

Exploring Aspects of Memory in Healthy Ageing and following Stroke

Dr Marianna Evangelia Kapsetaki

Department of Brain Sciences
Imperial College London

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Abstract

Memory is critical for everyday functioning. Remembering an event with rich detail requires the ability to remember the temporal order of occurrences within the event and spatial locations associated with it. But it remains unclear whether it also requires memory for the perspective from which we encoded the event, whether these three aspects of memory are affected following stroke, and which are the key brain regions upon which they rely. These questions are explored in this thesis.

In the first study presented here, I examined young and elderly healthy subjects with an autobiographical memory interview and a 2D spatial memory task assessing self-perspective, and found no correlation between performance on these tasks.

In the second experimental study, by assessing stroke patients on a 3D spatio-temporal memory task, I found that damage to the right intraparietal sulcus was associated with poorer memory for temporal order. However, voxelwise analyses detected no association between parietal lobe regions and accuracy in the egocentric condition of this task, or between medial temporal lobe regions and accuracy in the allocentric condition, one possible reason being that performance was near ceiling.

In the third experimental study, by assessing a considerably larger group of stroke patients on a spatial memory task, I found that, as a group, patients performed worse than healthy controls, and performance was correlated with an activities of daily living scale. A spatial memory network was identified in right (but not left) hemisphere stroke patients.

These findings provide evidence that spatial memory impairment is common after stroke, highlight its potential functional relevance, and increase our understanding of which regions are critical for remembering temporal order and spatial information. Furthermore, they suggest a dissociation between the mechanisms underpinning recall of 2D scenes over relatively short intervals versus remembering of real-life events across periods of many years.

Declaration of Originality

Dr Paresh Malhotra and Dr Charlotte Russell supervised the preparation of this thesis. Some lesion analyses in Chapter 6 were performed in collaboration with Dr Paul Bentley (the specific analyses in which this occurred are stated in that chapter). Flavia Loreto was the second scorer for the autobiographical memory interviews in Chapter 4, and Roberta Calvo assisted in creating some of the pre-prepared videos in Chapter 5. The first few stroke patients that were included in the analyses of Chapter 6 were tested by myself together with Dr Ianto Redknap (9 out of the 112 patients). Also, Dr Elena Olgiati provided the names and contact details for some healthy subjects and patients that she had previously screened and/or tested (2 of those patients were included in the main experiment of Chapter 5, and 8 of those patients were included in the experiment of Chapter 6).

The resting-state functional magnetic resonance imaging (rs-fMRI) data in Neurosynth that were used in Chapter 6 were provided (in part) by the Brain Genomics Superstruct Project of Harvard University and the Massachusetts General Hospital (Principal Investigators: Randy Buckner, Joshua Roffman, and Jordan Smoller), with support from the Centre for Brain Science Neuroinformatics Research Group, the Athinoula A. Martinos Centre for Biomedical Imaging, and the Centre for Human Genetic Research. Twenty individual investigators at Harvard and Massachusetts General Hospital generously contributed data to GSP Open Access Data Use Terms Version: 2014-Apr-22 the overall project.

All other work presented in this thesis is my own and any information derived from others' research is referenced in the text. To my knowledge, this thesis conforms to the rules and guidelines for PhD theses set by Imperial College London.

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Publications and Presentations

The study presented in Chapter 4 is currently under review as part of a manuscript submitted to the *Journal of Cognitive Psychology*. Manuscripts for the results from Chapters 5 and 6 are in preparation.

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Some of the work undertaken as part of this thesis has also been presented orally or as a poster:

Elements of Chapters 2 and 3 (some patients' lesion data and performance on the star cancellation task) have been presented at the:

- Annual Meeting of the Organisation for Psychological Research into Stroke (OPSYRIS), Oxford, UK (October 2019). Poster title: Tracking spatial neglect recovery pattern following right-hemispheric stroke. Authors: Calvo, R., Olgiati, E., Kapsetaki, M. E., & Malhotra, P. A.

Elements of Chapters 4 and 5 have been presented at the:

- Rising Scientist Day, Imperial College London, UK (February 2018; poster presentation)

Elements of Chapter 6 have been presented at the:

- Meeting of the Minds Neuroscience Conference, London, UK (January 2019; poster presentation which received the People's Choice Award for Best Poster)

- Oxford Autumn School in Neuroscience, UK (September 2018; poster presentation)
- Imperial College London Brain Sciences Retreat, UK (September 2018; oral and poster presentation)
- Rising Scientist Day, Imperial College London, UK (February 2019; poster presentation)
- 4Cs Science Communication Competition, Imperial College London, UK (May 2019; oral presentation)
- Cumberland Lodge conference, Windsor, UK (August 2019; oral presentation)
- Annual Meeting of the Organisation for Psychological Research into Stroke (OPSYRIS), Oxford, UK (October 2019; oral presentation)

Abbreviations

AAL	Automatic Anatomical Labelling
ACE	Addenbrooke's Cognitive Examination
AICHA	Atlas of Intrinsic Connectivity of Homotopic Areas
ANOVA	Analysis of Variance
CI	Confidence Interval
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
EEG	Electroencephalography
FLAIR	Fluid-Attenuated Inversion Recovery
fMRI	Functional Magnetic Resonance Imaging
fPET	Functional Positron Emission Tomography
FSL	FMRIB software library
IQR	Interquartile Range
JHU	John Hopkins University
MAT	Microsoft Access Table
MEG	Magnetoencephalography
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
NIFTI	Neuroimaging Informatics Technology Initiative
NPM	Nonparametric Mapping
PET	Positron Emission Tomography
PWI	Perfusion Weighted Imaging

ROI	Region of interest
rs-fMRI	Resting-State Functional Magnetic Resonance Imaging
SD	Standard Deviation
SEM	Standard Error of the Mean
SPECT	Single-Photon Emission Computerized Tomography
SPM	Statistical Parametric Mapping
SWI	Susceptibility Weighted Imaging
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
2D	Two-dimensional
3D	Three-dimensional
4MT	Four Mountains Test

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1 General Introduction

In this chapter, I discuss the theories and models that have formed our current understanding of memory. I describe the neuroanatomy of memory for events, specifically memory for the spatial and temporal details of an event, and the self-related aspect of that event, based mainly on functional neuroimaging and lesion studies in humans, as well as some studies in non-human animals. I explore the memory changes that can occur in healthy ageing and following brain injury. Finally, I describe the aims and hypotheses of this thesis.

1.1 The importance of memory in daily life

Memory is one of the most important functions in our life. It can shape our personality, goals, and actions, and is essential for undertaking everyday activities such as driving, finding our way home, learning a language, and planning for the future. The importance of memory in our lives can be traced back to ancient Egyptian and Greek mythology in which there was a god and a goddess of memory, Thoth and Mnemosyne, respectively (Herrmann and Chaffin 1988). Interestingly, the name Mnemosyne was also given to a river which ran parallel to the river lethi (forget), from which many words are derived such as lathreos (not following the rules), alethia (truth), lathos (mistake), and lethargos (stupor).

1.2 Memory systems

The earliest notion of memory taxonomy came from Aristophanes (Mitchell 1820, p. 63):

*'...My memory is of two sorts, long and short:
With them who owe me aught, it never fails;
My creditors indeed complain of it,
As mainly apt to leak and lose its reck'ning.'*

A dichotomization of memory was also suggested by William James (1890), who used the terms primary memory (referring to short-term memory) and secondary memory (referring to long-term memory).

Experimental evidence that memory may be divided into multiple systems came from Brenda Milner's findings in the 1950s. She studied a patient (known as H.M.) who sustained damage involving medial temporal lobe regions bilaterally following resective surgery for the treatment of refractory epilepsy. There was a dissociation in the memory deficits of H.M.: a) he was able to learn new skills (implicit memory, which is the ability to perform a task without the need to consciously remember the learning event) but not new events (explicit memory), b) he was able to maintain information for a limited amount of time (working memory) but could not remember for a longer period, and c) he was able to remember with detail personal events that occurred prior to his brain surgery (although this was later proven to be untrue as he could only remember the gist of those events; Corkin 2002) but not personal events that occurred after his brain surgery (Corkin 1984; Scoville and Milner 1957). New theories were subsequently introduced; these attempted to explain how memories are consolidated, separating memory depending on the duration for which it was remembered (short- or long-term) and whether it has access to consciousness (declarative or non-declarative; Squire and Zola-Morgan 1991; Tulving 1972; Tulving and Schacter 1990; Figure 1.1).

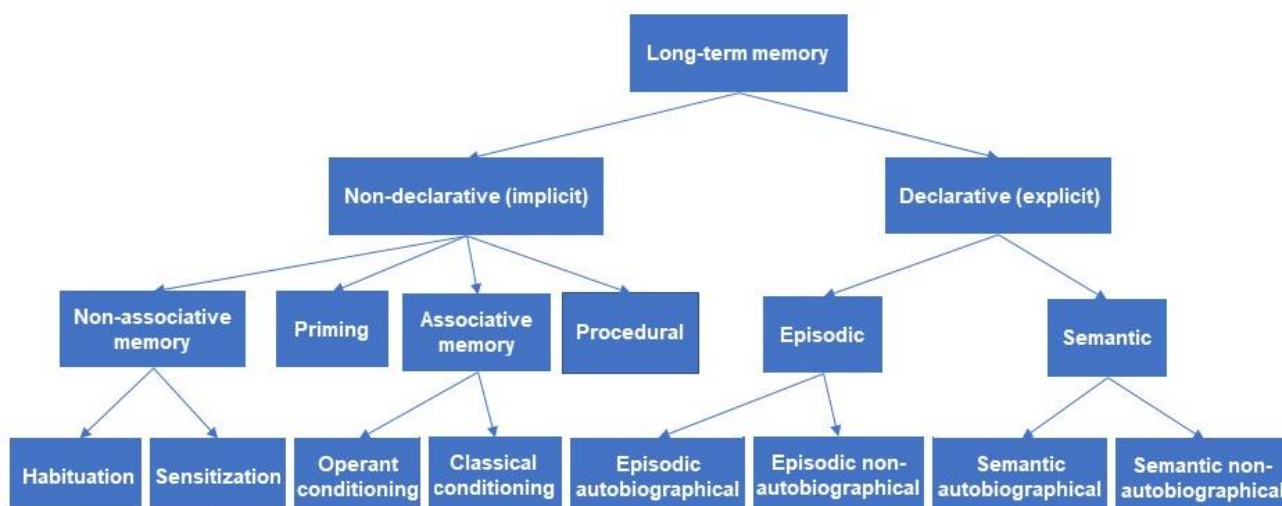


Figure 1.1. Classification of the multiple types of long-term memory

Although there is a tendency to think of each of these types of memory as entirely separate from each other, there is a lot of overlap between them.

Adapted from Gazzaniga, Ivry, and Mangun (2013).

1.3 Definitions of episodic, autobiographical, and semantic memory

1.3.1 Episodic memory

Tulving (1972, 1983, 2002) defined episodic memory as consciously accessible memory of personal events of a particular time and place, that is, the “what”, “where”, “when”, and related sensory and perceptual details such as smells or emotions, with reference to oneself as part of the event. The key features of episodic memory are that: a) it integrates the “what”, “where”, and “when” information rather than remembering each independently of the other (Burns et al. 2015; Ngo et al. 2019; Yim et al. 2013), b) it requires auto-noetic awareness which means being self-knowledgeable when re-experiencing an event (Tulving 1985, 2005), and c) it refers to events that happened only once and were encoded incidentally (without knowing that one needs to remember them; Cheke and Clayton 2013; Nadel and Hardt 2011; Zentall et al. 2001; Zentall, Singer, and Stagner 2008). These characteristics reflect how one would encode and retrieve real-life events.

The ability to retrieve an event (defined as a fragment of time in a specific location, which has a start and a finish, and is coherent and meaningful; Bird 2020; Zacks and Tversky 2001) does not only involve the ability to remember spatial information. It also involves the ability to retrieve the sequence of happenings within the event and at which timepoint in our life the event happened, either in absolute terms (absolute temporal order, e.g. remembering the exact date in which a trip to London occurred) or in relative terms (relative temporal order, e.g. remembering that a trip to London occurred after a friend’s birthday party; Friedman 2004; Wheeler, Stuss, and Tulving 1997). According to Tulving (1972, 1983, 2002), “when” is one of the three features of episodic memory, and it has been suggested that there are two processes involved in remembering the temporal order of events: reconstruction and distance processes (Friedman 1993, 2004). Reconstruction is the ability to infer when an event occurred by remembering contextual and other details associated with that event (Curran and Friedman

2003; Skowronski et al. 2003). On the other hand, distance processes rely on the vividness of the events (the strength of the memory trace). Reconstruction processes may be more effective for autobiographical events that occurred close in time (e.g. within the same day), whereas distance processes are thought to be more effective for autobiographical events that are temporally far apart (e.g. childhood compared to adulthood events; Burt et al. 2000). In laboratory-based episodic memory tasks, remembering the order of events (e.g. words or objects) tends to mainly rely on distance processes, because the stimuli are often not causally related, making it difficult to use reconstruction processes (St. Jacques et al. 2008).

Episodic memory involves the ability to remember an event with rich detail (recollection), rather than remembering it vaguely (familiarity). The doctrine of recollection was first proposed by Plato in ancient Greece (Jowett 1953), and since then, many models have emerged trying to examine the differences between recollection and familiarity. According to the dual-process models of recognition memory, recognition judgments such as discriminating whether an item was or was not presented in the encoding phase, are based on recollection and familiarity, which are functionally and neuroanatomically distinct processes (Atkinson and Juola 1973, 1974; Hintzman and Curran 1994; Mandler 1980; Yonelinas 2002).

1.3.2 Autobiographical memory

Autobiographical memory relies on both episodic and semantic memory. The ability to remember specific personal events with spatio-temporal, sensory, perceptual and emotional content is known as episodic autobiographical memory, whereas semantic autobiographical memory or personal semantics refers to semantic memory relating to the self (Piolino et al. 2006, 2009; Renoult et al. 2012; Tulving et al. 1988). Semantic autobiographical memory includes memory for repeated personal events (e.g. going to school every day), autobiographically significant concepts, and personal facts (e.g. personality characteristics,

names of friends, date of birth, and home address). This contrasts with semantic non-autobiographical memory, which refers to general non-personal knowledge (facts) about the world, e.g. encyclopaedic knowledge, and episodic non-autobiographical memory which refers to memory for specific details (“what”, “where”, and “when”) about events that have less personal significance, for example, remembering a list of words (Figure 1.1).

1.3.3 Distinction between episodic and semantic memory

Tulving (1972) was the first to propose an episodic-semantic distinction in declarative memory, which has been confirmed in many subsequent patient studies. For example, a patient with bilateral hippocampal damage had impaired memory for personal and non-personal events, both retrograde and anterograde (which means memory for information that was acquired prior and after brain injury, respectively), but intact retrograde semantic memory (Cipolotti et al. 2006). Impaired episodic memory but relatively intact semantic memory was also found in a patient with an infarct and atrophy affecting the temporal and parietal lobe bilaterally (Steinvorth et al. 2005), three patients with hypoxic brain injury affecting both hippocampi (Vargha-Khadem et al. 1997), and two patients with closed head injury (Rosenbaum et al. 2005; Tulving 1985). Furthermore, studies examining patients with semantic dementia, in which the affected regions include the anterior temporal lobes (mainly ventral), the amygdala and the head of the hippocampus (Barnes et al. 2006; Galton et al. 2001; La Joie et al. 2013; Tan et al. 2014), have shown that semantic memory is impaired whereas episodic memory is relatively intact, at least in the earlier stages of the disease (Bozeat et al. 2000; Chan et al. 2001; Graham and Hodges 1997; Hodges et al. 1992; Irish, Bunk, et al. 2016; Maguire et al. 2010; Moss et al. 2003).

On the other hand, many researchers have suggested that there is not a clear-cut separation between episodic and semantic memory; they seem to recruit both overlapping

and distinct brain regions, occur simultaneously, and interact (Glenberg 1997; Greenberg and Verfaellie 2010; Irish and Vatansever 2020; Levine et al. 2004; McClelland et al. 1995; Philippi et al. 2015; Svoboda et al. 2006; Toth and Hunt 1999; Weidemann et al. 2019). It has been noted that the episodic system involves all areas contributing to semantic memory, but also other areas which do not contribute to semantic memory, which is known as the “schema-plus-episodic” framework (Piolino et al. 2006). Thus, instead of acting as two separate systems, episodic and semantic memory could be viewed as a continuum in which each system lies at opposite ends (Grilli and Verfaellie 2014; Renoult et al. 2012). In keeping with this, Tulving (2002) posits that no (or very few) memory tasks involve a single memory system. Tasks that may be reported as examining episodic memory cannot avoid the fact that semantic memory is also contributing to some extent to an individual’s performance; information from the semantic system could be used when entering information into the episodic memory system (Tulving 1972), thus a semantic framework would be absolutely necessary when encoding an episodic memory.

1.4 Assessment of episodic and autobiographical memory

1.4.1 Episodic memory

The recollection-familiarity dissociation seems to underlie how episodic memory is defined and what is being measured in episodic memory. Various techniques have been used to distinguish recollection and familiarity (Yonelinas 2002). In the Remember-Know procedure, participants are asked to report if their recognition judgment is based on “remembering”, which means retrieving qualitative information about the stimuli presented in the encoding phase, or “knowing”, which means that the stimuli are familiar but participants cannot retrieve qualitative information about them (Knowlton and Squire 1995; Tulving 1985, 1989; Yonelinas and Jacoby 1995). In the “receiver operating characteristic” procedure, recollection and familiarity are estimated by relating accuracy to the subjects’ confidence in their judgments, using a

receiver operating characteristic curve (Rugg and Yonelinas 2003; Yonelinas 1994; Yonelinas and Parks 2007). In the “process-dissociation” procedure, the measure of recollection is the ability to retrieve the “when” and “where” features of each stimulus that was presented, which is not possible with familiarity alone (Jacoby 1991).

Episodic memory tasks can vary in the type of to-be-remembered information (e.g. verbal, spatial, or temporal order information), in how many episodic features are assessed, the dimensions of the stimuli (e.g. 2D or 3D), and the space in which they are presented (e.g. on a paper, in a virtual reality environment, or in a real environment). Tulving (1972) had initially suggested that remembering one of the words presented in a list is an episodic memory task, because one can retrieve its spatio-temporal relation to the other words and because it is a personal experience. But this view has recently been challenged. It has been reported that traditional laboratory experiments such as word list tasks, although in widespread clinical use, only examine the “what” of an experienced event and not the “where” and “when” and therefore do not capture the full nature of episodic memory, that is, the combination of “what”, “where” and “when” of an event (Nyberg et al. 1996; Tulving 2002). Cheke and Clayton (2013) assessed healthy young adults and showed that there was only a very weak correlation between a “what-where-when” memory task (a computer game in which participants were asked to find hidden coins) and a word list memory task, which suggests that these tasks assess different aspects of episodic memory. For example, the first task may involve the scene construction and autonoetic awareness features of episodic memory. The fact that many authors have used the term episodic memory to define tasks that assess different features of episodic memory, may be one of the reasons for the lack of consistent findings across studies.

Episodic memory tasks can also vary in the interval duration. Typically, episodic memory refers to information that is retained from a few minutes to many years, whereas information that is retained over shorter periods is processed mainly in working memory, specifically in the

so-called visuospatial sketchpad in the case of spatial information (according to the working memory model; Baddeley 2000; Baddeley and Hitch 1974). However, when cognitive load is high, even tasks with very short intervals may rely on episodic memory. For example, this may be the case in short-interval tasks in which: a) the integration of many elements is required (e.g. object-location binding of many different objects and locations as well as changes in viewpoint), b) the information cannot be easily rehearsed, c) the interval duration is slightly longer (e.g. one to three minutes), or d) participants are distracted (Jeneson and Squire 2012).

It is often challenging to develop tasks that examine whether memory for the “when” information is processed separately from the “where” and “what” information. In humans, one method to try to distinguish these features is to use two tasks, a “what-what-what” task and a “what-where-when” task, and then perform statistical elemental modelling to disentangle each feature from the others (Burns et al. 2015). Another method is to use tasks that manipulate either the location or temporal order of objects. Based on the findings from using the latter method, Rondina and colleagues (2017) suggested that spatial information may not be required for remembering temporal relations, but remembering spatial relations may require the incorporation of temporal information.

A phenomenon that can confound tasks that assess memory for temporal order is the serial position effect. Often when presented with a sequence of more than two stimuli, the first few stimuli (primacy effect) and last few stimuli (recency effect) tend to be remembered better than those in the middle of the list (Atkinson and Shiffrin 1968; Glanzer and Cunitz 1966; Murdock 1962). The serial position effect tends to be more pronounced for shorter retention intervals (Nairne et al. 1997), and the mechanisms that are thought to underlie the effect are that: a) the first stimulus is remembered because it was rehearsed for a longer time and thus was able to be stored in long-term memory, and b) the last stimulus is remembered because it is partly processed via working memory mechanisms (Atkinson and Shiffrin 1968).

It is important to note that in most studies examining episodic memory, subjects are aware that they are participating in a memory experiment. They are told that their memory is going to be tested, and often lists of images or words are repeated many times until participants obtain a specific score. Therefore, these experiments lack some of the key characteristics of episodic memory: incidental encoding and uniqueness of the event.

1.4.2 Autobiographical memory

Numerous studies have used structured tasks to assess autobiographical memory in patients with a stroke (Batchelor, Thompson, and Miller 2008; Berryhill et al. 2007; Drowos et al. 2010; Ernst et al. 2016; Grewal 2003; Hepner et al. 2007; Kitchener, Hodges, and McCarthy 1998; Steinvorth et al. 2005), encephalitis (Buccione et al. 2008; Calabrese et al. 1996; Fujii et al. 1999; Haslam et al. 2001; Hirano et al. 1999; Hokkanen et al. 1995; Insausti et al. 2013; Kopelman et al. 2009; Loveday and Conway 2011; Mimura et al. 2005; O'Connor et al. 1992; Reed and Squire 1998; Reinvang et al. 2000; Rosenbaum et al. 2008; Stanhope and Kopelman 2000; Stefanacci et al. 2000; Tsukiura et al. 2003; Warrington and McCarthy 1988; Wilson et al. 1995), traumatic brain injury (Conway and Tacchi 1996; Esopenko and Levine 2017; Hunkin et al. 1995; Kapur et al. 1992, 1996; Maravita et al. 1995; Markowitsch et al. 1993; Piolino, Desgranges, et al. 2007; Squire et al. 1989; Starkstein et al. 1997; Stracciari et al. 2008), or neurodegenerative conditions such as Alzheimer's disease and frontotemporal dementia (Addis et al. 2004; Barnabe et al. 2012; Hodges and Graham 1998; Hou et al. 2005; Irish et al. 2014; Irish, Kamminga, et al. 2016; Kumfor et al. 2016; Leyhe et al. 2009; Maguire et al. 2010; Meeter et al. 2006; De Simone et al. 2016; Snowden et al. 1996; Thomas-Antérion et al. 2000). In contrast, other studies have reported the presence or absence of autobiographical memory deficits in patients, but did not report exactly how autobiographical memory was assessed. Examples of this can be found in studies examining patients with a stroke (Benson et al. 1974; van Buren and Borke 1972; Carrera et al. 2004; Castaigne et al.

1981; Fukatsu et al. 1997; Kamble et al. 2015; Korematsu et al. 2010; Kurokawa et al. 2015; Miranda et al. 2015; Rahme et al. 2007; Turine et al. 2016), semantic dementia (Tu et al. 2013), encephalitis (Eslinger et al. 1993; Gorniak et al. 2006; Hierons et al. 1978; Hwang et al. 2016; Kataoka et al. 2008; McCarthy and Warrington 1992; Rose and Symonds 1960; Sellner et al. 2009; Starr and Phillips 1970), anoxic brain injury (Brown et al. 2016; Cummings et al. 1984; Victor and Agamanolis 1990; Volpe and Hirst 1983), or traumatic brain injury (Squire and Moore 1979; Vuilleumier and Assal 1995). Hence, it is difficult to obtain a clear understanding of whether autobiographical memory was affected in the latter studies. The structured tasks that are used to examine autobiographical memory usually examine the free recall of events that occurred in different lifetime periods and can sometimes include cueing in order to facilitate the generation of more details in the described events. Autobiographical memory questionnaires rely on the ability to understand the cue that is provided, search, retrieve an event, and describe it verbally. They also appear to require the ability to construct coherent scenes. This is supported by the finding that there is a correlation between performance on many autobiographical memory questionnaires and on a scene construction task (Clark and Maguire 2020).

The limitations of most of the autobiographical memory tasks are that the interviewer: a) does not have any control over the circumstances during encoding, for example, the level of involvement in the event and whether it was highly emotional, b) does not know how many times it has been previously retrieved, and c) does not know how accurate the report is. Another disadvantage of some autobiographical memory tasks is that they do not assess each lifetime period but allow the participant to choose which period they would like to describe an event from, making it difficult to systematically compare autobiographical memory between lifetime periods.

Some autobiographical memory tasks do not explicitly separate episodic from semantic information, for example, the Iowa Autobiographical Memory Questionnaire (Jones et al. 1998; Tranel and Jones 2006) and Borrini's autobiographical questionnaire (Borrini et al. 1989), whereas others do, for example, the Autobiographical Memory Interview (Kopelman et al. 1989) and the Autobiographical Interview (Levine et al. 2002). This is achieved by labelling the information in each participant's report regarding its specificity (whether it is a specific detail or a general fact) and its relation to the event (whether it relates to the event that is being described, i.e., internal detail, or not). Thus, from responses to these questionnaires, each event that is being described can be used to derive a score that reflects the degree of episodic specificity. The benefit of this process is that information that is non-episodic or irrelevant to the event is treated as separate. This way, one can exclusively assess the ability to remember details relating to one unique event, which is what defines episodic memory. The disadvantage of this process is that because episodic and semantic memory are highly integrated, it is not always clear whether the information in the autobiographical event being described is detailed and related to the event or fact-like, and thus scores can vary across different examiners (Strikwerda-Brown et al. 2019). For example, a schema can be used when describing a dinner out, and thus it is not clear whether remembering the order of happenings in that dinner should be labelled as episodic or semantic memory.

The Autobiographical Interview (Levine et al. 2002) and Autobiographical Memory Interview (Kopelman et al. 1989) do not examine the viewpoint from which the event is retrieved and the subjective experience of remembering the event. However, this can be assessed using the TEMPau task (Test Episodique de Memoire du Passe autobiographique; Episodic Memory Test of the Autobiographical Past; Piolino et al. 2003, 2009) which, in addition to separating episodic autobiographical memory from semantic autobiographical memory, also requires participants to report the state of consciousness (Remember/Know/Guess) and perspective ("field" or "own eyes" or first-person perspective versus "observer" or

third-person perspective) when retrieving each event. A first-person perspective means that they can see the event through their own eyes (as if being an actor), whereas a third-person perspective means that they can see themselves in the event (as if being a spectator; Piolino et al. 2006). As will be discussed later, these are important characteristics when examining autobiographical memory, since some patients may have intact episodic autobiographical memory when this is examined with objective measures but may have a lower subjective feeling of remembering. Additionally, some patients may have difficulty retrieving a past event from a first-person perspective which has been shown to be linked with reduced ability to retrieve many episodic details, i.e., details that are directly related to a particular event (Akhtar et al. 2017).

Autobiographical memory tasks also differ in other aspects, for example, in the number of lifetime periods, the number of events per lifetime period, in the type of cue that is given to retrieve the event (verbal cues or family photographs as used by some authors; Gilboa et al. 2004; Hodges and McCarthy 1993), whether the examiner or the participant is the rater, and in the scoring system that is used. Also, there is variation in how "impaired autobiographical memory" is defined. For example, some authors measure the number of incidents recalled, others the amount of detail recalled, and others the amount of internal details recalled. Therefore, slightly different results may be obtained in each study and it is not always the case that performance on different autobiographical memory tasks is strongly correlated. For example, some authors (Clark and Maguire 2020; Palombo et al. 2013) have found that there is no significant correlation between the Autobiographical Interview (Levine et al. 2002) Internal Details and the Episodic Score of the Survey of Autobiographical Memory (Palombo et al. 2013). On the other hand, Clark and Maguire (2020) found a significant (though only weak) correlation between the vividness score of the Memory Experience Questionnaire (Sutin and Robins 2007) and the vividness score of the Autobiographical Interview (Levine et al. 2002). The possible reason for this is that there are differences in who rates the vividness

and the amount of episodic details; in the Autobiographical Interview the details reported for each event are rated by an examiner, whereas in the Survey of Autobiographical Memory the participants rate their general ability to remember event details; the vividness in both the Memory Experience Questionnaire and the Autobiographical Interview is rated by the participant. Also, in the Autobiographical Interview, semantic autobiographical memory and episodic autobiographical memory are assessed using the same narrative and thus it is unconstrained by the examiner, whereas in the Survey of Autobiographical Memory these processes are assessed using separate questions. Clark and Maguire (2020) proposed that objective and subjective ratings seem to examine different autobiographical memory processes, and that the vividness score may be a more accurate indicator of the ability to recall an autobiographical event, than the amount of internal details. However, others argue that the amount of internal details is what indicates episodic re-experiencing (Levine et al. 2002; Palombo et al. 2015).

From the above studies, it can be seen that autobiographical memory has been studied by a number of different methods across populations, which makes it difficult to directly compare performance. Given that viewpoint in memory is potentially important, it is important to systematically examine the viewpoint from which each autobiographical event is retrieved, the subjective experience of remembering those events, and also to take into account which details are directly referring to that specific event (separate episodic from semantic information).

1.4.3 Comparison between autobiographical memory tasks and laboratory-based episodic memory tasks

There are many differences between autobiographical memory tasks and laboratory-based episodic memory paradigms. Autobiographical memory is mainly assessed using a structured

interview in which participants are asked to recall specific details (e.g. “what”, “where”, and “when”) of an event that they experienced in the past which usually occurred at least 24 hours before the testing session. In contrast, in laboratory-based episodic memory tasks the testing session usually occurs within a few hours after the encoding session (Conway 2001). Laboratory-based episodic memory tasks typically assess the ability to encode, store, and retrieve new information and the investigator has control over encoding conditions. Autobiographical memory tasks usually do not assess the participants’ current ability to encode information, and the investigator cannot be certain of the accuracy with which events are being recalled. In laboratory-based episodic memory tasks, participants tend to be instructed to remember 2D objects or words. Therefore: a) these tasks could be said to have less ecological validity (which is the concept that performance can be generalized to real world situations) compared to autobiographical memory tasks, b) participants do not encode the events naturally (incidentally), as would be the case with real-life autobiographical events, and c) the event that is encoded is likely to have less personal significance compared to a real-life autobiographical event (Mace 2019). The duration of the event being encoded can also differ between laboratory-based episodic memory tasks and autobiographical memory tasks. In the first, the duration for which each stimulus is presented (an event) is usually a few seconds, whereas in the latter, an event is defined as lasting minutes or hours (Peters et al. 2019).

The differences between autobiographical and laboratory-based episodic memory tasks are illustrated by the fact that: a) individuals with Highly Superior Autobiographical Memory obtain average or below average scores on laboratory-based episodic memory tasks, for example, remembering an abstract design, words, a story, or object locations (LePort et al. 2012; Mazzoni et al. 2019), and b) retrieving pictures of scenes that had been studied in the laboratory activates different functional brain networks compared to retrieving autobiographical events (using picture cues), even when controlling for vividness (Chen et al. 2017).

1.5 Neuroanatomy of memory for different types of information after different time intervals

1.5.1 Remembering episodic details after a long interval

1.5.1.1 Fronto-parieto-temporal network

Episodic memory is supported by a wide network including frontal, temporal (mostly medial temporal lobe) and parietal lobe regions, as has been shown in lesion and functional neuroimaging studies (Argyropoulos et al. 2019; Cabeza et al. 2008; Fletcher and Henson 2001; Simons and Spiers 2003). The “core recollection network” includes the hippocampus, parahippocampal cortex, ventral parietal cortex (including the angular gyrus), retrosplenial/posterior cingulate cortex, and medial prefrontal cortex, whereas the familiarity network includes the perirhinal cortex, anterior and dorsolateral prefrontal cortex, and dorsal parietal cortex (Aggleton and Brown 1999, 2006; Bowles et al. 2007, 2010; Brandt et al. 2009; Brown and Aggleton 2001; Diana et al. 2007; Eichenbaum et al. 2007; Holdstock et al. 2002; Mayes et al. 2002; Montaldi et al. 2006; Poppenk and Moscovitch 2011; Rugg and Vilberg 2013; Staresina et al. 2013; Vilberg and Rugg 2008; Wolk et al. 2011; Yonelinas 2002; Yonelinas et al. 2005). It should be noted that some studies suggest that the hippocampus is required for both recollection and familiarity (Kirwan et al. 2010; Manns et al. 2003; Merkow et al. 2015; Wais et al. 2006; Wixted and Squire 2010). Some of the reasons for these divergent findings could be that: a) some studies that have tried to examine the neural correlates of recognition and familiarity based on patients’ lesions lack high resolution scans, which makes it challenging to determine the exact location of damage (MacPherson and Della Sala 2019), and b) the hippocampus may be required for familiarity-based recognition for specific types of material (Bird 2017). The mechanism by which episodic recollection is thought to occur is that the features of an event, for example, the “what”, “where” and “when” information, which are represented in different neocortical areas, are linked together into “event engrams” in the

hippocampus, and by hippocampal pattern completion and neocortical reinstatement (via the entorhinal cortex; Staresina et al. 2019; Teyler and DiScenna 1986; Teyler and Rudy 2007) one is able to retrieve all features of that event (Horner et al. 2015; Staresina and Wimber 2019).

A meta-analysis of functional neuroimaging studies examining autobiographical memory showed that the core regions of the autobiographical memory network are the ventrolateral prefrontal cortex, the medial prefrontal cortex, retrosplenial/posterior cingulate cortex, temporo-parietal junction, medial temporal lobe, middle temporal gyrus, and cerebellum (Svoboda et al. 2006). These regions seem to significantly overlap with the so-called default mode network (Philippi et al. 2015; Spreng and Grady 2010), a network of regions that are particularly active during resting-state fMRI (Buckner, Andrews-Hanna, and Schacter 2008).

Further evidence about the important role of fronto-temporo-parietal regions in episodic memory comes from research carried out in patients with neurodegenerative disease. Patients with Alzheimer's disease, a condition that is characterized by extracellular amyloid-beta protein plaques and intracellular tau protein tangles which accumulate in temporal and parietal lobe regions, as well as in the frontal lobe at later stages of the disease (Braak and Braak 1996; Hardy and Selkoe 2002), tend to show episodic autobiographical memory impairment with no temporal gradient; they report a limited amount of internal details for both recent and remote autobiographical memory events (Irish, Hornberger, et al. 2011; Irish et al. 2018; Ivanoiu et al. 2006; Piolino et al. 2003). No temporal gradient in episodic autobiographical memory impairment seems to occur in patients with behavioural variant frontotemporal dementia (Irish, Hornberger, et al. 2011; Piolino, Chételat, et al. 2007). This is a condition that can affect prefrontal, lateral and medial temporal lobe regions (mostly anterior rather than posterior regions of the amygdalohippocampal structure), and basal ganglia (Barnes et al. 2006; Piguet and Hodges 2013). The impairment found in these patients is thought to be due

to deficient strategic retrieval processes (Hou et al. 2005; Irish, Hornberger, et al. 2011). La Joie and colleagues (2014) found that hippocampal connectivity within a network that includes the precuneus/posterior cingulate and angular gyrus, regions that are part of the “posterior medial system” (Ranganath and Ritchey 2012), underlies episodic memory, and that glucose metabolism in this network was lower in Alzheimer’s disease compared to semantic variant primary progressive aphasia. Ramanan and colleagues (2019) assessed patients with Alzheimer’s disease or corticobasal syndrome and found that the volume of fronto-parietal and medial temporal regions, as well as the integrity of fronto-parietal and fronto-temporal white matter tracts were related to performance on a delayed word-recall episodic memory task. A study which tested Alzheimer’s disease and frontotemporal dementia patients’ autobiographical memory for recent and remote events at two time points (one year apart) found that changes in the events’ internal details between the first and second testing session were related to cortical thinning in frontal regions (left inferior frontal gyrus/insula, right orbitofrontal cortex), temporal lobe regions (left middle temporal gyrus), and the right lingual gyrus (Irish et al. 2018). These authors also found that cortical thinning of the left temporo-parietal junction and posterior cingulate cortex/precuneus was related to changes in the amount of internal details for recent memories. Therefore, work in neurodegenerative conditions indicates that primarily regions of the default mode network seem to be critical for retrieving episodic details about past autobiographical events.

1.5.1.2 Temporal lobe

The most well-known individual to present with autobiographical memory impairment as a consequence of damage to the medial temporal lobe was the extensively studied case, H.M. (Corkin 1984; Scoville and Milner 1957). This patient, at the age of 27, underwent bilateral mesial temporal lobectomy for treatment of epilepsy, which damaged the medial temporal polar cortex, amygdaloid complex, entorhinal cortex, and parts of the hippocampal formation

(dentate gyrus, hippocampus proper, and subicular complex). Later, additional areas were found to be abnormal, with atrophy of the mammillary bodies and the cerebellum being detected using 1.5T Magnetic Resonance Imaging (Corkin et al. 1997), and damage in the left lateral orbital gyrus and frontal white matter being found at post-mortem examination (Annese et al. 2014; Winter 2018). Patient H.M. could not retrieve any autobiographical events from the 11 years prior to his brain surgery (Corkin 1984; Sagar et al. 1985; Steinvorth et al. 2005), but seemed to be able to retrieve autobiographical events for the period up to 16 years old (using the modified Crovitz test; Corkin 1984; Sagar et al. 1985). However, when using the Autobiographical Interview (Levine et al. 2002), which can more accurately separate episodic from semantic information, Steinvorth and colleagues (2005) found that he could not remember any episodic autobiographical events from any lifetime period; he could remember the gist of a personal event, but not its details; his autobiographical memories seemed to be “semanticized” (Corkin 2002).

Although work with H.M. highlighted the importance of the medial temporal lobe in episodic memory, it could not elucidate whether one hemisphere may be more important in episodic memory than the other. A study which used a similar approach in patients with unilateral rather than bilateral lesions, indicated that the right temporal lobe may have a more important role in episodic memory. Specifically, impaired memory for object locations (24 hour interval) was found in patients with right but not in those with left temporal lobe lesions (due to surgery for the treatment of epilepsy; Smith and Milner 1981).

Some studies have examined whether particular medial temporal lobe and deep brain structures are more important for episodic autobiographical memory than others. Stroke patients who have damage to the hippocampus but not bilaterally, or to only one region of the hippocampus, or to non-hippocampal medial temporal lobe regions, tend to have unimpaired ability to retrieve details about past autobiographical events (Batchelor et al. 2008; Eslinger

1998; Gray et al. 2010; Keven et al. 2018; Zola-Morgan et al. 1986). On the other hand, stroke involving both thalami can lead to episodic autobiographical memory deficits for all lifetime periods (Hodges and McCarthy 1993; Miller et al. 2001). Also, patients who suffered a left thalamic infarct (some of which also had damage in the right thalamus, right putamen, brain stem, or cerebellum) and reported memory complaints, performed significantly worse than healthy controls in a 2D object location recall task after a one day, one week, two weeks and four weeks interval but not after a one hour interval (Tu et al. 2014). Most of these bilateral thalamic lesions would likely have affected the functionality of both hippocampi, as the thalamus is connected to the hippocampus via the mammillothalamic tract, mammillary bodies and fornix (Aggleton et al. 2010), potentially explaining these findings.

Studies that have examined different regions within the hippocampus have shown that the posterior division appears to be involved in more detailed representations, whereas the anterior division appears to be involved in more broad/global representations (Poppenk et al. 2013). This is supported by literature in semantic dementia, in which the progression of the disease from the head of the hippocampus to other parts of the hippocampus may explain the absence of episodic memory deficits in the early stages and their presence in later stages of the disease (Tan et al. 2014). The progression of the disease along the longitudinal axis of the hippocampus could also explain the differences found in the number of incidents recalled and the amount of detail recalled in autobiographical memories across different semantic dementia patients. For example, some authors have found impaired autobiographical memory equally across all lifetime periods (Maguire et al. 2010); others found more impaired autobiographical memory for remote compared to recent events (Graham and Hodges 1997; Hou et al. 2005; Irish, Hornberger, et al. 2011; Nestor et al. 2002; Piolino et al. 2003); others found preserved autobiographical memory across all lifetime periods (McKinnon et al. 2006; Moss et al. 2003; Westmacott et al. 2001). Furthermore, functional neuroimaging studies have shown that the posterior division is more involved in retrieval whereas the anterior division is more involved

in encoding, known as the Hippocampal Encoding/Retrieval model (Lepage et al. 1998) or Hippocampal Encoding/Retrieval and Network model (Kim 2015), and that both the anterior and posterior hippocampus are activated for remote and recent autobiographical memories (Viard et al. 2007), but for recent autobiographical memories the activations seem to be distributed more towards the anterior part (Gilboa et al. 2004).

