degenerative diseases such as Alzheimer's amnesia.

Two contextual features that are especially important in our daily life are temporal information (when did something happen?) and spatial information (where did something happen?). Although Ellis, Katz & Williams (1987) found no effect of aging on spatial memory, most studies revealed profound effects on spatial memory. An important line of evidence concerning aging effects on spatial and temporal order memory comes from Naveh Benjamin (1987, 1988, 1990), who studied young and older adults to argue against automaticity of these processes. He clearly found impaired spatial memory, as well as temporal order memory in older adults. In contrast, Perlmutter, Metzger, Nezworski and Miller (1981) showed that spatial memory was impaired by aging, but not temporal order memory when using a recency task. Others also found profound effects of aging on spatial memory (Kessels, Te Boekhorst & Postma, in press; Cooney & Arbuckle, 1997). This spatial memory impairment in older adults is specifically found for allocentric spatial memory (Lemey & Proteau, 2003; Moffat & Resnick, 2002), while egocentric spatial memory is relatively spared (Desrocher & Smith, 1998). Interestingly, the initial encoding of spatial information seems to be largely spared in older adults (Olson, Zhang, Mitchell, Johnson, Bloise & Higgings, 2004). Chalfonte and Johnson (1996) showed that older adults were less accurate in relocating a number of objects within an array. However, not all features were affected by aging to the same extent, i.e. memory for spatial information was more affected by aging than item and color information, which were relatively spared.

Concerning memory for temporal order information, several studies found severe impairments due to aging (Howard, Howard, Dennis, Yankovich & Vaidya,

2004; Kausler & Wiley, 1990; Vakil, Weise & Enbar, 1997). Parkin, Walter and Hunkin (1995) showed that older adults' memory for temporal information is impaired, while memory for spatial information is spared, although this might be due to the egocentric nature of their task. Fabiani and Friedman (1997) also found impaired temporal order memory and suggested that this impairment was due to a specific age related decline in frontal lobe function, since performance on the recency task correlated with performance on the Wisconsin Card Sorting test. A direct relation between impaired temporal order memory in older people and defective prefrontal lobe functioning was reported by Cabeza, Anderson, Houle, Mangels and Nyberg (2000). By using positron emission tomography (PET) they showed reduced activation during temporal order retrieval in the right prefrontal cortex in older adults in comparison to younger adults.

Dumas and Hartman (2003) also reported impaired temporal order memory for verbal information in older people. They hypothesized that impaired performance on all types of memory tests is caused by a generalized decline in context memory, since they found that impaired temporal order memory could be eliminated after controlling for free recall. Similarly, although Cherry, Park and Donaldson (1993) did show impaired memory for three-dimensional spatial information in older adults, this impairment decreased when structural contextual cues were given, i.e. spatial landmark cues. In contrast, Denney, Dew and Kihlstrom (1992) found that older adults were impaired when asked to recall the locations of words in a quadrant. However, memory decline in older adults did not seem to be specific for contextual information, since the extent of the impairment was the same when the to be remembered locations were target or context information.

Although the foregoing studies have indicated impaired spatial and temporal order memory in older adults, it remains unclear whether aging impairs memory for these two features to the same extent. Therefore, the current study was aimed at making a direct comparison between memory for temporal order and spatial information. Interestingly, this will also give us important information concerning the underlying processing mechanism of spatial and temporal order memory. That is, spatial and temporal order information seem to be naturally linked, considering that an event always happens at a certain moment and at a certain place. This might suggest that these features are automatically integrated in memory, indicating that when you know when something happened you also now where it happened and vice versa. Accordingly, Healy (1975, 1977) suggested that spatial information is encoded in a primarily temporal representation, suggesting that when spatial order information is encoded in memory, this feature must be translated into a temporal

sequence of events. Similarly, Kohler, Moscovitch and Melo (2001) made a distinction between general and domain specific memory processes. General processes not only include encoding a target feature, but also the contextual features. In contrast, domain specific processes encode a single feature. For example, if spatial information is a general process, temporal order information would be automatically encoded, while if it is a domain specific process this would not be the case. Alternatively, spatial and temporal order memory might also depend on distinct processing systems, suggesting independent encoding. In line with this theory, Nairne and Dutta (1992) showed that temporal order and positional order scores are uncorrelated. Similarly, in a recent study it was shown that when presenting both spatial and temporal order information, temporal order memory improves when recall of this feature is expected and vice versa (Van Asselen, Van der Lube & Postma, submitted). Studying the influence of aging on spatial and temporal order memory will give us more insight in the nature of these important features. If temporal order and spatial information are automatically integrated, no difference is expected between the extent of the impairment between temporal order and spatial memory. Moreover, no additional binding effects are expected.

## Method

### *Participants*

A group of 19 young adults (7 men and 12 woman), with a mean age of 18 years ( $Sd = 2.2$ ) and 19 older adults (11 men and 8 woman), with a mean age of 65 years ( $Sd = 8.3$ ) participated in this study. A chi-square test indicated there was no significant difference in number of men and women in the two age groups [ $\chi^2(1) = 2.1$ ]. Older participants were living independent, and none of them suffered from a neurological disease. Level of education was rated on a scale of 1 to 7, with 1 being the lowest (less than elementary school) and 7 the highest score (University degree). Education rate of the young adults was 6 ( $SD = 1.2$ ) and the older adults 5 ( $SD = 0.7$ ). A Dutch version of the Annett Handedness Inventory (Briggs & Nebbs, 1975) was used to assess handedness. The younger adults included 17 right-handed and two left-handed participants, the older adults included one left-handed, one ambidextrous and 18 right-handed participants. All participants reported normal or corrected to normal vision and were paid for their participation or received a small present. Informed consents were obtained from all participants.

*Material and procedure*

For this experiment the Object Relocation program (Kessels, Postma & De Haan, 1999) was used. Over 200 different, easy-to-name, colored objects (e.g. ball, bike) were used, that were shown within a square of 14 by 14 cm on a 17 inch touch-screen computer. Although few objects were used twice, this was never so within one condition. For each trial, objects were randomly selected, although it was avoided to include objects of the same color or category (e.g. animal) within one trial.

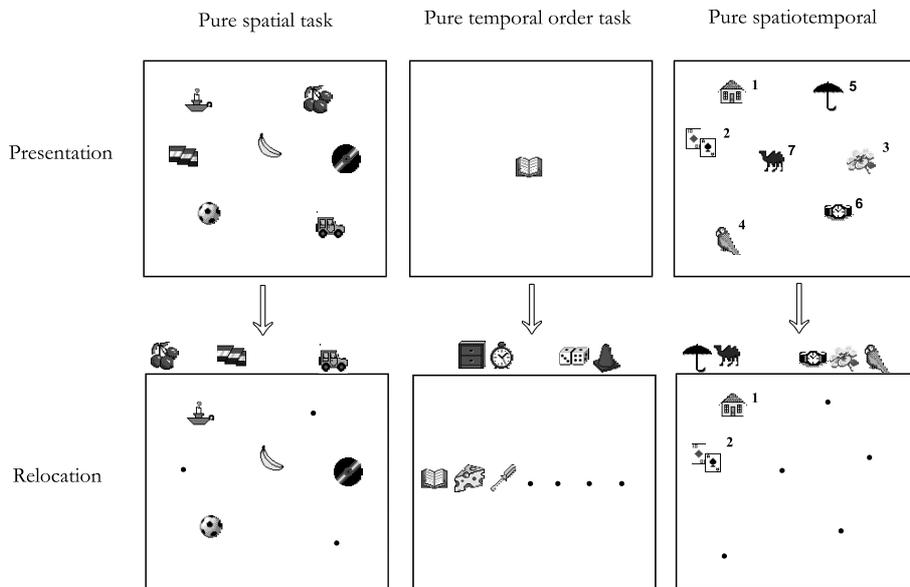


Figure 8.1: The presentation and relocation phase of the pure spatial pure, pure temporal order and mixed spatiotemporal order task (the numbers in the combined task indicate the temporal order of the objects).

Three conditions were created which were presented in a fixed order. Each condition included two practice trials of five objects and ten experimental trials of seven objects. The presentation and relocation phases of the three conditions are shown in Figure 8.1. First, the *pure spatial task* was administered, in which objects were presented simultaneously at different locations for 14 seconds. During the relocation phase, the objects were presented above the square and the locations were marked by dots. The participants were instructed to place the objects on the correct locations. Second, the *pure temporal order task*, in which objects were presented one by one on the same location in the middle of the square. Each object

was presented for two seconds. During the relocation phase, objects were presented again above the empty square and seven dots created a horizontal line within the square. Participants were asked to place the objects in the correct temporal order on the seven dots. Third, *the mixed spatiotemporal task*, in which the objects were presented one by one on different locations within the square for two seconds each. Again, the locations were marked by dots. Participants were instructed to place the objects both in the correct temporal order and at the correct spatial locations within the square.

## Results

The error percentages (Figure 8.2) of the pure spatial and pure temporal order task were analyzed with a 2 x 2 Repeated Measure Analyses, with within-subject variable Feature (spatial and temporal order task) and between-subject variable Age (young and older adults)<sup>3</sup>. This revealed a main effect for Age [ $F(1, 37) = 20.3, p < 0.001$ ], indicating that older adults made significantly more errors than younger adults. Importantly, although more errors were made on the temporal order task than the spatial task [ $F(1,37) = 20.1, p < 0.001$ ], no interaction effect between Feature x Age was found [ $F(1, 37) = 0.8$ ].

For the mixed spatiotemporal order task the error percentage was analyzed by means of ANOVA, with Age (young and older adults) and Gender (men and women) as fixed factors<sup>4</sup>. To control for performance on the pure temporal order and pure spatial condition, performance on these tasks was taken as covariates. Results showed that performance on the pure temporal order task partially accounted for the age effect found on the mixed spatiotemporal order task [ $F(1,34) = 4.6, p < 0.05$ ], but not the pure spatial task [ $F(1,34) = 1.9$ ]. Importantly, a significant age effect remained on the mixed spatiotemporal order task [ $F(1,34) = 6.6, p < 0.05$ ]. This indicates that the older adults performed worse than the younger adults when binding spatial and temporal order information in memory, even when controlling for spatial and temporal order memory in isolation.