1.5.1.3 Parietal lobe

A number of studies examining the close relationship between memory and attention in the parietal lobe have suggested that the parietal lobe's contribution to episodic memory may be only due to its vital role in attention (that is, it directs attention to memory contents), and have hypothesized a model known as the Attention to Memory model (Cabeza et al. 2008, 2011; Ciaramelli, Grady, et al. 2010; Ciaramelli et al. 2008). This model was mainly derived from the vast literature indicating that the parietal lobe has a key role in attention. However, many studies have shown that the parietal lobe does have a separate role in memory independently of attention; it appears that some regions within the posterior parietal cortex are associated with attention and other areas are associated with episodic memory retrieval (Hutchinson et al. 2014; Sestieri et al. 2017).

Recent neuroimaging, brain stimulation and patient case series have indicated that the parietal lobe seems to be involved in aspects of episodic memory. Inhibitory brain stimulation to the left angular gyrus can lead to reduced internal details when recalling autobiographical events (during free but not cued recall; Bonnici et al. 2018). Similarly, two patients with bilateral posterior parietal lobe infarction reported significantly less time, perceptual and thought internal details (but not significantly fewer event or place internal details) when recalling autobiographical events (Berryhill et al. 2007); this was found under free recall but not after specific probe questions, and it is important to note that the patients were significantly worse

than controls in one of the many mental imagery tasks that they performed. This dovetails with the finding that three stroke patients with right or left posterior parietal lobe damage who performed the Autobiographical Interview (Levine et al. 2002) and an anterograde memory task (words paired with definitions), were not significantly worse than healthy controls in either the internal details of the autobiographical events (in the specific probe condition) or in their accuracy in the anterograde memory task, but their subjective experience of remembering in the latter task was impaired (Davidson et al. 2008). Although cued recall on the anterograde memory task was not significantly different from controls, it was below average in two of these patients but above average in the other patient. This could be explained by the fact that the two patients were tested within one year post-stroke, whereas the latter was tested after four years. In all three patients, their lesion involved damage to the angular gyrus and temporo-parietal junction. Hippocampal function may have been affected in these two patients leading to a slightly (but not significantly) poorer cued recall, because: a) these regions seem to be connected with the hippocampus, as has been shown in studies with monkeys (Clower et al. 2001), and b) damage to the temporo-parietal junction is thought to cause the most extensive diaschisis (Alstott et al. 2009), a phenomenon that tends to occur in the early stages post-stroke. In summary, although these studies recruited very few patients, they provide preliminary evidence that the parietal lobe (particularly the angular gyrus) may be important for retrieving particular event-related details and for the subjective feeling of re-experiencing a past event.

Further evidence for the importance of the parietal lobe in memory can be found in patients with neurodegenerative syndromes such as posterior cortical atrophy. In this condition, the parietal lobes tend to be among the first regions to be affected and patients often present with visuospatial deficits (Andrade et al. 2012; Lehmann et al. 2011). Thus, it can be difficult to detect a memory deficit independent of the visuospatial deficits. Nevertheless, patients with posterior cortical atrophy seem to be impaired in the memory

subscale of the Addenbrooke's Cognitive Examination-Revised (ACE-R) even in the early stage of the disease (Ahmed et al. 2016) and also have impaired verbal recall (Tsai et al. 2011).

The role of the parietal lobe in egocentric episodic memory and in adopting a first-person perspective in autobiographical memory tasks is discussed in section 1.6.6 and Chapter 5.

1.5.1.4 Frontal lobe

Episodic autobiographical memory deficits have been found also in some stroke patients with frontal lobe involvement (Batchelor et al. 2008; Cole et al. 2014; Costello et al. 1998; Johnson et al. 1997; Della Sala et al. 1993); though another study did not find such deficits (Tranel and Jones 2006). These impairments can be explained by the fact that remembering autobiographical events relies on cognitive processes such as motivation, attention, effort, strategies, reasoning, monitoring, cognitive flexibility and working memory. These functions are often impaired following damage to the frontal lobe, potentially explaining a secondary effect on memory. This can be supported by Mangels' study (1997) in which memory for temporal details was impaired under the intentional but not under the incidental encoding condition in patients with frontal lobe damage, implying that the impairment was due to executive deficits at encoding rather than a deficit in retrieving the information. Further support for this comes from another study with frontal lobe patients, showing that performance on the autobiographical memory task correlated with performance on the executive tasks (Della Sala et al. 1993).

A study that assessed two patients with bilateral orbitofrontal damage due to anterior communicating artery aneurysm rupture, found that one patient (damage to Brodmann areas 10, 11, and 47) performed similarly to controls in an object location recall task, whereas the

other patient who had a smaller lesion (damage to Brodmann areas 10 and 11) was significantly impaired (Duarte et al. 2010). However, the latter was 22 years older than the mean age of the healthy controls. The influence of age can be further supported by the fact that the first patient (10 years under the mean age of healthy controls) performed well above the healthy controls' average score in all the standard neuropsychological tests (Rey Auditory Verbal Learning Test, Controlled Oral Word Association Task, Wisconsin Card Sorting Test, digit span, and Rey-Osterrieth Complex Figure Test delayed recall), but the older patient was borderline abnormal in all of these tests.

1.5.1.5 Other regions

Additional regions have also been associated with episodic autobiographical memory deficits after stroke. Firstly, damage to the basal forebrain can lead to impaired recall for autobiographical facts or events for all lifetime periods (Tranel and Jones 2006), or an episodic autobiographical memory deficit only for the childhood period (von Cramon et al. 1993), or no autobiographical memory deficits (Weniger et al. 1995). Second, a patient with occipital lobe damage had impaired recall for autobiographical facts or autobiographical events only for childhood, adolescence and young adulthood (Tranel and Jones 2006), which may have occurred due to the importance of the occipital lobe in mental imagery (D'Esposito et al. 1997).

1.5.2 Remembering spatial information after a short interval

1.5.2.1 Functional neuroimaging

Fronto-parieto-occipital regions seem to be recruited in spatial working memory tasks that involve 2D visual stimuli. Positron Emission Tomography (PET) studies have found activations in: a) prefrontal, premotor, parietal, and occipital regions (all in the right hemisphere) when performing a spatial working memory task (remembering the position of three black dots after

a 3-second delay; Jonides et al. 1993), and b) the dorsal prestriate and posterior parietal cortices both when encoding the location of 2D objects and when recognizing the objects' location immediately after they had all been presented (Owen et al. 1996). A fMRI study showed that similar regions were activated during a 3D tactile and a 2D visual spatial working memory task: posterior parietal, dorsolateral prefrontal and anterior cingulate cortices (Ricciardi et al. 2006). On the other hand, when spatial working memory tasks involve visual stimuli that are more 3D-like, medial temporal lobe regions seem to also be recruited. For example, the parahippocampal cortex and hippocampus were involved in processing the spatial location of 3D-like objects shown in a grid on a screen (Hannula and Ranganath 2008; Libby et al. 2014), and a fronto-parieto-temporal network (including the precuneus, inferior parietal cortex, and posterior parahippocampal gyrus) was activated when recognizing the location of 3D-like objects in a virtual environment (Schmidt et al. 2007).

Many fMRI studies have shown that the left hemisphere appears to be involved mostly in nonspatial working memory, whereas the right hemisphere appears to be involved mostly in spatial working memory (D'Esposito et al. 1998; Nagel et al. 2013; Walter et al. 2003). Bellgowan and colleagues (2009) asked participants to remember the identity or location of fractal images (18-second delay) and found that item encoding and recognition were biased to the left perirhinal and entorhinal cortices, whereas spatial encoding and recognition were biased to the right perirhinal and entorhinal cortices. Other studies have challenged these findings. Although Ray and colleagues (2008) found greater activation in the left hemisphere for verbal compared to spatial working memory, they did not find that the right hemisphere was more active for spatial compared to verbal working memory. Also, Nystrom and colleagues (2000) found bilateral frontoparietal activations in both verbal and spatial working memory tasks, but there was no hemispheric difference. The difficulty in discerning whether there is a hemispheric lateralization for spatial and verbal information may partly lie in the fact that scene visual imagery strategies are used more frequently than verbal strategies in some

verbal memory tasks, and that verbal strategies can be used to remember spatial information (Clark et al. 2020).

Functional neuroimaging studies can indicate which regions are involved in a particular function, but in order to understand which regions are critical, one needs to examine patients with brain lesions (Adolphs 2016; Fellows et al. 2005; Malhotra and Russell 2015; Rorden and Karnath 2004). These authors suggest that in lesion studies the relationship between impaired task performance and the lesioned region is causative, whereas in functional neuroimaging studies of healthy individuals the relationship between task performance and brain activations is correlational. Some activated regions may not be essential for performing a particular task; they may have been activated solely because they are connected to the regions that are critical for performing that task, for example, due to the strong homotopic connections between the hemispheres (Rorden and Karnath 2004).

1.5.2.2 Lesion studies

A number of studies have assessed the ability to remember spatial locations after a short interval in patients with brain damage due to different aetiologies. One study found that among patients with no visual field deficit, neither the right nor the left hemisphere group performed significantly worse than healthy controls on the Corsi block task (De Renzi et al. 1977). This is a commonly used task to assess spatial working memory, in which participants observe a sequence of up to nine tapped blocks (or highlighted squares) located in different positions and are asked to immediately repeat it in the forward or backward order (Corsi 1972). Also, amnesic patients (due to Korsakoff's syndrome, viral encephalitis, stroke causing bilateral thalamic damage, or a colloid cyst in the third ventricle) were not impaired in a delayed (maximum forty seconds) matching-to-sample spatial task of abstract black and white patterns, and a subject with damage involving the mammillary bodies bilaterally (due to a

traumatic accident) performed at the lower end of the normal range (Holdstock et al. 1995). In contrast, Mayes, Meudell and MacDonald (1991) presented a series of short words in one of four positions on a computer screen, and found that a cohort of amnesic patients (due to different pathologies) were significantly impaired in recalling the location at which they had seen the words, with no significant difference between the different pathologies. The majority of these studies did not include neuroanatomical lesion delineation.

Studies that have looked more closely at the lesion anatomy, have indicated the importance of the frontal and medial temporal lobe in spatial working memory. Patients with brain damage involving the dorsolateral prefrontal cortex (due to stroke or cortical excision for the relief of epilepsy) performed adapted versions of the Corsi block task (Ferreira et al. 1998). They were impaired in spatial and spatio-temporal delayed recall (10-second delay), but not in spatio-temporal delayed recognition. Among patients with temporal lobe damage (due to surgery for the treatment of epilepsy), the right but not the left hemisphere group showed impaired memory for object-locations (no interval or one minute delay; Abrahams et al. 1997; Bohbot et al. 1998; Smith and Milner 1981). Evidence for the important role of medial temporal lobe regions in binding elements, which is one of the key characteristics of episodic memory, comes from a study showing that patients with medial temporal lobe damage (due to anoxia or encephalitis) were not impaired in remembering features on their own, but were impaired when they needed to remember object-location conjunctions (both after a 1-second and 8-second delay; Olson, Page, et al. 2006). Bilateral hippocampal damage (though in most cases this was not focal) seems to cause impaired recall and recognition for topographical stimuli (Cipolotti et al. 2006), impaired ability to remember the positions of objects within a scene after a three seconds or a longer delay (Hannula et al. 2006), and impaired ability to remember the location of 2D squares after a 4-second delay (Olson, Moore, et al. 2006).

In conclusion, work with patients who have lesions of different aetiologies has shown that the dorsolateral prefrontal cortex and the medial temporal lobe (particularly the right hippocampus) seem to be important for remembering item locations after a short delay. However, in addition to these regions, fMRI studies have consistently found parietal lobe involvement in memory for spatial locations, and this has been further explored in patients, particularly individuals who have suffered a stroke (see below).

1.5.2.3 Stroke

Studies that have examined spatial working memory in stroke patients, using the Corsi block task or more purely spatial memory tasks, have found conflicting results.

1.5.2.3.1 Corsi block task (micro-scale version)

Many studies have shown that stroke patients' performance on the Corsi block task (or a very similar version) was not significantly worse than healthy controls (Annoni et al. 2003; van Asselen et al. 2008, 2009; Böttger et al. 1998; Claessen, Visser-Meily, de Rooij, et al. 2016; van der Ham et al. 2011, 2012; Jaillard et al. 2009; De Nigris et al. 2013; Nys et al. 2006) and that performance did not differ between left and right hemisphere stroke patients (van Asselen et al. 2008, 2009; van Asselen, Kessels, Neggers, et al. 2006; van der Ham et al. 2011, 2012; Kessels, de Haan, et al. 2002; Kessels, Kappelle, et al. 2002; Martin et al. 1996). Studies that have examined the lesion anatomy found that there was no significant difference in performance between patients with posterior parietal cortex involvement, patients with dorsolateral prefrontal cortex involvement or patients with hippocampal involvement; they all performed within the normal range (van Asselen, Kessels, Neggers, et al. 2006). Case studies and case series have shown that performance on the Corsi block task was not impaired after damage to the: a) right parietal lobe (Russell et al. 2019), b) right parietal cortex and bilateral

occipital cortices (van Assche et al. 2016), c) right parietal area and right parahippocampal gyrus (Luzzi et al. 2000), d) right basal ganglia (Mazzoni et al. 1997), e) dorsal paramedial region of the right thalamus (Della Sala et al. 1997), or f) right temporal lobe (Piccardi et al. 2011). There are many possible reasons why these studies did not detect any spatial working memory deficits. Firstly, most of them did not test patients within the first week post-stroke, but usually many months after, and thus patients may have recovered from any potential memory deficit. Second, the Corsi block task is not a complex or ecological task, and thus subtle memory deficits may have been missed.

In contrast, other studies have found that stroke patients performed significantly worse than healthy controls on the Corsi block task (Carelli et al. 2011; Hanley et al. 1991; Kant et al. 2017; Karimian et al. 2018; Kessels, Kappelle, et al. 2002; Malouin et al. 2004; Vallat-Azouvi et al. 2014) and case studies have found impaired performance when the lesion involves the thalamus (Ghika-Schmid and Bogousslavsky 2000; Kraft et al. 2015; Rusconi et al. 2014) or inferior parietal lobe (Baldo and Dronkers 2006). However, there are some confounds associated with these studies. First, some of these studies (Baldo and Dronkers 2006; Karimian et al. 2018; Rusconi et al. 2014; Vallat-Azouvi et al. 2014) did not report whether patients had spatial neglect on the day of the experiment. Spatial neglect, also known as unilateral neglect, hemineglect, or visuospatial neglect, a syndrome which is often present in the acute stage post-stroke, could have potentially aggravated patients' performance on the task because patients with this condition are unable to attend to (and thus encode) stimuli in the contralesional side of space (Parton et al. 2004). Second, because performance on the Corsi block task depends on the ability to remember both the temporal order and the location of the stimuli (Berch et al. 1998; Cavallini et al. 2003; Malhotra et al. 2005), impaired performance may have been due to the inability to remember their temporal order rather than their location.

1.5.2.3.2 Pure spatial working memory tasks

Many studies have examined spatial working memory in stroke patients using tasks that assess only the ability to remember the location of stimuli (after a few seconds or no interval), as opposed to remembering both the location and temporal order of the stimuli. Although most of these studies have found that stroke patients perform worse than healthy controls (van Asselen et al. 2008, 2009; van Asselen, Kessels, Neggers, et al. 2006; Berryhill and Olson 2008; Duffin et al. 2012; van Geldorp et al. 2013; van der Ham et al. 2012; Hartley et al. 2007; Kessels, Kappelle, et al. 2002; Kubat-Silman et al. 2002; Rossit et al. 2011), often spatial neglect was not screened for on the day of testing (van Asselen et al. 2008; van Geldorp et al. 2013; Hartley et al. 2007; Kubat-Silman et al. 2002). As discussed previously, if patients did have this condition, their lateralized bias may have been the reason for their poor performance on the tasks. Future studies of spatial aspects of memory in stroke patients need to carefully address the possible effects of lateralized bias by meticulous assessment for and documentation of the presence of spatial neglect.

Some studies have examined whether lesion location affects performance on purely spatial working memory tasks. Using a 2D object-location working memory task, one study found that right hemisphere (but not left hemisphere) stroke patients performed significantly worse than healthy controls (van Asselen, Kessels, Neggers, et al. 2006), other studies found no significant difference in performance between left and right hemisphere stroke patients (Kessels, de Haan, et al. 2002) and that both groups were unimpaired (Kant et al. 2017), while another study found that patients with left hemisphere stroke were impaired when they were asked to place the objects on a 7 x 7 grid but were unimpaired when there was no grid, and the exact opposite occurred in the right hemisphere group (van Asselen et al. 2008).

In a group of thirty stroke patients, those with damage involving the left hippocampus, right hippocampus, right posterior parietal cortex, or right dorsolateral prefrontal cortex were

impaired on a 2D object-location working memory task (van Asselen, Kessels, Neggers, et al. 2006). The importance of the right posterior parietal cortex has also been shown in a study in which right hemisphere stroke patients with spatial neglect who had (but not those who did not have) posterior parietal cortex involvement were impaired on a purely spatial working memory task, even for targets presented in their ipsilesional side (Pisella et al. 2004). Furthermore, researchers examining patients who had a stroke involving the right posterior parietal cortex (Berryhill and Olson 2008), or thalamus unilaterally (Kubat-Silman et al. 2002), found that these patients were impaired on a purely spatial working memory task (one to three seconds interval), though others found that a stroke patient with damage involving the left thalamus was not impaired in a task with a slightly longer interval (recognizing the location of abstract designs after a 3-minute interval; Parkin et al. 1994).

1.5.2.3.3 Conclusion

In conclusion, the fact that some stroke patients show deficits on the Corsi block task suggests that they may have difficulty in remembering the spatial location of stimuli within an event, their temporal order, or both. In tasks that assess purely spatial memory after a short interval, most studies have found that stroke patients are impaired, and damage involving the hippocampus, thalamus, or right posterior parietal cortex, seems to lead to the worst performance. However, there are some limitations in these studies that need further clarification. Firstly, most of them included patients who had (or had not been screened for) the following conditions: spatial neglect, visual impairments and/or aphasia. A lateral bias and the inability to understand instructions may be the reason why some patients were found to perform poorly on memory tests, rather than having a memory deficit per se. Second, most of these studies used stimuli that were: a) dots, 2D shapes, or 2D objects, b) presented on a white background or on a 2D grid, and c) shown on a screen. Although this indicates that these experiments were well-controlled, it also means that more work is needed using ecological tasks because these might

more accurately illustrate how patients perform in real-life situations. They might thus be more effective for screening and for examining the effect of therapeutic agents on real-life spatial memory deficits. Third, most studies did not examine lesion-behaviour relationships by performing statistical analyses, but rather examined single cases or small groups of patients whose lesion involved damage to one region of interest. As will be discussed in Chapter 3, voxelwise statistical analyses can more accurately infer which regions are related to a specific function. Hitherto, no study examining stroke patients' ability to remember spatial information has all the following characteristics: a) patients do not have deficits such as hemianopia, spatial neglect, or aphasia, b) ecological task which assesses spatial information separately from other types of information (e.g. temporal order), and c) voxelwise statistical analysis. The experiments described in Chapters 5 and 6 were designed to meet these characteristics; by assessing a patient group with clearly defined lesions they aimed to provide a fuller understanding of the critical networks and mechanisms underpinning spatial memory.

1.5.3 Remembering temporal information

1.5.3.1 Functional neuroimaging

Functional neuroimaging studies have shown that encoding and maintenance of temporal order relies on a dorsal fronto-parietal network including the dorsolateral prefrontal cortex and posterior parietal cortex (Amiez and Petrides 2007; Marshuetz et al. 2000; Roberts et al. 2018), independent of whether the stimuli are verbal or visual (Majerus et al. 2007, 2010). In another study, judging the temporal order in which squares were presented activated the temporo-parietal junction bilaterally, the right supramarginal gyrus, the right inferior frontal gyrus, and the superior frontal gyrus bilaterally (Davis et al. 2009). Also, Knutson, Wood and Grafman (2004) found greater bilateral frontal lobe activations when participants made judgments about the order of past events or the order of happenings in common everyday schemas compared to judging whether the events were semantically related to the

category/script group title. Specifically, the prefrontal cortex seems to be involved in memory for temporal order, as encoding activity in the prefrontal cortex is greater for subsequent accurate (compared to inaccurate) recall of the absolute temporal order of 2D objects (Jenkins and Ranganath 2010), and the greater the precision with which the order of movie scenes are recalled the greater the activity bilaterally in the medial prefrontal cortex, angular gyrus, and posterior cingulate cortex (Montchal et al. 2019). Kwok and colleagues (2015, 2012) found that the ability to retrieve the temporal order of scenes from a movie was associated with activations in the precuneus and the angular gyrus. Furthermore, greater activation was found in bilateral parietal lobe regions when participants judged the order of syllables they had heard a few seconds before, compared to judging the gender of the speaker (Moser et al. 2009). One may argue that this does not necessarily indicate that bilateral parietal regions are involved specifically in memory for temporal order; the greater activation could have been due to the greater working memory load in the first task. However, this idea can be partly ruled out by findings of another study in which the control task was slightly more taxing. Specifically, Majerus and colleagues (2006) found greater bilateral parietal lobe activity when participants recognized the order of words they had seen a few seconds before, compared to making old/new recognition judgments about the identity of the words.

Functional neuroimaging studies have also found medial temporal lobe involvement in memory for temporal information. Medial temporal lobe regions such as the posterior hippocampus and perirhinal cortex, were more active when encoding and maintaining temporal order information (compared to “what” information) in a working memory task involving 2D shapes (Roberts et al. 2018). Studies have found that encoding activations in the hippocampus and parahippocampal cortex predicted the subsequent accurate recall of the relative and absolute temporal order of 2D objects, respectively (Jenkins and Ranganath 2010), and the ability to retrieve the order of sequentially presented word triplets (Tubridy and Davachi 2011). These two regions were also found to be involved in recalling the sequence of

scenes in a movie (Lehn et al. 2009). However, the accuracy with which the absolute or relative temporal order of these scenes were recalled was associated with the hippocampus and the perirhinal and anterolateral entorhinal cortices, but not the parahippocampal cortex (Lehn et al. 2009; Montchal et al. 2019). The hippocampus is activated during event boundaries, it integrates information across events (Koster et al. 2018), that is, it joins temporal gaps so that it can link separate events (Hales et al. 2009; Hales and Brewer 2010; Staresina and Davachi 2009), and its activity is related to the retrieval of object or face sequences (DuBrow and Davachi 2016; Ezzyat and Davachi 2014; Hsieh et al. 2014; Jenkins and Ranganath 2016).

Thus, the hippocampus and parahippocampal gyrus, in addition to spatial memory, seem to be involved in memory for temporal order. Some authors have proposed that these processes may not be separate but in fact they may be one single process, that is, the hippocampus may be involved in content-independent sequence processing (linking spatial and temporal gaps; Buzsáki and Tingley 2018; Friston and Buzsáki 2016). As many of the above-mentioned types of stimuli are present in real-life events, these findings indicate that these two regions may be important for remembering the temporal details of personal real-life events.

1.5.3.2 Lesion studies

Although functional neuroimaging studies have shown that a fronto-temporo-parietal network seems to be involved in memory for temporal information, assessing patients with brain damage can reveal whether these regions are critical for this function.

Most studies assessing patients whose lesions involve the medial temporal lobe found deficits in remembering the temporal order of different types of stimuli. Although patient H.M., whose surgery involved both medial temporal lobes, was unimpaired in recency discrimination

tasks of verbal and non-verbal material (Sagar et al. 1990), subsequent studies with a larger sample size found temporal order memory deficits in such patients. For example, patients with bilateral hippocampal damage (unknown aetiology or hypoxic brain injury) were impaired in recognizing the order of verbal and non-verbal stimuli (Hopkins et al. 1995), both within a list and between lists (Mayes et al. 2001, 2004). Spiers and colleagues (2001) found that left (but not right) temporal lobectomy patients were impaired in remembering the order in which they received objects (no delay interval). Also, Thaiss and Petrides (2008) assessed patients with excisions for the treatment of epilepsy and showed that the unilateral temporal lobe group who all had damage to the amygdala, hippocampus, and parahippocampal cortex were impaired in remembering temporal details about recent personal real-life events (the left temporal lobe group was impaired in remembering the order of the events, and both the left and right temporal lobe group were impaired in remembering the day on which each event occurred). However, these impairments were not present in the frontal lobe group.

In contrast, other lesion studies have shown that the frontal lobe also appears to be important in remembering the temporal order of stimuli. Butters and colleagues (1994) examined ten patients with frontal lobe damage (right, left, or bilateral; due to stroke, tumour resection, or traumatic brain injury) and found that as a group they were unimpaired in recognizing 3D objects, but were impaired in remembering the order in which they appeared. Although as a group, patients with prefrontal cortex damage (due to stroke, traumatic brain injury, tumour, or atrophy) were unimpaired in recognizing abstract pictures, words, and the location of "Xs", they were impaired in recalling the order in which these stimuli appeared (Kesner et al. 1994). Similarly, patients with frontal lobe lesions were unimpaired in recalling and recognizing words and public events, but were impaired in recalling their temporal order (Shimamura et al. 1990). Deficits in memory for temporal order after a long delay were also found by Daum and Mayes (2000) who showed that patients with unilateral frontal lobe damage (due to traumatic brain injury, stroke, tumour resection, or aneurysm surgery) had

impaired ability to remember the temporal order of the faces that they had recognized (the faces had been presented thirty minutes previously). McAndrews and Milner (1991) used a task that assessed the ability to remember the temporal order of items that participants had named or for which they had performed an action, and found that patients with unilateral temporal lobe excisions were unimpaired, whereas patients with unilateral frontal lobe excisions were impaired only in the condition in which they had been asked to name the items. In summary, consistent with the functional neuroimaging literature, patients with frontal lobe damage tend to perform poorly in tasks involving memory for temporal order independent of the type of stimulus and independent of the duration of the delay interval.

One caveat of the work discussed above is that the lesion localization in some patients was imprecise compared to currently available methodologies. For example, in one study (McAndrews and Milner 1991) the lesion was not localized based on a brain scan but on the surgeon's drawings during the operation, and in some studies all (Kesner et al. 1994; Shimamura et al. 1990) or some (Butters et al. 1994; Daum and Mayes 2000) of the patients had only a computed tomography (CT) scan, which is relatively low resolution. Another limitation of these studies is that most of them included patients with multiple different aetiologies, some of which cause widespread brain damage. In some patients the epileptogenic lesion was a tumour, which means that the diffuse infiltration into surrounding regions (in the case of malignancy) cannot be clearly seen on conventional MRI (Swanson et al. 2004). This indicates that the lesion-behaviour relationships that were found may not be very accurate, and further insight might be gained from systematic examination of a patient group with relatively well-defined lesions.

1.5.3.3 Stroke

From the stroke literature, it is not yet absolutely clear which regions are critical in memory for temporal order. A study that examined stroke patients with damage to many different regions, found that they were impaired in remembering the temporal order of the tests of a neuropsychological test battery, but temporal order performance did not differ between left and right hemisphere stroke patients nor did it appear to be related to lesion location (Schoo et al. 2014). This dovetails with a study that found that stroke patients were impaired in recalling the absolute or relative temporal order of scenes from a route they had watched on a video (Claessen, Visser-Meily, Jagersma, et al. 2016), and performance did not significantly differ between right and left hemisphere stroke patients. Though, in Claessen and colleagues' study the route was shown twice during encoding and therefore lacks the "uniqueness" feature of episodic memory. In contrast, Kant and colleagues (2017) found that left hemisphere stroke patients were impaired in remembering the order of 2D items immediately after they had been presented on a screen, but patients with right hemisphere or bilateral stroke were unimpaired.

Other studies were able to show that damage to specific regions can lead to deficits in memory for temporal information. Mangels (1997) found that patients with frontal lobe infarcts were impaired in reconstructing the order of words in a semantically related list and on word free recall under intentional learning; tests of word free recall and recognition using similar encoding manipulations indicated that order performance was dissociable from item memory. In line with this, remembering the temporal order of landmarks which patients saw while navigating in a real environment was weakly correlated with the amount of damage to the dorsolateral prefrontal cortex (van Asselen, Kessels, Kappelle, et al. 2006). Impaired memory for temporal details was also found in a patient with a left thalamic infarct (temporal discrimination; Parkin et al. 1994) and a patient with a right inferior capsular genu infarct and possibly additional damage to the right anterior thalamus (temporal order judgment of words;

Schnider et al. 1996). Thus, it seems that damage to the thalamus (possibly due to this region's connectivity with the hippocampus) and frontal lobe regions (possibly due to the executive deficits that are often present in these patients) can impair the ability to remember the temporal order of different types of stimuli. However, it should be noted that these findings are in small groups and need further evaluation.

1.5.3.4 Conclusion

In conclusion, both functional neuroimaging and lesion studies have shown that fronto-parieto-temporal regions appear to have an important role in memory for temporal order. These studies though have not been able to disentangle whether the involvement of the frontal lobe in this function is separate or due to its important role in executive functions. Furthermore, no previous study has assessed long-term memory for the temporal order of non-word stimuli within one single event in a large group of stroke patients who do not have spatial neglect, nor which brain regions are critical for this function by performing voxelwise statistical analyses. An experimental paradigm to assess this aspect of memory in stroke patients, along with the results obtained, are discussed in Chapter 5.

1.6 Spatial representation

1.6.1 Reference frames

Two different reference frames are thought to be involved when we process spatial information: a) egocentric, which means representing the location of objects from our perspective (body-centred spatial representations; Figure 1.2), or b) allocentric, which means representing the location of stimuli in relation to each other, independent of our position in space (world-centred spatial representations; Wolbers and Wiener 2014). However, there has been debate regarding this division. Some authors suggest that there may only be one

reference frame, i.e., only the egocentric (Filimon 2015) or only an integrated egocentric-allothetic map, rather than two separate reference frames (Niemeier and Karnath 2002). It is not yet clear whether, how much, and how these reference frames interact. Evidence for the close interaction between the body- and world-centred reference frame is the Roelofs effect, which is the mislocalization of a person's subjective midline when an offset frame is present (Bridgeman et al. 2018; Roelofs 1935). Functional neuroimaging and lesion studies have shown that separate but partly overlapping regions are involved in each reference frame (Chechlacz et al. 2010; Galati et al. 2000; Neggers et al. 2006; Rorden, Hjalton, et al. 2012). The dominant account is that these two reference frames exist in parallel and the use of one or the other depends on how much the subject has moved between encoding and retrieval, how much prior experience one has within that space, and the structure and size of the space (Burgess 2006).

The size of spaces that we encounter can be: a) spaces smaller than the body, that is, non-navigable spaces such as an object or a small number of objects, b) large spaces which can be directly navigated, for example, rooms or a neighbourhood, or c) very large spaces which cannot be apprehended directly through navigation, for example, geographical spaces (Montello 1993; Tversky 2003). Researchers have suggested that small-scale spaces may rely mainly on an egocentric reference frame, whereas large spaces may rely mainly on an allothetic reference frame (Ekstrom and Isham 2017; Iachini et al. 2014). The fact that one cannot experience a large-scale environment (e.g. London) within the timeframe of a single episode, but instead one needs to accumulate many experiences in different locations within that area in order to create a mental image of the large space (a cognitive map), indicates that large-scale environments are more likely to be processed in an allothetic reference frame and may be closely linked to semantic (autobiographical) memory (i.e., accumulation of many episodes rather than one unique episode), whereas small-scale environments may be mainly

processed in an egocentric reference frame and could be closely linked with episodic (autobiographical) memory (Figure 1.2).

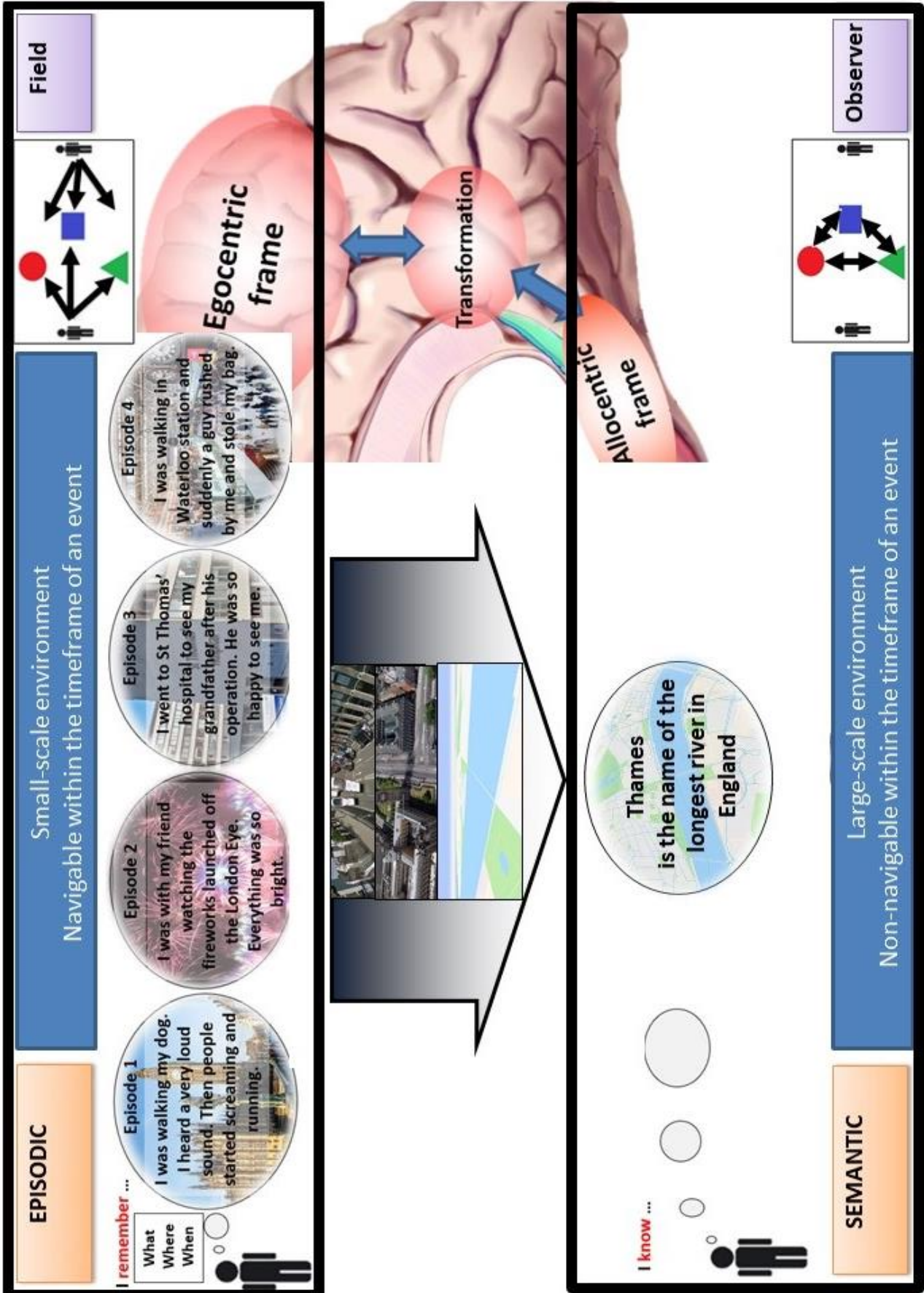


Figure 1.2. Illustration of a possible close relationship between navigation, the scale of the environment, memory, and reference frames, and how different brain regions may interact to support these processes

It illustrates that by linking many events one can acquire the gist, and by linking many egocentric representations one can acquire an allocentric representation of an environment. This figure is mainly based on a model of spatial memory and imagery derived from rodent studies (Bicanski and Burgess 2018), a review discussing the relationship between memory, navigation and reference frames (Buzsáki and Moser 2013), and on the finding that performance on egocentric navigation tasks seems to be positively linked to performance on episodic, but not semantic, memory tasks (Committeri et al. 2020).

In line with this, dissociations have been found in brain-damaged patients' ability to perform micro- compared to macro-space tasks, e.g. performing the Corsi block task (blocks shown on a table) compared to navigating within a room (Piccardi et al. 2008), in visuospatial planning compared to navigational planning abilities (Bocchi et al. 2020), and only a weak correlation was found between performance on a scene construction task (e.g. imagining being on a beach) and navigation questionnaires (Clark and Maguire 2020). Also, Piccardi and colleagues (2011) assessed two patients with damage involving fronto-temporal regions: one patient showed impaired performance in learning a sequence in the macroscale version of the Corsi block task (walking onto the squares), but not in the microscale version (tapping blocks), whereas the other patient showed the reverse pattern. Similarly, a stroke patient with right superior parietal lobe damage (it was reported as focal damage, though only a CT scan was performed) had no deficit in wayfinding, but was impaired in spatial tasks at a micro-scale (Passini et al. 2000). Many studies (with Alzheimer's disease patients [Bianchini et al. 2014], patients with temporal lobe resections [Piccardi et al. 2010], or functional neuroimaging in healthy subjects [Nemmi et al. 2013]), have shown that the working memory network involved in small-scale environments (Corsi block task) appears to be partly different to that involved in large-scale environments (walking Corsi task). Studies examining mental imagery in brain-damaged patients, have found double dissociations between non-topographical mental images (small non-navigable spaces) and topographical mental images (navigable spaces; Guariglia et al. 2013; Guariglia and Pizzamiglio 2007; Palermo et al. 2010).

1.6.2 Neuroanatomical evidence of reference frames in spatial processing

Following Tolman's (1948) introduction of the term cognitive map, many studies have found cells specialized in processing our position in space. Studies have found place cells in the hippocampus (O'Keefe and Dostrovsky 1971; O'Keefe and Nadel 1978), grid cells in the medial entorhinal cortex and pre/parasubiculum (Boccaro et al. 2010; Hafting et al. 2005), object-vector cells in the medial entorhinal cortex (Høydal et al. 2019), boundary vector cells in the subiculum (Lever et al. 2009), border cells in the medial entorhinal cortex and parasubiculum (Solstad et al. 2008), and head direction cells in many regions including the pre/postsubiculum and anterior dorsal thalamic nuclei (Ranck Jr 1984; Taube 1995, 2007; Taube et al. 1990). Although all the above studies focused on rodents in a small-scale laboratory environment, such cells seem to exist in bats (Ulanovsky and Moss 2007; Yartsev et al. 2011), non-human primates (Ono et al. 1991; Robertson et al. 1999), and humans (Doeller et al. 2010; Ekstrom et al. 2003; Hassabis et al. 2009; Jacobs et al. 2013; Vass and Epstein 2013). In humans, there may be head-direction cells in the retrosplenial cortex, thalamus (Shine et al. 2016), and medial parietal cortex (Baumann and Mattingley 2010), and anchor cells mainly in the parahippocampal cortex (Kunz et al. 2020). All the above cells are thought to process allocentric information (Madl et al. 2015), except the anchor cells which may process egocentric information and the transformation from egocentric to allocentric representations (Kunz et al. 2020). Apart from being active while the subject traverses a visible environment, some of these cells can be active even in the absence of visible stimuli. For example, grid and place cells in rats can be active in a dark environment (Hafting et al. 2005), which can be explained by the fact that these cells may also use auditory, olfactory and tactile cues (Bao et al. 2019; O'Keefe and Nadel 1978; Zhang and Manahan-Vaughan 2015). Also, grid cells can be active during imagined navigation in humans (Horner et al. 2016).

1.6.2.1 Non-human animals

Apart from the studies mentioned above that have found spatially tuned cells in the hippocampus, there have been many other studies in non-human animals showing that the hippocampus, which is essential for episodic memory, is also involved in spatial (particularly allocentric) processing. Hippocampal volume is associated with spatial ability in several species of birds and small mammals (Krebs et al. 1989; Lee et al. 1998; Sherry et al. 1992). Navigation using allocentric strategies tends to be impaired in rodents with hippocampal damage (Packard and McGaugh 1996; Pearce et al. 1998). Similarly, in monkeys, the hippocampus is activated during allocentric representations (Rolls et al. 1997).

Research in monkeys has shown that the posterior parietal cortex is activated when processing egocentric information (Andersen et al. 1985), while others found that area 7a (a region in the superior parietal lobule; Scheperjans et al. 2008) is involved in egocentric representations, and the lateral intraparietal cortex is involved in allocentric representations (Snyder et al. 1998). Studies recording neural activity in rodents have found that the posterior parietal cortex may be involved in the integration of allocentric and egocentric information (Wilber et al. 2014); though other rodent studies recording neural activity indicate that the retrosplenial cortex is involved in this process (Alexander and Nitz 2015).

1.6.2.2 Functional and structural neuroimaging in healthy humans

Many neuroimaging studies in humans have investigated the neural correlates of egocentric and allocentric representations by using predominantly virtual reality navigation tasks. Parietal lobe activity seems to be associated with spatial learning navigation tasks that involve egocentric representations and position judgments (compared to landmark recognition; Aguirre et al. 1996; Aguirre and D'Esposito 1997; Burgess et al. 2001; Maguire, Frackowiak, and Frith 1997), as well as in orienting, tracking, reaching and recognizing objects in space

from unusual viewpoints (Faillenot et al. 1997; Kosslyn et al. 1994; Sugio et al. 1999). Wolbers and colleagues (2008) showed that the precuneus was involved in making updated representations as participants moved in a virtual environment. In a virtual navigation task, egocentric processing activated mainly a posterior parietal-premotor network, and also frontal areas, whereas allocentric processing mainly activated an occipito-temporal network (Gramann et al. 2006). The use of an allocentric navigational strategy tends to be associated with activity in the hippocampus (Iaria et al. 2003; Maguire 1998) and entorhinal cortex (Doeller et al. 2010), as well as with a larger posterior (compared to anterior) hippocampus (Brunec et al. 2019). In another study, the parahippocampal place area was involved in selectively discriminating different viewpoints, whereas the retrosplenial cortex seemed to combine different views of the same space which were presented continuously (Park and Chun 2009). In conclusion, neuroimaging studies indicate that the parietal lobe tends to be associated with egocentric representations, medial temporal lobe regions (mainly the hippocampus) with allocentric representations, and the retrosplenial cortex with the transformation between these two reference frames (Figure 1.2).