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<sup>3</sup> Although the current study was not aimed at investigating the effect of gender on spatial and temporal order memory and no statistical differences were found between the number of men and women in both age groups, we did look at a possible influence of gender on our results. When the between-subject variable Gender was added to the Repeated Measures Analyses, a significant effect for Gender was found [ $F(1, 35) = 17.2, p \leq 0.001$ ], indicating men made more errors than women. Importantly, no interaction effects between Gender x Age and Gender x Condition was found [ $F(1, 35) < 2.2$ ].

<sup>4</sup> When Gender was included as a fixed factor in this ANOVA, no significant Gender effect was found [ $F(1,32) = 0.1$ ], nor a interaction effect between Gender x Condition [ $F(1,32) = 0.7$ ].

In order to analyze whether performance of the young and older adults is above chance level in the three conditions, three One-sample t-tests were performed. For the pure spatial and pure temporal order task, chance was 85.7 percent incorrect (one of seven objects correct) and for the mixed spatiotemporal task it was 97.96 percent correct (one of forty-seven objects correct). Performance was significantly above chance level for the pure spatial [ $t(37) = 32.0, p \leq 0.001$ ], the pure temporal order [ $t(37) = 15.63, p \leq 0.001$ ] and the mixed spatiotemporal task [ $t(37) = 10.8, p \leq 0.001$ ].

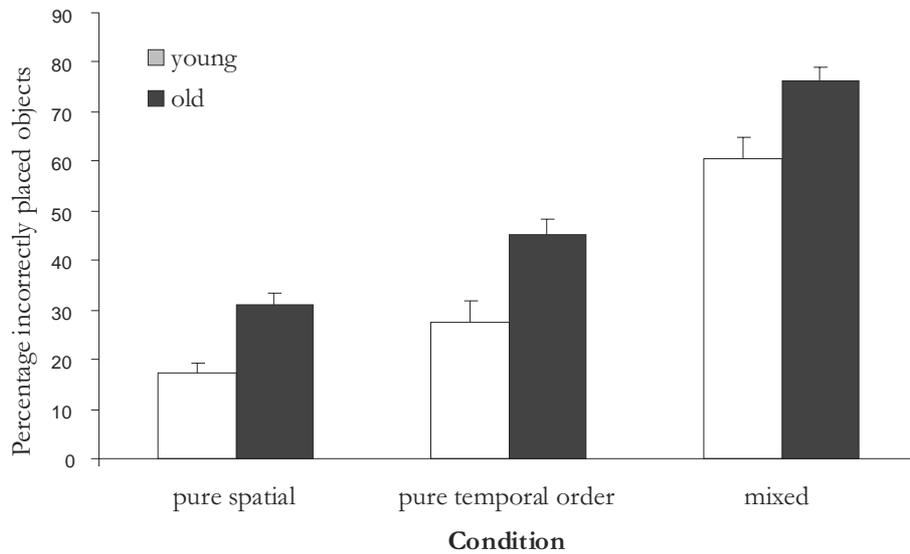


Figure 8.2: Mean error percentages in the pure spatial, pure temporal and mixed spatiotemporal task for the young and older adults separately.

## Discussion

The first goal of the current research was to directly compare the effect of aging on memory for temporal order and spatial information. It was shown that older adults were impaired when asked to reconstruct the temporal order of seven sequentially presented objects. Moreover, older adults were also impaired when they had to relocate seven objects that were presented simultaneously in an empty square to their correct location. An important aspect of the current study is the comparability of the spatial and temporal order tasks, considering both required relocation of seven objects that were presented under the same circumstances and for the same

time-period. By directly comparing aging effects on both tasks it was shown that the extent of the impairment due to aging was the same for both spatial and temporal order memory. Previously, impairments were found due to aging for both spatial (Chalfonte & Johnson, 1996; Perlmutter, 1981) and temporal order memory (Fabiani & Friedman, 1997; Howard et al., 2004; Kausler & Wiley, 1990; Parkin et al., 1995; Vakil et al., 1997). By designing an experiment in which performance on a temporal order task could be compared to a spatial memory task, we have managed to demonstrate that these important contextual features deteriorate to the same extent. Notably, this is in line with the idea that the prefrontal lobes, which are particularly vulnerable for the degenerative effects of aging (Raz et al., 2000), are important for both spatial memory (Kessels, Postma, Wijnalda & De Haan, 2000; Teixeira Ferreira, V erin, Pillon, Levy, Dubois, Agid, 1998) and temporal order memory (Kopelman, Stanhope & Kingley, 1997; Shimamura, Janowsky, & Squire, 1990).

Furthermore, this research was aimed at studying the effect of aging on integrating contextual features of an event in memory. When both the temporal order and spatial locations of objects had to be recalled, the older adults performed worse than the younger adults. This effect persisted when accounted for the deficits found in the pure spatial and pure temporal order tasks. Thus, the current study clearly shows that the ability to integrate spatial and temporal order features in memory is impaired in older people, in specific the ability to integrate temporal order and spatial information. Importantly, this would suggest that temporal order and spatial information are not automatically integrated in memory. Moreover, these results are in line with previous studies of Chalfonte and Johnson (1996), who found impaired feature binding in older adults when participants were asked to remember both object and color, or object and location information in long-term memory. Mitchell, Johnson, Raye and Mather (2000a) used a recognition task to test feature binding in working memory in older people. They showed that the binding deficit that is found in long term memory due to aging has its origin, at least in part, at the encoding process. The same group of researchers used this recognition task in a subsequent fMRI study including old and young participants and showed that the binding deficit as a result of aging is most likely due to decreased function in the anterior hippocampus (Mitchell, Johnson, Raye & Mather, 2000b). Studies using tests of associative learning have also shown marked deficits when testing older people. Collie, Myers, Schnirman, Wood and Maruff (2002) showed that older people with cognitive decline related to impaired hippocampal function perform worse than controls on tasks of associative learning. They concluded that cognitive decline in some older people might result from

deteriorating hippocampal function, causing impaired functioning on tasks of associative learning, particularly when novel stimuli are used or stimuli that are thought to be related to the hippocampal function, such as spatial location information.

In conclusion, memory for contextual information, including both spatial and temporal order features, was clearly impaired in older people. Importantly, the extent of this impairment was the same for temporal order and spatial memory. Moreover, an additional impairment due to aging has been found when both features have to be integrated in memory and connected to an event. Possibly, the memory problems that older adults encounter increase when multiple features have to be integrated. This would imply that they might benefit from controlled and limited presentation of information.

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## CONCLUSIONS



## **Chapter 9**

### **Summary and Discussion**

## Summary

The present thesis focused on two important aspects of spatial memory. First, the different processes involved in spatial memory and their neural correlates were studied using three different spatial memory paradigms: a spatial working memory task, an object-location memory task and a navigation task. In the second part of this thesis the extent to which the different components of spatial memory function automatically was examined. In this final chapter, the main findings of the different studies will be summarized and the implications of these results for our knowledge about spatial memory will be discussed.

In chapter two, the different processes involved in object-location memory were studied by examining patients with a focal lesion in either left or right hemisphere and comparing the performance of these two patient groups with age- and education-matched healthy controls. It was found that patients with a lesion in the right hemisphere were impaired on a coordinate position task, whereas patients with a lesion in the left hemisphere were impaired on a categorical position task. These results confirm previous results suggesting hemispheric specialization for categorical and coordinate position information (e.g. Laeng, 1994, Kosslyn, 1989). In contrast, no hemispheric specialization was found when position information had to be integrated with object information. Additionally, performance on the categorical and coordinate object-location tasks were clearly correlated, suggesting they tap on the same underlying process. Importantly, these results reveal that multiple areas of the human brain are involved in storing position information and binding it to objects.

Chapter 3 and 4 examined an important aspect of spatial memory, i.e. the ability to search through an environment and to keep track of previously learned spatial locations. In chapter three, a spatial search task was performed by Korsakoff patients. Although long-term memory is clearly impaired in these patients, particularly for context features such as spatial information (Holdstock, Mayes, Cezayirli, Aggleton & Roberts, 1999; Kessels, Postma, Westers & De Haan, 2000; Kopelman, Stanhope & Kingsley, 1997; Mayes, Meudell & MacDonald, 1991; Shoquierat & Mayes, 1991), it is unclear whether working memory is also impaired, or preserved to some extent (Brokate, Hildebrandt, Eling, Fichtner, Runge & Timm, 2003; Haxby, Lundren & Morley, 1983; Joyce & Robins, 1991; Mayes, Daum, Markowisch, & Sauter, 1997). It was demonstrated that Korsakoff patients' ability to keep spatial information active in memory over both a short and a more extended time period was impaired compared to controls. In contrast, their ability to keep spatial information passively in working memory, as was assessed with the

Corsi-Block tapping task, was spared. Interestingly, this spatial working memory impairment could not be ameliorated by adding contextual color cues to the boxes. This implicates an additional impairment for the integration of spatial information with other types of context information, such as color (chapter 3). These findings extend the context-deficit hypothesis (Mayes, Meudell & Pickering, 1985), according to which amnesia is the result of an inability to encode contextual information, such as the moment and place that an event occurs. Additionally, they have an important clinical application by demonstrating that cueing cannot be used to help patients remember specific information.

The same spatial search-task was assessed in a group of patients with focal lesions due to stroke. By using a lesion-overlap technique it was possible to define the relation between the extent of damage to a specific brain area (i.e. the posterior parietal cortex, the dorsolateral prefrontal cortex and the hippocampus) and performance on two different tasks assessing spatial working memory. A spatial search task was used, in which target objects have to be located in a number of closed boxes presented on a computer-screen. Moreover, the Corsi Block-Tapping tasks requires participants to remember a sequence of blocks mounted on a board that was previously tapped by the experimenter. The right dorsolateral prefrontal cortex and the right posterior parietal cortex were found to be involved in keeping spatial information active in memory over a short time period, as was assessed with the within-search errors of the Box task and the Corsi Block-Tapping task. Moreover, both right and left hippocampal formation seem to play a fundamental role in maintaining spatial information in working memory over an extended time period, as was assessed with the between-search errors. The role of the left posterior parietal and left dorsolateral prefrontal cortex in spatial working memory seems to be limited.

In chapter five the same lesion-overlap technique is used to study the different processes involved in route learning, including landmark recognition, remembering the order of the landmarks, drawing a map of the route, and retracing the route. It was shown that the right hippocampal formation is important for more basic aspects of route learning, such as processing landmark information, but also for processing allocentric spatial information (e.g. Parslow, Morris, Fleminger, Rahman, Abrahams, Recce, 2005). Additionally, the right temporal cortex seems to be involved in allocentric spatial memory as well, as measured with a map-drawing test. Encoding the temporal-order of the landmarks is dependent on prefrontal cortical areas. Moreover, damage to the dorsolateral prefrontal cortex, which is though to be particularly involved in spatial working memory (Chapter 4), resulted in impaired route retracing.