1.6.2.3 Lesion studies in humans

Many of the above findings have also been confirmed by studies in patients with brain lesions. Patients with right hemisphere lesions (damage due to stroke, neurosurgery, tumour, or cyst) were impaired in the ability to process changes in spatial perspective (Descloux and Maurer 2020). However, this study had some confounds in that: a) some patients had spatial neglect and/or visual field deficits, b) there was a very large variety in the time that the assessment occurred (from 14 days to 17 years after the onset of the brain damage), c) patients with lesions due to many different aetiologies were included, and d) the investigators did not examine which regions were associated with worst performance. Studies that have examined the lesion anatomy in more detail have shown that patients with parietal lobe involvement

(different aetiologies) tend to perform worse than patients with frontal lobe involvement and healthy controls on an egocentric virtual navigation task (Seubert et al. 2008). Also, patients with lesions in the posterior parietal cortex (due to stroke or tumour) were impaired in reporting the most efficient route from one landmark to another (egocentric), but were also impaired in drawing a map of a familiar environment (allocentric; Ciaramelli, Rosenbaum, et al. 2010). Importantly, in the first task, their subjective experience of mental navigation was also reduced. Others have found that stroke patients with parietal lobe damage are unable to visualize an array of items from different perspectives (Passini et al. 2000), have difficulty in learning routes when given only egocentric cues (Weniger et al. 2009), and experience topographical disorientation (Kaski et al. 2016; Ruggiero et al. 2014).

In patients with brain damage, reference frames have often been examined in the context of spatial neglect. In egocentric spatial neglect, patients are unable to attend to the contralesional side of space in reference to their own body, whereas in allocentric spatial neglect, patients are unable to attend to the contralesional side of stimuli (Rorden, Hjaltason, et al. 2012; Figure 1.3). There appears to be a strong association between egocentric and allocentric spatial neglect (Li et al. 2014; Rorden, Hjaltason, et al. 2012), as they tend to co-exist in over 50% of patients with left-sided spatial neglect (Yue et al. 2012), and lesion studies have shown that separate but largely overlapping regions are involved in each of these types of spatial neglect (Medina et al. 2009; Yue et al. 2012; Figure 1.3). Tasks that assess egocentric spatial neglect include the Behavioural Inattention Test star cancellation task and Mesulam task (Mesulam 1985; Wilson et al. 1987), whereas tasks typically used to assess allocentric spatial neglect include the Broken Hearts Test (Demeyere et al. 2015) and Apple Cancellation Test (Humphreys et al. 2012). In all these tests, subjects are asked to detect targets which are presented randomly on an A4 paper, but the key difference lies in the type of targets and distractors which are used. In the Behavioural Inattention Test star cancellation task (Figure 2.2A), the targets are small stars among big stars, words, and letters, and in the

Mesulam task (Figure 2.2B) subjects need to find sun-like targets among multiple different shapes. Contrarily, in the Broken Hearts Test and the Apple Cancellation Test, the difference between targets and distractors is not the size or type of stimuli (as both distractors and targets can be small or large—either hearts in the Broken Hearts Test, or apples in the Apple Cancellation Test), but rather in the presence or absence of one side of the shape, that is, targets are closed shapes whereas distractors are open shapes in which the left or right side of the shape is missing. In these two tasks, none of the shapes are rotated. Thus, they cannot differentiate between stimulus- and object-centred spatial neglect (Figure 1.3).

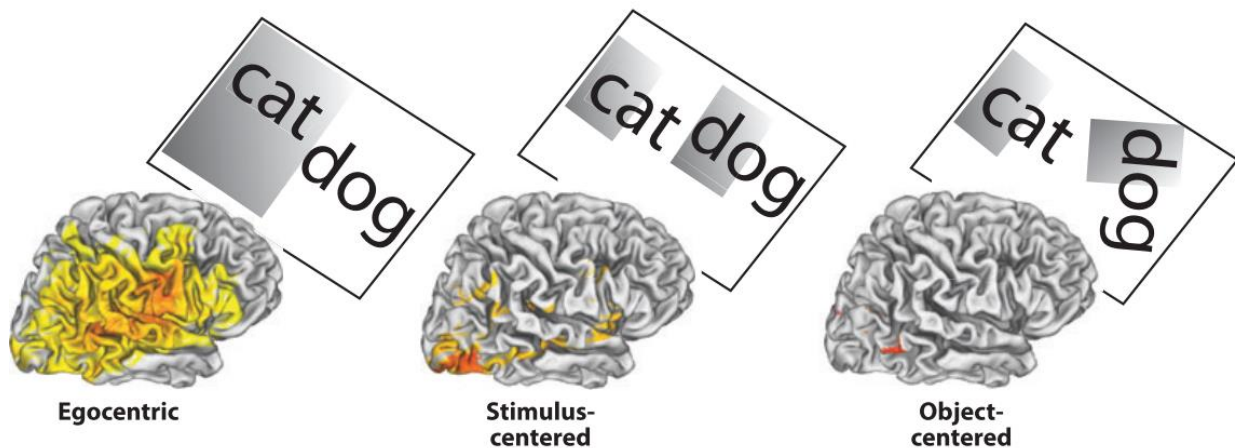


Figure 1.3. Brain regions involved in different types of spatial neglect

Figure from Corbetta and Shulman (2011) which was based on data of Medina and colleagues (2009). Image reproduced with permission of the rights holder, Annual Reviews.

1.6.3 Neuroanatomy of scene perception

According to Henderson and Hollingworth (1999, p. 244), scene is a ‘semantically coherent (and often nameable) view of a real-world environment comprising background elements and multiple discrete objects arranged in a spatially licensed manner’. The three key areas that tend to be selective for perceiving complex scenes in the human brain include the

parahippocampal place area, occipital place area, and the medial place area (Aguirre et al. 1998; Bar and Aminoff 2003; Çukur et al. 2016; Dilks et al. 2013; Epstein and Kanwisher 1998; Kamps et al. 2016; Silson et al. 2016). Although some authors have used the terms medial place area, retrosplenial cortex, and retrosplenial complex interchangeably (Aminoff et al. 2007), the medial place area is thought to be located in the posterior part of the ventral parieto-occipital sulcus and does not include the retrosplenial cortex (Brodmann areas 29 and 30; Silson et al. 2016). Some studies have proposed that there may be an anterior-posterior subdivision in scene-selective areas: the anterior part may be mainly involved in memory of scenes whereas the posterior part may be predominantly involved in the perception of scenes (Baldassano et al. 2016; Silson et al. 2019; Figure 1.4).

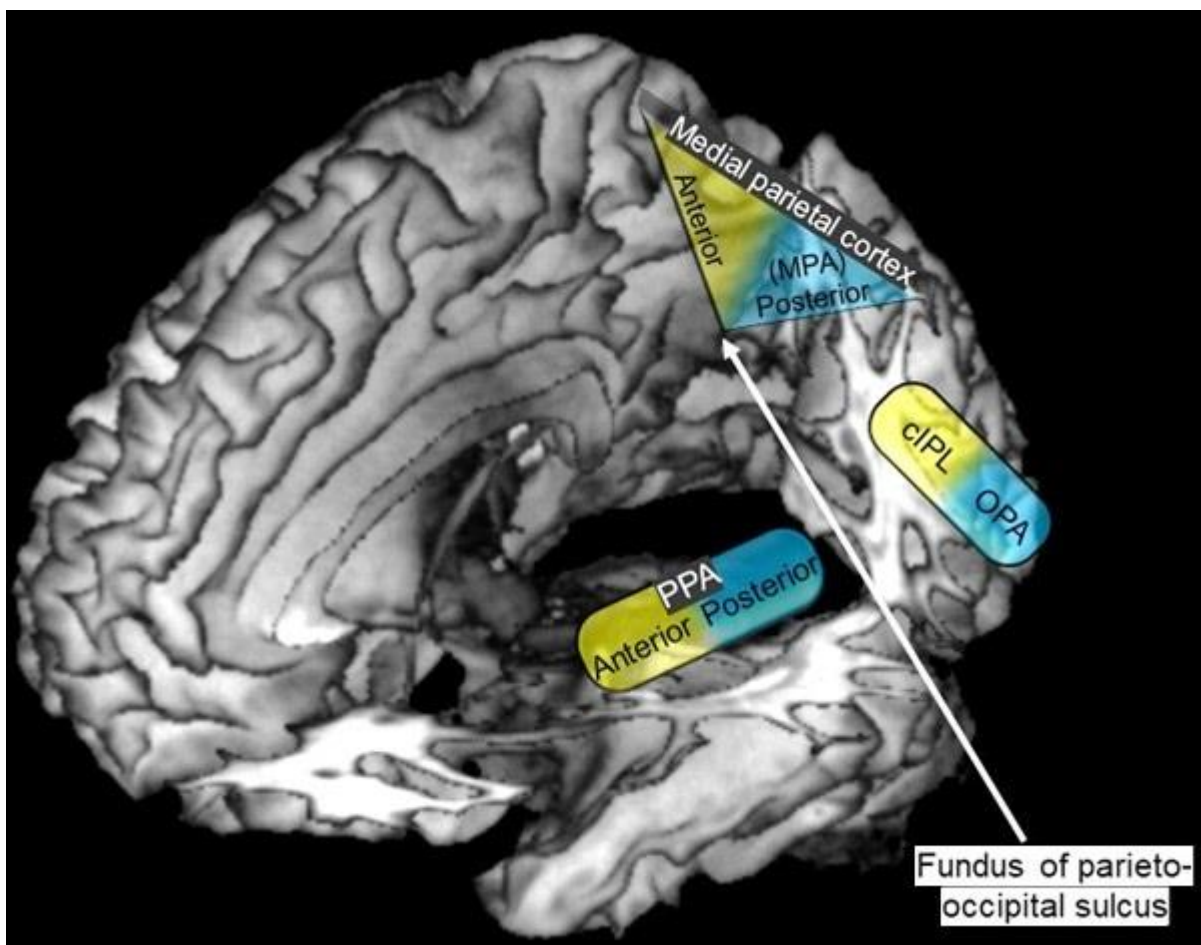


Figure 1.4. Illustration of the subdivisions proposed for scene-selective areas

In yellow are areas that may be more involved in memory of scenes, whereas in blue are areas that may be more involved in scene perception. The fundus of the parieto-occipital sulcus seems to be where mnemonic representations separate from perceptual representations (Silson et al. 2019). cIPL: caudal inferior parietal lobule; OPA: occipital place area; PPA: parahippocampal place area; MPA: medial place area. Adapted from Baldassano and colleagues (2016).

Other regions may also be involved in scene perception. A fMRI study showed that apart from the areas mentioned above, the superior parietal lobule also was involved in judging distances in a virtual environment (distances between objects, between objects and a landmark, and between the observer and two objects; Committeri et al. 2004). Wilson and colleagues (2020) assessed the ability to generate scenes in patients with Alzheimer's disease and patients with behavioural variant frontotemporal dementia. They provided word cues of scenes (e.g. a beach) and asked participants to imagine and describe them in detail. The ability to generate scenes that are contextually detailed and spatially coherent was impaired in these patients, and these deficits may be related to the integrity of posterior parietal and medial temporal lobe areas such as the right parahippocampal gyrus and right hippocampus.

1.6.4 How spatial processing relates to memory

There is a close relationship between memory and processing spatial information. Remembering spatial details (e.g. distances between items or their location) and binding information is integral to episodic memory. It seems that many regions that are involved in episodic memory are also involved in scene construction, e.g. the hippocampus, parahippocampal gyrus, retrosplenial, posterior cingulate, posterior parietal, middle temporal, and medial prefrontal cortices (Hassabis et al. 2007). The hippocampus, which is widely understood to be critical for episodic memory, is also important in combining and relating information (e.g. in binding object with context information; Davachi 2006; Eichenbaum et al.

2007; Horner et al. 2015), in representing space (O'Keefe and Dostrovsky 1971), and perceiving and constructing spatially coherent scenes (Zeidman et al. 2015); scene construction theories suggest that these abilities are the reason why the hippocampus is so important for episodic memory, navigation, imagining and future-thinking (Bird and Burgess 2008; Eichenbaum 2017; Hassabis and Maguire 2007, 2009; Maguire and Mullally 2013; O'Keefe and Nadel 1978; Rubin and Umanath 2015). In order to construct spatial representations, one needs to maintain the spatial information and sometimes also manipulate it, for example, changing viewpoints. These are processes that require working memory, in particular the visuospatial sketchpad (Baddeley 2000; Baddeley and Hitch 1974).

1.6.5 The status of spatial information in autobiographical memory

When recalling an autobiographical event, one can retrieve it as if seeing it from one's own eyes, or as if observing it (how a spectator would have seen this event), or both (Nigro and Neisser 1983; Rice and Rubin 2009). Some authors have argued that not everyone tends to use both of these perspectives when recalling past events and there may be differences across individuals in how much one uses the "observer" or "own eyes" perspective (Radvansky and Svob 2019).

Many studies in healthy young adults indicate that the perspective from which an event is retrieved may be strongly associated with the precision and richness of recall, as measured by objective and subjective measures. Retrieving an event from a first-person perspective tends to be associated with greater accuracy, uniqueness, emotional intensity, vividness, and sense of subjective experience, more "remember" responses (even when the memories which are retrieved are remote; Crawley and French 2005), more episodic detail, and with recalling many details about the physical sensations, feelings and thoughts during that event (Akhtar et al. 2017; Marcotti and St. Jacques 2018; McIsaac and Eich 2002; Piolino et al. 2006; Siedlecki

2015; Sutin and Robins 2010; Verhaeghen et al. 2018; Figure 1.2). Higher spontaneity (which refers to a low number of prompts required to retrieve a specific event rather than a generic event) is related to higher specificity, more “remember” and “own eyes” responses, but fewer “know” and “observer” responses when retrieving autobiographical events (Piolino et al. 2006). Recent autobiographical memories, which in healthy young subjects tend to be more specific, vivid, coherent, and detailed than remote autobiographical events (Sutin and Robins 2007; Tollenaar et al. 2009; Verhaeghen et al. 2018), are more likely to be reported from an “own eyes” perspective (Akhtar et al. 2017; Nigro and Neisser 1983; Sutin and Robins 2007), and their retrieval triggers more and shorter lasting eye fixations (El Haj, Boutoleau-Bretonnière, et al. 2020).

In contrast, retrieving an event from a third-person perspective tends to be associated with less sensory and emotional reliving (Berntsen and Rubin 2006), more “know” responses (Crawley and French 2005; Piolino et al. 2006), and with recalling many details about one’s appearance and actions, and the relative location of objects (relative to the other objects and relative to oneself; McIsaac and Eich 2002). When young adults were required to change the perspective from which they retrieved personal events, from a first-person to a third-person perspective, this led to retrieving fewer episodic details (Akhtar et al. 2017), less sensory and emotional reliving (Berntsen and Rubin 2006), and reduced emotional intensity (Robinson and Swanson 1993; Sekiguchi and Nonaka 2014). Encoding an event from a third-person perspective (rather than a first-person perspective), led to it being rated as less self-relevant (when participants provided a rating immediately after they encoded it) and having less vividness (when they rated it after a week but not immediately after they encoded it; Mooren et al. 2016). Also, when young adults recalled past events in which aspects of themselves had changed, they tended to retrieve them from a third-person perspective and with reduced feeling of reliving (Libby and Eibach 2002).

1.6.5.1 The impact of healthy ageing

Healthy ageing can affect the ability to remember personal events, despite priming, procedural and semantic memory remaining relatively intact (Churchill et al. 2003; Hartshorne and Germine 2015; Laver and Burke 1993; Nyberg et al. 2003). Although remembering the “what” information appears to be unaffected, healthy elderly subjects seem to have deficits in remembering specific episodic details, that is, details directly related to a unique event and specific to time and place (Diamond and Levine 2020; Folville, Bahri, et al. 2020; Gaesser et al. 2011; St. Jacques and Levine 2007; Levine et al. 2002; Peters et al. 2019; Piolino et al. 2006; Robin and Moscovitch 2017), such as the “when” feature (Blachstein et al. 2012; Fabiani and Friedman 1997; Madsen and Kesner 1995; Parkin et al. 1995), the “where” feature (Chalfonte and Johnson 1996; Mazurek et al. 2015; Puglisi et al. 1985), contextual details, e.g. the colour of stimuli (Park and Puglisi 1985), and binding stimuli to their spatio-temporal context (Kessels et al. 2007; Kinugawa et al. 2013; Old and Naveh-Benjamin 2008; Plancher et al. 2010). They also tend to require more prompts in order to retrieve a specific rather than a generic event (Piolino et al. 2006). Apart from objective deficits, they appear to have a lower sense of vividness and reliving when retrieving autobiographical events (Piolino et al. 2006) (though others have found that this was higher in healthy elderly subjects; Janssen, Rubin, and St. Jacques 2011; Rubin and Berntsen 2009; Rubin and Schulkind 1997) and they tend to report fewer “remember” and more “know” responses compared to young subjects (Piolino et al. 2006).

It remains unclear whether allocentric and egocentric aspects of memory are affected in healthy ageing. Although a systematic review showed that healthy elderly have impairments in the use of allocentric (but not egocentric) frames in spatial navigation, it found that there have been discrepancies regarding which of the two reference frames are impaired in laboratory-based tasks assessing memory for spatial information (Colombo et al. 2017).

However, a recent study found that healthy elderly subjects had a relative egocentric episodic memory deficit; specifically they were worse than healthy young subjects in remembering the perspective from which they had viewed scenes a day before (Russell et al. 2019). There is also no clear consensus in the autobiographical literature. Piolino and colleagues (2006) found that, compared to young subjects, healthy elderly individuals tend to give more “observer” responses when retrieving autobiographical memories, but the same amount of “own eyes” responses, while Rathbone and colleagues (2015) found that they are more likely to recall autobiographical events from an “own eyes” perspective. The advantage of the first study is that viewpoint responses were analysed separately for different lifetime periods, and they found that age differences in viewpoint responses can differ depending on which lifetime period is examined. It is important to note that in the second study, the memories reported by young subjects were from a different lifetime period to those that were reported by elderly subjects, which may have led to an invalid comparison.

In conclusion, the possible link between perspective and (a) precision and (b) richness of recall (as measured by both objective and subjective measures) may be different in healthy elderly subjects, because memories tend to be more semanticized and recalled from a third-person perspective as we age (Piolino et al. 2002, 2006). An experimental method to assess this relationship in both young and elderly healthy subjects, along with the results obtained, are discussed in Chapter 4.

1.6.6 Neuroanatomical evidence of reference frames in memory

1.6.6.1 Functional Neuroimaging

Functional neuroimaging studies have found that many regions are activated when participants perform spatial memory tasks involving egocentric, allocentric, or both reference frames (Agarwal et al. 2017; Chen et al. 2014, 2018; Dhindsa et al. 2014; Galati et al. 2010;

Gomez et al. 2014; Parslow et al. 2004; Postle and D'Esposito 2003; Rosenbaum et al. 2004; Schmidt et al. 2007; Sormaz et al. 2017; Sulpizio et al. 2013; Wallentin et al. 2008). Studies assessing memory for object locations throughout different viewpoints have found that parahippocampal cortex and lingual gyrus (but not hippocampal) activity was proportional to how much the viewpoint had changed (Schmidt et al. 2007). Also, Sulpizio and colleagues (2013) found that regions such as the posterior intraparietal sulcus, parieto-temporal-occipital junction, precuneus, supramarginal gyrus, frontal eye fields, anterior lingual gyrus, posterior parahippocampal gyrus, and retrosplenial complex were associated with the amount of viewpoint change in a virtual room. However, the retrosplenial complex was activated by how much the viewpoint changed selectively for the environmental frame. In their paradigm, this frame refers to changes in the position of an object relative to the walls of the room rather than relative to: a) the furniture positioned at the centre of the room, or b) the viewer. Furthermore, in healthy elderly subjects the angular gyrus bilaterally was able to differentiate whether a scene was the same or a different perspective from which they had viewed it the previous day (Russell et al. 2019). Also, hippocampal activity was found during allocentric but not egocentric encoding in a spatial memory task (Parslow et al. 2004).

Most of the above findings using laboratory-based spatial memory tasks are in line with findings in the autobiographical memory literature. During autobiographical memory retrieval, the precuneus (Freton et al. 2014) and angular gyrus (St. Jacques, Conway, Lowder, et al. 2011) are involved in adopting a first-person perspective, whereas other studies have found that the precuneus is involved in adopting a third-person perspective (Grol et al. 2017), or both a first and a third-person perspective (Eich et al. 2009). For example, when retrieving an autobiographical event, the precuneus was sensitive to changes in visual perspective, irrespective of whether the change was from a first- to a third-person perspective or from a third- to a first-person perspective (St. Jacques et al. 2018). Additionally, the hippocampus, precuneus and angular gyrus seem to be activated when retrieving an autobiographical

memory from either a first- or third-person perspective (Eich et al. 2009; Grol et al. 2017; Iriye and St. Jacques 2020; St. Jacques et al. 2017).

In summary, most functional neuroimaging studies that have used laboratory-based memory tasks with scenes or autobiographical memory tasks, suggest that the angular gyrus may be involved mainly in egocentric representations, the hippocampus may be involved mostly in allocentric representations, whereas the precuneus may be involved in both representations.

1.6.6.2 Lesion studies with patients

Although memory for egocentric and allocentric representations has been examined in many functional neuroimaging studies, it has been rarely examined in patients with brain damage. Using allocentric spatial memory tasks, impaired performance was found in three patients with bilateral hippocampal damage due to: a) autoimmune limbic encephalitis (on a task with an interval of one minute; Banta Lavenex et al. 2014), b) uncertain aetiology (impaired after a 20-second and 60-second but not a 5-second interval; Holdstock et al. 2000), or c) perinatal anoxia (King et al. 2002). In contrast, four patients with unilateral frontoparietal damage (due to stroke or closed head injury) were impaired in remembering the distance between 3D objects and themselves (egocentric), but not in remembering the distances between the objects (allocentric; Iachini et al. 2009).

There is even more limited research looking at egocentric and allocentric memory exclusively in stroke patients. Hartley and colleagues (2007) found that a patient with a right hemisphere infarct in the occipital and temporal lobe, including damage to the posterior hippocampus, and lingual and parahippocampal cortices, was impaired on the Four Mountains Test (4MT), a task that examines memory for spatial information, mainly allocentric memory.

Another study (Russell et al. 2019) assessed six stroke patients with right posterior parietal lobe involvement (maximal overlap in the supramarginal gyrus) using a 3D spatial memory task. In this task, participants saw 3D real-life objects on a 2 x 2 grid, and after two hours they saw the same objects but these were either in a different position, or the scene was shown from a different viewpoint, or it was an unchanged scene; participants were asked to choose which was the exact scene they had seen during encoding. The patients were not impaired in remembering what items they had seen, where they were placed, nor in standard neuropsychological tasks such as the Corsi block task and a task that involved delayed recognition of line-drawings; but they were impaired in remembering the perspective from which they had viewed the scenes. The 4MT and adapted versions of the task used by Russell and colleagues are further discussed in the experimental chapters.

1.6.6.3 Conclusion

Spatial reference frames in the context of memory have very rarely been studied in stroke patients. Although egocentric representations seem to be processed in the parietal lobe, allocentric representations in the medial temporal lobe, and the transformation between these representations may occur in the retrosplenial cortex, these anatomical findings have been based on non-human animal studies, neuroimaging studies and small groups of patients with brain lesions, and most of them have used non-memory tasks. To date, no study has examined egocentric and allocentric spatial memory in a large sample of stroke patients to accurately determine which brain regions are critical for these functions. The fact that fMRI data in healthy elderly subjects have shown that both angular gyri seem to be able to discriminate whether scenes were the same or a different perspective from which they had been viewed the previous day (Russell et al. 2019), suggests that stroke patients with damage to the right and/or left angular gyrus may have deficits in egocentric spatial memory. In Chapters 5 and 6, egocentric and allocentric spatial memory were assessed using the 4MT

as well as an adapted version of Russell and colleagues' (2019) paradigm, in a large group of left and right hemisphere stroke patients.

1.7 Hypotheses and Aims of Remaining Thesis Chapters

The main hypotheses underlying this thesis are that: a) self-perspective is a key component of episodic memory, and b) memory for spatial information relies on a network of brain regions including the hippocampus, parahippocampal gyrus, retrosplenial cortex and posterior parietal cortex; specifically, egocentric memory relies on the posterior parietal cortex, whereas allocentric memory relies on the hippocampus.

As discussed earlier, patients included in previous studies have often suffered from spatial neglect, hemianopia and/or aphasia, which may have led to confounding results. Therefore, in this thesis, patients with such deficits on the day of testing were excluded. Chapter 2 describes the tests that were used to screen stroke patients and the standard neuropsychological tests that were used in the experiments of the subsequent chapters. Also, the results from the screening procedure are presented.

In Chapter 3, the techniques used to perform neuroanatomical analyses are described. The benefits and limitations of lesion symptom mapping and lesion network mapping are discussed.

The aim of Chapter 4 was to examine the importance of self-perspective in episodic memory by exploring whether there is a relationship between (a) how accurately one is able to remember their viewpoint at encoding, and (b) the amount of episodic detail and the viewpoint reported in their autobiographical memories. Additionally, I examined whether this relationship is affected by age as previous studies have shown that healthy elderly subjects

tend to recall autobiographical memories with fewer episodic details and provide more “observer” responses. This was explored by comparing performance on an adapted egocentric episodic memory paradigm and performance on an adapted autobiographical memory task in healthy individuals across two different age groups.

The main aim of Chapter 5 was to explore the role of the posterior parietal lobe in egocentric episodic memory. One previous study with right hemisphere stroke patients showed that the posterior parietal lobe (particularly in the area of the angular gyrus) seems to be important for egocentric episodic memory (Russell et al. 2019), but it has yet to be explored whether the left posterior parietal lobe is also essential for this function. Furthermore, most studies examining episodic memory in stroke patients have not incorporated memory for egocentric representations, allocentric representations and for temporal order into one task. Thus, an experimental paradigm was developed to assess these features of episodic memory in stroke patients. Its feasibility was examined in a pilot study with healthy young, healthy elderly and stroke patients. The neural correlates of each of these aspects of memory were investigated by assessing left and right hemisphere stroke patients.

The aim of Chapter 6 was to assess whether memory for spatial information is impaired following stroke and explore the network of critical brain regions for this function, in particular egocentric and allocentric spatial memory. Although there have been studies examining spatial memory in stroke patients, most of them: a) have assessed a small group of patients, b) have not performed a comprehensive lesion analysis, and c) have used tasks such as the Corsi block task which requires a motor response as well as intact memory for sequences (Berch et al. 1998; Cavallini et al. 2003; Malhotra et al. 2005), and is not very ecological. As discussed earlier, many regions seem to be involved in spatial memory but none of the previous studies have explored the neural correlates of spatial memory using a lesion network mapping approach. Thus, spatial memory was examined by using the 4MT, a more ecological

and “purer” spatial memory task compared to tasks used in other studies. Performance was compared between left and right hemisphere stroke patients, but also between these stroke groups and data from previously published studies, for example, healthy controls, patients with mild cognitive impairment, Alzheimer’s disease, or semantic dementia. Lesion symptom mapping and lesion network mapping were the techniques used to examine the neuroanatomical correlates of memory for spatial information.

Lastly, Chapter 7 contains a general discussion of the experimental findings and their implications. The limitations of the experiments are addressed as well as possible future directions.

2 Methods

2.1 Introduction

In this chapter I describe the screening tests that I administered to stroke patients, the results of the screening procedure, the standard neuropsychological tests that were used in the experiments of Chapters 5 and 6, and the inclusion criteria for the subjects that took part in my experiments.

2.2 Aims of screening and neuropsychological assessment

As mentioned in Chapter 1, the main aim of the experiments described in Chapters 5 and 6 was to examine aspects of memory in stroke patients. Thus, identifying patients with concomitant deficits was crucial, as these might potentially contribute to poor performance on the memory tasks being used. At initial screening I tested for spatial neglect, hemianopia, and aphasia. Although the presence of these deficits could potentially impair performance on the memory tasks employed in my experiments, their presence at screening did not automatically exclude patients, as all these deficits may improve spontaneously. For this reason, I re-tested patients at the time of participation, and if they continued to have signs of these disorders that might affect performance, they were not invited to participate. The battery of tests that I employed was chosen to be as comprehensive as possible to detect these deficits, but also to be quick and relatively easy for the patients, in order to avoid potential drop-out due to fatigue.

There are many conditions which are sometimes present in stroke patients that may affect performance on the memory tasks used in the current thesis. These include: spatial neglect, constructional apraxia, deficits in spatial or object perception, in recognizing objects (object agnosia), in judging the orientation of objects (object orientation agnosia), in perceiving

more than one object at a given time (simultanagnosia), in perceiving depth (astereopsis), or in perceiving spatial relations between objects or between oneself and other objects (visuospatial agnosia). Importantly, the presence of most of these conditions could be detected by using the standard neuropsychological and screening tests mentioned in this chapter, but also by administering a practice session in the 4MT which included perception trials, a practice session in the Corsi block task, and by including an encoding check in the spatio-temporal task of Chapter 5.

My general aim was to be inclusive in order to be able to examine the widest possible range of brain lesions. A large proportion of patients have spatial neglect at presentation (Stone et al. 1993), particularly those with damage to the temporal and parietal lobes (Ringman et al. 2004). Therefore, to be inclusive, I felt it would be appropriate to include such patients as long as their spatial neglect had recovered by the time of participation. As discussed in Chapter 1, the temporal and parietal lobes are particularly relevant to this thesis, as they seem to be involved in memory and in the specific aspects I explored: allocentric and egocentric representations, respectively. The angular gyrus appears to be involved in egocentric aspects of episodic memory (Russell et al. 2019), while the parahippocampal gyrus appears to be involved in processing spatial scenes (Mormann et al. 2017). These regions seem to be highly interconnected; specifically the parietal lobe with the parahippocampal gyrus, and the latter with the hippocampus (Dalton and Maguire 2017).

Also, standard neuropsychological tasks were used, such as the ACE-III, the Rey-Osterrieth Complex Figure Test, the Corsi block task, and a representational neglect task, to examine the relationship between performance on these tasks and my experimental tasks.

2.3 Screening stroke patients

2.3.1 Visual fields and acuity

Visual field deficits were detected by using the traditional confrontation visual field technique (Elliott, North, and Flanagan 1997; Figure 2.1). These deficits are often difficult to disentangle from spatial neglect, especially when assessing patients with severe spatial neglect whose head and eyes may be maximally rotated towards the ipsilesional side (Parton et al. 2004). If patients had hemianopia when they were first screened, I examined them again at minimum one month later. This interval was chosen because although hemianopia due to stroke recovers usually within 10 days (Pambakian and Kennard 1997), complete recovery occurs within a month in up to 20% of patients (Ali et al. 2013; Gray et al. 1989). Patients whose hemianopia had not recovered were not included in the experiments, as their inability to see one half of the visual arrays used in the memory tasks would likely affect their performance. Patients with quadrantanopia were not excluded because this would not necessarily worsen performance, and in fact one other study involving the 4MT did include a patient with quadrantanopia (Hartley et al. 2007).

Visual acuity was examined in patients who reported blurry vision in the 4MT study, by using the Jaeger eye chart version which contains short paragraphs of 11 different font sizes (Runge 2000). Patients who could not read any of these paragraphs were excluded.

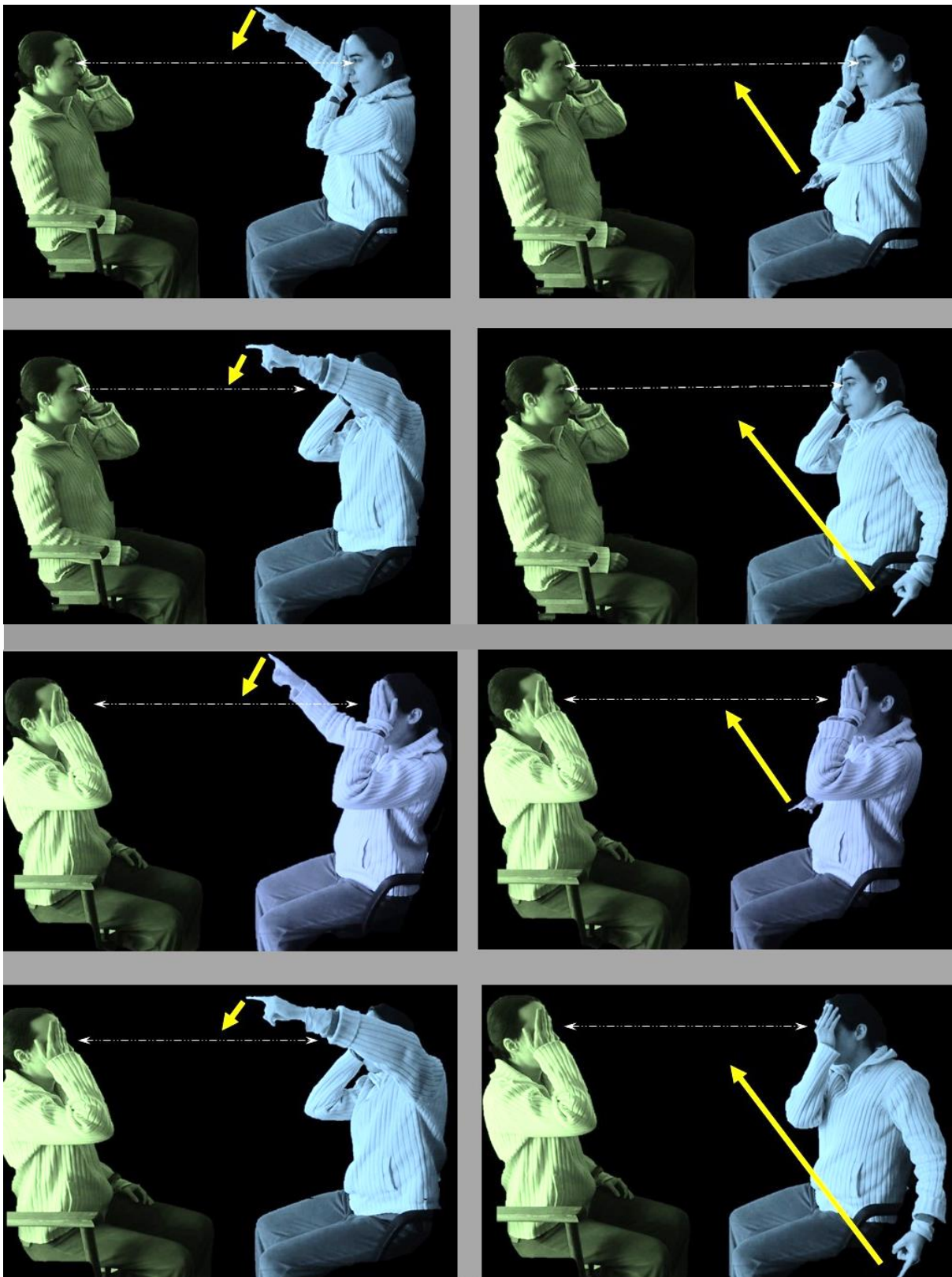


Figure 2.1. Confrontation visual field technique

The examiner is shown in blue and the patient is shown in green. The patient is asked to fixate on the examiner's eye (white dashed line) and respond when they are able to see the examiner's moving finger (the movement of the finger is shown with the yellow arrow).

2.3.2 Spatial neglect

Spatial neglect is a heterogeneous syndrome which is present more often in right (compared to left) hemisphere stroke patients, possibly because of the difficulty in assessing patients with severe aphasia (Bowen et al. 1999). There is large variability in reported rates. Reasons for this include variability in the: a) sample size, b) number of days between stroke onset and testing, c) spatial neglect tests that are used, and d) lesion location (Bowen et al. 1999). For example, Stone and colleagues (1993) found that 82% of right and 65% of left hemisphere stroke patients had spatial neglect, whereas Pedersen and colleagues (1997) found that it was much lower (38% of right and 7% of left hemisphere stroke patients). Even though both studies tested patients within one week post-stroke, the first used more sensitive tests and examined a much smaller sample. At three months post-stroke, neglect is less prevalent and was found in 17% of right and 5% of left hemisphere stroke patients in a study of 849 people by Ringman and colleagues (2004).

At present, there is no single standard procedure for detecting spatial neglect following stroke; therefore, the techniques used, and their limitations, need to be evaluated. Because of the heterogeneity of this condition, a combination of tasks is often used (Agrell et al. 1997). The following were the main spatial neglect tasks used in this thesis: the line bisection task, the Behavioural Inattention Test star cancellation task (Wilson et al. 1987), and the Mesulam shape cancellation task (Mesulam 1985). The line bisection task was administered because some patients may show a lateralized bias on this task but not on the cancellation tasks (Ferber and Karnath 2001; Rorden et al. 2006). The star cancellation and Mesulam tasks (in which spatial neglect patients often start from the ipsilesional side) are thought to assess egocentric neglect, whereas the line bisection task does not selectively assess only one type of spatial neglect, that is, performance can be based on an egocentric or an object-based (allocentric) reference frame (Bickerton et al. 2011; Chechlacz et al. 2010). This is important as different regions are thought to be associated with each of these types of spatial neglect

(Medina et al. 2009; see section 1.6.2.3 for further discussion about these types of spatial neglect). There was no time restriction in performing these tasks; each task was stopped when the patient reported that they had finished. Time to completion was not recorded.

In the Behavioural Inattention Test star cancellation task (Wilson et al. 1987), patients are asked to circle all the small stars presented randomly on an A4 paper (27 of them are located on the right and another 27 on the left side of the paper) and omit the distractors (52 big stars, 12 letters, and 10 words; Figure 2.2A). At the start of the task, the 2 central small stars are circled by the administrator to indicate to the patient which stars to search for. Spatial neglect was operationally defined as omitting more than two small stars on the contralesional compared to the ipsilesional side of the paper (Li et al. 2016).

In the Mesulam shape cancellation task (Mesulam 1985), patients are asked to circle a target (an unfilled circle which has 8 spikes and a line at 135 degrees; Figure 2.2B). There were 15 targets presented randomly in each quadrant of an A4 paper. Across the whole paper there were 311 distractors (filled and unfilled shapes of different sizes, for example, circles, triangles, stars, and rectangles). Spatial neglect was operationally defined as omitting more than two targets on the contralesional compared to the ipsilesional side of the paper (Li et al. 2016). This task was not administered to patients who showed very severe spatial neglect on the star cancellation task (looking for stars outside the page). These patients were often very fatigued, and piloting showed that they could not find any targets on the Mesulam task which is more demanding than the star cancellation task.

In the line bisection task, patients were presented with 6 black horizontal lines of 3 different lengths (25 cm, 14.8 cm, 9.85 cm; Figure 2.2C). Each line was 1 mm in width shown in the centre of a white A4 paper. Patients were asked to draw a vertical line through the middle of the horizontal line. The order in which each line length was presented, was

randomised. Spatial neglect was operationally defined as mean line bisection deviation of more than 5 mm towards the ipsilesional side (Li 2016). A contralesional bias is sometimes found in patients who only have visual field defects such as hemianopia or quadrantanopia, which is known as hemianopic line bisection error (Barton and Black 1998; Schuett et al. 2011), though others (Sperber and Karnath 2016) have reported an ipsilesional bias in these patients. A small leftward bias on this task is often found in neurologically healthy individuals, which is known as pseudoneglect (Jewell and McCourt 2000).

In the Behavioural Inattention Test picture copying task (Wilson et al. 1987), patients are presented with 3 line drawings on the left side of an A4 paper and are asked to copy them on the right side of the paper (Figure 2.2D). Patients with contralesional omissions were defined as having spatial neglect.

Apart from peripersonal neglect (which was assessed by using the neglect tasks mentioned above), extrapersonal neglect was detected by asking patients to name and/or point to 10 objects in the room (Stone et al. 1991; Figure 2.2E). Patients were defined as having this type of neglect if they identified more objects in the ipsilesional compared to the contralesional side of the room.

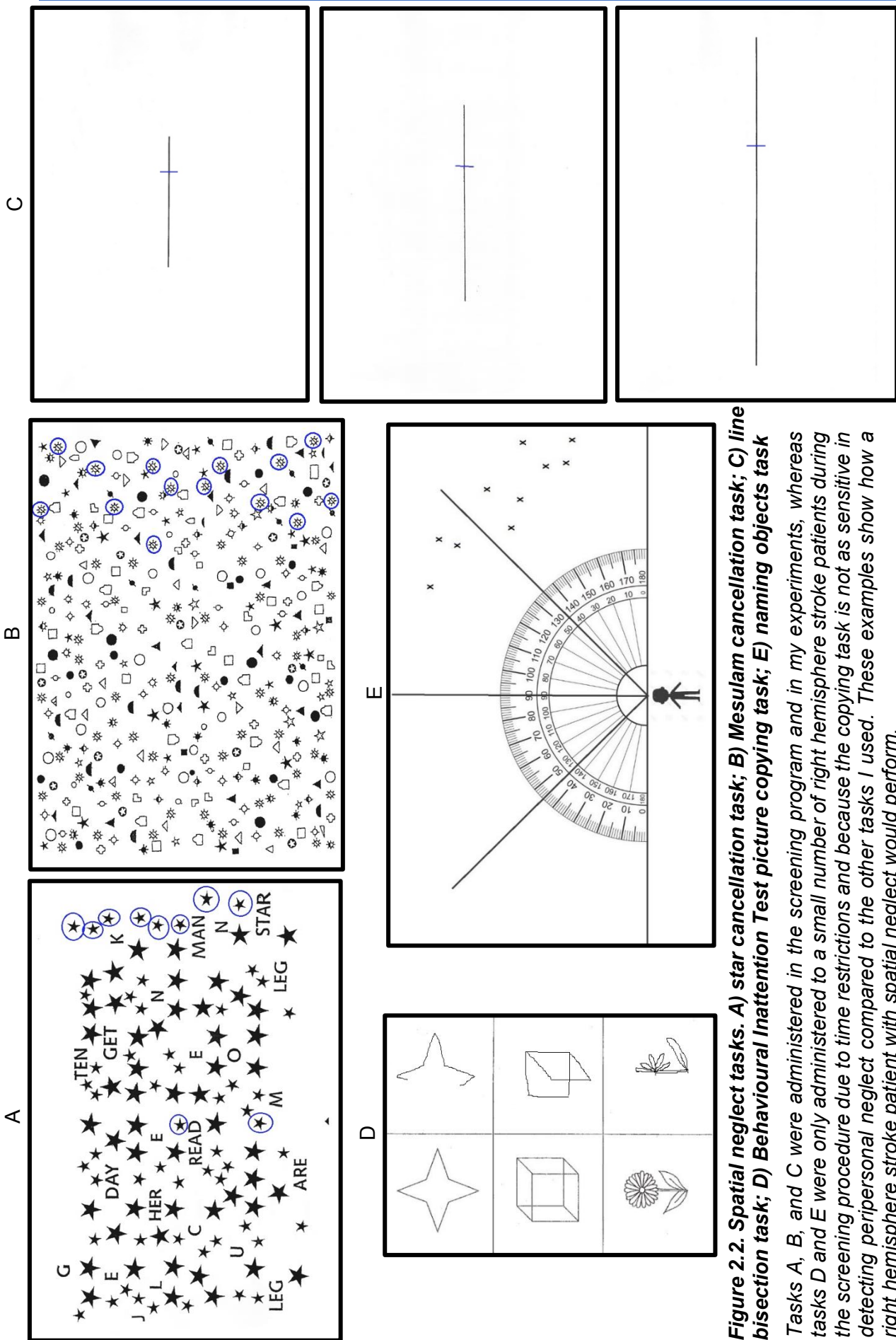


Figure 2.2. Spatial neglect tasks. A) star cancellation task; B) Mesulam cancellation task; C) line bisection task; D) Behavioural Inattention Test picture copying task; E) naming objects task
 Tasks A, B, and C were administered in the screening program and in my experiments, whereas tasks D and E were only administered to a small number of right hemisphere stroke patients during the screening procedure due to time restrictions and because the copying task is not as sensitive in detecting peripersonal neglect compared to the other tasks I used. These examples show how a right hemisphere stroke patient with spatial neglect would perform.

2.3.3 Visual extinction

A phenomenon that often presents concurrently with spatial neglect is visual extinction (Driver and Mattingley 1998). Patients with visual extinction are able to detect stimuli when they are presented on their own (either on their ipsilesional or contralesional side), but when the two stimuli are presented simultaneously they are only able to detect the ipsilesional stimulus (Driver and Mattingley 1998). This phenomenon is more common after right (rather than left) hemisphere stroke (Stone et al. 1993).

To test visual extinction, the examiner's right and left index fingers moved simultaneously in the patient's left and right visual hemifield, respectively. If a patient had a visual field deficit, both fingers were presented in the intact visual field. Patients were defined as having visual extinction if they reported seeing only the examiner's finger in their ipsilesional side when the examiner moved both fingers.

2.3.4 Aphasia

Aphasia is found in 12–38% of stroke patients (Berthier 2005; Ellis et al. 2012) and leads to poorer outcome (Ellis et al. 2012). It was important to exclude patients with this language deficit for many reasons, including possible inability to: a) understand the instructions (e.g. in receptive aphasia), and b) ask questions to clarify their understanding of the tasks (e.g. in expressive aphasia).

The aphasia screening test that I used was the Sheffield screening test for acquired language disorders (Syder et al. 1993). This particular test was chosen because it: a) screens for both expressive and receptive language abilities, b) includes questions about patients' functional communication, and c) is relatively straightforward and brief (about 5–10min) which is particularly important because many stroke patients experience fatigue.

Although aphasia occurs mostly after damage to the left hemisphere, in some cases it is present in right hemisphere stroke patients (Gajardo-Vidal et al. 2018). Because it is so rare in the latter group and because this test is not sensitive enough to detect their language deficits (Syder et al. 1993), it was only administered to left hemisphere stroke patients on the day of memory testing (experiments in Chapters 5 and 6). It was not administered at the screening stage because piloting showed that it was not feasible. Also, at the screening stage I did not approach patients with severe aphasia.

2.3.5 Results from the screening procedure

On a daily basis, in the period between September 2017 and March 2020, I went through the inpatient lists of the three Stroke Units of Charing Cross Hospital, London (the Hyperacute, Subacute, and Rehabilitation Units). Firstly, I examined patients' medical notes to check whether they met the eligibility criteria of my studies (see section 2.5.1). After shortlisting patients according to their medical notes, I went through all their radiology reports and visibly inspected their MRI (if available) and CT brain scans to assess whether: a) the stroke was confirmed on the scan, b) they had had a previous stroke, and c) the lesion was sufficiently visible to delineate. I then liaised with the multidisciplinary team to ensure that the patients would be capable of going through the screening assessment.

Using this approach, I screened 430 patients (Table 2.1). This number does not include: a) patients whose screening assessment I observed (I did not personally administer the tests), and b) patients who were initially screened by another colleague and then rescreened by myself to examine whether they were eligible for the studies presented in this thesis (i.e., whether they had recovered from spatial neglect and hemianopia). The complete set of screening tests was not performed by all patients for many reasons, including inability to move either of their hands, severe visual impairment, fatigue, language barrier, and aphasia. The

percentage of patients with spatial neglect (lateralized bias in at least one of the spatial neglect tests) was 40.7% in my sample (Table 2.1). This percentage is larger than a previous study which tested 602 patients within the first week post-stroke and found that 23% had spatial neglect (Pedersen et al. 1997).

Table 2.1. Results from screening stroke patients

The ratios refer to how many patients showed impairment out of all the patients that performed the task. Here I report only the results from the first time I assessed the patients (and do not include results from immediately prior to participation).

	Right hemisphere stroke	Left hemisphere stroke
Number of patients assessed	276	154
Visual field deficit	50/262 (19.0%)	17/151 (11.2%)
Visual extinction	11/250 (4.4%)	0/148 (0%)
Hemiparesis	168/270 (62.2%)	77/152 (50.6%)
Hemianesthesia	59/259 (22.7%)	14/145 (9.6%)
Aphasia	–	48/154 (31.1%)
Spatial neglect on the Behavioural Inattention Test star cancellation task	75/256 (29.2%)	18/136 (13.2%)
Spatial neglect on the Mesulam shape cancellation task	42/148 (28.3%)	8/109 (7.3%)
Spatial neglect on the line bisection task	69/247 (27.9%)	26/132 (19.6%)
Spatial neglect on the Behavioural Inattention Test shape copying task	4/15 (26.6%)	–
Extraperosnal neglect (naming/pointing to objects in the room)	3/6 (50.0%)	–
Ipsilesional start on the Behavioural Inattention Test star cancellation task	117/256 (45.7%)	93/136 (68.3%)
Ipsilesional start on the Mesulam shape cancellation task	84/148 (56.7%)	85/109 (77.9%)
Lateralized deficit on ≥ 1 spatial neglect task	121/264 (45.8%)	43/139 (30.9%)
Lateralized deficit on ≥ 1 spatial neglect task and ipsilesional start on ≥ 1 cancellation task	92/258 (35.6%)	34/136 (25.0%)
Lateralized deficit on ≥ 2 spatial neglect tasks	55/247 (22.2%)	10/131 (7.6%)

2.4 Standard neuropsychological tasks

2.4.1 Assessment of cognition across domains

The Addenbrooke's Cognitive Examination (ACE-III; Hsieh et al. 2013) is a quick and relatively easy-to-administer test which is widely used to screen for cognitive impairment. It examines five cognitive domains: attention, memory, fluency, language, and visuospatial abilities. This test was used because it provides a more accurate general cognitive profile compared to other tests such as the Montreal Cognitive Assessment (MoCA) and the Mini Mental State Examination (MMSE), especially in the memory domain (Matias-Guiu et al. 2017a, 2017b). It was administered to healthy elderly controls and stroke patients who took part in the experiment described in Chapter 5, to make sure that healthy elderly participants did not have undiagnosed cognitive impairment and to examine whether score differences in the spatio-temporal task might relate to differences in any of the ACE-III domains, particularly memory and visuospatial processing.

2.4.2 Corsi block task

In this task, first described by Corsi (1972), subjects observe a sequence of up to nine tapped blocks (or highlighted squares) located in different positions and are asked to immediately repeat it in the forward or backward order. Although it has been widely used to examine visuospatial working memory in stroke patients (see section 1.5.2.3.1), it could be argued that it is not such a “pure” measure because it also requires manual motor coordination and the ability to remember sequences (Berch et al. 1998; Cavallini et al. 2003; Malhotra et al. 2005). It has been proposed that, in both forward and backward recall on this task, the visuospatial sketchpad appears to be recruited initially and then the central executive is increasingly involved as sequences become longer (Vandierendonck et al. 2004). It seems that the

backward (compared to the forward) condition places a heavier load on the ability to represent sequences (Higo et al. 2014).

In the electronic version that I used (Draine 2016), participants saw nine blue squares (dimensions: 25 mm x 25 mm) on a black background, which were present on a 9.7-inch iPad touchscreen for the whole duration of the task (Figure 2.3). On each trial, 2 to 9 squares were highlighted in yellow in a specific sequence and the participant was asked to remember the exact squares and the exact sequence in which they were highlighted. As soon as the sequence finished, they were required to tap the same squares in the same temporal order that they lit up, to replicate the sequence. To indicate that each response was recorded, when the participant tapped a square, it turned yellow, and it automatically became blue again once they took their finger off the screen. Self-corrections were allowed. After completing each sequence, feedback was provided on the screen indicating whether they had responded correctly or incorrectly. Two attempts were given for each sequence length; on these two attempts, the number of squares was the same but there was a change regarding which squares were highlighted and in what sequence. In each sequence: a) the squares were highlighted at random, and b) no square was highlighted twice. The test began with two squares and the number of highlighted squares increased by one whenever the participant was correct in at least one of the two attempts. There was no interval between trials. The task ended when the participant was incorrect in both trials of the same sequence length.

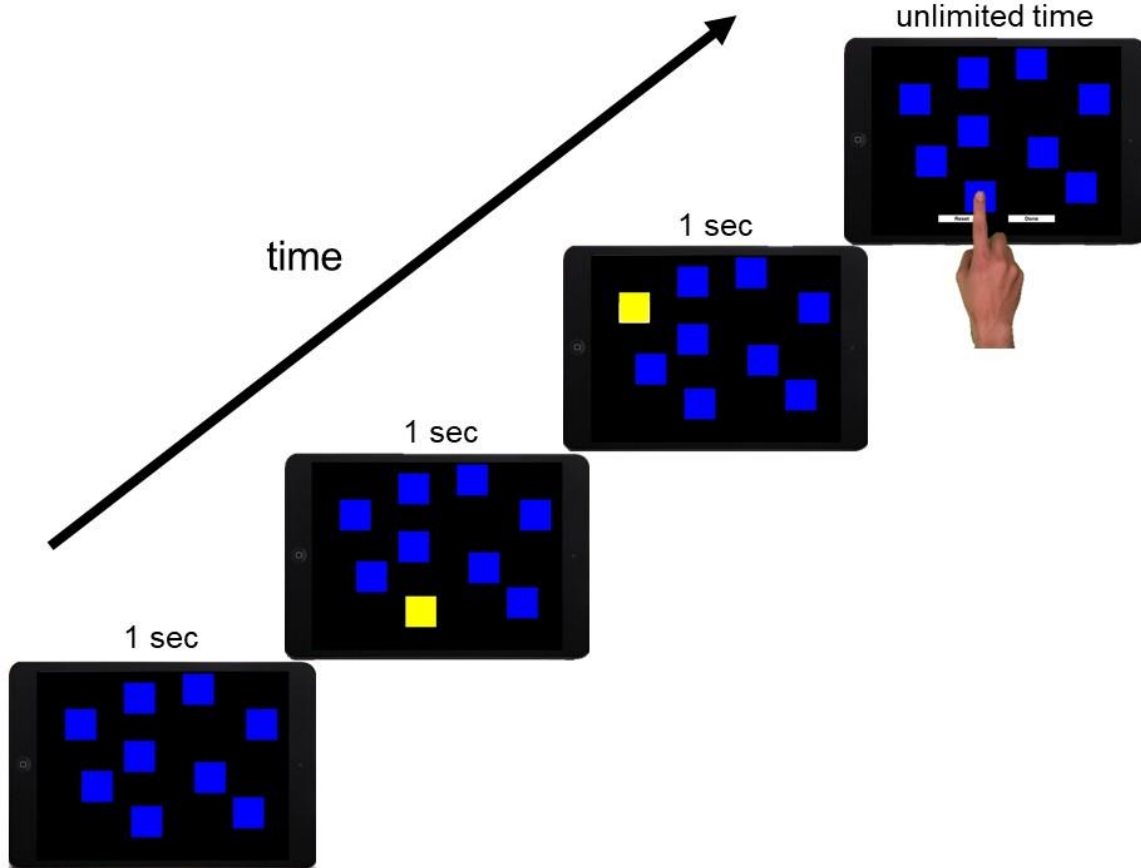


Figure 2.3. Example of a two-square sequence on the electronic version of the Corsi block task

The task provides two scores: the block span and total cumulative score. The former is the longest sequence that is reproduced (maximum = 9), whereas the latter considers one's performance across both trials of each length (Span x Number of Correct Trials; maximum = $9 \times 16 = 144$). Thus, the latter may provide a more reliable measure of the participants' performance (Kessels et al. 2000). Although participants must remember both the temporal order and spatial location of the squares, the task does not provide a separate score for each.

To ensure that participants thoroughly understood what to do, they went through a practice session (which I created) before starting the actual task. They read the instructions of the task and observed two examples of two-square sequences and one example of a three-

square sequence. The span examples in the practice sessions were not the same as the sequences in the experimental task.

Two studies that compared the electronic to the non-electronic version did not find a significant difference in Corsi forward recall (Brunetti et al. 2014; Robinson and Brewer 2016), but one study did (better forward recall when using the non-electronic version but no difference in backward recall; Claessen, van der Ham, and van Zandvoort 2015). The main difference between the electronic and the non-electronic version is that the first is 2D whereas the latter is 3D and thus has higher ecological validity. Hence, the superior performance that was found by Claessen, van der Ham, and van Zandvoort (2015) may be because 3D objects (compared to 2D images of objects) enhance memory (Snow et al. 2014) and are more attention provoking (Gomez et al. 2018). Another possible reason for the enhanced recruitment of these cognitive functions in the non-electronic version, is that extra cues are provided (e.g. the sound of tapping the blocks and the motion of tapping them). On the other hand, though, these cues may be regarded as distracting. In the electronic version, participants can focus only on the colour change, thus avoiding any other possible distractions.

The electronic version of the task was administered to subjects who participated in the experiments of Chapters 5 and 6 (only the forward condition was administered in the latter) for three reasons. First, to examine whether there was any relationship with performance on the experimental tasks, and second, whether spatial working memory deficits persist in patients who have recovered from spatial neglect. Stroke patients with spatial neglect perform poorly even on a vertical adaptation of this task with no requirement in remembering sequences, which indicates a non-lateralized spatial working memory deficit (Malhotra et al. 2005). Although no spatial working memory deficits were found in patients who never had spatial neglect, Malhotra and colleagues (2005) did not test patients who had recovered from spatial neglect. Third, I wanted to explore whether there is any overlap in the brain regions

that are associated with performance on the 4MT, the spatio-temporal task of Chapter 5, and the Corsi block task. Processes that are required in the 4MT and in the spatio-temporal task of Chapter 5 are mainly allocentric memory, egocentric memory and the ability to translate between these perspectives, which are thought to be primarily dependent on the hippocampus, the posterior parietal lobe, and the retrosplenial cortex, respectively. There is no clear consensus on the reasons for hippocampal involvement in spatial episodic/working memory tasks. It could be purely due to the spatial element of these tasks, as suggested in the cognitive map theory (O'Keefe and Nadel 1978), purely due to the episodic/working memory element instead, or due to both the spatial *and* episodic/working memory elements (Baddeley et al. 2011; Leszczynski 2011). Thus, examining the neural correlates of performance on the 4MT, the spatio-temporal task of Chapter 5, and the Corsi block task, might also provide a clearer understanding of hippocampal function.

2.4.3 Representational neglect task

Patients with representational neglect or mental imagery neglect have a deficit of mental imagery in which they cannot describe or explore the contralesional side of their mental images (Bisiach and Luzzatti 1978; Salvato et al. 2014). This affects about 14–17% of spatial neglect patients with right hemisphere damage (frontal, temporal, or parietal; Bartolomeo, D'Erme, and Gainotti 1994; Guariglia et al. 2005, 2013; Rode et al. 2004), and leads to poorer recovery (Cocchini et al. 2001). Very rarely it can also be found in patients who do not have spatial neglect (Beschlin et al. 1997; Coslett 1997; Ortigue et al. 2001). There are dissociations between personal and extrapersonal representational neglect (Ortigue et al. 2003, 2006), as well as between topographical and non-topographical representational neglect.

Representational neglect was assessed only in stroke patients participating in the experiment of Chapter 6. I used a topographical representational neglect task, specifically the

“Description of a topographical scene from memory”, because among all topographical memory tests this is the one that is most similar to the 4MT (assessing the spatial layout of a scene). I used a paradigm adapted from that described by Kaski and colleagues (2016). Patients were asked to imagine standing in front of their house and recall what would be visible from their viewpoint; firstly looking at the house and secondly having their back to the house (Figure 2.4). Total responses from the left and right side (for each viewpoint) were recorded. Answers were checked by observing the area (in patients that I tested at their home) or using Google Street View from the Maps application (<http://maps.google.com>).

This test was used for two reasons. Firstly, I wanted to try to differentiate between general and lateralized deficits. General means that a limited number of stimuli are reported on both sides of space in the representational neglect task, whereas lateralized means that fewer stimuli are reported in the contralesional side compared to the ipsilesional side. As I did not include patients with spatial neglect, it may be more likely that some patients have a generalized rather than a lateralized deficit in mental imagery. Secondly, I wanted to examine whether performance on the representational neglect task was related to performance on the 4MT. This is probable because both tasks require a high level of mental imagery, and the ability to remember a complex visuospatial environment, maintain it, and manipulate the viewpoint from which they observe that environment. The main difference between these tasks is that the environment is much more familiar in the representational neglect task (their neighbourhood) compared to the 4MT (scenes observed for a few seconds) and thus the former may be easier to manipulate.



Figure 2.4. Example of imagining two different viewpoints in the representational neglect task

2.4.4 Rey-Osterrieth Complex Figure Test

In the Rey-Osterrieth Complex Figure Test (Lezak et al. 2012; Osterrieth 1944; Rey 1941), participants are shown a complex figure (Figure 2.5) which they are asked to copy. This is performed with different coloured pens so one can examine the process by which participants draw the figure, for example, whether they start from the ipsilesional side. Additionally, it can examine a number of cognitive processes including visuospatial praxis, construction planning, executive functioning, and the ability to perceive, attend to and maintain a complex visuospatial representation (Massa et al. 2015). Crucially participants are not told to remember the figure or that their memory for that figure will be tested later. In order to examine incidental anterograde memory for visuospatial material, participants are given surprise memory tests in which they are asked to draw the figure from memory (immediately after copying it and also after approximately 20 minutes). Time to completion was recorded for each trial.

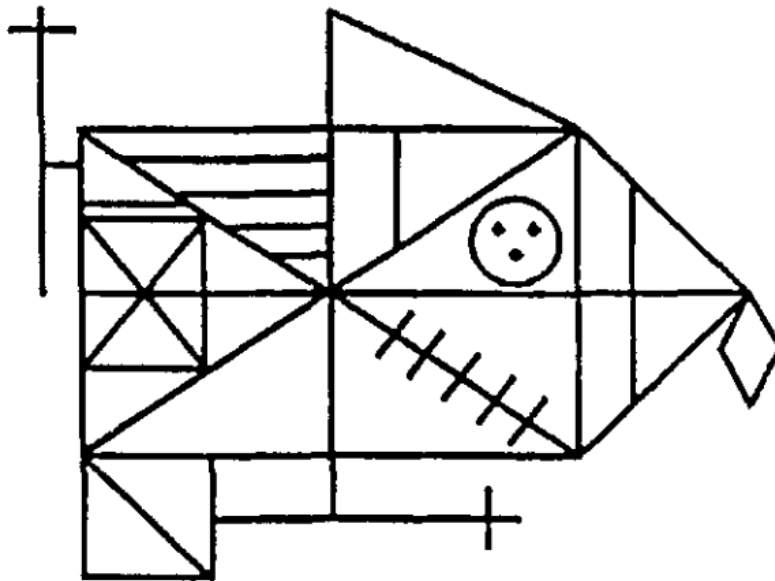


Figure 2.5. The Rey-Osterrieth Complex Figure

Image reproduced from Stern and colleagues (1994) with permission of the rights holder www.tandfonline.com.

This test was administered to patients and healthy subjects in the experiment described in Chapter 5. One of the reasons for using it, was to examine whether patients had constructional apraxia. In this disorder, although patients are able to produce individual movements, they are unable to accurately copy, draw, or assemble 3D objects or even simple drawings; this condition has been linked to impairments in position judgments and is thought to occur due to an inability to remember visuospatial information from one eye fixation to the next (Russell et al. 2010). Patients' inability to copy the figure could be secondary to reduced ability to encode it. Even if some patients with constructional apraxia are able to remember the figure clearly, their recall score would be low because of their inability to draw it in the recall trials. Because patients who recover from spatial neglect may still present with constructional apraxia (Hier et al. 1983), it was important to examine whether this condition was present as it may have affected performance on the memory tasks employed in my experiments.

In the current thesis, the presence, accuracy, and placement of the different elements of the Rey figure were manually scored according to the Boston Qualitative Scoring System (Stern et al. 1994, 1999; 3 Rey figures per each of the 43 patients in the experiment of Chapter 5). Immediate and delayed retention scores were computed by comparing performance between copy and immediate recall, and between immediate and delayed recall, respectively. Raw scores were converted to cumulative percentages and T-scores by using age- and gender-matched normative data (Stern et al. 1999).

2.5 Inclusion criteria for subjects in my experiments

2.5.1 Stroke patients

The inclusion criteria for participation of stroke patients in my experiments are shown in Table 2.2. Regarding the last row in this table, it should be noted that although recent evidence supports that the cerebellum (Andreasen et al. 1999; Noroozian 2014; Tomlinson et al. 2014) and brain stem (Fu et al. 2017; Garrard et al. 2002) are involved in non-motor cognitive functions, and that transient ischaemic attacks (van Rooij et al. 2016) and small vessel disease (especially if it is severe; Charidimou and Werring 2012; Poels et al. 2012; Staals et al. 2015) can be associated with cognitive dysfunction, I did not exclude patients if in addition to their cerebral stroke they had imaging markers of small vessel disease (lacunes, microhaemorrhages, white matter hyperintensities), brain calcifications, established lesions located in the cerebellum or brain stem, or previous transient ischaemic attacks. White matter changes are common in the general population without any cognitive deficits (de Leeuw et al. 2001; Liao et al. 1996; Longstreth et al. 1996, 1998). Although their interaction with large vessel stroke has yet to be fully investigated (Wardlaw et al. 2013), I decided to include them in my experiments unless there was evidence of pre-existing cognitive impairment that was secondary to these.

Patients were tested regardless of the presence of reported post-stroke memory problems, as I did not want to bias my selection to only those patients in which memory problems had already been identified (by the patient or carer). There is no clear consensus as to whether stroke patients' self-reported memory complaints are associated with impaired performance on objective tests (van Rijsbergen et al. 2014). Some patients may be overreporting memory problems as they would be highly conscious of the difference between their pre- and post-stroke cognitive abilities. Another advantage of taking this non-selective approach is that the measurement of behaviour using a continuous scale with large variability in patients' scores (from no errors to the maximum number of errors), leads to increased power and sensitivity in voxel-lesion symptom mapping analyses (Baldo et al. 2012).

Table 2.2. Inclusion criteria for stroke patients in my experiments

Clinical stroke affecting only one cerebral hemisphere with evidence of haemorrhage or infarct on CT and/or MRI
Age \geq 18 years
No spatial neglect at time of testing in any of these tasks: star cancellation task, Mesulam task, line bisection task
Able to fully cooperate study procedures, e.g. understand and follow instructions, and complete the tasks. Having English as a first language was not a requirement for participation.
Willing and able to give informed consent
No aphasia in left hemisphere stroke patients at time of testing. If they had aphasia when I screened them, I contacted them to take part in the study after a minimum of 3 months, at which point I administered the “Sheffield screening test for acquired language disorders” (Syder et al. 1993). Patients scoring less than 15/20 were excluded.
Glasgow Coma Scale = 15/15 at time of testing
Normal or corrected-to-normal colour vision at time of testing. Patients with hemianopia were excluded but not those with quadrantanopia or visual extinction.
No current alcohol or drug abuse
Absence (according to their medical notes) of any co-existing psychiatric, neurological, or medical condition that affects the central nervous system, for example: <ul style="list-style-type: none"> - Previous cerebral stroke - Traumatic brain injury requiring admission to hospital - Clinically diagnosed dementia or mild cognitive impairment - Clinically diagnosed depression (though patients with mild post-stroke depression were not excluded) - Conditions that lead to metabolic encephalopathy, e.g. severe hepatic failure

2.5.2 Healthy subjects

The inclusion criteria for participation of healthy subjects in my experiments are shown in Table 2.3. Healthy participants were recruited mainly by advertisements placed on campuses of

Imperial College London, at local gyms, and through the Imperial College Neuroscience Society newsletter.

Table 2.3. Inclusion criteria for healthy subjects in my experiments

Medically stable
Age \geq 18 years
Able to fully cooperate study procedures, e.g. understand and follow instructions, and complete the tasks. Having English as a first language was not a requirement for participation.
Willing and able to give informed consent
Normal or corrected-to-normal colour vision
No alcohol or drug abuse
No psychiatric, neurological, or medical condition that affects the central nervous system

2.6 Ethical approval

In order to recruit stroke patients for my experiments, when I screened patients on the wards I obtained their consent to be contacted in the future. All studies were approved by the Imperial College Research Ethics Committee. All participants in my experiments gave informed written consent according to the Declaration of Helsinki and any travel expenses were reimbursed if needed. Performance on all tasks was unobtrusively and continuously observed to make sure that participants were actively engaging on the tasks and could understand and follow the instructions.

3 Anatomical Analysis of Focal Lesions and Lesion-Behaviour Mapping

3.1 Introduction

This chapter refers to the methodologies used to perform lesion-behaviour analyses in stroke patients in Chapters 5 and 6. I describe the imaging methods that I used, the techniques for delineating and normalizing the patients' lesions and relating them to their behavioural scores, as well as the limitations involved. I also discuss the lesion network mapping techniques that were performed in Chapter 6.

3.2 How to examine the functional organization of the brain

Prior to modern imaging techniques, the ability to infer the function of brain regions was limited because behaviour could only be related to post-mortem brain abnormalities (e.g. Broca 1861; Wernicke 1874). With the advent of CT and then MRI, which allow a fast and more accurate examination of brain anatomy, the field has advanced rapidly. Currently, there are many ways to examine whether a region is associated with performance on a task (Figure 3.1). Each method differs in its spatial and temporal resolution, whether it is invasive or not, whether or not it interferes with brain function, and in which population groups it is often used.

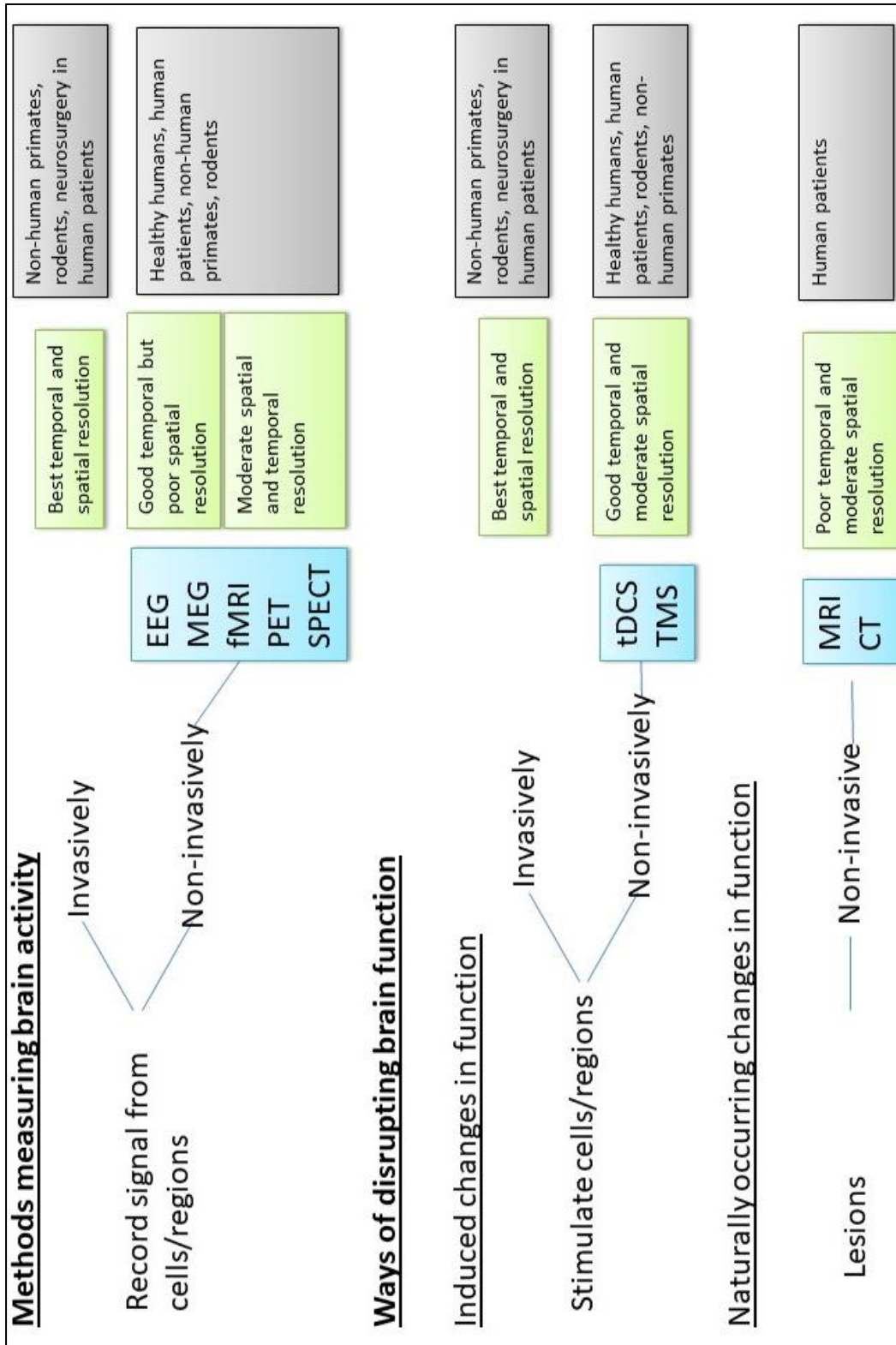


Figure 3.1. Some of the methods often used to examine brain function

Their spatial and temporal resolution are shown in green. The population groups in which each method is most often used is shown in grey. EEG: electroencephalography; MEG: magnetoencephalography; SPECT: single-photon emission computerized tomography; tDCS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation.

Most studies on allocentric, egocentric memory, and memory for temporal order have tested rodents and healthy humans. But to understand which areas in the human brain are essential for these aspects of memory, it could be argued that the most suitable method is lesion-behaviour mapping. Lesion-based studies allow us to detect which brain regions are *critical* for a given behaviour, in contrast to functional neuroimaging-based studies in healthy subjects which can only show whether brain regions are *involved* in a behaviour (Malhotra and Russell 2015; Rorden and Karnath 2004; Tyler et al. 2005).

In this thesis, I performed analyses that relate performance on specific memory tasks with lesion anatomy (lesion symptom mapping), and further analyses which then directly relate those findings with task-based and resting-state brain activations (lesion network mapping). With these methods, I attempted to examine: a) the contribution of each brain region to temporal order and spatial memory, b) whether different regions are associated with egocentric and allocentric memory, c) whether larger lesions lead to more severe impairment, and d) whether spatial memory utilizes a widely distributed neural network.

3.3 Procedure

The procedure for conducting the patient studies in this thesis is illustrated in Figure 3.2. The first step was described in Chapter 2. A description of the cognitive tasks used in the second step is found in Chapters 2, 5, and 6. The next four steps, from manual lesion delineation to lesion network mapping, are discussed below.

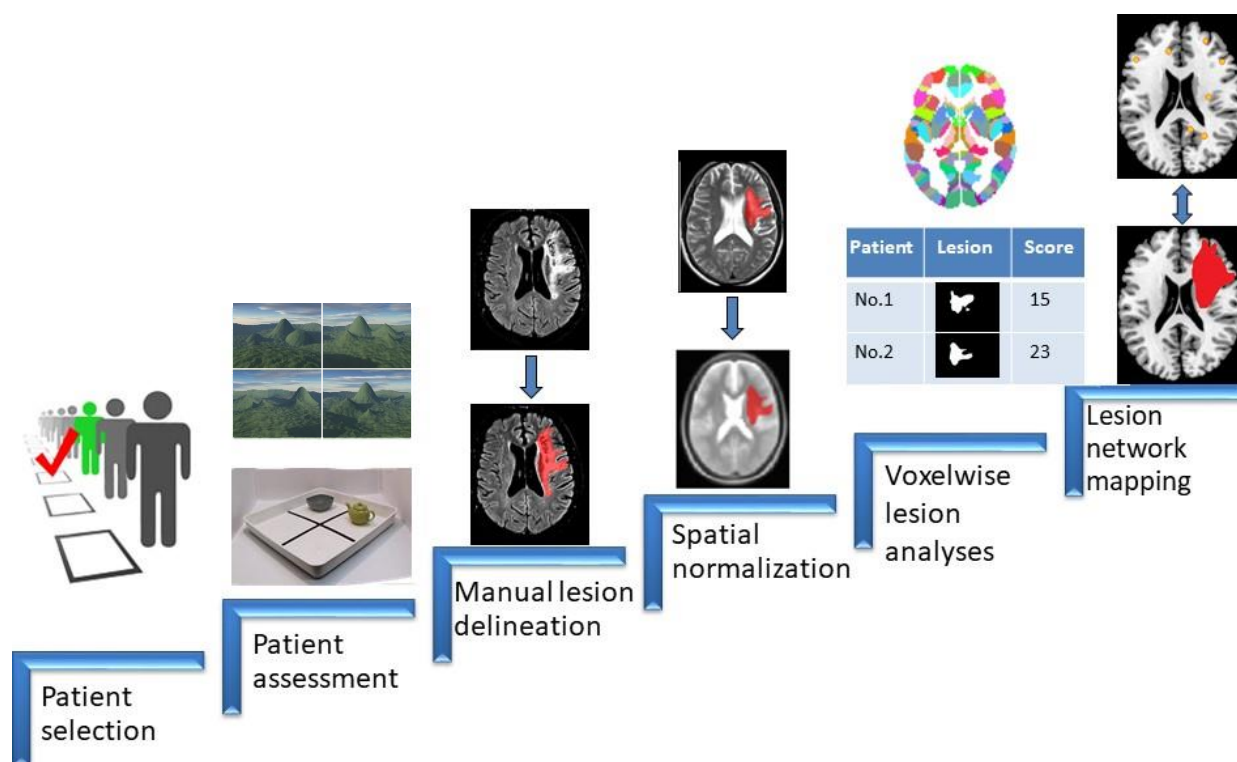


Figure 3.2. Workflow diagram

3.3.1 Lesion delineation

In this thesis, I performed manual lesion delineation (the current gold standard; de Haan and Karnath 2018; Ito, Kim, and Liew 2019) on the clinical scans of 123 stroke patients. In the majority of patients, I used their MRI scans to map the lesion; a CT scan was used only in patients who did not have a MRI scan. Specifically, I delineated the lesions of 50 right hemisphere stroke patients (40 using MRI scans, 10 using CT scans) and 50 left hemisphere stroke patients (37 using MRI scans, 13 using CT scans) for the experiment described in Chapter 6, and an additional 15 right hemisphere stroke patients (14 using MRI scans, 1 using a CT scan) and 8 left hemisphere stroke patients (all using MRI scans) for the experiment in Chapter 5. All MRI scans were performed on a Siemens 1.5T scanner, and CT scans were performed on Siemens SOMATOM Definition, General Electric Optima CT 660, Philips iCT 257, or Philips Ingenuity CT scanners; these were performed within approximately seven days

after stroke as part of standard clinical investigations. If patients had more than one MRI scan available, I selected the MRI scan that showed the lesion most clearly. The choice of MRI sequences on which I mapped their lesion depended on the amount of time elapsed since stroke onset: diffusion weighted imaging (DWI) sequence if the scan was performed within 48 hours, T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence if the scan was performed after 48 hours (de Haan and Karnath 2018; Figure 3.3). These sequences have been used for lesion mapping in previous stroke studies (e.g. Karnath and Rennig 2017).

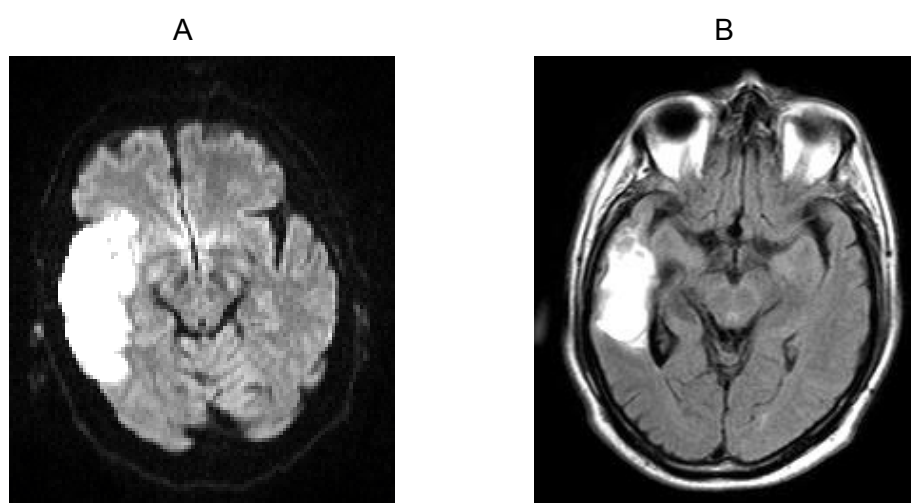


Figure 3.3. Lesions of two patients (bright white) shown on axial slices of different MRI sequences

A) DWI showing the acute lesion; B) FLAIR showing the subacute lesion.

Initially, I converted the Digital Imaging and Communications in Medicine (DICOM) files into Neuroimaging Informatics Technology Initiative (NIFTI) files using a tool available in the MRIcron software package (Version 2016; [www.mccauslandcenter.sc.edu/mricron](http://www.mccauslandcenter.sc.edu/mricron/mricron)). I then manually mapped the lesions directly onto patients' native scans (slice-by-slice on the axial plane) using MRIcron. In order to delineate the lesions as accurately as possible I also inspected the patients' other sequences and scans (if available), for example, T1, T2, FLAIR, DWI, and susceptibility weighted imaging (SWI). I was blind to the behavioural results when

mapping their lesion. The quality of delineation in some of the lesions for which I had doubts was evaluated by a consultant neurologist (Dr Paresh Malhotra) who was also blind to results.