The importance of route learning or navigation in our daily lives suggests that this complex function could have developed at least partly into an automatic process, requiring little focused attention. In order to study the automaticity of these different aspects of route learning, the same route-learning experiment was performed under intentional and incidental learning conditions. It was hypothesized that an automatic process would not improve in the condition in which attention was paid to the route during navigation, in contrast to the condition in which no attention was given. Results showed that performance on the tasks assessing route knowledge (landmark recognition, landmark ordering) did not improve with attention. In contrast, performance of the tasks assessing survey knowledge (knowledge with which to reverse the route and draw a map of the route) did improve significantly when learned under intentional learning conditions.

In everyday life, context features are usually not presented alone, but rather together with other features. It thus could be possible that these features are automatically integrated in memory by a unitary mechanism. For example, when you process the temporal order of a number of ongoing events in memory you may automatically encode where these events took place, and vice versa. Therefore, chapters 7 and 8 examine the relation between encoding temporal-order and spatial information, by representing objects one by one on different locations on a display. Subsequently, participants had to relocate the objects in the correct temporal order or to the correct spatial location when recall was either expected or unexpected. Performance on both the spatial and temporal-order task improved when recall was expected, compared to when it was not expected. The finding that intention to learn either the location or temporal order of objects improved performance suggests both features are not automatically integrated in memory.

In line with these findings, the final study in this thesis showed that memory for temporal-order and spatial information deteriorates with age. Considering that automatic processes are expected not to be influenced by aging (Hasher & Zacks, 1979), these results suggest that both temporal-order and spatial memory are effortful memory processes, at least to an important extent. Moreover, an additional impairment was found in older adults on task conditions in which two important contextual features had to be integrated in memory. These findings further support the idea that spatial and temporal-order information are not automatically integrated in memory.

## Discussion

A substantial part of the current thesis was aimed at studying spatial memory in patients with cerebral dysfunction, i.e. Korsakoff amnesia or focal lesions due to stroke. This has revealed a number of interesting conclusions regarding the neural network involved in spatial memory. Although the common idea that spatial memory is largely dependent on the right hemisphere was supported, it was also demonstrated that the left hemisphere is clearly involved in some aspects of spatial memory. That is, categorical spatial information seems to be encoded by brain areas in the left hemisphere, whereas coordinate position information is encoded by brain areas in the right hemisphere. However, this hemispheric specialization for categorical and coordinate spatial representations was not found when positional information had to be integrated with object information. Therefore, remembering the exact or relative positions of objects is probably dependent on the same underlying process. However, it seems unlikely that the categorical/coordinate distinction can only be applied to position information and not to object-location memory, considering that spatial representations usually give information about the positions of objects. Possibly, when encoding the locations of multiple simultaneously presented objects, the objects serve as 'landmarks' characterizing the different locations, suggesting the positions of these objects are remembered in relation to each other (i.e. categorical representation). Alternatively, a coordinate representation of the exact positions of objects might be made when the location of a single object has to be remembered (cf. Alexander, Packard, Peterson., 2002). Therefore, it would be interesting to study hemispheric specialization for categorical and coordinate position information when the positions of only few objects have to be remembered.

In order to study the effect of damage to specific brain areas on spatial memory in more detail, an innovative lesion-overlap technique was developed. By transforming CT or MR images of patients to a standard brain template, it was possible to study the relation between the amount of damaged tissue in a brain area of interest and the observed behaviour in standard neuropsychological tests. This offers an interesting way of studying the neural mechanisms involved in spatial memory, as well as other cognitive processes, conveying the behavioural-neuropsychological approach with neuroimaging techniques. Future studies with larger patient groups can use a more explorative approach to unravel neural circuitries, whereas this technique can also be used to compare the overlap of lesions of patients with similar cognitive deficits, giving another way of defining the brain area(s) that is (are) involved in a particular function.

By using this lesion-overlap technique it was demonstrated that the hippocampal system is involved in several aspects of spatial memory, including the transition from spatial information from working memory into long-term memory (Chapter 4). However, it is not clear whether the hippocampal formation is specifically involved in the transition from working memory into long-term memory, or whether it is also involved in retrieving information from long-term memory and transferring it into working-memory. Additionally, the hippocampal system is involved in route retracing (e.g. Burgess, Maguire & O'Keefe, 2002) as well as recognizing landmarks, whereas it plays no significant role in remembering the order of these landmarks or drawing a map of the route. The latter two functions rely on prefrontal and temporal cortical brain areas respectively, underlining the idea that route learning involves a large and complex neural circuitry, including both allocentric and egocentric information processing (Burgess, Spiers, Paleologou, 2004).

Other brain areas that are important for spatial memory are the right posterior parietal cortex and the dorsolateral prefrontal cortex (Chapter 4). It was shown that these areas have a particular role in keeping spatial information active in working memory during a short time period. These results are in line with animal and fMRI studies showing a network underlying spatial working memory, involving the prefrontal cortex and parietal cortices (Constantinidis & Wang, 2004; Friedman & Goldman-Rakic, 1994; Glabus et al., 2003; Goldman-Rakic, 1988; Jonides, Smith, Koeppel, Awh, Minoshima & Mintun, 1993). Additionally, damage to these areas resulted in impaired navigation, further supporting their role in active or dynamic aspects of spatial memory. That is, navigation requires continuous updating of spatial information and additionally, using information that is stored in memory to find one's way around.

Two experiments with similar methods (Chapter 7 and 8) indicated that spatial and temporal-order information are not automatically processed in memory. However, when temporal-order or spatial recall was unexpected (i.e. incidental learning), performance was above chance level, suggesting some information was encoded without focused attention. These results indicate that the distinction between automatic and effortful processes is not dichotomous, but continuous. Possibly, spatial and temporal-order memory work to a certain extent automatically, but can be optimized by effort. Additionally, automaticity of spatial memory was studied in a more natural setting, i.e. when learning a route through a building (Chapter 6). The finding that basic aspects of route learning (route knowledge) were processed more automatically than the more complex aspects (survey knowledge) underlines the notion that these distinct processes involved in spatial

memory differ in the amount of attention they require. The extent of automaticity might depend on features such as complexity and amount of information. Moreover, the latter study demonstrated that future studies should not only focus on examining spatial memory in controlled, artificial circumstances, such as computer experiments, but also study spatial memory under more natural circumstances.

Interestingly, route learning was examined in a group of stroke patients with focal lesions and healthy subjects under intentional and incidental learning. Since both studies involved the same route-learning tasks, we can draw some preliminary and indirect conclusions concerning the effect of brain damage on automatic and effortful memory processes. One of the hypotheses is that automatic processes might be largely spared after brain damage, in contrast to effortful processes, such as found in patients with Alzheimer's disease (Knight, 1998; Koivisto, Portin, Seinela & Rinne, 1998; Rohlin, Ellis & Scogin, 1991). By studying route learning under intentional and incidental learning conditions it was demonstrated that tasks assessing landmark recognition and landmark-order information were largely automatic (Chapter 6). However, these tasks were impaired by damage to the right hippocampal formation and the dorsolateral prefrontal cortex respectively. Additionally, effortful memory processes, assessed with the map-drawing and route-retracing task, were also impaired by brain damage, in particular after damage to the right hippocampal formation, right temporal cortex and dorsolateral prefrontal cortex. These findings suggest that both automatic and effortful memory processes can be impaired (cf. Grafman, Weingartner, Lawlor, Mellow, Thompsen-Putnam & Sunderland, 1990). Although the current route-learning studies offer indirect and inconclusive data concerning the impact of brain damage on automatic and effortful memory process, it does indicate the importance of systematically examining this interesting subject. This would have clear benefits for the clinical assessment of cognitive deficits after acquired brain damage and might help to improve revalidation of neurological patients.

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## **Nederlandse samenvatting**

*Hersengebieden betrokken bij het ruimtelijk geheugen*

Ruimtelijk geheugen is een belangrijke cognitieve functie, die er voor zorgt dat informatie over onze omgeving wordt opgeslagen. Deze informatie kan bijvoorbeeld worden gebruikt om van A naar B te komen of te onthouden waar we onze auto hebben geparkeerd. De hoeveelheid en variëteit van ruimtelijke informatie om ons heen suggereert dat ruimtelijk geheugen niet één proces betreft, maar bestaat uit verschillende subprocessen (cf. Nadel & Hardt, 2004; Postma, 2005), bijvoorbeeld om informatie gedurende een korte of langere periode op te slaan of om de relaties tussen voorwerpen in onze omgeving in het geheugen op verschillende wijzen te representeren. Deze variëteit zien we terug wanneer we kijken naar de hersengebieden die betrokken zijn bij het opslaan en opdiepen van ruimtelijke informatie. In plaats van één enkel hersengebied dat verantwoordelijk is voor het ruimtelijk geheugen, lijkt er een netwerk te bestaan van hersengebieden die een verschillende rol in de informatieverwerking vervullen. Om de rol van deze hersengebieden nader te onderzoeken werd in het eerste deel van dit proefschrift het effect van hersenbeschadigingen op verschillende ruimtelijk geheugenprocessen bestudeerd, zoals het ruimtelijk werkgeheugen, object-lokatiegeheugen en het leren van een route.

De betrokkenheid van de rechter en linker hersenhelft in het object-lokatiegeheugen werd bestudeerd in *hoofdstuk 2*. Om de posities van verschillende objecten om ons heen te onthouden zijn een aantal processen vereist. Zo moet bijvoorbeeld object en positie informatie in het geheugen worden opgeslagen, waarbij een derde proces nodig is om deze informatie te integreren. Deze drie processen zouden functioneel verschillend zijn en ook van verschillende hersengebieden afhankelijk zijn (Moscovitch, Kapur, Kohler & Houle 1995). Recent hebben Postma, Kessels en Van Asselen (2004) gesteld dat een onderscheid kan worden gemaakt tussen relatieve, categorische (boven/beneden, links/rechts) en exacte, ‘coördinate’ positie informatie (exacte, metrische informatie). Deze verschillende vormen van ruimtelijke relaties zouden respectievelijk door neurale netwerken in de linker en rechter hersenhelft worden verwerkt (Kosslyn, 1989). Het is echter nog onduidelijk of deze zogenaamde lateralisatie effecten ook aanwezig zijn wanneer categorische en coordinate positie informatie moet worden geïntegreerd met object informatie. Om de betrokkenheid van de rechter en linker hersenhelft bij deze processen te onderzoeken werden patiënten met een laesie ten gevolge van een herseninfarct of een hersenbloeding getest met een object-lokatietest. Patiënten met een laesie in de rechter hersenhelft bleken slechter te scoren op een test die coördinat posities meet, terwijl patiënten met een laesie in de linker hersenhelft slechter scoorden op een taak die categorische posities meet. Het