3.3.2 Spatial normalization

Afterwards, I performed spatial normalization of patients' lesion maps and scans onto a common template. This procedure aligns patients' brains (it minimises interindividual variability in brain position, size, shape, and any possible rotation of the skull; Ashburner and Friston 2003) so that the lesions can then be superimposed on a brain template and voxels can correspond to the same coordinates across all patients. The lesion maps and the scans were normalized using the Clinical Toolbox provided by the statistical parametric mapping (SPM) 12 software (Penny et al. 2011; <https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) by following the guidelines on "CT normalization" and "MRI normalization" (<https://www.nitrc.org/docman/view.php/881/1853/manual.pdf>).

For patients whose lesion was mapped using a MRI scan, I used the routine "MRI normalization", in which SPM's default Montreal Neurological Institute (MNI) 152 template is based on 152 healthy young adults with a mean age of 25 years, standard deviation (SD) of 4.9, and of which 66 are females (Rorden, Bonilha, et al. 2012). I inputted: a) the anatomical scan (each patient's T2 scan; thus the chosen modality was T2), b) the lesion map (the NIfTI file that I had created in MRICron), and c) the pathological scan (either the patient's DWI or FLAIR image, depending on which of the two I had mapped the lesion on). For patients whose lesion was mapped using a CT scan, I performed CT normalization. In CT normalization, SPM's default MNI template for elderly people was used (mean age: 61.3 years old, which matches the average age of stroke patients; Rorden, Bonilha, et al. 2012). I inputted the patient's CT scan and lesion map (the NIfTI file that I had created in MRICron). In both CT and MRI normalization the voxel sizes were 1 x 1 x 1 mm, no brain mask was applied to the

template, the bounding box was [-78 -112 -50] and the origin was set automatically.

I then visually inspected each patient's normalized lesion map and normalized scan (T2 if I performed MRI normalization, or CT if I performed CT normalization) to assess whether normalization was successful (whether they were aligned to the average template) by using CheckReg in SPM12. I also looked at the normalized lesion on a template brain in MRIcron and extracted the lesion volume (voxels).

3.3.3 Voxelwise lesion analyses

Voxelwise lesion analyses examine lesion-behaviour relationships on a voxel-by-voxel basis. These analyses can be descriptive (lesion subtraction analysis) or statistical. In descriptive methods one can only use binary behavioural scores, whereas in statistical methods one can use either binary or continuous scores. The use of continuous scores (a gradient rather than dichotomizing patients into impaired and unimpaired groups), allows the identification of regions related to worst performance. This approach leads to increased power and sensitivity (Baldo et al. 2012).

3.3.3.1 Voxelwise statistical analyses

In voxelwise statistical analyses, when entering continuous behavioural data, each voxel in the brain undergoes the following computations: initially subjects are separated into two groups depending on whether their lesion has or has not damaged that voxel, then behavioural data are compared between the two groups, and therefore a t-statistic is generated for that voxel (Bates et al. 2003; Karnath et al. 2019). The output of this analysis is a statistical map showing the voxels for which there is a significant association between behaviour and voxel status (damaged versus undamaged; Karnath et al. 2019).

One possible reason that voxelwise statistical analyses have rarely been used in the memory literature is that most lesion studies on memory have focused on single cases or small case series. This technique requires quite a large sample size to avoid over- or underestimation of the effect sizes (Lorca-Puls et al. 2018); voxel-lesion symptom mapping studies typically include 30–100 patients (Baier et al. 2010; Benavides-Varela et al. 2017; Buxbaum et al. 2014; Campanella et al. 2014; Cohen-Zimmerman et al. 2020; Deng et al. 2020; Fellrath and Ptak 2015; Frenkel-Toledo et al. 2020; Ghaleh et al. 2018; Grajny et al. 2016; Kenzie et al. 2015; Kinkingnéhun et al. 2007; Laredo et al. 2018; Liu et al. 2019; Lunven et al. 2015; Machner et al. 2018; Mandal et al. 2020; Michaelis et al. 2020; Mihulowicz et al. 2014; Pflugshaupt et al. 2020; Pillay et al. 2017; Ptak and Schnider 2010; Ripamonti et al. 2018; Ronchi et al. 2016, 2020; Salazar-López et al. 2016; Schwartze et al. 2015; Skipper-Kallal et al. 2017; Sperber et al. 2020; Strölin et al. 2017; Timpert et al. 2015; Ubben et al. 2020; Umarova et al. 2016; Vossel et al. 2011; Vossel and Fink 2016; Weiss et al. 2016; Xing et al. 2016; Zündorf et al. 2014); this is the sample size I aimed to have in my experiments.

In this thesis, I performed mass-univariate and low (but not high) dimensional multivariate voxelwise statistical analyses using two software packages: nonparametric mapping (NPM) and NiiStat. By mass-univariate analyses I am referring to anatomically and behaviourally mass-univariate analyses (they do not regress for behavioural variables); by low dimensional multivariate analyses I am referring to anatomically mass-univariate but behaviourally multivariate analyses (that is, some behavioural covariates are included); in contrast, high dimensional multivariate analyses use machine learning techniques and are anatomically multivariate analyses (Xu, Jäger, et al. 2018; Xu, Jha, et al. 2018). Nonparametric mapping and NiiStat are the most up-to-date toolboxes for exploring associations between behavioural and neuroimaging data (Karnath et al. 2019). Both toolboxes can be used to perform voxel- and region of interest (ROI)- based analyses, but the NPM toolbox does not include any atlases in order to carry out the latter. NiiStat also allows one to regress for multiple

possible confounding factors such as lesion volume (Karnath et al. 2019) and thus one can perform low dimensional multivariate analyses. For these reasons, NiiStat was preferred for the majority of lesion analyses carried out in this thesis.

3.3.3.1.1 NiiStat in MATLAB

NiiStat (<https://www.nitrc.org/projects/niistat/>) is a collection of MATLAB scripts for analysing many different types of neuroimaging data. In analyses in which there is a single dependent variable of interest and there are continuous behavioural data, the following are true for NiiStat: a) statistics are computed using the general linear model (the results being the same as those from a two-sample t-test), and b) results are the same as those produced in NPM except for small rounding error differences (Karnath et al. 2019).

In NiiStat, I performed both voxel- and ROI- based analyses. These complement each other at least to some degree and thus can lead to more accurate conclusions if used in tandem (Snook et al. 2007). In a ROI-based analysis, one can examine whether the percentage of damage in a specific ROI is significantly related to performance on a task. It therefore detects which brain regions are critical for a particular cognitive function. This method is less prone to false positives and has greater statistical power compared to a voxel-based analysis, because it compares regions rather than single voxels (thus performs fewer comparisons; Rorden and Karnath 2004). Some disadvantages though of the ROI-based analysis are that: a) significance may be lost because it averages all the voxels within a ROI (Snook et al. 2007), b) each ROI is defined slightly differently depending on the atlas that is used, and c) it is only able to examine the predefined ROIs that are inputted (Rorden et al. 2009). For example, if the hippocampus is split into an anterior and a posterior hippocampal ROI, as is the case in the Atlas of Intrinsic Connectivity of Homotopic Areas (AICHA; Joliot et al. 2015), one cannot differentiate symptoms corresponding to CA1 versus CA3 damage.

Thus, although with the advent of new atlases one can perform a ROI-based analysis to examine whether performance is related to specific subregions, a voxel-based analysis can investigate even finer within-subregion differences, that is, it has higher spatial precision (Rorden et al. 2009), and thus can reveal which specific voxel or voxels are significant without being biased by predefined regions.

To perform analyses in NiiStat, I converted the lesion maps (which are binary, i.e., damaged or not damaged voxel) from NIfTI to Microsoft Access Table (MAT) files using MATLAB. I then entered them into NiiStat as MAT files. The significance level was set to $p < 0.05$ and permutation thresholding was used to control for familywise error rate. For mass-univariate analyses I used 5,000 permutations, which is the gold standard, whereas for low dimensional multivariate analyses I used the Freedman-Lane Permutation method (“-5000”; <https://github.com/neurolabusc/NiiStat>; Rorden, Karnath, and Bonilha 2007). In order to avoid a Type I error and possible outlier effects, the voxel-based analyses were conducted only on voxels that were damaged in at least 10% of the patient sample. Although some voxel-lesion symptom mapping studies have used a lower threshold (2–8%; Arnoux et al. 2018; Baier et al. 2010, 2011; Benavides-Varela et al. 2017; Buxbaum, Shapiro, and Coslett 2014; Campanella et al. 2014, 2018; Chouiter et al. 2016; Cohen-Zimmerman et al. 2020; Deng et al. 2020; Gläscher et al. 2009; Kenzie et al. 2015; Kinkingnéhun et al. 2007; Manuel et al. 2013; Mihulowicz et al. 2014; Payabvash et al. 2018; Pedrazzini and Ptak 2020; Pillay et al. 2017; Pisoni et al. 2019; Sagnier et al. 2019; Tsuchida and Fellows 2012; Ubben et al. 2020; Vossel et al. 2011; Weaver et al. 2019; Weiss, Ubben, and Kaesberg 2016), and others have used a higher threshold (13–30%; Boccia et al. 2020; Fellrath and Ptak 2015; Frenkel-Toledo, Ofir-Geva, and Soroker 2020; Kaski et al. 2016; Ludolph et al. 2019; Machner et al. 2018; Migliaccio et al. 2014; Pedrazzini and Ptak 2019; Pestalozzi et al. 2018; Ptak and Schnider 2010; Ripamonti et al. 2018; Ronchi et al. 2016, 2020; Rorden, Hjaltason, et al. 2012; Salazar-López, Schwaiger, and Hermsdörfer 2016; Skipper-Kallal et al. 2017; Teghil et al. 2020;

Vossel and Fink 2016; Wong et al. 2019; Zündorf, Karnath, and Lewald 2014), a 10% threshold has been suggested by Karnath and colleagues (2019) and has been used in many previous voxel-lesion symptom mapping studies (Benavides-Varela et al. 2016; Christensen et al. 2014; Dafsari et al. 2019; Ding et al. 2020; Ernst et al. 2016; Ghaleh et al. 2018; Grajny et al. 2016; Hebscher et al. 2016; Hoogkamer et al. 2015; Ilg et al. 2013; Im Moon et al. 2016; Lacey et al. 2017; Laredo et al. 2018; Liu et al. 2019; Lunven et al. 2015; Mandal et al. 2020; Michaelis et al. 2020; Papageorgiou et al. 2012; Pflugshaupt et al. 2020; Schwartz, Stockert, and Kotz 2015; Sperber, Nolingberg, and Karnath 2020; Strölin et al. 2017; Thieme et al. 2013; Timpert et al. 2015; Tsuchida and Fellows 2009; Umarova et al. 2016; Xing et al. 2016; Zihl et al. 2009).

3.3.3.1.2 NPM in MRICron

Further voxel-based analyses were performed using the Brunner-Munzel test (Brunner and Munzel 2000) available in the Nonparametric Mapping (NPM) toolbox in MRICron (Version 2016; Rorden et al. 2007; <http://people.cas.sc.edu/rorden/mricron/stats.html>). The Brunner-Munzel test is a non-parametric rank-order test which can compare continuous behavioural data between two groups of interest. Following the recommendation by Karnath and colleagues (2019), I applied 8,000 permutations in order to control for multiple comparisons. As in the NiiStat toolbox, the voxel-based analyses in the NPM toolbox were conducted only on voxels that were damaged in at least 10% of the patient sample.

3.3.3.1.3 Atlases used in the ROI-based analyses

Variability in results when using different atlases has been demonstrated for white matter tracts (de Haan and Karnath 2017), but has yet to be investigated in grey matter ROI atlases. For this reason, it has been proposed that more than one atlas should be used to interpret the data (Karnath et al. 2019). The choice of which atlases to use in the lesion analyses in this

thesis depended on the method that was used to derive the atlases (e.g. the number of subjects and the resolution of the scanner), whether they include grey and/or white matter ROIs, and whether they include particular regions or networks which may be relevant to the aspects of memory examined in the current thesis. Three atlases that contain only grey matter ROIs were used, the AICHA (Joliot et al. 2015), Harvard-Oxford (Desikan et al. 2006), and FOX (Fox et al. 2005) atlas, and two atlases with which I could explore white matter ROIs, the JHU (Faria et al. 2012) and Julich (Zhang et al. 2010) atlas.

The AICHA atlas contains 384 cortical and subcortical grey matter ROIs, which were parcellated based on resting-state fMRI data (3T scanner) from 281 healthy subjects (Joliot et al. 2015). The reason for using this atlas is that it is derived using high-resolution imaging from a large dataset of healthy subjects which was balanced for gender and handedness (this dataset is much larger than the datasets used in the other atlases that are available in NiiStat), and has extensive region parcellations which may be relevant to the analyses in this thesis. Specifically, it is the only atlas available in NiiStat that separates the parahippocampal gyrus into 5 subdivisions, the hippocampus into 2 subdivisions (anterior and posterior), the cingulum into 8 subdivisions, and the precuneus into 9 subdivisions (Joliot et al. 2015). This is important as many of these regions have been shown to be involved in episodic memory and visuospatial processes, and subdivisions within them may be functionally distinct (Cavanna and Trimble 2006; Jones et al. 2013; Kivisaari et al. 2020; Margulies et al. 2009; Nadel et al. 2013).

Another grey matter atlas which was used in the current thesis, the FOX atlas, contains 10 ROIs from the default mode and the task-positive networks, that is, areas which often exhibit task-related deactivations and areas which often exhibit task-related activations, respectively (Fox et al. 2005). These regions were parcellated based on fMRI data (3T scanner) from 10 healthy subjects. The reason for using this atlas was that it could be

particularly relevant to the aspects of memory that I explored; the default mode network is thought to be involved in scene construction (Hassabis and Maguire 2007) and seems to significantly overlap with the core autobiographical memory network (Philippi et al. 2015; Spreng and Grady 2010).

Faria and colleagues (2012) acquired structural MRI and resting-state fMRI data (3T scanner) from 20 healthy subjects and created the John Hopkins University (JHU) atlas which contains 189 grey and white matter and ventricular ROIs. This atlas was used in the current thesis because it contains both grey and white matter ROIs, and is the only atlas available in NiiStat that separates the fornix into different subdivisions and includes mammillary body ROIs.

Another two atlases, the Harvard-Oxford atlas (Desikan et al. 2006) and the Julich atlas (Zhang et al. 2010), were used only in order to perform further analyses on the association between lesion location and total errors on the 4MT. These atlases are included in the FMRIB Software Library (FSL; <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>) but not in the NiiStat toolbox. The Harvard-Oxford atlas implemented in FSL includes grey matter ROIs which were parcellated based on macroscopic anatomical landmarks on MRI scans (1.5T) from 40 healthy individuals (Desikan et al. 2006). Additional divisions were made to some ROIs of this atlas, and thus the total number of grey matter ROIs were 152. On the other hand, the Julich atlas contains 59 white matter ROIs, which were parcellated based on diffusion tensor imaging data (1.5T scanner) from 20 healthy subjects (Zhang et al. 2010).

I did not use the Brodmann (Brodmann 1909), Automatic Anatomical Labelling (AAL; Tzourio-Mazoyer et al. 2002), or CAT (Catani and de Schotten 2008) atlases which were available in NiiStat, because the Brodmann and AAL atlases were derived from just one

subject (thus may be less reliable), and the CAT atlas is derived from fewer subjects and using a lower resolution scanner compared to the other atlas that I used in NiiStat to examine white matter ROIs, the John Hopkins University atlas (JHU; Faria et al. 2012).

3.3.3.1.4 Flipped lesions

A number of previous stroke studies have used a technique in which all lesions are flipped onto a single hemisphere in order to increase statistical power (because of the greater lesion overlap; Cheng et al. 2014; Payabvash et al. 2018; Rinne et al. 2018; Seifert et al. 2016; Stoodley et al. 2016; Urra et al. 2017). A limitation of the “flipped lesion” technique is that it is unable to reveal hemispheric differences in behaviour (Stoodley et al. 2016). It assumes that each region has the same function as the contralateral region and thus may lead to inaccurate findings (Wu et al. 2015). This is especially important in this thesis, because spatial processing is thought to be lateralized to the right hemisphere (Vogel et al. 2003). This limitation can be partly bypassed by examining whether there is any significant difference in performance between the two hemispheric groups prior to flipping the lesions. Distorted results can also occur due to natural structural hemispheric asymmetries such as petalia and Yakovlevian torque (Toga and Thompson 2003; Zhao et al. 2009).

The “flipped lesion” technique was used in selected voxelwise statistical analyses in Chapter 6. Specifically, all left hemisphere lesions were flipped onto the right hemisphere using MRIcron. The decision to do this, rather than flipping the right hemisphere lesions onto the left hemisphere, was arbitrary and based on other studies which have used this technique (Ilg et al. 2013; Kraft et al. 2014; Payabvash et al. 2018; Rinne et al. 2018; Seifert et al. 2016; Stoodley et al. 2016; Urra et al. 2017).

3.3.3.2 Voxelwise descriptive analysis

As an adjunct to the above analyses, I also performed lesion subtraction analysis, which is a voxelwise descriptive analysis. This examines which areas are associated with a deficit and which are not, because it is able to compare between a patient group that has a deficit of interest and a control patient group in which that particular deficit is not present. The output of this analysis is a map showing brain areas in which damage is descriptively (not statistically) more frequent in subjects who have, compared to those who do not have a deficit (Karnath et al. 2019). Having such a control group is advantageous; analyses that overlap lesions only of the impaired patients can be misleading, because the areas that are found may just indicate areas that happen to be more vulnerable to damage, for example, due to the vascular anatomy (Caviness et al. 2002); they may not be directly related to the function of interest (Rorden and Karnath 2004).

Lesion subtraction analysis is not as reliable as voxelwise statistical analyses because it is a purely descriptive method and does not allow any statistical conclusions (de Haan and Karnath 2018). Also, it does not analyse continuous behavioural scores; patients are dichotomized depending on their score, which leads to decreased statistical power (Cohen 1983). When performance is measured using a continuous variable (as was the case in my experiments), it is difficult to determine the cut-off score for separating the groups (the impaired from the unimpaired group; Bates et al. 2003). MRICron was used to carry out lesion subtractions for the work carried out in this thesis.

3.3.4 Lesion network mapping

Lesion network mapping is a recent methodology which allows the localization of a memory (or any other cognitive function) network from focal lesions, by integrating a network approach with the traditional lesion mapping method. It stems from the extensive fMRI literature

demonstrating the importance of networks in cognitive functions. Functional neuroimaging detects blood-oxygen-level-dependent (BOLD) signals either while performing a given task or during resting conditions. Task-based fMRI is able to detect widely distributed areas that are activated when performing a task. On the other hand, resting-state fMRI is able to detect correlation patterns in the spontaneous fluctuations of the BOLD signal, which is known as functional connectivity (Fox and Greicius 2010). Two areas are thought to be functionally connected if their activity over time is strongly correlated (Constable et al. 2013). In other words, resting-state fMRI is able to detect networks of functionally connected areas in the brain (Fox 2018). In lesion network mapping, functional connectivity maps are preferable to structural connectivity maps (derived from DTI), because the former include a wider network (extensive polysynaptic connections rather than point-to-point connections; Fox 2018).

Lesion network mapping also stems from the observation that lesions located in different areas of the brain can cause similar symptoms (Corbetta et al. 2015). These authors found that the amount of spatial memory impairment variance that could be explained by the location of structural damage was only 4%. A weak association between memory and structural damage has also been found by other authors (Awh and Jonides 2001; Siegel et al. 2016). This cannot be explained if we assume that each cognitive function is processed by only one region in the brain, but can be explained if the cognitive process relies on the united function of many connected areas, that is, a network (Fox 2018). This suggests that a widely distributed network of connected regions may be critical for memory function. Therefore, by integrating fMRI with lesion data, symptoms that cannot be localized to a single region can be mapped to a wider network.

Both lesion network mapping and high dimensional multivariate voxelwise statistical analyses are capable of revealing such wide networks (which is not possible with mass-univariate analyses or low dimensional multivariate analyses; Boes et al. 2015; Fox 2018;

Karnath et al. 2019; Karnath, Sperber, and Rorden 2018). In this thesis, I used lesion network mapping rather than high dimensional multivariate analyses in order to detect brain networks, for two reasons. Firstly, high dimensional multivariate analyses have as many limitations as mass-univariate analyses (Ivanova et al. 2020; Sperber et al. 2018) and require a very large group of patients due to the large number of variables; typically, high dimensional multivariate analyses have included at least 72 stroke patients with damage to one hemisphere (Mah et al. 2014; Smith et al. 2013; Yourganov et al. 2015, 2016; Zhang et al. 2014) and another study found that the optimal sample size should be at least 100–120 patients (Sperber et al. 2018). Secondly, lesion network mapping provides a much greater depth of understanding compared to multivariate and univariate voxelwise analyses since it combines both lesion and functional neuroimaging data. This means that it can overcome the limitations of using just fMRI data (such as the fact that fMRI can identify a correlative but not a causative relation between a brain region and a cognitive function) or just lesion data (Price and Friston 2002), and can take into account remote neuronal dysfunction (Klingbeil et al. 2020). For example, Klingbeil and colleagues (2020) found that the key node associated with anosognosia for hemiplegia was the right posterior hippocampus when they performed lesion network mapping, but this region was not revealed by voxel-lesion symptom mapping; possible reasons for this discrepancy are that none of their patient group had damage to this region and that voxel-lesion symptom mapping does not identify regions of dysfunction secondary to diaschisis.

Recent lesion network mapping studies have revealed brain circuits involved in conditions such as hallucinations (Boes et al. 2015), coma (Fischer et al. 2016), hemichorea (Laganiere et al. 2016), pain (Boes et al. 2015), Capgras syndrome (Darby et al. 2017), aphasia (Boes et al. 2015), depression (Padmanabhan et al. 2019), mania (Cotovio et al. 2020), prosopagnosia (Cohen et al. 2019), cervical dystonia (Corp et al. 2019), Holmes tremor (Joutsa et al. 2019), parkinsonism (Joutsa et al. 2018), freezing of gait (Fasano et al. 2017), and impaired decision-making (Sutterer et al. 2016). To my knowledge, one study to date has

used this approach to reveal a memory network and its key node (Ferguson et al. 2019). Importantly, the authors did not focus specifically on one type of memory (patients had a range of different memory deficits, e.g. verbal, visual, autobiographical, semantic, and/or temporal order). Also, because their analysis was based on amnesic stroke cases derived from previous studies, their findings may have been distorted by the following issues. First, some of those patients had other conditions such as spatial neglect, visual field deficits, aphasia, and/or depression, which may have been the reason for their impaired performance on the memory tasks. Second, some of the case studies included in the analysis did not report what tasks were used to assess memory and thus we cannot know what type of memory deficit those patients had. For example, in the study by Chen, Zayas and Gold (2008) which was incorporated into the lesion network mapping analysis, it was reported that the patient could not learn new information. This means that the patient had anterograde amnesia, but we do not know for what type of information (whether it was for personal events, public events, words, or scenes). Third, lesions were drawn on a template brain by looking at 2D brain slices which were available in the case studies. However, for about half of the patients, a limited number of brain slices were available, and thus the 3D lesion reconstruction may not have been highly accurate.

In the current thesis, lesion network mapping was performed by integrating lesion and behavioural data from patients that I tested, with fMRI data (task-based and resting-state) from healthy individuals reported in previous studies. I did not use fMRI data from stroke patients (which was used in a previous lesion network mapping study; Lim et al. 2020) because this may not be as effective in detecting the critical brain network for a cognitive function, as the BOLD signal can be severely affected by the regional blood flow changes occurring from the brain injury (Rorden and Karnath 2004).

The task-based fMRI study from which I obtained coordinates, used a task similar to the task that I used. Sphere-ROIs were created from brain activations reported in that study. One limitation of creating spheres is that their size is chosen arbitrarily (mainly based on previous studies), and thus the results may alter depending on the sphere size that is chosen (Eickhoff et al. 2006). Resting-state fMRI data were obtained from Neurosynth (<http://neurosynth.org>; Yarkoni et al. 2011), an online platform that contains and combines results from many functional neuroimaging studies (either task-based or resting-state). The main reason I used this platform is that one can perform a seed-based resting-state fMRI analysis (analyse functional connectivity for a seed region based on resting-state fMRI activity) using resting-state fMRI data from 1,000 healthy adults (Holmes et al. 2015; Yeo et al. 2011). The normative functional connectivity maps extracted from this large dataset can be used in combination with lesion data to derive a common network for a given cognitive function (Fox 2018). The region of interest (e.g. a voxel that is found to be significant in the voxel-lesion symptom mapping analysis) can be entered into Neurosynth, and then by using the resting-state fMRI data, Neurosynth provides a map showing areas whose spontaneous activity is positively or negatively correlated with activity in the region of interest (Yarkoni et al. 2011). In other words, this method can detect areas that are functionally connected to the seed region.

Despite lesion network mapping being one of the most advanced methods for symptom localization, it does have some caveats. First, symptoms can change over time due to alterations that occur in the brain after the injury (e.g. plasticity), but this temporal component is not incorporated into lesion network mapping analyses (Fox 2018). Second, fMRI datasets are usually not matched to each stroke patient in regards to age, gender, education, and amount of small vessel disease. Third, in the healthy population there is a high degree of interindividual differences in the functional connectivity between different brain regions (Finn et al. 2015, 2017), which may be even higher in healthy elderly subjects (Bastin et al. 2012). This means it may be inaccurate to infer that the areas that would be normally connected to

the seed-region in one particular patient (prior to the damage to this region) are the same as those that are found when using resting-state fMRI data from a large dataset of healthy young adults. Finally, although lesion network mapping infers that damage to any of the network nodes will lead to symptom formation, this cannot be certain for the central node of the network (Fox 2018).

3.4 Discussion

3.4.1 Chronicity of patient assessment

The timepoint post-stroke at which patients are tested varies across voxel-lesion symptom mapping studies; some studies tested patients only in the acute stage (Døli et al. 2020), others only in the chronic stage (Liu et al. 2018), while others tested patients in both the acute and chronic stage (Abela et al. 2012; Karnath et al. 2011; Wu et al. 2015). However, there are important limitations present at both stages, which are addressed below.

In the acute stage, standard clinical sequences (CT, T1, T2, DWI, and FLAIR) cannot identify all of the brain regions that are impaired. They can identify the ischaemic core, but not functional changes which can occur in the ischaemic penumbra or in remote areas. The ischaemic penumbra is an area of electrically unexcitable cells around the ischaemic core; the cells' integrity and ionic homeostasis is preserved, but if the blood flow is not restored quickly they may undergo necrosis (Markus 2004). The ischaemic penumbra can be visible on sequences such as CT perfusion imaging (Campbell et al. 2011) or by combining DWI with perfusion weighted imaging (PWI). In the latter approach, the penumbra is defined by subtracting the DWI lesion volume from the PWI lesion volume, also known as PWI/DWI mismatch (Albers 1999). However, brain perfusion images are not acquired clinically in the majority of patients (Thirugnanachandran et al. 2018). Second, in the acute stage, brain function can be disrupted by oedema. Although the extent of oedema can be inferred from the

presence of midline distortion, sulcal effacement, and compression of the ventricles (Vemmos et al. 2003), it cannot be quantitatively measured accurately on standard clinical scans. Third, dysfunction secondary to diaschisis is undetectable on structural scans. Diaschisis is defined as the presence of neurophysiological alterations in remote brain regions (even in the opposite hemisphere) which: a) are directly caused by the lesion, b) are related to behavioural changes, c) often recover with time, and d) may be detected using functional neuroimaging techniques, e.g. fMRI or functional positron emission tomography (fPET; Carrera and Tononi 2014). Lesions that cause the most extensive diaschisis seem to be located in the cortical midline, the temporo-parietal junction, or the frontal cortex (Alstott et al. 2009). Hence, if, for example, a patient with a small lesion in the temporo-parietal junction is assessed in the acute stage, they may be impaired on a given task due to transient functional changes to distant brain regions; but because these are not detected on standard clinical scans, the lesion-mapping analysis would lead to distorted findings.

If one waits until all the above phenomena resolve, other important issues may occur. Structural and functional changes that may be present in the chronic stage include: a) ventricular enlargement and displacement of healthy tissue due to liquefactive necrosis of the lesioned area (Wilke et al. 2011; Zbesko et al. 2018), b) gliosis and demyelination in the border zone of the lesion which can cause lesion expansion (Alexander et al. 2010; Huang et al. 2014; Seghier et al. 2014), and c) widespread brain atrophy (particularly though in regions connected to the lesion via diaschisis; Cheng et al. 2020; Seghier et al. 2014). The changes that occur may lead to recovery of function (known as positive or adaptive plasticity), or to disruption of function (known as negative or maladaptive plasticity; Woolf 1989). Therefore, patients' performance is likely to depend both on the presence of the lesion and on the presence of any of the above possible processes; compared to the acute stage, a patient may perform worse (e.g. due to brain atrophy or maladaptive plasticity), better (e.g. due to positive neuroplasticity), or similar (e.g. if a mixture or none of these structural and functional changes

occur). For some of the patients in this thesis (and as has been the case in many previous lesion studies), testing took place in the chronic stage and their lesion was delineated on scans performed in the acute stage, that is, testing was not performed on the day of imaging. This means that lesion-behaviour relationships may have been imprecise since the phenomena that may have been present in the chronic stage would not have been taken into account.

The undetectable (on standard clinical scans) neurophysiological changes in the acute stage and the structural and functional reorganization of the brain in the chronic stage make it challenging to select the most appropriate time to assess patients. However, brain alterations occurring in the chronic stage are thought to be more impactful on behaviour compared to the changes in the acute stage. Although the presence of the ischaemic penumbra seems to lead to behavioural changes (Shahid et al. 2017), there is no clear evidence for the behavioural relevance of diaschisis (Carrera and Tononi 2014). Thus, it has been recommended that when the aim of a voxel-lesion symptom mapping study is to examine the brain's functional architecture, all patients should be tested in the acute stage (de Haan and Karnath 2018; Karnath et al. 2019; Karnath and Rennig 2017). But testing in the acute stage is unfeasible for many patients (especially if they have large lesions) because: a) they may be too poorly to be assessed, and b) they may have deficits such as spatial neglect, hemianopia, or aphasia, which may affect their performance on memory tasks. On a practical level, recruiting patients at only one time period post-stroke decreases the sample size which leads to inadequate statistical power in voxel-lesion symptom mapping analyses (Mechelli et al. 2005; Medina et al. 2010). Thus, in this thesis, I aimed to test all patients in the acute stage and if this was unfeasible for some patients (due to the above-mentioned deficits), I tested those patients in the more chronic stage.

3.4.2 Lesion characteristics and coverage of the brain

Although recruiting many patients can lead to adequate lesion coverage, a disadvantage of the lesion method is that usually the coverage is not as complete as with functional neuroimaging. In lesion-behaviour analyses one cannot make any conclusions about the function of areas that have not been damaged in an adequate number of patients. If the lesion coverage of the patients as a group does not include some brain regions, then no significant association will be found between these regions and the behavioural scores, thus one would have the potentially wrong impression that these regions are not related to that particular function.

Although the inclusion of patients with large lesions would partly solve this issue, if only such lesions were included then the spatial resolution of my results would be very low. Small lesions can enhance the spatial resolution, but the disadvantages are that: a) it would require many years to recruit an adequate enough sample so that a complete coverage of the brain is obtained, and b) by causing only slight damage to a functional module they may not lead to a cognitive deficit (due to vicariation, which is the process by which undamaged brain regions can take over the function of the damaged region; Rorden and Karnath 2004; Slavin, Laurence, and Stein 1988). Thus, it is beneficial to include lesions of different sizes.

It has been argued that one of the limitations of performing lesion-behaviour analyses with stroke patients is that ischaemic lesions are biased by the vascular architecture, which means that the lesions' shape and distribution is not random (Chatterjee 2005; Husain and Nachev 2007; Mah et al. 2014). This can occur to a similar extent in both mass-univariate and multivariate analyses (Ivanova et al. 2020; Sperber et al. 2018). In my experiments, I tried to reduce this bias by including patients with both haemorrhagic and ischaemic stroke. Unlike

ischaemic strokes and haemorrhagic infarcts, primary haemorrhages can cross vascular boundaries (Rowley 2012), leading to more randomly distributed lesions.

By including patients with stroke in any brain region, I could make inferences about the contribution of each and every area. For example, if I had included only patients with medial temporal lobe damage (based on the wide literature about its role in memory), I could have missed other regions which are potentially important for this function. Whereas some stroke studies examining memory have focused only on one vascular territory, e.g. posterior cerebral artery (Busigny et al. 2014; von Cramon et al. 1988), this was not the case in the experiments presented here because I wanted to take an inclusive approach (wide range of lesion locations) which is arguably preferable when conducting voxelwise lesion analyses. Even though there is inter-subject variability in the vascular architecture (e.g. the posterior cerebral artery may supply different regions in each subject), if I had included patients with damage to only one territory, the lesion analysis would be based only on regions that are most commonly supplied by this territory. One of the key regions that I am exploring in this thesis is the parietal lobe, which is supplied by all three cerebral arteries (Standing 2016). Thus, it was important to include all strokes independent of the territory affected.

3.4.3 Imaging modalities and lesion delineation

Differences in image quality make it difficult to analyse combined data. This thesis and previous studies (Karnath et al. 2004, 2011; Verdon et al. 2010) included patients with either CT or MRI, even though these modalities have different resolutions. The reason for this is that with the advent of CT templates for lesion normalization (Rorden, Bonilha, et al. 2012) it has been recommended that patients who have only CT scans should not be excluded (de Haan and Karnath 2018). This enables the inclusion of more patients, thus increasing statistical

power, which is important especially in lesion mapping studies (Mechelli et al. 2005; Medina et al. 2010).

Accuracy in lesion delineation is crucial when performing voxel-lesion symptom mapping (Liew et al. 2020). Inter-rater variability can also affect the precise delineation of a lesion. Although inter-rater variability can be avoided by the use of fully automated methods, these methods do not delineate the lesion as accurately as manual tracing, particularly when delineating periventricular regions and the contours of the brain (Mehta et al. 2003; Wilke et al. 2011). Further, the large inter-patient variability in the size and shape of the brain, and the number and orientation of brain slices, may lead to inaccurate delineation of the lesion onto a template (Mort et al. 2003). The advantage of mapping lesions on the native scan is that these factors do not affect the accuracy of the delineation. Rather, they are automatically incorporated into the spatial normalization algorithms. Thus, mapping on the native scan is preferable in order to obtain a more accurate representation of the lesion.

During lesion mapping, if any of the following were visible on the scan they were not delineated: imaging markers of small vessel disease (lacunes, microhaemorrhages, white matter hyperintensities), calcifications, intraventricular extension of the lesion, enlarged ventricles, widened sulci, Wallerian degeneration, atrophy, and any additional cerebellar or brain stem lesions. It is important to note that many of these can be associated with cognitive dysfunction (as discussed in Chapter 2). Also, when delineating a lesion it is often challenging to: a) separate markers of small vessel disease from stroke lesions (Dalca et al. 2014), and b) delineate the borders of a haemorrhagic stroke because the haemorrhage can cause large dislocations and may extend into the ventricles (de Haan and Karnath 2018).

3.4.4 Spatial normalization

Interindividual differences are present in the healthy human brain, for example, in the: a) location of cytoarchitecturally defined areas (Amunts et al. 2004), and b) size of grey matter and white matter tracts (Bartolomeo et al. 2017). These differences seem to be present mostly at the cortical level and less so at the subcortical level (Duffau 2017). They can lead to variability in cognition, including memory (Kanai and Rees 2011; Machizawa et al. 2020); hence, structural differences (which are present even prior to the stroke) may contribute to the variance in patients' performance on the tasks employed in this work. Spatial normalization discards such variations in the brain because it adjusts each subject's brain to match a "normal" brain template.

Secondly, when performing normalization, an issue arises as to what template to use: a template based on healthy young or healthy elderly adults. In studies that use mixed modalities (such as this thesis), it is beneficial to use templates approximately age-matched across modalities, e.g. a "healthy young" MRI template and a "healthy young" CT template (Rorden, Bonilha, et al. 2012). The advantage of using a "healthy young" template in stroke populations, is that it allows a close connection between most functional neuroimaging studies (in which participants are usually young adults) and studies with stroke patients (Rorden, Bonilha, et al. 2012), which is important in lesion network mapping. The advantage of using a "healthy elderly" template is that it matches the average age of stroke patients. Though it is important to note that in some stroke studies there may be large age variations (as was the case in this thesis).

I used a "healthy elderly" template for the CT normalization and a "healthy young" template for the MRI normalization, as these were the default templates in the SPM12 Clinical Toolbox. Although this toolbox includes a routine called "MRI segment-normalize" in which

one can perform enantiomorphic normalization (which appears to be beneficial especially for large lesions; Nachev et al. 2008) and choose between “healthy young” and “healthy elderly” templates, it was impossible to use this routine in this thesis because it requires T1-weighted images and high resolution scans (Karnath et al. 2019).

3.4.5 Voxelwise lesion analyses

Even though mass-univariate voxelwise statistical analyses can infer lesion-behaviour associations more accurately than other methods such as lesion subtraction analysis, they are prone to false positive errors (finding that a region is necessary for a given task when in reality it is not). The frequency of lesioned voxels and the possible impact that one damaged voxel may have onto another can distort findings (Mah et al. 2014). A realistic example is shown in Figure 3.4. Insular damage is associated with larger lesions and occurs in almost 80% of middle cerebral artery occlusions, the most commonly affected vascular territory in stroke (Kodumuri et al. 2016; Ng et al. 2007). The hippocampus, and parahippocampal, retrosplenial, and posterior parietal cortices are some of the regions that seem to be involved in spatial memory (Herweg and Kahana 2018; Kessels et al. 2001). Although the insula is not thought to be involved in spatial memory, if it happens to be damaged coincidentally with voxels damaged in these other regions (e.g. due to the vascular architecture), then results will be misleading. It will erroneously find that the insula is more significantly associated with spatial memory than these other regions. Furthermore, by applying a threshold (e.g. only analyse voxels damaged in at least two patients), it will identify the insula, but not the other regions, as significant. This is another reason why it is beneficial to take a lesion network mapping approach (as mentioned above).

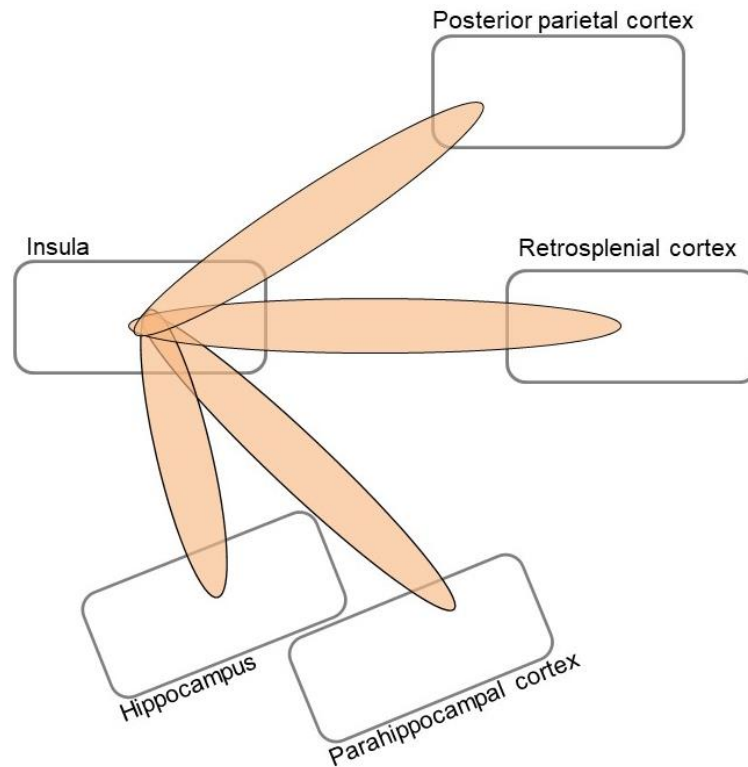


Figure 3.4. Illustration of how damage to a voxel may be dependent on damage to other voxels

*Four patients' lesions are represented in orange.
Adapted from Mah and colleagues (2014) and Nachev (2015).*

Another reason that voxelwise statistical analyses can lead to an increase in false positive results is the large number of statistical tests which make comparisons across thousands of voxels, also called familywise error rate (Rorden and Karnath 2004). Although this can be reduced with the Bonferroni correction, the false discovery rate, or permutation-based thresholding, these corrections do not fully eliminate this error rate. The Bonferroni correction is the most conservative of the above methods; it can lead to decreased statistical power which means that real effects may not be found (Karnath et al. 2019; Rorden et al. 2009; Rorden and Karnath 2004). The most lenient of the above methods is the false discovery rate, which controls the percentage of Type I error among the observed positives (Benjamini and Hochberg 1995; Yekutieli and Benjamini 1999). This means that if no positives are

observed, the control provided by the false discovery rate will be equal to that provided by the Bonferroni correction (Karnath et al. 2019). Permutation thresholding offers increased statistical power (compared to the Bonferroni correction) when voxels may not be truly independent, and is thought to be the gold standard (Karnath et al. 2019; Mirman et al. 2018; Poldrack et al. 2017; Rorden et al. 2009); this is why it was used in the voxelwise lesion analyses in the current thesis.