onderscheid tussen categorische en coordinate relaties verdween wanneer positie informatie moest worden geïntegreerd met object informatie. Dit laatste resultaat suggereert dat er één proces verantwoordelijk is voor het opslaan van de posities van meerdere objecten.

Daarnaast werd het ruimtelijk werkgeheugen onderzocht, waarin ruimtelijke informatie gedurende een korte periode wordt opgeslagen. In *hoofdstuk 3* werden patiënten met het syndroom van Korsakov getest. Deze patiënten hebben een ernstig verstoord geheugen, vooral wanneer informatie gedurende een langere periode moet worden onthouden. Door een ruimtelijke zoektaak te gebruiken (de 'Box task') werd aangetoond dat deze patiënten tevens een gestoord ruimtelijk werkgeheugen hebben. Deze stoornis kon niet worden verminderd door het aanbieden van contextuele (kleur) cues, die de posities van de objecten markeerden.

Vervolgens werden in *hoofdstuk 4* de exacte hersengebieden die betrokken zijn bij het ruimtelijk werkgeheugen bestudeerd, door patiënten met een focale laesie in de hersenen ten gevolge van een herseninfarct of een hersenbloeding te testen met dezelfde ruimtelijke zoektaak als in hoofdstuk 3. Hiervoor werd een laesie-overlaptechniek gebruikt, waarbij CT/MRI scans van de patiënten werden genormaliseerd naar een standaard T1-template. Door het omzetten van scans van verschillende hersenen naar een standaard-formaat konden de locaties van de laesies direct met elkaar worden vergeleken. Vervolgens werd het effect van een laesie in een bepaald hersengebied op de score van patiënten op de ruimtelijke zoektaak bepaald. Hieruit bleek dat beschadiging van de rechter dorsolaterale prefrontaal cortex en de rechter posterieure parietale cortex een verstoring van het actief houden van ruimtelijke informatie gedurende een zeer korte periode (seconden) veroorzaakt, terwijl de hippocampus betrokken is bij de verwerking van deze informatie op de langere termijn.

Dezelfde laesie-overlaptechniek werd gebruikt om de hersengebieden die betrokken zijn bij het leren van een route door de ruimte te bepalen (*hoofdstuk 5*). Voor het leren van een route kunnen verschillende aspecten van de ruimte om ons heen worden gebruikt, zoals 'landmarks' (voorwerpen die een bepaalde positie langs de route kenmerken) of sensorische en motorische informatie. Tevens kan een 'mentale kaart' van de route worden gemaakt, waarin de verschillende posities langs de route ten opzichte van elkaar worden onthouden. In dit onderzoek werden patiënten met een focale lesie ten gevolge van een herseninfarct of hersenbloeding gevraagd om een route door het universiteitsgebouw te lopen. Vervolgens moesten deze patiënten 'landmarks' herkennen, foto's van landmarks in de juiste volgorde leggen, de route in een plattegrond van het gebouw tekenen en de route teruglopen. Door dezelfde techniek te gebruiken als in hoofdstuk 4, konden de hersengebieden

die betrokken zijn bij deze processen in kaart gebracht worden. Dit toonde aan dat de hippocampale formatie in de rechter hersenhelft betrokken is bij het herkennen van landmarks. Beschadiging van de temporale cortex in de rechter hersenhelft verstoort het tekenen van de route in een plattegrond, terwijl de hippocampale formatie, de posterior parietale cortex en de prefrontale cortex in de rechter hersenhelft belangrijk zijn voor het teruglopen van de route. De prefrontale cortex is tevens betrokken bij het onthouden van de volgorde van de landmarks.

#### *Automaticiteit van het ruimtelijk geheugen*

De hoeveelheid en variëteit van ruimtelijke informatie om ons heen heeft tot gevolg dat we niet altijd onze aandacht kunnen richten op deze informatie en ook niet alles in ons geheugen kunnen opslaan. Een deel van de informatie zou echter automatisch in ons geheugen worden opgeslagen, zonder dat we de intentie hebben om dit te onthouden. Van de processen die verantwoordelijk zijn voor de automatische opslag van deze informatie wordt verondersteld dat deze niet beïnvloed worden door oefening, veroudering of individuele verschillen (Hasher & Zacks, 1979). Hierdoor is het mogelijk om bijvoorbeeld een auto te besturen en tegelijkertijd een gesprek te voeren met een medepassagier. Echter, wanneer we in een nieuwe, drukke omgeving rijden, zullen we onze aandacht weer moeten richten op deze omgeving om niet te verdwalen. De mate waarin verschillende aspecten van het ruimtelijk geheugen automatisch verlopen, is in het tweede deel van dit proefschrift onderzocht.