Thus, in this thesis I aimed to take the most accurate approach possible for lesion delineation, normalization, lesion symptom mapping, and lesion network mapping, given practical limitations such as the availability of only clinical scans.

4 The Relationship Between Episodic Recall of Visual Perspective and Autobiographical Memory

4.1 Introduction

As discussed in Chapter 1, there seems to be a close relationship between the viewpoint from which a personal event is retrieved and how much detail (as measured by both objective and subjective measures) is retrieved from that event. Evidence for this relationship comes from studies in: a) healthy young subjects, b) healthy elderly subjects, and c) patients with posterior parietal lobe damage, which are discussed below.

First, when healthy young adults perform autobiographical memory tasks, a first-person perspective tends to be associated with increased episodic detail (Akhtar et al. 2017), “remember” rather than “know” responses when retrieving remote memories (Crawley and French 2005), and increased vividness (Sutin and Robins 2010; Verhaeghen et al. 2018). In these subjects, recent personal events are more often retrieved from a first-person perspective (Akhtar et al. 2017; Nigro and Neisser 1983; Sutin and Robins 2007). Researchers have also examined the effects of experimentally induced posterior parietal lobe disruption in this group (Bonnici et al. 2018). They found that in healthy young adults, inhibitory brain stimulation over the left angular gyrus affected the ability to retrieve autobiographical events from a first-person perspective and with rich event-related details.

Second, when healthy elderly subjects perform episodic memory laboratory-based tasks, they tend to have deficits in remembering specific details when objectively rated (Blachstein et al. 2012; Chalfonte and Johnson 1996; Fabiani and Friedman 1997; Kessels et al. 2007; Kinugawa et al. 2013; Madsen and Kesner 1995; Mazurek et al. 2015; Park and

Puglisi 1985; Parkin et al. 1995; Plancher et al. 2010; Puglisi et al. 1985). In autobiographical memory tasks they seem to report more “observer” responses (Piolino et al. 2006) and fewer event-related details (compared to young subjects), as has been found from both objective (Gaesser et al. 2011; Levine et al. 2002; Peters et al. 2019; Piolino et al. 2006; Robin and Moscovitch 2017) and subjective ratings (Piolino et al. 2006). In addition, the results of a recent study by Russell and colleagues (2019) suggest that healthy elderly individuals seem to be less accurate in identifying their own encoded perspective in a recognition task. This study showed that elderly subjects performed as well as young subjects on the delayed recall of the Rey-Osterrieth Complex Figure Test, on the Corsi block task, and in recognizing line drawings (after a 30-minute interval). However, crucially, they were worse than young subjects in distinguishing whether scenes were shown from the same or different perspective to what they had seen the previous day.

Third, poor memory for details related to one’s past personal events and for egocentric perspective also seem to be a consequence of posterior parietal lobe damage and dysfunction. In autobiographical memory tasks under free recall conditions, patients with posterior parietal lobe damage tend to report fewer internal details relating to time, perception and thoughts, as has been shown in objective ratings (Berryhill et al. 2007). Further, on a second experiment from the paper cited above, Russell and colleagues (2019) assessed patients with right posterior parietal lobe lesions and found that they were less accurate than healthy age-matched subjects in identifying their own encoded perspective in a recognition task, even though their performance on standard neuropsychological memory tasks was intact.

The “own eyes” and “observer” viewpoints in autobiographical memory tasks have been assessed in many different ways. Some authors have asked participants to remember whether they retrieve the memory from an “own eyes” or an “observer” perspective (Akhtar et al. 2017;

Crawley and French 2005; Piolino et al. 2006), while others have used a continuous scale for “own eyes–observer” perspective (Berntsen and Rubin 2006; Sekiguchi and Nonaka 2014; Siedlecki 2015; Verhaeghen et al. 2018). Piolino and colleagues (2006) additionally used a separate score (which they named “field / observer”) if participants shifted from one perspective to another. In order to make it easier for participants to interpret correctly the question about the viewing perspective they showed pictures that illustrated the “field” (two eyes) and “observer” (a camera) viewpoint. Notably, these are subjective ratings. For example, participants may report that they retrieve the event from a first-person perspective (the viewpoint from which they had originally experienced the event). However, we cannot be sure that they provide an accurate representation because: a) they may not understand what the experimenter means, b) they may have more than one perspective at recall, and c) we do not know whether the position from which the event was viewed at encoding matches that at retrieval. The reason for the latter is that studies examining autobiographical memory across people’s lifespan, usually do not have control over the circumstances during encoding and participants are typically not asked to report the exact position from which they are viewing the event as they retrieve it. A more objective way of directly examining egocentric episodic memory would be to employ a task in which the experimenter has control over the viewpoint from which participants view the scenes at encoding, and can then manipulate the viewpoint to examine whether participants are actually able to remember the viewpoint accurately.

The studies mentioned above (Akhtar et al. 2017; Bonnici et al. 2018; Crawley and French 2005; Piolino et al. 2006; Sutin and Robins 2010; Verhaeghen et al. 2018) suggest an important role for self-perspective in episodic memory. This link between viewpoint and episodic detail seems to occur in both autobiographical memory tasks and laboratory-based episodic memory tasks. However, an underexplored area of research is whether the results in autobiographical memory tasks (fewer event-related details and less vividness linked to fewer first-person perspective responses) are similar to those found in episodic memory laboratory-

based tasks (low objective and subjective scores in the degree of episodic details, and egocentric memory deficits). Specifically, further work is required to examine whether the accuracy of one's memory for the viewpoint from which they had seen an event (2D, 3D-like, or real-life; recent or past) is related to how detailed their memory is for real-life personal events (recent or past). Also, more work is needed to examine whether there is a relationship between self-perspective in autobiographical memory tasks ("own eyes" and "observer" responses; a more subjective measure of self-perspective) and self-perspective in laboratory-based episodic memory tasks (a more objective measure of self-perspective).

4.2 Aims, hypotheses, and predictions

The main aim of the study described in this chapter is to examine the importance of self-perspective features of episodic memory across different ages, by investigating whether there is any correlation in performance between an adapted version of the TEMPau interview (Piolino et al. 2003, 2009) and an episodic picture task (an adapted computerized version of a previously used memory task; Russell et al. 2019). The first task examines autobiographical memory (memory for multi-featural real-life 3D events that are highly related to the self). The second task assesses spatial aspects of memory using pictures of objects. It includes some pictures in which the viewpoint is different to that at encoding, and some in which the object's location, rather than the viewpoint, is different to that at encoding. These manipulations have been shown to be able to probe memory for one's own perspective when the objects are presented in a 3D real environment (Russell et al. 2019). However, it is unknown whether this is also the case when the objects are presented as pictures on a screen. This is one of the questions that the current study aims to explore.

The hypotheses of this study are that self-perspective is a key component of episodic memory, and that age affects episodic autobiographical memory, laboratory-based episodic

memory, and the ability to remember the original viewpoint from which an event was seen (real-life autobiographical event or laboratory-based 2D event).

The first prediction is that performance on the episodic picture task will be linked with performance on the autobiographical memory interview; specifically, discrimination ability in the angle shift condition of the episodic picture task will be correlated with the amount of vividness, episodic details, and first-person perspective responses in the events reported in the autobiographical memory interview.

The second prediction is that, compared to healthy young subjects, healthy elderly subjects will perform worse in the episodic picture task (particularly in the condition in which there is a change in the viewpoint of the scenes), and in the autobiographical memory interview (fewer episodic details, less vividness, and more “observer” responses when retrieving autobiographical events).

4.3 Methods

4.3.1 Participants

This study included 20 healthy young subjects (age range: 19–35 years old; mean age \pm standard error of the mean [SEM]: 25.4 ± 1.20 ; 13 females; 19 right-handed, 1 left-handed) and 26 healthy elderly subjects (age range: 65–82 years old; mean age \pm SEM: 74.42 ± 1.09 ; 12 females; 22 right-handed, 4 left-handed). Detailed inclusion criteria are described in section 2.5.2. The number of participants was based on previous similar studies (Folville, Bahri, et al. 2020; Gaesser et al. 2011; St. Jacques and Levine 2007; Kinugawa et al. 2013; Levine et al. 2002; Peters et al. 2019; Puglisi et al. 1985; Robin and Moscovitch 2017; Russell et al. 2019). A parametric t-test showed that there was a significant difference in the years of education

between the young (mean = 19.3 years, SEM = 0.98) and the elderly group (mean = 15.34 years, SEM = 0.96; $t(44) = 2.822$, $p = 0.007$, Cohen's $d = 0.846$).

4.3.2 Episodic picture task

The episodic picture task was an adapted version of a paradigm that has identified an impairment in egocentric spatial perspective aspects of episodic memory (remembering the viewpoint from which they had seen scenes) in healthy elderly subjects and in patients with posterior parietal lobe damage (Russell et al. 2019). This adapted version was created using Psychopy software (Peirce 2009).

4.3.2.1 Stimuli

The stimuli included in the episodic picture task were full-colour pictures that contained one everyday/familiar object on a 2 x 2 grid (Figures 4.1 and 4.2). These pictures were of real 3D objects and were taken from one of two different angles which differed by 90 degrees, as used in a previous study (Russell et al. 2019). These objects belonged to one of twelve different categories: clothing, garden equipment, bathroom items, wild animals, fruit and vegetables, packaged food, musical instruments, sports, stationery, vehicles, tools, or kitchen equipment (3 objects per category, except for the musical instruments category in which 2 objects were used). Each object did not belong to more than one object category, was easily nameable, was recognizable when shown from a different angle (it could be seen clearly and did not look completely different), and was not a human figure (as this may affect the viewpoint that is adopted; see Tversky and Hard 2009). These pictures were displayed on a white background in the centre of a 14-inch laptop computer screen (Lenovo Thinkpad T440), placed at a distance of approximately 50 centimetres from the participant.

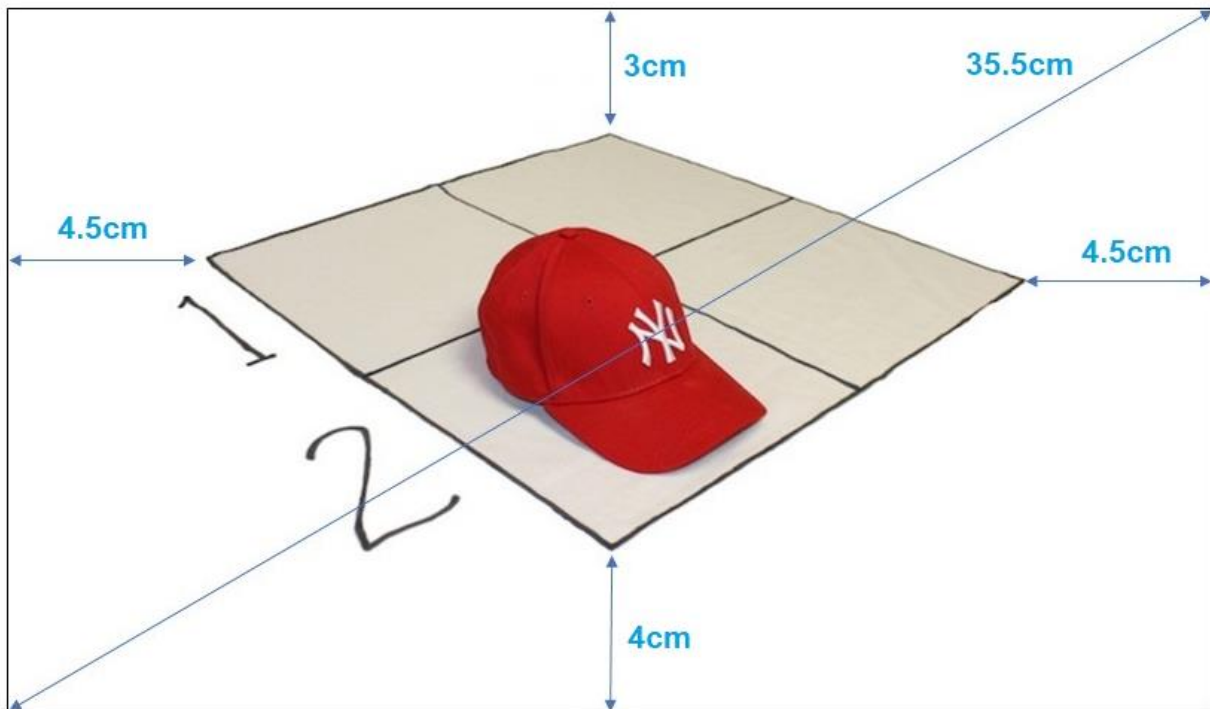


Figure 4.1. Dimensions of the pictures as displayed on a 14-inch (35.5 cm) laptop computer screen

Note that whatever is shown in blue in this figure was not displayed on the screen; it is displayed here solely for illustration purposes.

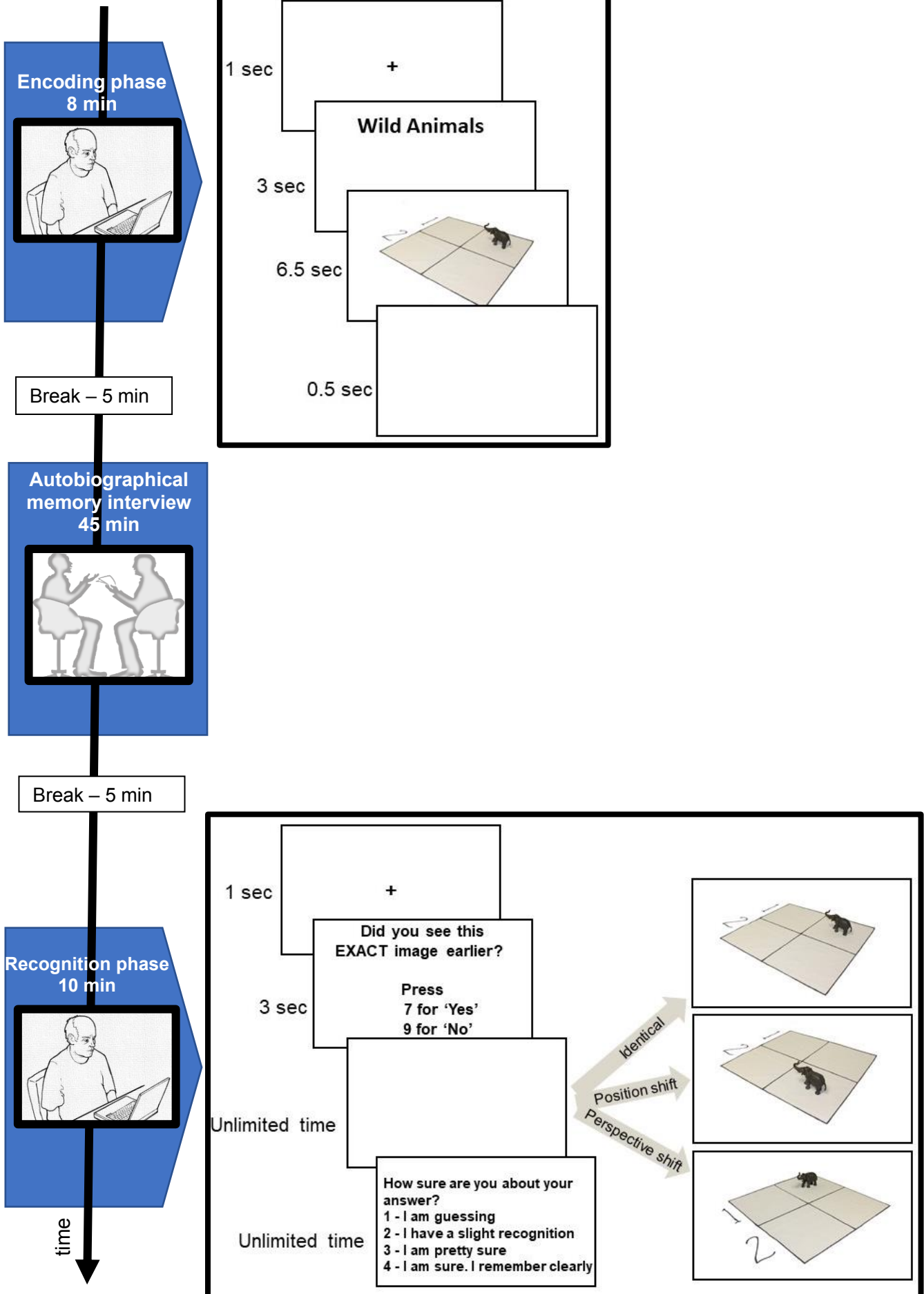


Figure 4.2. Procedure of the experimental study

All tasks were performed within one session which lasted about 90 minutes. The order of the sessions and their approximate duration are shown on the left, and an example of a trial in the encoding and recognition phase of the episodic picture task is shown on the right. The key conditions in the recognition phase are shown at the bottom right.

4.3.2.2 Encoding phase

In the encoding phase of the episodic picture task, participants were presented with 35 pictures (for example, picture in Figure 4.1) which were displayed for 6.5 seconds each, preceded by the name of the object category, and followed by a blank white screen of 500 milliseconds. Participants were asked to remember the object, where exactly it was on the grid, and what the whole image looked like to them. These pictures were presented in 3 blocks (12 pictures, then another 12 pictures, then another 11 pictures) and the pictures' order was randomized across participants. Thirty-five pictures were included to avoid a ceiling effect—in a pilot study that I conducted (involving 10 healthy subjects across the age span) in which the task included 24 pictures, the mean total number of errors of the elderly subjects was only 3.

The encoding phase was the main aspect by which this episodic picture task differs from the paradigm used by Russell and colleagues (2019). In that study, the scenes in the encoding phase were real-life 3D scenes, that is, real objects placed on a table. One aim of the current study was to develop a 2D computerized version of their paradigm, which would be easier to deliver to larger participant numbers.

4.3.2.3 Recognition phase

In the recognition phase of the task, participants saw 35 images which were presented in a random order in the centre of the laptop computer screen: 19 were unaltered (original) pictures from the encoding phase, in 8 pictures the position of the object had changed, and in 8 other

pictures the viewpoint had changed (Figure 4.2). They were asked to make a forced choice decision about whether the picture was exactly the same as the one viewed earlier by pressing with their right index finger one of the two buttons on a standard keyboard ('7' for yes; '9' for no). Then, participants reported how confident they felt about their answer by pressing one of the numbers 1, 2, 3, or 4 on the laptop keyboard (1 being the least confident). For both of the above questions, participants had unlimited time to provide their response. The examiner did not provide feedback to participants during the task. Each participant completed one of three versions of the recognition phase of the task. Each version had the same number of angle shift pictures, object position shift pictures, original pictures, and the same objects as they saw in the encoding phase, but the only feature that changed was which objects were shown in each condition. This was a pseudo-randomization to ensure that the objects shown in the encoding phase were presented in different conditions across participants. The selection of which version would each participant perform, and the order of the pictures displayed in each version were randomized. The order in which participants viewed the images in the recognition phase was also different to the order in the encoding phase. There were no practice trials in the encoding or in the recognition phase of the task.

4.3.3 Autobiographical memory interview

The autobiographical memory instrument was an adapted version of the TEMPau interview (Piolino et al. 2003, 2009). Participants were asked to recall nine specific autobiographical memories from three lifetime periods: 3 memories from childhood (up to 12 years old), 3 memories from the last 5 years (except the last year), and 3 memories from the most recent year, in response to general cues which were presented auditorily (e.g. "Could you recall details of a particular journey you made—either local or far away—in the last year?"). This interview was used because, as discussed in Chapter 1, apart from separating episodic autobiographical memory from semantic autobiographical memory, it also requires

participants to report the perspective from which they are retrieving each event, and how vividly they remember it. An adapted version was used so that the lifetime periods could be matched across the different age groups. Participants were not asked about memories from adolescence or early adulthood, that is, age 13–30 years (except if a participant was 18–34 years old in which case the last five years included this period). They were asked to describe as many details as possible about a single event which lasted less than a day and was not repeated (the time, the place, any thoughts and emotions while it was happening, and with whom it happened). Participants reported their memories verbally and the administrator wrote them down. There was no response time limit. They were given set prompts (until they said “I cannot remember anything else”) and the total number of prompts was tabulated. The following general prompts were the only ones used: “Can you add any specific details?” (if the participant had not given enough details) and “Remember I want to hear about a specific event” (if the event that was described lasted more than a day or had been repeated). After recalling each event, however specific it was, participants were asked to report how vividly they remembered it (on a scale from 0 to 4, where 4 is the greatest vividness), and if they recalled it as if they were observing the event (third-person perspective) or if they were seeing it as if from their own eyes (first-person perspective). They were asked to choose only one of the two. A strict protocol was used to maximize consistency across participants, because in the pilot study the interview time varied significantly across subjects.

4.3.4 Analyses

4.3.4.1 Episodic picture task discrimination ability (d-prime)

In the recognition phase of the episodic picture task, participants were asked whether the pictures were exactly the same as the ones they had seen earlier. If the pictures did not have any changes (original) the correct response would be “yes”, whereas if the pictures had an angle change or an object position change then the correct response would be “no”. To answer

this question, some participants may have a response bias. For example, they may have a tendency to respond "no" to most or all trials, which could lead to 100% correct in the angle and the object position shift conditions. However, this does not mean that the participant was able to discriminate the original pictures from the changed pictures. If their performance is analysed just on the proportion of correct responses, then one will not be able to assess their discrimination ability. Therefore, I calculated d-prime (d'), a measure of sensitivity that is based on signal detection theory (Green and Swets 1966; see equation below). This score takes into account the hit rate, which is the proportion of target trials in which the participant responded that it was the target, and the false alarm rate, which is the proportion of non-target trials in which the participant responded that it was the target. If d' is close to 0 it indicates chance performance. The higher the score, the better the participant can differentiate targets from non-targets. To avoid d' being equal to infinity, if a participant's hit rate was 1 it was recorded as $1 - \frac{1}{2v}$, whereas if a participant's false alarm rate was 0 it was recorded as $\frac{1}{2v}$, where v is the number of lures (Macmillan and Creelman 1991).

$$d' = z \left(\underbrace{\frac{\text{N of correct in original scene trials}}{\text{N of original scene trials}}}_{\text{Hit rate}} \right) - z \left(\underbrace{\frac{\text{N of errors in changed scene trials}}{\text{N of changed scene trials}}}_{\text{False alarm rate}} \right)$$

Separate d' scores were also calculated for the angle shift condition and the object position shift condition.

$$d'_{\text{angle}} = z \left(\underbrace{\frac{\text{N of correct in original scene trials}}{\text{N of original scene trials}}}_{\text{Hit rate}} \right) - z \left(\underbrace{\frac{\text{N of errors in angle shift trials}}{\text{N of angle shift trials}}}_{\text{False alarm rate}} \right)$$

$$d'_{\text{position}} = z \left(\underbrace{\frac{\text{N of correct in original scene trials}}{\text{N of original scene trials}}}_{\text{Hit rate}} \right) - z \left(\underbrace{\frac{\text{N of errors in position shift trials}}{\text{N of position shift trials}}}_{\text{False alarm rate}} \right)$$

4.3.4.2 Autobiographical memory interview scoring

The interview was scored following the scoring system described by Piolino and colleagues (2003). Each of the nine memories per participant was scored on a five-point episodic scale which takes into account the uniqueness of the event, and the amount and type of details: 0 = they did not report any memory or provided very general information; 1 = they reported a repeated or extended event with no spatio-temporal context; 2 = they reported a repeated or extended event with some spatio-temporal context; 3 = they reported a specific event with spatio-temporal context and a few other event-related details; 4 = they reported a specific event with spatio-temporal context and many other event-related details.

The interviews were scored by two independent examiners who were blind to the age of each subject. The final score for each event was calculated in the following way: if there was a discrepancy of 1 point between the scores given by the two examiners, a mean score was given; if the discrepancy was more than one then a third independent examiner gave a score; the third score was then averaged with whichever of the previous scores it was within one point of. Only one of the three scorers had been in any one participant's interview. There was good inter-rater reliability for the episodic score between the two main raters (intraclass correlation coefficient = 0.802).

4.4 Results

4.4.1 Episodic picture task

4.4.1.1 Discrimination ability

A Mann-Whitney U test revealed no significant difference in the d' scores between the two age groups in any condition ($U = 211$, $p = 0.277$, Cohen's $d = 0.326$ for perspective shift; $U = 240$, $p = 0.657$, Cohen's $d = 0.126$ for object position shift; $U = 214.5$, $p = 0.313$, Cohen's $d = 0.3$ for both conditions; Figure 4.3). A Wilcoxon signed-rank test revealed that within each age group there was no significant difference between the d' score of the angle shift condition and the d' score of the object position shift condition ($Z = -1.042$, $p = 0.297$, Cohen's $d = 0.334$ in the young group; $Z = -1.092$, $p = 0.275$, Cohen's $d = 0.306$ in the elderly group). These non-parametric tests were used because there were outliers.

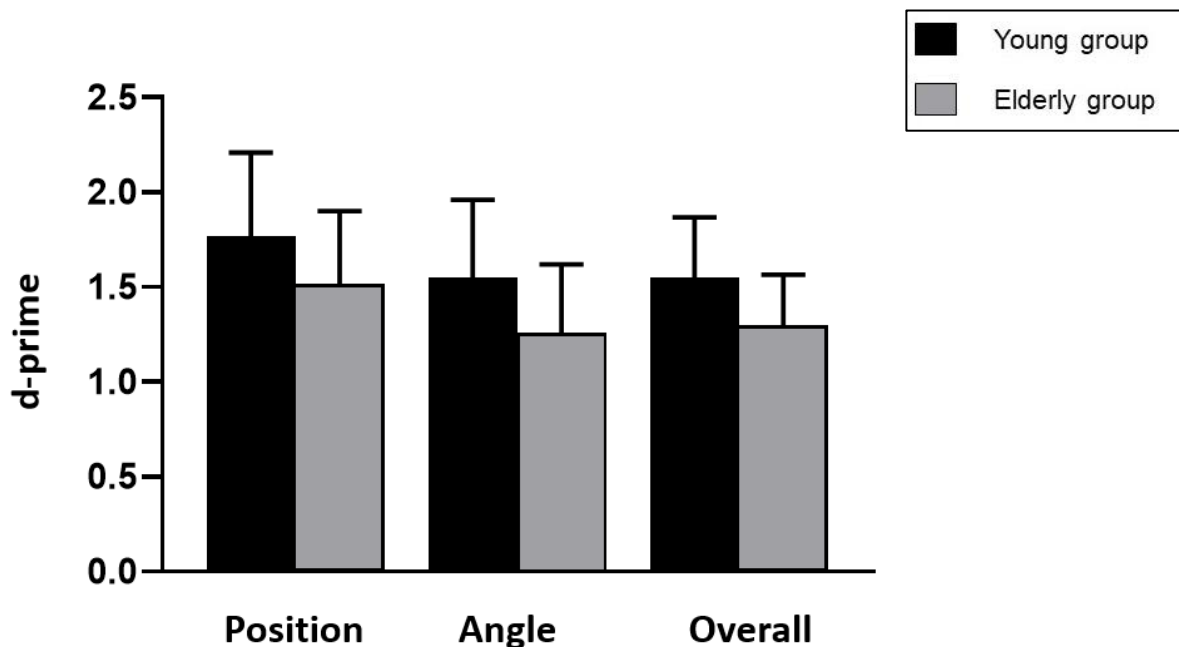


Figure 4.3. *D-prime score for each age group and for each condition*

Each column and error bar represents the mean and 95% confidence interval (CI), respectively.

4.4.1.2 Confidence ratings

Across the whole group of subjects (all 46 subjects), the mean (\pm SEM) confidence rating was 3.02 ± 0.068 across all trials, 3.06 ± 0.074 for the original pictures trials, 2.97 ± 0.071 for the object position shift trials, 2.97 ± 0.080 for the angle shift trials. Confidence ratings separately for correct and wrong responses are shown in Table 4.1.

Table 4.1. Confidence ratings depending on the condition and on whether their answer was correct or wrong in the two age groups

Mean and SEM.

		Confidence	
		Young	Elderly
Object position shift trials	Correct responses	3.13 (0.11)	2.96 (0.11)
	Wrong responses	2.26 (0.15)	2.82 (0.17)
Angle shift trials	Correct responses	3.01 (0.13)	2.96 (0.16)
	Wrong responses	2.77 (0.18)	2.81 (0.13)
Original pictures trials	Correct responses	3.26 (0.09)	3.15 (0.10)
	Wrong responses	2.51 (0.17)	2.59 (0.16)

Firstly, a Mann-Whitney U test was used to examine between-age-groups differences in the ability to judge one's memory performance. High confidence for trials in which participants were incorrect, and low confidence for trials in which participants were correct, would suggest a potential deficit in this ability. The fact that confidence judgments are a subjective measure suggests that they may be more linked to self-related processes and thus these judgments may differ between the angle shift condition and the other conditions of the task. This is because the angle shift condition assesses the ability to remember one's own encoded perspective of a scene. These analyses showed that there was no significant difference between the two age groups in any condition in the confidence ratings for correct responses or in the confidence ratings for incorrect responses ($U = 251.5$, $p = 0.850$, Cohen's $d = 0.063$ for confidence in correct responses in the angle shift trials; $U = 219$, $p = 0.823$, Cohen's $d = 0.270$ for confidence in wrong responses in the angle shift trials; $U = 216.5$, $p = 0.33$, Cohen's

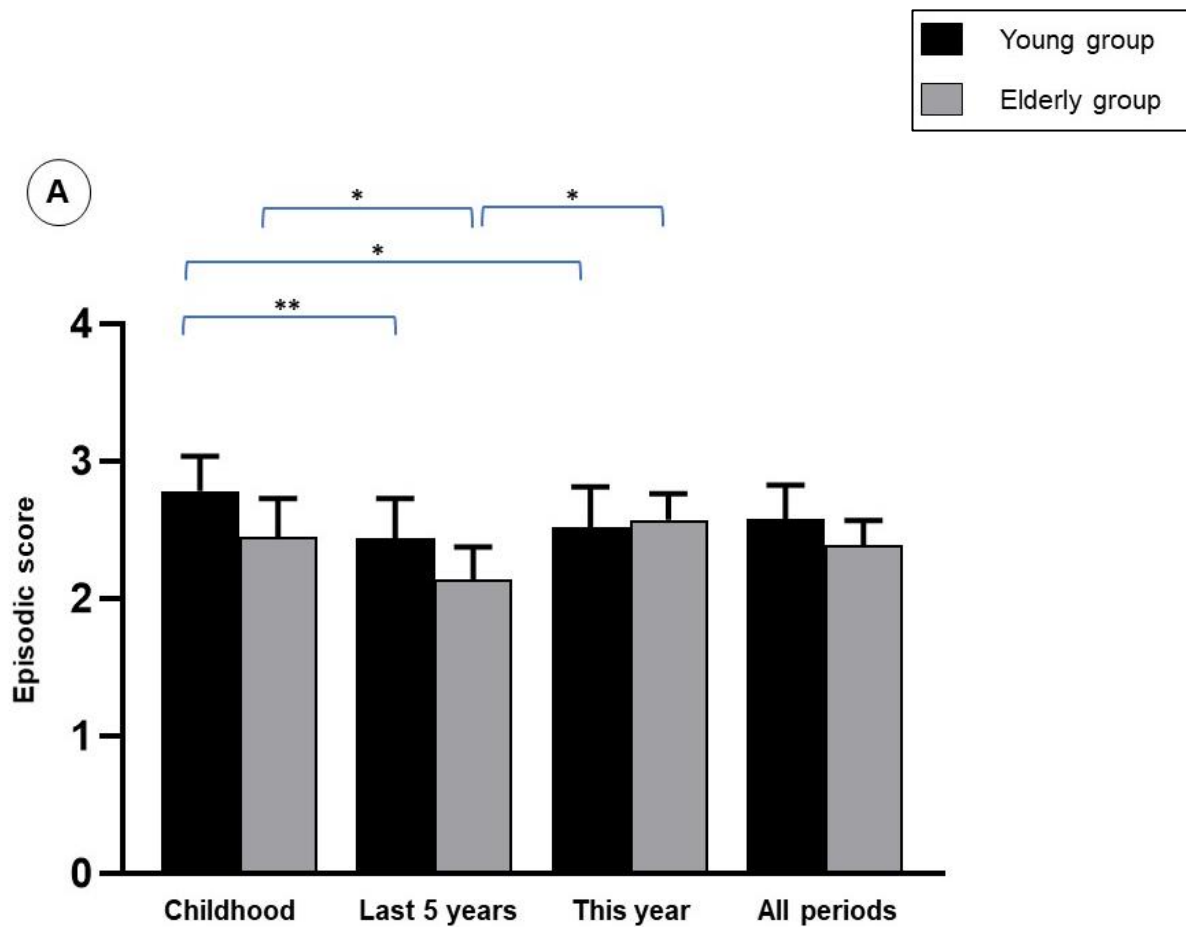
$d = 0.285$ for confidence in correct responses in the object position shift trials; $U = 236$, $p = 0.595$, Cohen's $d = 0.155$ for confidence in correct responses in the original trials; $U = 235.5$, $p = 0.585$, Cohen's $d = 0.155$ for confidence in wrong responses in the original trials). The only exception is in the wrong responses in the object position shift trials, for which the elderly group were significantly more confident compared to the young group ($U = 91$, $p = 0.007$, Cohen's $d = 1.324$; this difference survives Bonferroni correction for multiple comparisons; Table 4.1).

Secondly, I examined whether within each age group there was any significant difference in the confidence ratings depending on the condition (correct and wrong responses were examined separately). A Friedman test was used because there were outliers. There was no significant difference in the confidence ratings for wrong responses depending on the condition (young group: $\chi^2(2) = 2.561$, $p = 0.278$; elderly group: $\chi^2(2) = 5.233$, $p = 0.073$). A significant difference in the confidence ratings for correct responses depending on the condition was found in the young group ($\chi^2(2) = 7.487$, $p = 0.024$), but not in the elderly group ($\chi^2(2) = 4.188$, $p = 0.123$). Pairwise comparisons were performed using a Wilcoxon signed-rank test, because there were outliers in the differences between the paired data. Young subjects provided higher confidence ratings for their correct responses in the original trials than for their correct responses in the angle shift trials ($Z = -2.053$, $p = 0.040$, Cohen's $d = 0.686$).

In sum, an effect of age on confidence in one's memory judgments was found only in the object position shift trials. Specifically, when elderly subjects provided an incorrect response in these trials, they were more confident about this response than young subjects. Also, when young subjects provided a correct response, they felt more confident about it in trials showing the original picture than in trials showing an angle shift picture.

4.4.2 Autobiographical memory interview

The episodic score for each lifetime period and for each age group is shown in Figure 4.4A. Examination of this figure suggests that there were no gross differences in the amount of episodic details between the age groups, and that all subjects recalled fewer episodic details for events that occurred in the “last 5 years” period.



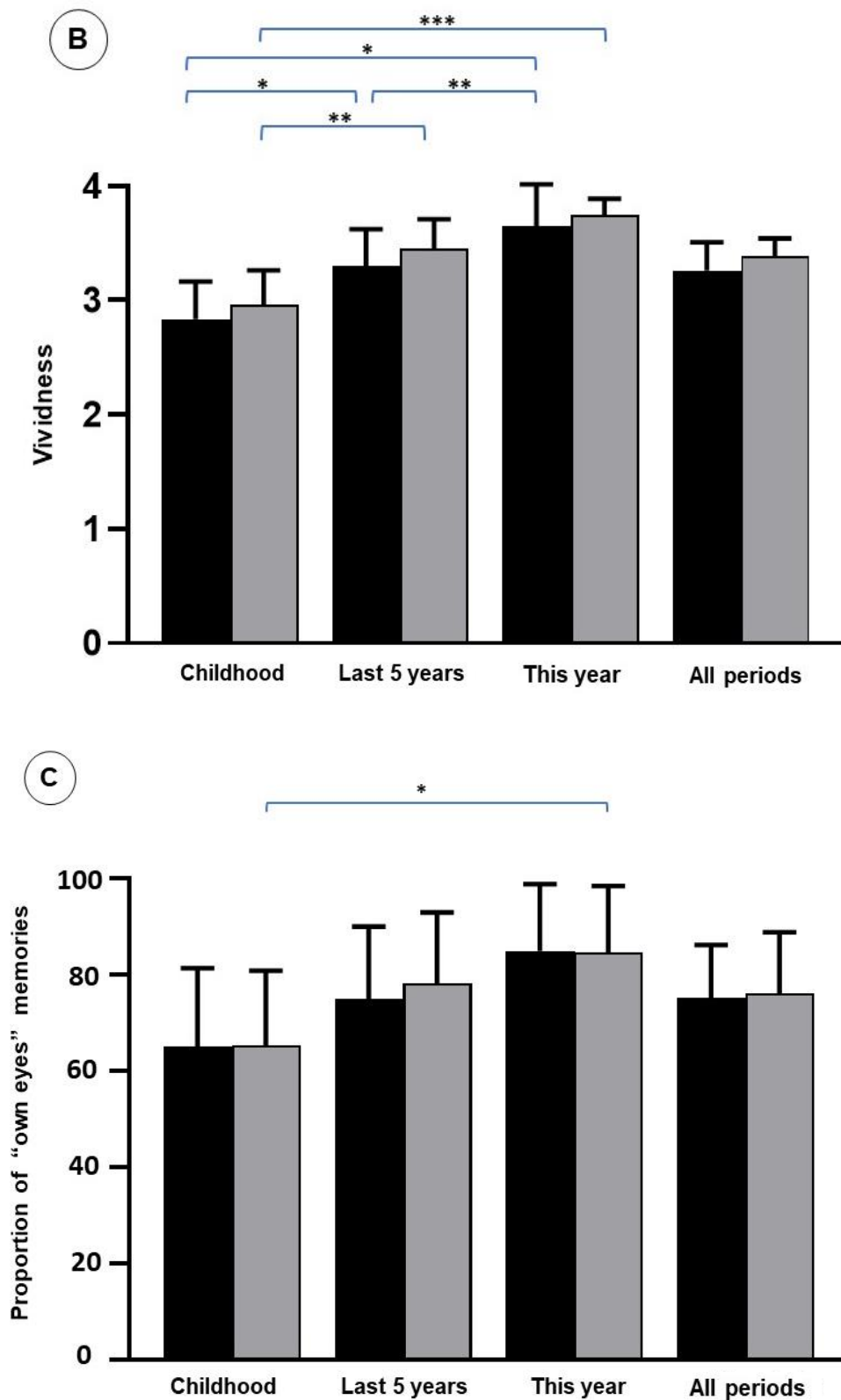


Figure 4.4. Comparisons between age groups and lifetime periods for the: A) episodic score; B) vividness; C) proportion of memories retrieved from an "own eyes" viewpoint

Only the comparisons shown with asterisks were significant. The \cap points to each individual bar, not to a combination of bars. Each column and error bar represents the mean and 95% CI, respectively.

*: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$.

Firstly, I examined whether there were any differences between the two age groups in the episodic score (overall and for each lifetime period) using a Mann-Whitney U test (because there were outliers). There was no significant difference in the episodic score between the two age groups in any of the three lifetime periods ($U = 188$, $p = 0.109$, Cohen's $d = 0.482$ for childhood period; $U = 186.5$, $p = 0.101$, Cohen's $d = 0.496$ for the "last 5 years" period; $U = 234$, $p = 0.562$, Cohen's $d = 0.167$ for the "this year" period; $U = 216.5$, $p = 0.335$, Cohen's $d = 0.285$ for all lifetime periods; Figure 4.4A).

Secondly, I examined whether, within each age group, the episodic score significantly differed between the three lifetime periods by using a Friedman test. This test was used because there were outliers in both age groups for the episodic score of the "last 5 years" period. There was a significant difference in the episodic score depending on the lifetime period in both the young ($\chi^2(2) = 9.270$, $p = 0.010$) and elderly group ($\chi^2(2) = 9.521$, $p = 0.009$). Pairwise comparisons were performed using a Wilcoxon signed-rank test. The episodic score was higher for the childhood period compared to the "last 5 years" period (young group: $Z = -2.855$, $p = 0.004$, Cohen's $d = 1.012$; elderly group: $Z = -2.178$, $p = 0.029$, Cohen's $d = 0.634$; Figure 4.4A). Also, the young subjects' episodic score for the childhood period was higher than for the "this year" period ($Z = -2.382$, $p = 0.017$, Cohen's $d = 0.813$), whereas the elderly subjects' episodic score for the "this year" period was higher than that for the "last 5 years" period ($Z = -3.073$, $p = 0.002$, Cohen's $d = 0.942$).

Also, self-rated scales in the autobiographical memory interview were analysed (Figure 4.4B), unlike the previous measure which was rated by the researchers. Firstly, between-age-groups differences in vividness scores (overall and for each lifetime period) were examined using a Mann-Whitney U test. This revealed that between the two age groups there was no significant difference in: a) the overall vividness score (averaged across all lifetime periods; $U = 237$, $p = 0.608$, Cohen's $d = 0.155$), or b) the vividness score of each lifetime period (all p 's

> 0.24 and all Cohen's d 's < 0.345). Secondly, within-age-group differences in vividness scores were examined using a Friedman test. There was a significant difference in the vividness score depending on the lifetime period in both the young ($\chi^2(2) = 13.211, p = 0.001$) and the elderly group ($\chi^2(2) = 16.578, p < 0.001$). Pairwise comparisons were performed using a paired t -test, except for the childhood versus "last 5 years" period in the elderly group for which a Wilcoxon signed-rank test was used (because there were outliers in the differences between the two related groups), and the childhood versus "this year" period comparison in the young group, and the "last 5 years" versus "this year" comparison in the elderly group for which a Sign test was used (because the distributions of the differences between the two related groups were neither normal nor symmetrical in shape). Significant differences in the vividness scores are shown in Figure 4.4B.