In *hoofdstuk 6* is automatische verwerking van ruimtelijk informatie tijdens het lopen van een route onderzocht. Hiervoor werd hetzelfde experiment gebruikt als in hoofdstuk 5. Gezonde volwassenen werden gevraagd een route door het universiteitsgebouw te lopen. Hierbij werd een intentionele en incidentele leerconditie gebruikt, waarbij de helft van de proefpersonen de opdracht kreeg om de route zo goed mogelijk te onthouden, terwijl de andere helft dezelfde route liep zonder bewust op te letten. Uit de resultaten bleek dat basale aspecten van het leren van een route, zoals het herkennen van landmarks en het onthouden van de volgorde van deze landmarks automatisch worden opgeslagen in het geheugen. Daarentegen werden complexe aspecten, zoals het teruglopen van de route of het tekenen van de route in een plattegrond beter verwerkt wanneer bewust aandacht aan deze informatie gegeven werd.

In ons dagelijks leven vinden gebeurtenissen niet alleen plaats op een bepaalde locatie, maar ook op een bepaald moment. Deze natuurlijke ‘link’ tussen ruimtelijk en temporele informatie zou kunnen betekenen dat deze aspecten automatisch worden geïntegreerd in het geheugen. Dit houdt in dat wanneer we weten wáár iets

gebeurt, we automatisch weten wannéér iets gebeurt. De integratie van ruimtelijke informatie met temporele informatie is bestudeerd door objecten één voor één aan te bieden op verschillende locaties op een computerscherm (*hoofdstuk 7*). Wanneer proefpersonen de opdracht kregen om de volgorde of de positie van een object te onthouden was de presentatie beter dan wanneer ze deze opdracht niet kregen. Hieruit bleek dat ruimtelijk en temporele informatie niet automatisch worden geïntegreerd in het geheugen. Echter, ook wanneer proefpersonen niet wisten dat ze ruimtelijk of temporele informatie moesten onthouden onthielden zij meer informatie dan op basis van kans zou kunnen worden verwacht. Dit geeft aan dat een klein gedeelte van de informatie automatisch wordt verwerkt.

Het idee dat ruimtelijke en temporele informatie niet automatisch wordt verwerkt of geïntegreerd wordt verder ondersteund in *hoofdstuk 8*. Gezonde ouderen bleken minder goed in staat om ruimtelijke of temporele informatie op te slaan in het geheugen dan jong volwassenen. Aangezien automatische processen niet zouden worden beïnvloed door veroudering (Hasher & Zacks, 1979), werd hiermee wederom aangetoond dat het onthouden van temporele en ruimtelijke informatie niet automatisch verloopt. Daarnaast blijkt dat wanneer ruimtelijke en temporele informatie beide moeten worden onthouden, ouderen een additioneel probleem hebben met het integreren van deze informatie.

In dit proefschrift werd de rol van verschillende hersengebieden die betrokken zijn bij het onthouden van ruimtelijke informatie onderzocht. Hierbij werd gebruik gemaakt van een nieuw ontwikkelde laesie-overlap techniek. Door deze techniek kan in de toekomst meer gericht onderzoek worden gedaan naar bijvoorbeeld de relatie tussen beschadiging van specifieke hersengebieden en cognitief functioneren. Het tweede deel van dit proefschrift richtte zich op de vraag of aandacht noodzakelijk is voor het verwerken van ruimtelijke informatie. Hier werd aangetoond dat geheugenprocessen die nodig zijn voor het leren van een route en het integreren van temporele en spatiële informatie verschillen in de mate waarin zij aandacht vereisen. Vervolgonderzoek zal moeten aantonen wat de exacte kenmerken zijn van deze processen en in hoeverre zij afhankelijk zijn van factoren zoals complexiteit en hoeveelheid informatie.



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*Marieke, Maart 2005*

**Curriculum vitae**

Marieke van Asselen werd geboren op 8 januari 1977 in Vinkeveen. In 1995 behaalde zij het VWO diploma aan het Alkwin Kollege in Uithoorn, waarna zij psychologie ging studeren aan de Universiteit van Amsterdam. Nadat zij in 1999 zeven maanden als Erasmusstudent onderzoek had gedaan aan de Universiteit van Porto (Portugal) heeft zij negen maanden stage gelopen aan de afdeling Neuropsychologie van het Wilhelmina Kinderziekenhuis in Utrecht. In januari 2001 studeerde zij af in de richtingen Klinische psychologie en Psychonomie met als studieroute Neuropsychologie. Zij begon haar promotieonderzoek aan de afdeling Psychonomie van de Universiteit Utrecht in februari 2001.

Marieke van Asselen was born on January 8, 1977 in Vinkeveen, The Netherlands. In 1995 she completed her secondary school education at the Alkwin Kollege in Uithoorn, after which she studied Psychology at the University of Amsterdam. After doing research during seven months as an Erasmus student in Porto (Portugal), she performed her clinical internship at the Department of Neuropsychology of the Wilhelmina Children's hospital. In January 2001 she obtained her masters degree, majoring in Psychonomics and Clinical psychology, specializing in Neuropsychology. She started working on her Ph.D. project at the Department of Psychonomics at the Utrecht University in February 2001.