Furthermore, I examined whether there was a link between the episodic score (an objective measure) and the vividness score (a subjective measure). Correlation analyses were performed between the vividness score given for a particular lifetime period and the episodic score of that lifetime period. These analyses showed that there was no significant correlation between the vividness score for a particular lifetime period and the episodic score for that period, in neither of the two age groups (young group: $r_s = 0.244, p = 0.299$ for childhood period, $r_s = 0.053, p = 0.825$ for "last five years" period, $r_s = 0.254, p = 0.281$ for "this year" period, $r_s = 0.187, p = 0.429$ across all periods; elderly group: $r_s = 0.016, p = 0.937$ for childhood period, $r_s = 0.089, p = 0.666$ for "last five years" period, $r_s = -0.004, p = 0.986$ for "this year" period, $r_s = -0.094, p = 0.648$ across all periods; in this thesis r_s indicates a Spearman's correlation).

As can be seen in Figure 4.4C, the results for the proportion of "own eyes" memories replicate the known effect of more "own eyes" responses for recent memories (Akhtar et al. 2017; Nigro and Neisser 1983; Piolino et al. 2006; Sutin and Robins 2007; Verhaeghen et al.

2018). Within-age-group comparisons (using a Friedman test because there were outliers and the normal distribution assumption was violated), revealed significant differences in the elderly ($\chi^2(2) = 11.476, p = 0.003$) but not the young group ($\chi^2(2) = 4.531, p = 0.104$). Pairwise comparisons were performed using a Wilcoxon signed-rank test. In the elderly group, the proportion of “own eyes” responses was higher in the “this year” period than in the childhood period ($Z = -2.390, p = 0.017, \text{Cohen's } d = 0.702$). Between-age-groups comparisons (using a Mann-Whitney U test) revealed that between the two age groups there was no significant difference in: a) the overall proportion of “own eyes” memories (averaged across all lifetime periods; $U = 217.5, p = 0.335, \text{Cohen's } d = 0.278$), or b) the proportion of “own eyes” memories for each lifetime period (all p 's > 0.55 and all Cohen's d 's < 0.167).

For each of the nine memories of the interview, a Mann-Whitney U test was used to assess whether the episodic score for that memory was higher in participants who reported it as from their “own eyes” compared to participants who reported it as “observed”. These comparisons were performed across all participants, but also for each age group separately. In the whole group analysis, the episodic score for each of the 9 memories was not significantly different in participants who reported that memory as “own eyes” compared to participants who reported that memory as “observed” (all p 's > 0.063 and all Cohen's d 's < 0.577). When examining each age group separately, the only significant differences were for two different events in the “last 5 years” period; the episodic score for those events was higher in participants who remembered them from their “own eyes” compared to participants who remembered them as “observed” ($U = 19.5, p = 0.030, \text{Cohen's } d = 1.037$ in the young group for one type of event from that period; $U = 20, p = 0.011, \text{Cohen's } d = 1.086$ in elderly group for a different type of event from that period).

For each of the nine memories of the interview, a Mann-Whitney U test was used to explore whether the vividness score for that memory was higher in participants who reported

it as from their “own eyes” compared to participants who reported it as “observed”. These comparisons were performed across all participants, but also for each age group separately. In the whole group analysis, only for one of the memories from the “last 5 years” period ($U = 97$, $p = 0.030$, Cohen’s $d = 0.593$) and one of the memories from the “this year” period ($U = 56.5$, $p = 0.024$, Cohen’s $d = 0.491$) was the vividness score higher in participants remembering them from their “own eyes” compared to participants remembering them as “observed”. None of the comparisons were significant when examining each age group separately (all p ’s > 0.072 and all Cohen’s d ’s < 0.648).

4.4.3 Correlations between the autobiographical memory interview and the episodic picture task

The Spearman’s Rank-Order Correlation was used to explore associations between the autobiographical memory interview and the episodic picture task. These analyses were performed in order to examine the hypothesis that self-perspective is a key component of episodic memory. A strong correlation between performance on these tasks would suggest that the key aspect that autobiographical interviews and laboratory-based episodic memory tasks (involving scenes) have in common, is the ability to recall the original perspective from which the event was encoded (one’s own self-perspective). The episodic picture task is laboratory-based, events are encoded under controlled conditions (thus we know exactly what the correct answers are), and involves spatial aspects. The perspective that photos are taken from can vary and might reflect a viewing perspective we would have in memory. Thus, it is interesting to assess whether this relates to episodic details in autobiographical memory and possibly to specific subjective aspects of autobiographical memory.

First, correlations were performed between the d -prime score for each condition in the episodic picture task and the episodic score in the autobiographical memory interview (overall

score and for each lifetime period). No significant correlations were found when analysing the whole group of participants (all p 's > 0.277). When analysing each group separately, the only significant correlation was found in the elderly group between the d-prime for the angle shift condition in the episodic picture task and the episodic score for the childhood period ($r_s = -0.393$, $p = 0.047$).

Second, correlations were performed between the d-prime score for each condition in the episodic picture task and the vividness score in the autobiographical memory interview (overall score and for each lifetime period). No significant correlations were found when analysing the whole group of participants. However, when analysing each age group separately, the only significant correlation was found in the young group between the d-prime score for the position shift condition in the episodic picture task and the vividness score for the childhood period ($r_s = 0.523$, $p = 0.018$).

Third, correlations were performed between the d-prime score for each condition in the episodic picture task and the proportion of "own eyes" memories in the autobiographical memory interview (overall and for each lifetime period). No significant correlations were found when analysing the whole group of participants nor when analysing each age group separately (all p 's > 0.132).

4.5 Discussion

This study assessed healthy subjects' memory accuracy and confidence on an episodic picture task. This task included conditions in which scenes were shown from an altered angle or with an altered object position to that at encoding. As previous work (Russell et al. 2019) has shown that these manipulations can reflect one's ability to accurately remember the viewpoint from which 3D scenes had been seen, one aim of the current study was to examine whether this would also be the case when the scenes are 2D. Participants were also assessed

in their ability to recall autobiographical memories from three different lifetime periods by using an adapted autobiographical memory interview (Piolino et al. 2003, 2009). The second aim of this study was to examine the relationship between performance on these two tasks. As the episodic picture task involves 2D scenes which are shown from an altered perspective to that at encoding, I wanted to examine whether this would relate to autobiographical memory (episodic details and subjective aspects). Performance on these tasks may be correlated for the following reasons. First, autobiographical memory relies to a large extent on episodic memory. Second, self-related processing (self-perspective) may be a common feature underlying autobiographical memory, subjective aspects of memory, and the angle shift condition of the episodic picture task.

Elderly subjects were as accurate as young subjects in remembering the viewpoint from which they had seen 2D scenes and in remembering the position of the object in those scenes. Also, their autobiographical memories were as vivid, episodically rich, and with the same amount of “own eyes” responses as young subjects in each and every lifetime period. Correlation analysis showed that discrimination ability for the angle shift condition was weakly correlated with the episodic score for the childhood period. However, this was a negative correlation and was only present in the elderly group. This result suggests that there is no strong relationship between performance on this particular laboratory-based episodic memory task involving 2D scenes and autobiographical memory tasks. The task that I employed, which involved 2D scenes, may not be an effective way of probing memory for self-perspective. This is discussed in more detail below.

4.5.1 Episodic picture task

Subjects' discrimination ability (d' -prime) in the episodic picture task did not differ depending on age or condition. This contrasts with a study that assessed memory for egocentric perspective and memory for allocentric relationships using a similar task to the one described

here, and found a deficit in memory for egocentric perspective in the elderly group (Russell et al. 2019). Although, in the viewpoint change condition, their elderly group performed similarly to my elderly group, their young group performed better than my young group. Factors that possibly increase the difficulty of their task compared to the one used in this chapter are that testing was performed one day after encoding, and there were two objects in each scene. In contrast, factors that may make Russell and colleagues' task easier than the one used here are that the scenes at encoding were presented for a longer duration (60 seconds rather than 6.5 seconds), twice, were 3D, and almost three times larger (real objects on a table rather than pictures of these objects on a computer screen; differences between 2D and 3D representations, e.g. in their memorability [Snow et al. 2014], are further discussed in sections 4.5.3, 4.5.4, and 7.3.1). Furthermore, the scenes were fewer (28 instead of 35). The argument about the differences in the dimensions of the scenes is supported by work showing that when the encoding phase of a memory task involves real-life 3D scenes, discrimination accuracy is poorer in healthy elderly subjects compared to young subjects, whereas when these scenes are encoded in a 2D environment no age differences are found (Diamond et al. 2020). Thus, it may be that a memory task involving small-scale 2D scenes showing one object on a grid which are presented only once for a short duration and are tested after a relatively short delay cannot effectively probe memory for self-perspective, and therefore does not reveal age differences in this aspect of memory.

In the current study, the elderly group were more confident compared to the young group when they provided an incorrect response about the object's position. This is line with other studies showing that, compared to young subjects, healthy elderly subjects were less accurate in their high confidence judgments on a scene-face pairs recognition task (only when the scenes at encoding were highly similar to those presented in the recognition phase; Greene, Chism, and Naveh-Benjamin 2020), and more confident when they were incorrect in a word-pairs recognition task (Shing et al. 2009). However, this age effect was not found when using

an object location recall task (Salvato et al. 2016). These discrepancies could be due to the: a) different duration of the interval, b) different types of stimuli, c) whether the task involved recall or recognition, d) whether it involved making associations between stimuli, and e) whether the age groups were education-matched, as it has been shown that subjects with lower levels of education are more confident in their incorrect responses on a memory task (Szajer and Murphy 2013). For example, in my study, elderly subjects were less educated compared to young subjects (a pattern that has also been observed in a number of previous healthy ageing studies; Clarys et al. 2002; Janssen et al. 2011; Piolino et al. 2006; Souchay et al. 2007).

4.5.2 Autobiographical memory interview

A recency effect (higher scores for recent compared to remote memories) occurred for the episodic score, vividness score, and proportion of “own eyes” responses in both age groups. However, this effect did not reach significance for the episodic score and proportion of “own eyes” responses in the young group, which could be due to the smaller sample size (20 young versus 26 elderly subjects). Previous studies have shown that in both young and elderly healthy subjects, recent (compared to remote) autobiographical memories tend to be more specific, vivid, coherent, and detailed, and are more likely to be reported from an “own eyes” perspective (Akhtar et al. 2017; Gardner et al. 2015; Irish, Lawlor, et al. 2011; Nigro and Neisser 1983; Piolino et al. 2006; Sutin and Robins 2007; Tollenaar et al. 2009; Verhaeghen et al. 2018; Wang and Conway 2004). Also, the current study partially replicated previous findings which have shown that retrieving an autobiographical event from a first-person perspective is linked with greater accuracy, a stronger sense of subjective experience, and more “remember” responses (Marcotti and St. Jacques 2018; Piolino et al. 2006; Siedlecki 2015).

There was no age effect in the amount of episodic details in any of the three lifetime periods, which is in contrast to previous research (Gaesser et al. 2011; Levine et al. 2002; Peters et al. 2019; Piolino et al. 2006; Robin and Moscovitch 2017). This discrepancy could be due to differences in the administration of the interview such as using the probes differently. In the current study, the mean number of times that the “Can you add any specific details?” prompt was used per memory was 0.52, whereas, for example, Piolino and colleagues (2006) seemed to have used a higher number of prompts. When prompting participants, Piolino and colleagues (2006) did not only provide a general prompt (which was done in the current study), but they also sometimes provided specific prompts such as “When did the event occur?”. Furthermore, compared to the current study, in the study of Piolino and colleagues (2006) participants were asked to recall more events per period.

Also, I did not find any significant difference in the proportion of “own eyes” responses between the two age groups. This is in accord with the findings of Piolino and colleagues (2006). However, it is difficult to directly compare the results of these two studies because Piolino and colleagues (2006) analysed the proportion of “own eyes” responses differently; unlike the approach undertaken in this thesis, they also allowed participants to give an “own eyes / observer” response if they shifted between the two viewpoints.

Furthermore, I did not find any significant difference in vividness between the age groups in any of the lifetime periods. As discussed in Chapter 1, there is no clear consensus about age effects in vividness when retrieving autobiographical events. Some authors (Piolino et al. 2006) have found that, compared to young subjects, healthy elderly subjects have a lower sense of vividness when recalling autobiographical events, whereas others (Comblain et al. 2005; Janssen et al. 2011; Rubin and Berntsen 2009; Rubin and Schulkind 1997) found that it was higher. Compared to the current study, these studies (Comblain et al. 2005; Janssen et al. 2011; Rubin and Berntsen 2009; Rubin and Schulkind 1997) used a larger range scale for

rating vividness, and some of them differed in which lifetime period was examined and in how many events participants were asked to retrieve per period. For example, Rubin and Berntsen (2009) asked each participant to report their vividness for only one event (either from the previous week or from adolescence), and Comblain and colleagues (2005) asked participants to provide vividness ratings for only six events (that occurred in the past 5 years). Another difference between the current and these studies, which could potentially explain the discrepancy in these findings (Fitzgerald 2010; Wang and Conway 2004), is the participants' culture. A recent review showed that the subjective feeling of remembering in healthy elderly tends to be greater or the same as in young subjects (Folville, Simons, et al. 2020). A potential reason for this is that elderly subjects may make subjective memory judgments based not (or not only) on the number of episodic details, but on other types of information such as semantic information, or based on just one type of episodic detail, e.g. emotional aspects of the event (Comblain et al. 2004; Folville, Simons, et al. 2020; Hashtroudi et al. 1990; Johnson et al. 2015).

In both age groups, the amount of episodic detail reported for the childhood period was significantly more than for the "last 5 years" period. This profile has also been found in an elderly group in a previous study (Piolino et al. 2006), and could reflect the reminiscence bump. Although the reminiscence bump is thought to occur on average (worldwide) in adolescence and early adulthood, in the United Kingdom population the peak may be at about 12 years old (Conway et al. 2005), which was the maximum age for the childhood period in the autobiographical memory interview I used. Arguably, events experienced early in life are often attached to photographic evidence, and may be more self-defining and more frequently rehearsed compared to recent events (Conway and Holmes 2004; Conway and Pleydell-Pearce 2000; Rubin et al. 1998; Wells et al. 2014). These factors could potentially explain the greater amount of episodic detail for childhood memories.

In line with the study by Clark and Maguire (2020), which used the Autobiographical Interview (Levine et al. 2002), I did not find any significant correlation between the vividness score and the episodic score in any of the two age groups. However, this is inconsistent with a study by Folville and colleagues (2020), which found that in both age groups there was a significant link between the subjective score (how vividly participants remembered scenes) and the objective score (amount of details they recalled about those scenes), and this link was stronger in the young compared to the elderly group. These discrepancies could be attributed to differences in the task that Folville and colleagues (2020) used. That is, in their task, participants encoded pictures on a screen (these were non-self-related and not from previously experienced events), the encoding session was controlled (thus the researchers could examine the accuracy of participants' reports), and the delay interval was a few seconds. Thus, it may be that young and elderly subjects in the current study were not willing or able to report all the event-related details, or did not rely on episodic content to make vividness judgments.

It is important to note that the type of cues used may influence the retrieval of autobiographical events (Goddard et al. 2005). The cues that I used in the interview were verbal cues (e.g. "Give details about a particular event that stands out to you, that took place when you were at primary school"). However, if instead of words I had used other types of cues such as pictorial (e.g. a cartoon of a child or a cartoon of a school) or auditory cues (e.g. sounds of children), then it is possible that participants would have described other autobiographical events which may have involved a different amount of episodic detail and vividness (Chu and Downes 2002; Goddard et al. 2005; El Haj, Kapogiannis, et al. 2020; Herz and Schooler 2002; St. Jacques, Conway, and Cabeza 2011; Mazzoni et al. 2014). Potential reasons for these differences are that verbal, odour, auditory, and picture cues tend to differ in how distinct they are, how much information they provide, and how similar this information is to autobiographical events (Mazzoni et al. 2014; Nelson 1979). For example, compared to

the information provided by verbal cues, the information provided by picture cues (colour, depth, landscape) is arguably more similar to an autobiographical event.

4.5.3 Correlation between the autobiographical memory interview and the episodic picture task

By examining the relationship between performance on the autobiographical memory interview and the episodic picture task, I wanted to explore what features of a controlled laboratory-based episodic memory task reflect our ability to remember autobiographical events with great detail, vividness and from a first-person perspective. Even though these tasks differ in many ways (e.g. remoteness of the encoded events), I wanted to examine whether there is a relationship between them because what they supposedly have in common is that they rely on episodic memory and involve self-related processes. Events typically encoded in laboratory-based episodic memory tasks (e.g. word lists) arguably have less personal significance than autobiographical events. However, the laboratory-based episodic memory task used in the current study aimed to probe more self-related processes, and this was one reason why it was expected that performance on these two tasks would be correlated. Autobiographical memory may be more related to first-person perspective memories in a controlled laboratory-based episodic memory task, because autobiographical events are possibly more related to the self.

A significant correlation was found between discrimination ability in the angle shift condition of the episodic picture task and the episodic score in the autobiographical memory interview. However, this was a weak correlation, was the opposite direction to that expected, and was found only in the elderly group and only for the childhood period. This finding, that the more semanticized their childhood memories, the better they were at discriminating between the scenes shown from an altered viewpoint and those shown from an unaltered

viewpoint, suggests that elderly participants may possibly have used a verbal strategy (more like a semantic strategy or like a cognitive map) to discriminate between these scenes. Also, this finding reflects work indicating that autobiographical memories in the elderly, especially for remote events, may be more semanticized (as discussed in Chapter 1). A significant correlation was also found between the discrimination ability in the position shift condition of the episodic picture task and the vividness score in the autobiographical memory interview. However, this again was a weak correlation and was found only in the young group and only for the childhood period. This finding indicates that young subjects' vividness of a childhood event seems to be linked to how much allocentric spatial information they actually remember, which reflects work showing that remote events tend to be more semanticized—more like a cognitive map. Below, I discuss potential reasons why no strong correlation was found between performance on the autobiographical memory interview and the episodic picture task.

First, it is possible that not having an incidental paradigm worked against the aim of the current study to find the shared resources of these two memory types (autobiographical memory and episodic memory). In the autobiographical memory interview participants encoded the events incidentally (without being instructed to remember them), whereas in the episodic picture task they were asked to remember the scenes. Second, the episodic picture task involved only one sensory modality (vision) and measured the ability to remember spatial information, whereas the autobiographical memory interview not only involved vision but also multiple other features (e.g. auditory, olfactory, gustatory, somatosensory, motor, and vestibular) and gauged the ability to remember not only spatial information but also other types of information (e.g. temporal details and emotions). Thus, future studies could compute a separate score in the autobiographical memory interview, which would only take into account the amount of spatial details reported, and examine whether this score correlates more strongly with performance on the episodic picture task.

Third, in the autobiographical memory interview the events which were encoded were real-life 3D scenes, in contrast to the episodic picture task which involved 2D scenes. The 2D scenes may have not been able to represent self-perspective in the way that 3D scenes can. This argument is supported by neuroimaging evidence showing that somewhat different regions underlie memory for real-life events compared to memory for events encoded in laboratory-based paradigms (involving auditory, olfactory stimuli, words, or pictures of objects, faces, or scenes; Cabeza et al. 2004; Chen et al. 2017; Fink et al. 1996; Gilboa 2004; McDermott, Szpunar, and Christ 2009; Monge et al. 2018; Nyberg et al. 2002), and by another experiment (see section 4.5.4; differences in how we process stimuli depending on the number of their dimensions are further discussed in the last chapter). It is also supported by the finding that when retrieving details about scenes which had been encoded in a real-life 3D environment (compared to equivalent scenes that were encoded in a 2D environment), subjects reported a greater sense of seeing the details in their “mind’s eye” (Diamond et al. 2020). Arguably, in a real-life 3D environment one sees their own body within the event, whereas if an event is shown as a picture on a screen then one does not see their body within that picture. The presence or absence of our body within a scene at encoding, seems to impact the encoding and consolidation of the scene (Gauthier et al. 2020). Therefore, a task involving the encoding of events in which the participant is part of them, i.e., present within them, may be more effective in probing memory for self-perspective.

Lastly, unrelated to task features, another reason that no strong correlation was found between the autobiographical memory interview and the episodic picture task could be that the current study may not have been sufficiently powered. Although it included similar numbers to previous studies that compared performance between young and elderly groups of healthy subjects (Folville, Bahri, et al. 2020; Gaesser et al. 2011; St. Jacques and Levine 2007; Kinugawa et al. 2013; Levine et al. 2002; Peters et al. 2019; Puglisi et al. 1985; Robin and

Moscovitch 2017; Russell et al. 2019), this number of subjects may have been insufficient for a correlation analysis.

4.5.4 Comparison to an experiment using 3D stimuli

A linked experiment to the one described in this chapter has also been conducted by other group members in the same team (described along with this study in Kapsetaki et al., under review). They recruited a different set of participants (young and elderly groups of healthy subjects whose age range was almost exactly the same as the groups in the current study) who completed an autobiographical memory interview and a laboratory-based episodic memory task; performance was compared between the two age groups and correlations were examined between the two tasks. The autobiographical memory interview was the same as the one used here, and the laboratory-based episodic memory task included the same types of objects placed on the same grid as I used. However, crucially, the main difference between that experiment and the experiment described in this chapter is that the stimuli presented at encoding were real-life 3D objects (not pictures of these objects), as in the study carried out by Russell and colleagues (2019). Other differences include that there were two objects instead of one object on the grid, 22 instead of 35 scenes, the duration for which each scene was presented at encoding was longer (60 instead of 6.5 seconds), and at the end of each encoding block their memory for the scenes was assessed and they were given a verbal reminder in the case of incorrect responses. Furthermore, participants changed their seating position in order to see the scenes from different angles (in my experiment they did not change seating position) and a camera was placed on the participants' head which supposedly took a still of the scene they were observing (no head-camera was used in my experiment). Thus, these two factors may have provided more emphasis on the importance of remembering their viewpoint.

That experiment had three key findings which contrast with the results of the experiment in this chapter. First, there was a significant positive correlation between the episodic score in the autobiographical memory interview and discrimination ability for the viewpoint shift condition in the laboratory-based episodic memory task, which was driven by the young group. Second, in the laboratory-based episodic memory task, age had a negative effect on the ability to discriminate between previously seen scenes and changed scenes (altered location of one of the objects or changed viewpoint; importantly, the effect was greater for the changed viewpoint). Third, compared to the young group, the elderly group had a significantly lower overall episodic score (averaged across all lifetime periods), which was particularly driven by the “this year” and “last 5 years” lifetime periods.

Therefore, the differences in the findings between that experiment and the one described in this chapter suggest that: a) memory for 2D scenes is quite different to memory for 3D scenes, and b) a task involving 2D scenes may not be able to effectively probe memory for self-perspective.

4.5.5 Limitations and future directions

This section discusses the limitations of this study and the possible ways by which they could be addressed in the future.

Interindividual differences in the amount of detail in episodic memories can occur not only due to interindividual differences in the ability to *retrieve* details, but also due to interindividual differences in the ability to *report* details about an event. First, the amount of details reported in the interview may depend on one’s character. For example, reticent people may report fewer details even if they do remember all the details relating to the event (Cohen and Taylor 1998; Kessler and Wethington 1991). One method that I could have used to control

this is to calculate the ratio of internal to external details or the ratio of internal to total details, as has been used in previous studies (e.g. Barnabe et al. 2012; Levine et al. 2002; Meulenbroek et al. 2010; Murphy et al. 2008). This was not performed in the current thesis because whenever participants started referring to information that was unrelated to the event, they were interrupted (to remind them that they needed to talk about one specific event). Second, the amount of details reported may depend on language capabilities and descriptive ability. Thus, the current study could have included a control task in which participants would be shown a picture of a scene and would be asked to describe it, as has been done previously (e.g. Gaesser et al. 2011; Madore, Gaesser, and Schacter 2014).

Future studies could further probe people's memory by using a mental imagery questionnaire and a scene construction task, because autobiographical memory seems to require mental imagery and the ability to construct a scene (Aydin 2018). There is a high degree of overlap between these processes (Hassabis et al. 2007), as suggested by Clark and Maguire's (2020) finding that there was a significant correlation between the vividness score in the Autobiographical Interview (Levine et al. 2002) and performance on a mental imagery questionnaire. Even though in some scene construction tasks participants are told to not describe a memory (e.g. Hassabis and Maguire 2007), it is almost impossible to form a mental scene without basing it on our memory (scenes we have seen before). Mental imagery questionnaires may ask participants to imagine a scene, but often the scene refers to a past experience. For example, many questions in the Object-Spatial Imagery Questionnaire (Blajenkova et al. 2006) and the Plymouth Sensory Imagery Questionnaire (Andrade et al. 2014), which were used by Clark and Maguire (2020), clearly involve memory, for example, "...entering a familiar store...", "I have photographic memory", "I can easily remember...", "imagine the appearance of the front door of your house", and "imagine the appearance of a friend you know well". Therefore, the relationship found between memory questionnaires and mental imagery questionnaires in the study by Clark and Maguire (2020) is likely because

these questionnaires are drawing on the same cognitive processes. This is why, in the current study, I tried to examine which aspects of a scene are remembered in the episodic picture task (the position of stimuli or self-perspective), and whether the ability to remember one's self-perspective is the key link between the autobiographical memory interview and the episodic picture task.

Another potentially important factor, which I did not take into account when using the autobiographical memory interview and should be considered in future studies, is how many times the participant has retold this event or rehearsed it. This would have influenced how detailed the described event was, and may have been one of the reasons that I did not find a significant difference in the episodic score between the young group and the elderly group. For example, a possible reason why elderly subjects reported an equal amount of details compared to young subjects is that, as mentioned in previous studies (e.g. Alea and Vick 2010; Luchetti and Sutin 2018), they may have rehearsed and retold those events many times. In contrast, young participants may have remembered an equal amount of details but with fewer rehearsals and less retelling. Participants were asked to report three autobiographical memories per lifetime period, and it is likely that they chose events that they would have rehearsed the most as these would have been remembered well enough to describe in detail. This issue could be addressed by asking participants to provide an estimate of how many times they have rethought and talked about each event they are describing, as has been done previously (e.g. Conway et al. 2005; Wang 2001; Wardell et al. 2020).

Additionally, many participants appeared to find it very difficult to appreciate the difference between the "own eyes" and the "observer" perspective in the autobiographical memory interview. However, I did not systematically record which particular individuals found it difficult. Thus, I could not examine whether one age group found it particularly difficult compared to the other age group. A continuous scale for "own eyes" – "observer" viewpoint

in the autobiographical memory interview, as has been used previously (Berntsen and Rubin 2006; Rice and Rubin 2009; Sekiguchi and Nonaka 2014; Siedlecki 2015; Verhaeghen et al. 2018), may have possibly been easier for participants to understand and a more accurate measure of one's viewpoint. This scale may have also been more sensitive in detecting a relationship between the viewpoint reported in the autobiographical memory interview and performance on the episodic picture task.

There were some further limitations in the autobiographical memory interview that I used, which are common in studies assessing autobiographical memory across different age groups (e.g. Levine et al. 2002; Piolino et al. 2006). First, the time between encoding and retrieval of the autobiographical events differed across participants. For example, for the childhood period, the retention interval in the young group was about 7–33 years, whereas in the elderly group it was about 53–70 years. Second, each participant experienced a different event, as I did not have any control over the circumstances during encoding. Third, some participants could not describe an event because their daily life did not include the activities that were used as cues in the interview, so they were asked to describe a similar event.

Regarding the episodic picture task, there may have been some degree of proactive and retroactive interference because the grid that was used was the same across all trials. Furthermore, future studies could examine what types of strategies are used to solve this task. For example, participants may encode the objects' position relative to themselves or relative to the numbers shown outside the grid.

4.6 Conclusion

In conclusion, no strong correlation was found between episodic memory for 2D scenes and episodic memory for real-life autobiographical events, and there was no significant difference between young and elderly subjects in their discrimination ability in the object location or

viewpoint change condition. This suggests that the way we remember 2D scenes presented on a screen may be quite different to how we remember real-life events, and an episodic memory task involving 2D scenes may not be able to effectively probe memory for one's own self-perspective. Many studies use the umbrella term "episodic memory", but often what each of them measures can be very different. Findings from studies that have used laboratory-based 2D episodic memory tasks cannot always be inferred to how one remembers real-life events. Therefore, the main task in the next chapter employs a three-dimensional approach rather than 2D scenes at encoding.

5 Spatial and Temporal Information in Episodic Memory following Stroke

5.1 Introduction

As discussed in Chapters 1 and 4, previous studies have shown that in healthy elderly people (compared to young people) personal events tend to be retrieved with fewer specific details (Devitt et al. 2017; Gaesser et al. 2011; Levine et al. 2002; Peters et al. 2019; Piolino et al. 2006; Robin and Moscovitch 2017), less vividness (Piolino et al. 2006), reduced subjective experience of remembering (Piolino et al. 2006), more often from a third-person perspective (Piolino et al. 2006, 2009), and healthy elderly subjects appear to be poorer at recalling events from their own perspective (Russell et al. 2019). There is increasing evidence that autobiographical memory can be affected in stroke patients with posterior parietal lobe damage and these patients appear to have particular difficulty in correctly recalling their previously encoded perspective in an episodic memory task (Berryhill et al. 2007; Davidson et al. 2008; Russell et al. 2019). I will therefore review work on the posterior parietal lobe's involvement in episodic memory processes.

5.1.1 The role of the posterior parietal lobe in episodic memory

Episodic memory is not traditionally thought to be affected by damage to the posterior parietal lobe, but rather by damage to the medial temporal lobe (mainly the hippocampus; Squire, Stark, and Clark 2004). Even though the posterior parietal lobe is almost ubiquitously found to be activated in episodic memory tasks, patients with damage to this region are not typically impaired on such tasks, which remains a complex puzzle in the episodic memory literature (Berryhill 2012; Cabeza et al. 2008; Schooler et al. 2011; Vilberg

and Rugg 2008). Below, I discuss functional neuroimaging and lesion studies examining the role of the posterior parietal lobe in episodic memory.

5.1.1.1 Evidence from functional neuroimaging studies

There appears to be strong evidence from functional neuroimaging studies supporting a particular role of the posterior parietal lobe in episodic memory: it appears that it is essential for binding and remembering specific details about an event, which are key features of episodic memory (Tulving 1972, 1983, 2002). For example, greater activity is found in posterior parietal regions when participants recall details associated with previously presented words (Hutchinson et al. 2014; Wheeler and Buckner 2004; Yonelinas et al. 2005) or 2D objects (Dobbins and Wagner 2005; Vilberg and Rugg 2007), compared to when they are not able to recall contextual details associated with these stimuli. The involvement of ventral regions of the posterior parietal cortex (in particular the angular gyrus) in binding episodic features across multiple modalities (Seghier 2013; Tibon et al. 2019), is known as the Cortical Binding of Relational Activity theory (CoBRA; Shimamura 2011), and such an account may explain why (a) the angular gyrus is one of the few brain regions at which episodic, semantic, and default mode network activations overlap (Humphreys et al. 2020; Irish and Vatansever 2020) and (b) it may be involved in scene construction, as greater activity in the posterior parietal cortex is found when subjects imagine fictitious scenes compared to fictitious objects, and when they recall autobiographical memories compared to previously seen 2D objects (Hassabis, Kumaran, and Maguire 2007).

Apart from objective aspects of episodic memory retrieval, functional neuroimaging studies (see below) have shown that the posterior parietal lobe seems to also be involved in subjective aspects of retrieval (e.g. vividness and confidence), and that objective and

subjective aspects may be processed by different regions within this lobe. Richter and colleagues (2016) found that greater activity in the angular gyrus and the precuneus was associated with higher precision and higher vividness, respectively, when recalling 2D objects (their colour, orientation and location) that were associated with a background scene. Furthermore, greater posterior parietal lobe activity was found when participants provided confidence ratings about previously learnt name-face pairs than when recognizing these pairs (Chua et al. 2006), and when they reported higher confidence (compared to lower confidence) in their "know" responses in a word recognition task (Yonelinas et al. 2005). The posterior parietal lobe's involvement in subjective aspects of memory suggests that its main role may be in self-related processes. This may be the reason why it has been found to be involved in objective aspects of episodic memory retrieval, specifically, in binding episodic features (as adopting a first-person perspective seems to be linked with retrieving a greater amount of episodic details; Akhtar et al. 2017; Marcotti and St. Jacques 2018; Piolino et al. 2006; Verhaeghen et al. 2018).

5.1.1.2 Evidence from lesion studies

Although the functional neuroimaging studies discussed above indicate that the posterior parietal lobe is involved in binding multiple episodic details and remembering them with high vividness and confidence, dysfunction of this region (due to naturally occurring lesions or inhibitory brain stimulation; see below) can lead to poor ability to remember event-related details (objective measures) in autobiographical memory tasks under free recall conditions, poor ability to remember events with high confidence, but relatively intact ability to remember stimuli and the contextual details linked to them (objective measures) in laboratory-based episodic memory tasks. Therefore, the deficits manifested by these patients may be too subtle to result in impaired performance on standard clinical memory tests.

Stroke involving the posterior parietal lobe does not seem to affect the ability to recall details that are associated with previously presented single words, sentences, 2D items, or faces (Ciaramelli et al. 2017; Simons et al. 2008, 2010), free or cued word recall accuracy (Drowos et al. 2010; Godefroy et al. 2009), word recognition accuracy (Ciaramelli et al. 2017; Godefroy et al. 2009; Haramati et al. 2008; Hower et al. 2014), or object recognition accuracy (Ally et al. 2008). Thus, the posterior parietal lobe does not appear to be critical for episodic memory accuracy in laboratory-based tasks. In contrast, when retrieving autobiographical events under free recall conditions, posterior parietal lobe disruption due to inhibitory brain stimulation can lead to reduced internal details (Bonnici et al. 2018), and posterior parietal lobe damage due to stroke can lead to reduced internal details relating to time, perception, and thoughts (Berryhill et al. 2007); though these deficits seem to disappear under cued recall conditions (Berryhill et al. 2007; Bonnici et al. 2018; Davidson et al. 2008). Furthermore, in line with the functional neuroimaging literature, lesion studies have shown that this region appears to be important for subjective aspects of memory. Patients with posterior parietal lobe involvement have reduced confidence in their memory judgments on an old/new word recognition task (Ciaramelli et al. 2017; Hower et al. 2014) and on a task examining memory for contextual details related to sentences and 2D items (Simons et al. 2010), even though their accuracy on these tasks is unimpaired. Reduced confidence in one's memory judgments on a task examining memory for contextual details related to particular stimuli has also been found after inhibitory stimulation of the left angular gyrus (in this paradigm the stimuli were words; Yazar, Bergström, and Simons 2014). This suggests that one reason why deficits in remembering event-related details (objective measures) have been found when subjects with posterior parietal lobe damage (or dysfunction) perform autobiographical memory tasks but not when they perform laboratory-based episodic memory tasks may be that autobiographical events are possibly more related to the self.

Lesion studies (temporary inactivation or permanent damage of brain regions) suggest that the posterior parietal lobe, apart from remembering event-related details in autobiographical memory tasks and the subjective experience of remembering (e.g. confidence about one's own memory performance; as discussed above), seems to also be important in egocentric representations (see below). In fact, these aspects of episodic memory may be linked as they are all referring to one's self-experience of an event. Many lesion studies have revealed the posterior parietal lobe's role in egocentric representations in the context of attention, navigation, and spatial processing (Ciaramelli, Rosenbaum, et al. 2010; Hillis et al. 2005; Iachini et al. 2009; Medina et al. 2009; Seubert et al. 2008; Weniger et al. 2009). However, its potentially critical role in egocentric representations in the context of autobiographical memory has only been shown by temporarily damaging brain regions in healthy subjects; specifically Bonnici and colleagues (2018) found that inhibitory brain stimulation to the left angular gyrus seems to affect the ability to retrieve autobiographical events from a first-person perspective. Only one study has examined the posterior parietal lobe's role in egocentric representations in the context of episodic memory following stroke (though this was a small group of patients; Russell et al. 2019). From the evidence discussed above, it appears likely that the posterior parietal lobe is involved in egocentric episodic memory, as the autobiographical memory literature in healthy subjects has shown that greater subjective experience of remembering an event (which seems to be a key function of the posterior parietal lobe as discussed above), is associated with retrieving the event from a first-person perspective (Crawley and French 2005; Sutin and Robins 2010; Verhaeghen et al. 2018). This is because, arguably, to feel that one is fully re-experiencing a past personal event one needs to look (with their "mind's eye") at that event from the same viewpoint as that which was taken at encoding (as if stepping into those same shoes).

Therefore, further work is needed to explore the potential role of the posterior parietal lobe in egocentric episodic memory, by using a task that is able to probe this aspect of memory in a larger group of patients with damage to this region.

5.1.2 Development of a 3D spatio-temporal task

The first aim of the current study was to develop an episodic memory task and assess its feasibility by administering it to healthy young subjects, healthy elderly subjects, and stroke patients. This task was developed by taking into consideration: a) studies that have used “what-where-when” tasks (Burns et al. 2015; Cheke 2016; Cheke and Clayton 2013; Mazurek et al. 2015; Smulders et al. 2017), b) a task that has previously been used in stroke patients, healthy young, and healthy elderly individuals to assess egocentric aspects of episodic memory separately from allocentric aspects of episodic memory (Russell et al. 2019), and c) a 3D spatio-temporal task which is currently being used at King’s College London with healthy young and healthy elderly individuals (unpublished work). Furthermore, I took into account the essential criteria that should be met by tasks that assess episodic memory (Pause et al. 2013).

This task assessed episodic memory, not autobiographical memory. Rather than assessing memory for real-life personal events across periods of years or decades, it assessed memory for scenes that were encoded in a laboratory setting under controlled conditions after a relatively short interval. Real 3D footage was presented at encoding (real-life 3D objects were placed on a tray instead of showing pictures of objects on a screen), to allow control and manipulation of every aspect of the task, and to create episodes which resemble real-life events. Participants viewed these episodes while wearing a head-camera. By using video footage from this camera at recognition (instead of still images which were used in some previous studies, e.g. St. Jacques et al. 2011; Russell et al. 2019),

I could assess whether participants could remember the event (as defined by Tulving) exactly as *they* experienced it, with all its details such as the viewpoint from which they saw the event, the position of the objects in that event, and the temporal order in which they saw those objects. This task assessed both spatial and temporal aspects of episodic memory—importantly the latter has not been extensively explored in the stroke literature. Although Tulving defined episodic memory as including the "what", "where", and "when" information, most studies that assess episodic memory do not assess memory for the temporal details of the event, i.e., although they report that they are assessing episodic memory, they most often assess memory for spatial but not temporal order information. The ability to remember temporal information within an event has been mainly tested after a short interval, i.e., seconds to a few minutes, which could be argued to predominantly draw on working memory. The task used in the current study assessed memory for temporal order within an event, following the proposal by Kant (1998) that this is the type of temporal information that is retrieved when re-experiencing an event. Therefore, three aspects of episodic memory (egocentric, allocentric, and temporal information) could be assessed separately by using one paradigm.

5.1.3 Examination of which brain regions are necessary for different elements of episodic memory

By carrying out systematic neuroanatomical analyses of the patients participating in this study, I was able to assess which brain regions might be critical for each feature of episodic memory (egocentric, allocentric, and temporal order information), which was the second aim of the current study.

The first anatomical hypothesis is that posterior parietal lobe regions (particularly the angular and supramarginal gyrus) are important for egocentric aspects of memory, with the prediction being that stroke patients with damage to these regions will be less accurate in

the angle shift condition of the spatio-temporal task and will have a diminished subjective experience of remembering (confidence about their memory judgments) on this task, compared to stroke patients who do not have damage to these regions. The second hypothesis is that medial temporal lobe regions (particularly the hippocampus) are important for allocentric aspects of memory, with the prediction being that patients with a stroke involving these regions will be less accurate in the object position shift condition of the spatio-temporal task than stroke patients who do not have damage to these regions.

The evidence to date suggests that a network of brain regions including the posterior parietal cortex, prefrontal cortex, and hippocampus, are important for memory for temporal order (as discussed in Chapter 1). However, the lesion anatomy associated with impaired memory for the temporal order of non-word stimuli within a single event after a long interval has not been examined. My prediction prior to carrying out this experiment, was that stroke patients with damage to regions that are part of this network, would have impaired performance in the temporal order shift condition of the spatio-temporal task.

Findings from previous neuroimaging, volumetric, and lesion studies suggest that there may be a lack of hemispheric lateralization in memory for spatial and temporal order information (van Asselen, Kessels, Neggers, et al. 2006; van Asselen et al. 2008, 2009; Claessen, Visser-Meily, Jagersma, et al. 2016; van der Ham et al. 2011, 2012; Kant et al. 2017; Kessels, de Haan, et al. 2002; Kessels, Kappelle, et al. 2002; Martin et al. 1996; De Renzi et al. 1977; Schoo et al. 2014; Thaiss and Petrides 2008). Specifically, regarding the ability to recall episodic memories from one's own perspective, which was the main interest of the current study, Russell and colleagues (2019) who used a very similar task to here found that this process: a) recruited both angular gyri (fMRI data in healthy elderly subjects) and b) was impaired in stroke patients with right posterior parietal lobe damage. However, this was a small group of patients and patients with left posterior parietal lobe damage were

not assessed. Studies that have examined only patients with right hemisphere lesions have shown that these patients seem to be impaired in the ability to process changes in spatial perspective (Descloux and Maurer 2020; Passini et al. 2000). Studies that assessed patients with either left or right hemisphere damage have found that both groups are equally impaired in the ability to learn the position of a target in a virtual reality maze which required the use of egocentric navigation strategies (all patients had parietal cortex involvement; Weniger et al. 2009) and in remembering the distance between 3D objects and themselves (egocentric; all patients had frontoparietal involvement; Iachini et al. 2009). In contrast, egocentric neglect seems to be more frequent in patients with right (rather than left) hemisphere damage (Demeyere and Gillebert 2019; Hillis et al. 2005; Kleinman et al. 2007). Adding further support to this account, in healthy subjects, the volume of both left and right posterior parietal regions seems to be correlated with adopting a first-person perspective during autobiographical memory retrieval (Freton et al. 2014).

5.2 Methods

5.2.1 Subjects

This study included 43 patients with a first unilateral cerebral hemispheric stroke (22 in the right hemisphere, 21 in the left hemisphere; Figure 5.1) and 2 healthy elderly subjects (age over 55 years; 1 female). The healthy subjects were tested as pilot participants. I did not include a control group of healthy subjects because patient groups offer controls themselves. Detailed inclusion criteria are listed in section 2.5. This patient sample size is in line with many previous lesion symptom mapping studies (Fellrath and Ptak 2015; Ghaleh et al. 2018; Grajny et al. 2016; Laredo et al. 2018; Liu et al. 2019; Lunven et al. 2015; Machner et al. 2018; Michaelis et al. 2020; Mihulowicz et al. 2014; Pillay et al. 2017; Salazar-López et al. 2016; Skipper-Kallal et al. 2017; Strölin et al. 2017; Timpert et al. 2015; Ubben et al. 2020; Umarova et al. 2016; Vossel and Fink 2016; Weiss et al. 2016; Zündorf

et al. 2014). In order to make sure these subjects were blind to the paradigm, none of them had participated in the pilot phase of the current study nor in the study described in Chapter 4. However, 21 of these subjects had participated in the study described in Chapter 6. This is unlikely to have affected their performance on the tasks of the current chapter because: a) the scenes presented in the spatio-temporal task described here are sufficiently different from those presented in the 4MT, and b) the time between participation in the two studies was at least 7 months. As the main aim of the current study was to explore whether the posterior parietal lobe is involved in recalling episodic memories from one's own perspective, the 43 patients that I recruited were categorized into four groups: patients whose lesion involved the left posterior parietal lobe (N = 9; Figure 5.5A), patients whose left hemisphere lesion did not involve the posterior parietal lobe (N = 12; Figure 5.5B), patients whose lesion involved the right posterior parietal lobe (N = 11; Figure 5.5C), patients whose right hemisphere lesion did not involve the posterior parietal lobe (N = 11; Figure 5.5D). The median age of the 43 stroke patients at the time of testing was 62 years (Interquartile Range [IQR] = 20), the mean age at which patients had left education was 19.5 years (SEM = 0.56), and the median days since stroke (duration between stroke date and date of testing) was 312 (IQR = 208). These demographic factors did not significantly differ between the four lesion groups ($\chi^2(3) = 0.886$, $p = 0.829$, $\eta_p^2 = 0.054$ for age at experiment; $\chi^2(3) = 5.181$, $p = 0.159$, $\eta_p^2 = 0.056$ for age left education; $\chi^2(3) = 4.815$, $p = 0.186$, $\eta_p^2 = 0.047$ for days since stroke; Kruskal-Wallis H Test; Table 5.1).

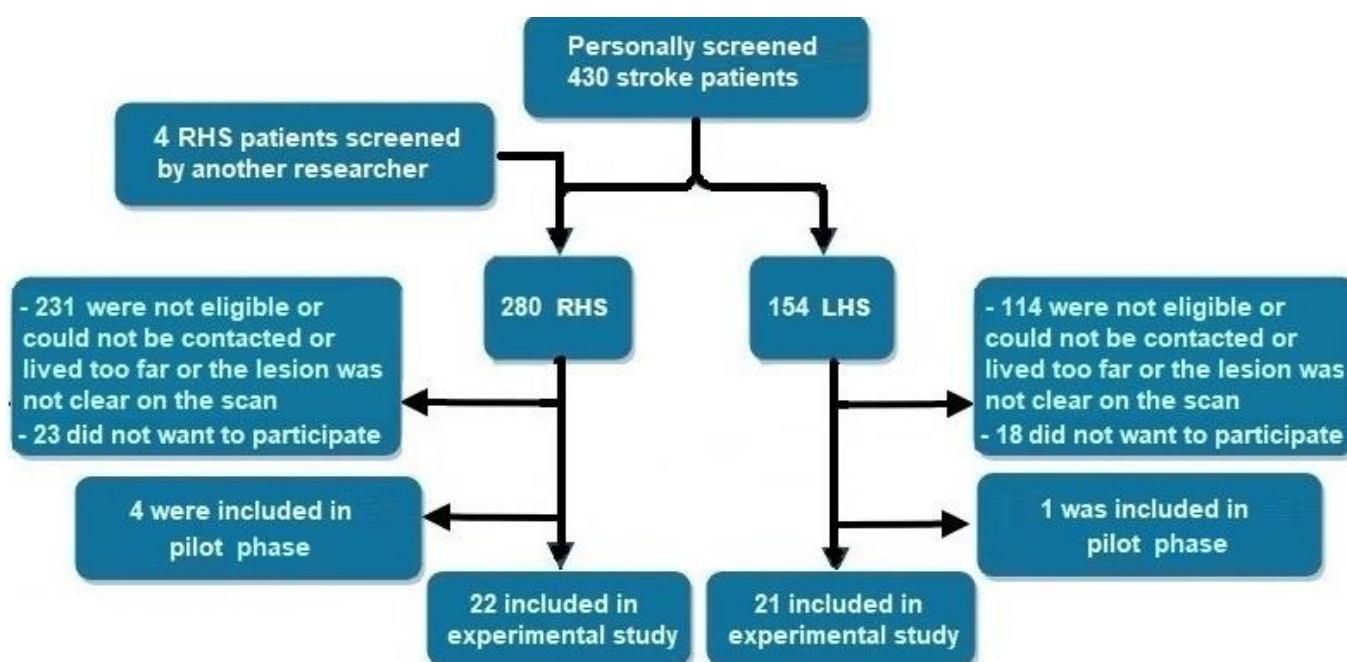


Figure 5.1. Flowchart of patient recruitment

RHS: right hemisphere stroke, LHS: left hemisphere stroke.

Table 5.1. Demographics per lesion group

Note that there is an outlier in the right posterior parietal group; one patient was tested approximately 10 years post-stroke. Mean and SEM (except gender for which the number of females is shown).

	Right posterior parietal lobe involvement	Left posterior parietal lobe involvement	Right hemisphere stroke without posterior parietal lobe involvement	Left hemisphere stroke without posterior parietal lobe involvement
Age (years)	64.72 (3.33)	62.33 (3.52)	68.63 (2.96)	63.83 (3.47)
Age left education (years)	21.40 (1.23)	18.72 (1.01)	19.86 (1.19)	18.04 (0.90)
Gender (N of females)	4	3	3	6
Days since stroke	734 (301)	278 (38)	362 (80)	245 (33)

5.2.2 Spatio-temporal task

In this task, temporal order, allocentric, and egocentric aspects of memory were assessed by presenting common everyday objects on a tray and examining patients' ability to remember the temporal order in which they were presented, their position, and the viewpoint from which they were seen, respectively, by using a two-alternative forced-choice recognition task (Figure 5.2). A recognition (rather than a recall) task was used because: a) one can manipulate features of the scene in order to differentiate egocentric, allocentric, and memory for temporal order deficits, and b) it is relatively easier to perform, making it more accessible for patient populations. A two-alternative forced-choice recognition task was used for two main reasons. Firstly, this paradigm maximizes the number of trials per condition, thereby leading to increased power in the analyses. If 21 scenes are presented at encoding, then a yes/no recognition task (which includes only one scene per trial) could include, for example, 10 trials with old scenes, 4 trials in condition A, 4 trials in condition B, and 3 trials in condition C. On the other hand, a two-alternative forced-choice recognition task could include, for example, 8 trials in condition A, 8 trials in condition B, and 5 trials in condition C. Secondly, a previous study that assessed stroke patients on a two-alternative forced-choice recognition task involving similar conditions to the ones used here, found that patients did not perform at ceiling (Russell et al. 2019).

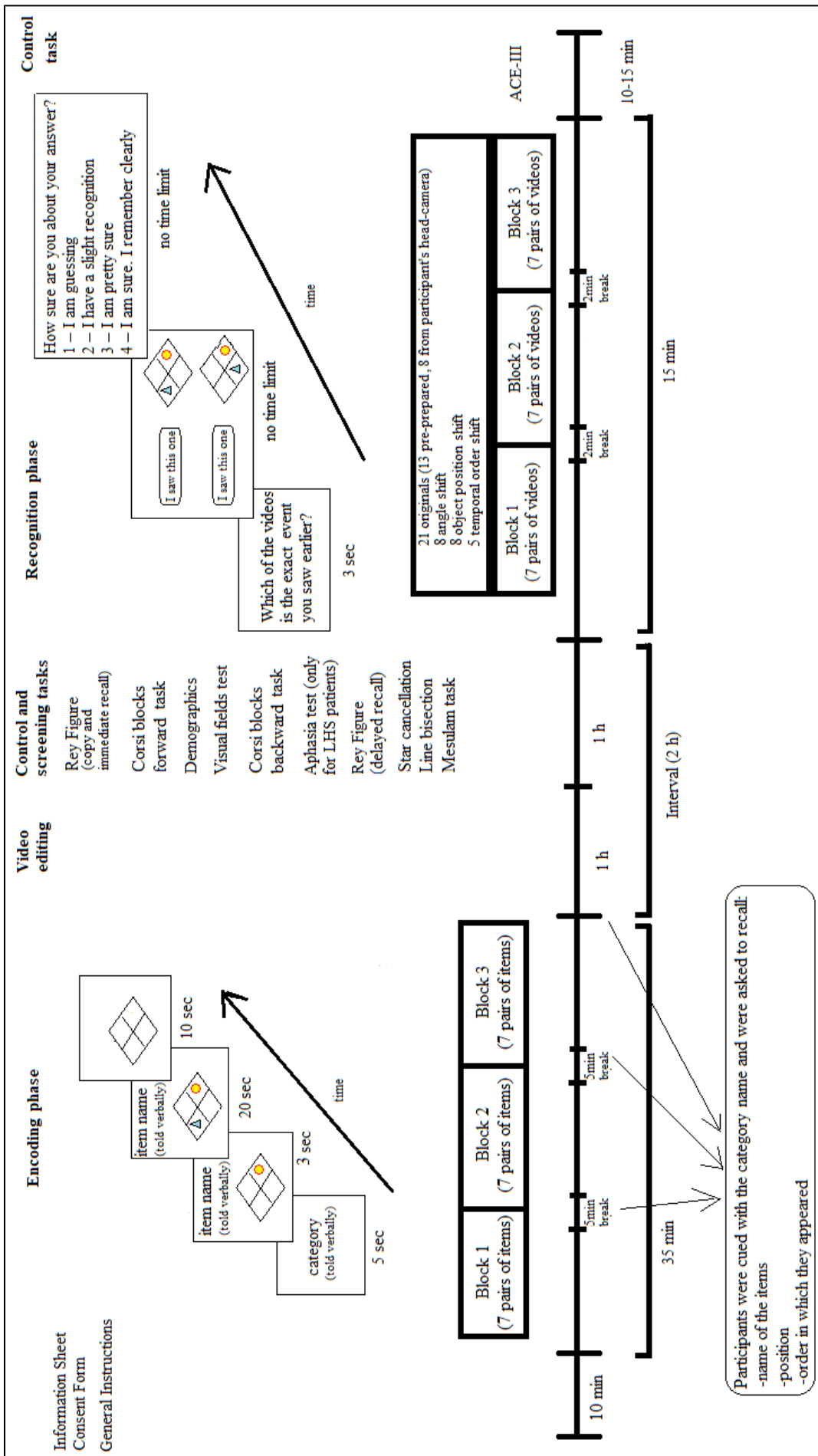


Figure 5.2. Diagram of the whole experiment

Note that in the encoding phase of the spatio-temporal task, participants saw real 3D objects on a real grid (not on a computer or iPad screen). In the recognition phase of the spatio-temporal task they saw the videos on a computer screen. LHS: left hemisphere stroke.

5.2.2.1 Stimuli

The stimuli used in the task were objects from seven different categories: kitchen, vehicles, animals, stationery, food, clothing, and musical instruments (six objects per category). These objects were three-dimensional, original- or toy-sized (big enough to be seen but small enough to fit within one square on the grid), easily nameable, were not human figures, were not completely white, were chosen to be as salient as possible, they could be seen clearly across the different conditions (i.e., original, angle shift, object position shift—see below), did not look completely different when shown from a different angle, and did not belong to more than one category.

The videos used in the recognition phase were edited using VSDC video editing software and an online video editor (www.ezgif.com). Specifically, by converting them to a different video format, adding grey background, and adjusting their duration and dimensions, they were transformed to videos resembling the images in Figure 5.3. The altered videos used in this phase of the task (object position shift, angle shift, temporal order shift) were created prior to the start of the experiment (using the same head-camera which was placed on a different person's head at a very similar height and distance as the participants). Due to the length of time needed for video editing, not all videos from each participant's head-camera could be edited within the 2-hour delay interval. The original video was from the participant's own footage in 3 out of the 8 angle shift trials, in 3 out of the 8 object position shift trials, and in 2 out of the 5 temporal order shift trials, and "pre-prepared" videos were used for the other trials. Exactly which of the participants' head-camera videos were going to be edited, was randomly chosen before starting the experiment. If some of those videos could not be used (e.g. due to excessive head movement), other videos from their head-camera were used. If all videos from their head-camera were unclear, then only pre-prepared videos were used.

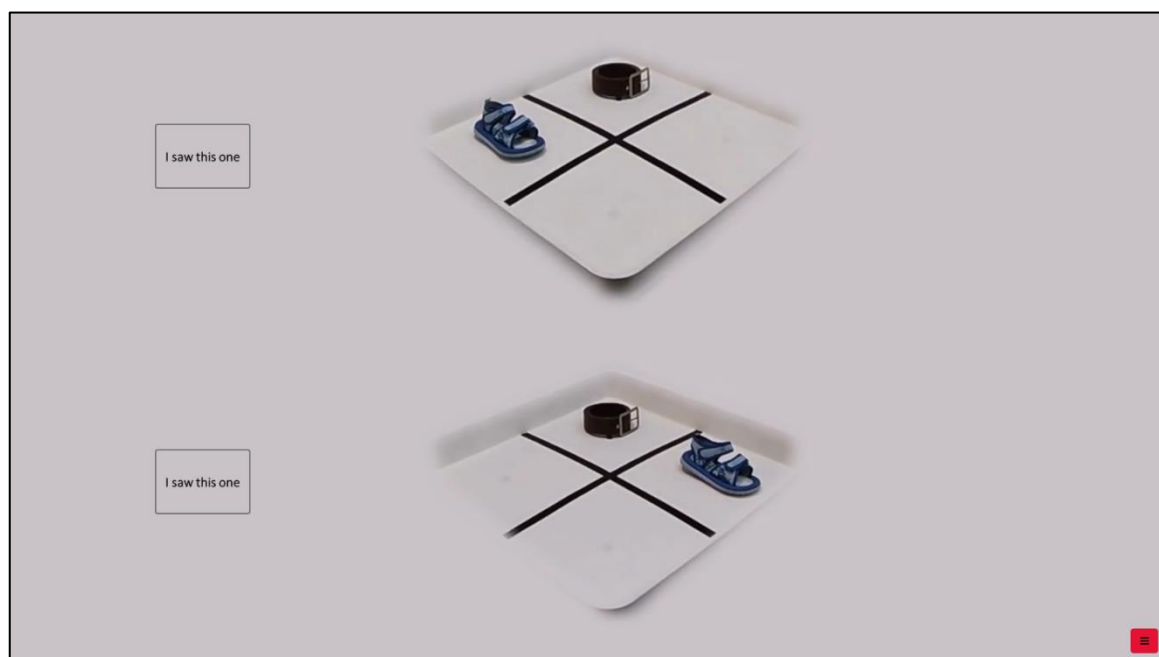


Figure 5.3. Snapshot of the end of a trial in the recognition phase showing the object position shift condition

As can be seen, the background of the videos was removed, i.e., the grid was surrounded by one homogenous grey colour which was the same colour as that from inside the tray.

5.2.2.2 Setting

Testing took place in a quiet windowless room with the same lighting conditions across participants. Each participant sat in front of a table upon which a 60 cm x 60 cm white plastic tray with a 2 x 2 grid was placed (Figure 5.4). In order to prevent participants from using external cues which could aid object-location memory, the grid was surrounded by three opaque white panels, and no numbers were shown within or outside the grid. The distance between the grid and the chair was approximately the same across all participants (about 50 centimetres). An adjustable chair was used to ensure that all participants looked at the grid from the same height. All objects were kept in a box which was not visible to participants. Across all participants and all trials, I wore the same white coat and white gloves while placing the objects, so that they could not discriminate their own from the pre-prepared videos.

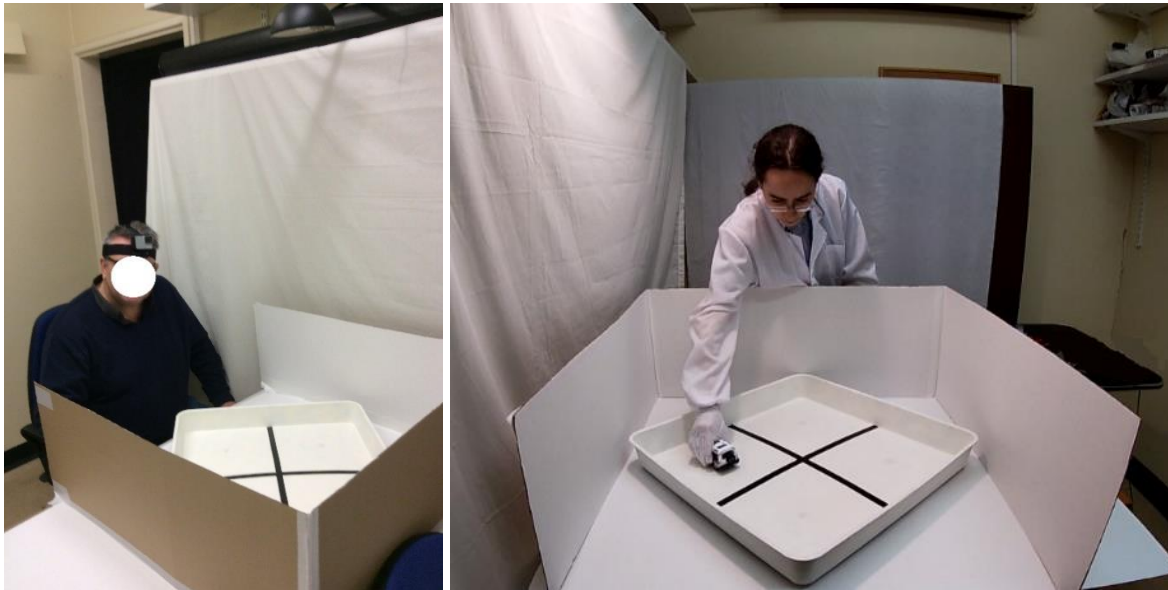


Figure 5.4. *The setting of the encoding phase of the spatio-temporal task*

The left image shows the position at which participants sat during this phase (this subject provided consent for the photo to be taken) and the right image is a snapshot from a participant's head-camera. The objects were placed from directly opposite the participant and the examiner's skin was not visible.

5.2.2.3 Procedure of the encoding phase

Initially, participants were told that they were going to be tested for the scenes presented on the grid and that they should try to remember as much as they could about the scenes and what the scenes looked like. However, they were not told what exact features of the scenes they were going to be tested on, i.e., the encoding of contextual details (e.g. position and temporal order) was incidental. The aim was to examine whether they could remember all these details without being instructed to do so, i.e., how one would normally encode events in real-life situations, which is arguably one of the critical features of episodic memory (Cheke and Clayton 2013; Zentall et al. 2001, 2008). Participants then wore a head-camera (GoPro Hero7 1440p HD Video) which was used to take videos of what the participant was looking at and to highlight that the perspective from which they saw the scenes was important.

At the start of each trial, the tray was shown in its original 0 degrees position, i.e., the horizontal edge of the tray was in front of the participant. Then the tray was turned 45 degrees clockwise or anti-clockwise by the examiner. Participants were first told the name of the object category, and while each of the two objects was sequentially presented in separate squares of the grid, they were told its name. The objects were placed at the exact centre of one of the grid's four squares (which was facilitated by using white Velcro tape), and there was a 3-second interval between the first and second object of each scene. The name of the category was given to participants so that it could be used as a cue during the encoding check, and it could facilitate encoding. The orientation of each object in relation to the bottom horizontal edge of the tray (the edge closest to the participant) was as one would see the object from a canonical position (how one would normally think of it). The objects were removed 20 seconds after both objects had been placed on the grid. The next trial started after a 10-second delay. Each participant saw a total of 21 object pairs (7 categories x 3 object pairs each). These were shown in 3 blocks, with a small break in between each block.

After each encoding block, an encoding check was performed to make sure that participants encoded the scenes correctly. This allowed me to determine whether poor performance in the recognition phase of the task was due to a deficit at encoding or at retrieval. Specifically, by using the category names as verbal cues, participants were asked to recall the name of the objects in each scene, their position, and the order in which they were presented. Any errors were corrected immediately, by telling participants the name of the objects, the order in which they were presented, or pointing to the location in which they were placed (depending on the type of error they made). However, participants were not shown the objects again.

The following aspects of the encoding phase were randomized. First, the square in which the first presented object was placed (out of the 2 objects of the pair) was random. Second, within each encoding block, no two sequential scenes had the first presented object positioned in the same square, there was only one pair of objects per category, half of the pairs were seen from a clockwise rotation of the grid and the other half from an anti-clockwise rotation of the grid (the order of these rotations was allocated randomly within each block), and out of the six possible position combinations of the object pairs only one was shown more than once. Third, across the three encoding blocks, the categories were not shown in the same order, the category that was presented first was not the same, the category that was presented last was not the same, and the order in which there was a clockwise or anti-clockwise rotation of the grid was not the same. Fourth, each participant was randomly allocated to one of three different versions of the encoding phase of the spatio-temporal task. These versions were created in order to control for any differences in the object saliency. The only difference between these versions was the order in which the scenes were presented.

After the encoding phase, there were 10 minutes of rest, to support memory retention (Craig and Dewar 2018). The interval between the encoding and recognition phase of the spatio-temporal task was approximately 2 hours (as used in a previous task assessing episodic memory in stroke patients; Russell et al. 2019). This duration was chosen mainly for the following practical reasons: a) at least 6 minutes were required to edit each video, b) patients would potentially be too fatigued if the overall duration of the experiment was overlong, and c) it was not feasible to bring these patients in on two consecutive days.

5.2.2.4 Procedure of the recognition phase

The recognition phase took place in the same room as the encoding phase and in the presence of the examiner. It was created and hosted in the online Gorilla Experiment Builder (www.gorilla.sc; Anwyl-Irvine et al. 2020).

In this phase, egocentric, allocentric, and memory for temporal order were assessed by using videos of four different conditions: an original, an angle shift, an object position shift, and a temporal order shift condition. In each of the 21 trials, participants were presented with two videos on a 17.3-inch laptop computer screen (Samsung RV720). At the start of each trial, two still images of the start of the videos (an empty grid) were shown—one at the top of the screen and the other at the bottom of the screen. The examiner clicked on each still image so that the videos could be watched in turn (first, the video that was positioned at the top of the screen and then the video that was positioned at the bottom of the screen). One of these videos was always identical to the one that participants saw at encoding (same angle, sequence, and position of objects; some of these were pre-prepared and some were their own), and the other varied according to condition. This alternative video could be either a temporal order shift (the objects were placed on the grid in a different sequential order compared to what participants had seen at encoding; this was used to test memory for temporal order), an angle shift (the angle of the encoded scene had changed by 90 degrees; this was used to test egocentric aspects of memory), or an object position shift (the position of one of the objects was different; this was used to test allocentric aspects of memory). In the object position shift video, the position of only one object was changed rather than shifting the position of both objects to the squares that were previously empty or transposing the position of the two objects. There are two main reasons for not using these alternative scenarios. Firstly, in these scenarios the tray may look as if it is rotated, i.e., resembling the egocentric condition. Secondly, in the second scenario (which we have run before) the object position change is not very salient. It is important to note that I did

not examine the “what” information about each event, for example, object recognition or recall; this was only examined in the encoding check.

Across the 21 pairs of videos, 8 pairs contained one original and one angle shift video, 8 pairs contained one original and one object position shift video, and 5 pairs contained one original and one temporal order shift video. After watching both possibilities, a still of the end of the two videos (two objects on the grid; see Figure 5.3) was present on the screen, and participants were instructed to select the video representing exactly what they saw at encoding. A correct answer would be to select the original video, but not the temporal order shift, object position shift, or angle shift video. The simultaneous presence of both videos on the screen (original and altered) minimised any requirement for mental rotation in the angle shift trials.

Participants then rated how confident they felt about their response (on a scale from 1 to 4, where 4 is the highest confidence). When choosing between the two videos and when providing confidence ratings, participants had unlimited time to provide a verbal response, which was inputted by the examiner. Therefore, the sequence of events in each trial was as follows: the examiner clicked the top video in order to start, when that finished the bottom video was clicked in order to start, and then depending on the verbal response of the participant, the examiner clicked the appropriate response buttons. For this reason, the response time was not used as an outcome measurement. After the completion of the experiment, the examiner provided feedback to the participants.

The following aspects of the recognition phase of the task were randomized. First, in the object position shift condition, the position to which one of the objects moved was random, the object whose position was changed was random (either the object that was positioned first or the object that was positioned second), and if two scenes had the same

pattern of object pair positions in the “original” condition, the position to which the object moved was not the same between these two scenes. Second, the position at which the video of the “original” condition was presented (top or bottom of the laptop screen) was randomly counterbalanced. Third, each participant was randomly allocated to one of three different versions of the recognition phase. The objects and the number of angle shift, object position shift, and temporal order shift conditions were the same across these versions, but the only difference was which type of shift occurred in each scene.

5.2.3 Screening and standard neuropsychological assessment

Screening and standard neuropsychological tasks (described in detail in Chapter 2) were performed either within the 2-hour interval (10 minutes or 60 minutes after the encoding phase) or after the recognition phase of the spatio-temporal task (depending on the preference of each participant). All patients (apart from two left hemisphere stroke patients: one with, and the other without, posterior parietal lobe involvement) opted to perform the screening and standard neuropsychological tasks within the 2-hour interval. The order in which these tasks were administered is shown in Figure 5.2.

Standard neuropsychological tasks were used to examine whether any impairment in the spatio-temporal task was related to any deficits in item recall, visuospatial processing, or visuospatial (working or episodic) memory, rather than specific egocentric, allocentric, or temporal order memory deficits. Visuospatial working memory was assessed using the forward and backward Corsi block task on a 9.7-inch iPad touchscreen using Inquisit 5 software (Draine 2016). All participants performed the Rey-Osterrieth Complex Figure Test (copy, immediate, and delayed recall; Lezak et al. 2012; Osterrieth 1944; Rey 1941) to examine visuospatial memory. The Addenbrooke's Cognitive Examination (ACE-III; Hsieh et al. 2013) was used in order to test for overall level of cognition (however, participants

were not excluded if their score was below cut-off, that is, below 88/100; Noone 2015; So et al. 2018; Takenoshita et al. 2019) and to compare these scores with performance on the spatio-temporal task.

Further assessments were performed in order to ensure that patients did not have aphasia, visual field deficits, or spatial neglect at the time of testing. These were the Sheffield screening test for acquired language disorders (Syder et al. 1993; which was performed only by left hemisphere stroke patients), the star cancellation task from the Behavioural Inattention Test (Wilson et al. 1987), the line bisection (6 lines of different lengths), and the Mesulam shape cancellation task (Mesulam 1985). Standard confrontation was used to ensure that patients did not have visual field deficits.

5.2.4 Pilot phase

The paradigm described above was developed after making multiple adaptations to a pilot paradigm in which I tested 20 subjects (5 healthy young subjects, 10 healthy elderly subjects, 4 right hemisphere stroke patients, and 1 left hemisphere stroke patient). The main adaptations that were made are discussed below.

Importantly, because in the pilot phase stroke patients' performance on the spatio-temporal task was similar to healthy elderly controls, the difficulty was increased from 14 trials to 21 trials. A total of 14 trials was originally chosen for the pilot phase because patients with right posterior parietal lobe stroke were not at ceiling with this number of trials using a similar paradigm (Russell et al. 2019). In the encoding phase, when placing objects on the grid, participants were told the name of each object (rather than telling them just the category name), the white glove was attached to the white coat, and objects were placed from directly opposite the participant (rather than from the right side of the participant). The

reason for the latter change is that when placing the objects from the right in all conditions, the condition that represents an angle shift would not really seem like an angle shift because in the video the participant would be seeing the hand coming from the right. In the encoding check, feedback was provided only if participants did not respond or provided an incorrect response after repeated questioning. For the recognition phase, the pre-prepared videos of all the conditions were created using footage from a real person's head-camera (not tripod videos), because piloting revealed that one could easily detect which were the tripod videos and which videos were from a participant's head-camera (as there was some slight movement in the latter). Also, instead of presenting the videos with full background, they were shown with a blurred background (Figure 5.3), so that participants could not rely on any external cues. At the start of the recognition phase of the spatio-temporal task, participants were not told what types of changes were made to the videos. If participants reported that they did not notice (or were not sure of) the difference between the two videos that were presented on the screen during a trial, they were not allowed to watch those videos for a second time and were not told what the difference was during that trial; instead, those pairs were examined separately after the computerized task had been completed. Following this, (a) participants were asked to report whether they used any strategy in the spatio-temporal task and to describe it, and (b) they performed the ACE-III. The ACE-III was performed at this stage in order to avoid as much as possible any interference with the objects that participants saw in the spatio-temporal task.

5.2.5 Lesion analyses

Voxelwise statistical (voxel- and ROI-based) analyses were performed separately for each hemispheric group. Three atlases were used in the ROI-based analyses for the following main reasons: a) the JHU atlas (Faria et al. 2012) because it contains both grey matter and white matter ROIs, b) the AICHA atlas (Joliot et al. 2015) because it has more granular grey

matter parcellations, and c) the FOX atlas (Fox et al. 2005) because it contains areas of the default mode network which is potentially relevant to the current study. These voxelwise analyses and atlases are discussed in more detail in section 3.3.3.

Additionally, I examined whether patients had damage to posterior parietal lobe regions, by looking at each patient's normalized lesion on the AICHA atlas in MRICron. Even if only a few voxels of their lesion were located in one of these regions, patients were classified as having posterior parietal lobe involvement. Comparisons on demographics and performance on the tasks were conducted between stroke patients with, compared to those without, (left or right) posterior parietal lobe involvement. Further comparisons on performance on the tasks were conducted between stroke patients with, compared to those without, (left or right) angular gyrus or supramarginal gyrus involvement.

5.3 Results

5.3.1 Lesion characteristics

Lesion overlaps of each of the four patient groups were created in order to examine the lesion distribution (Figure 5.5). These lesion overlaps show that there was larger lesion coverage in the right compared to the left hemisphere. All lesions were ischaemic apart from 1 in the right hemisphere stroke group and 3 in the left hemisphere stroke group which were haemorrhagic. Across all patients, the median lesion volume was 2822 voxels (IQR = 29288). A Kruskal-Wallis H Test showed that there was a statistically significant difference in lesion volume between the four lesion groups ($\chi^2(3) = 16.326$, $p = 0.001$, $\eta_p^2 = 0.342$); specifically, the right posterior parietal lobe group had greater lesion volume than every other lesion group (all p 's < 0.012 and Cohen's d 's > 1.383; Mann-Whitney U test).

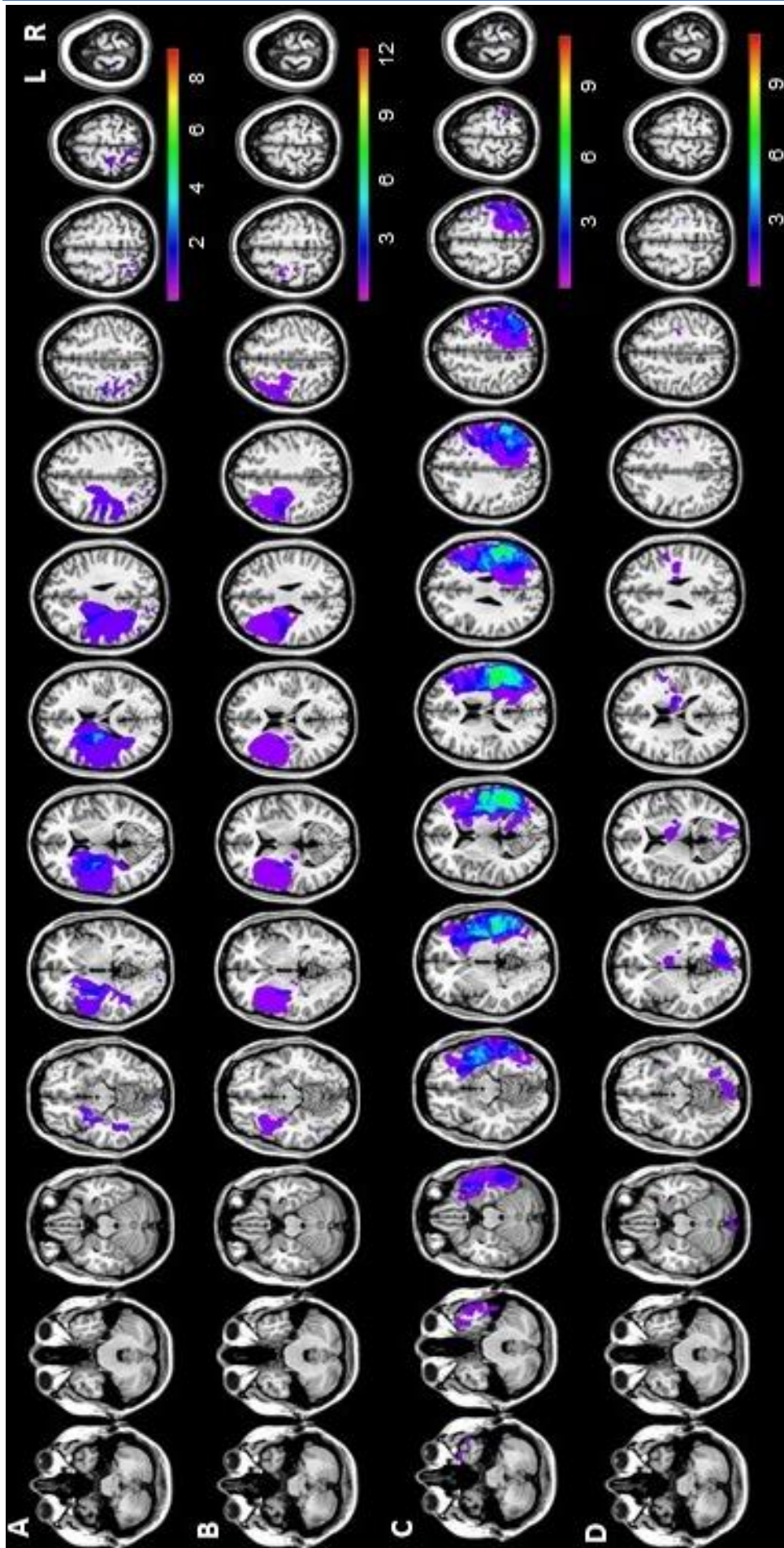


Figure 5.5. Lesion overlaps shown on axial slices of a ch2 brain template

A) Left hemisphere stroke patients with posterior parietal lobe involvement; B) Left hemisphere stroke patients without posterior parietal lobe involvement; C) Right hemisphere stroke patients with posterior parietal lobe involvement; D) Right hemisphere stroke patients without posterior parietal lobe involvement

The colour scales indicate how many individuals had damage to each voxel.

5.3.2 Accuracy in the spatio-temporal task

The performance of the four lesion groups on the spatio-temporal task is shown in Figure 5.6. The performance of the two healthy elderly subjects was: a) 1 temporal order error and 1 object position error in the female participant, and b) 0 errors in the male participant.

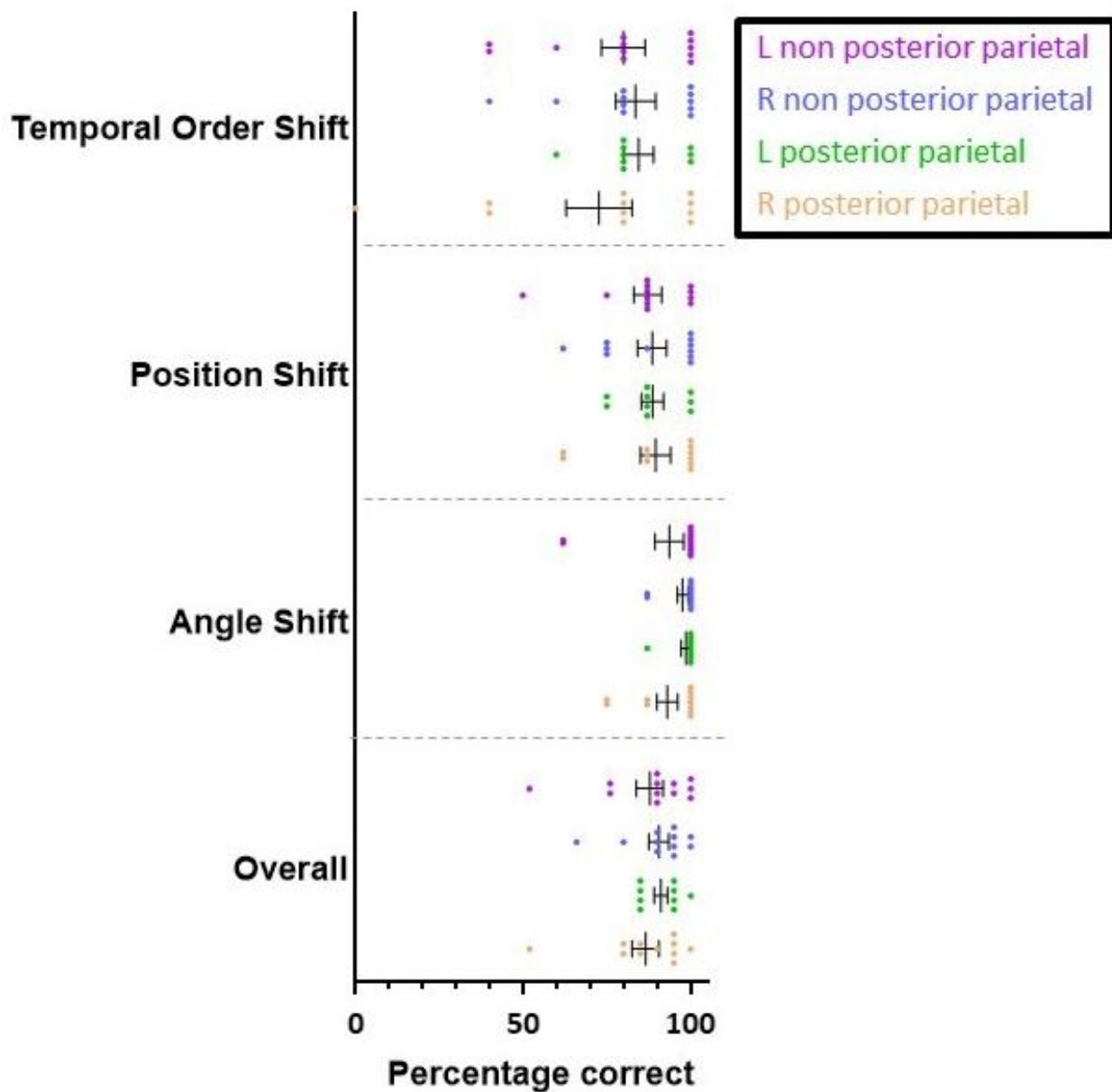


Figure 5.6. Percentage of correct responses in each condition and each lesion group

The black lines represent the mean and SEM.

A 3 (angle shift, temporal order shift, object position shift) x 4 (right posterior parietal, left posterior parietal, right hemisphere stroke without posterior parietal involvement, left hemisphere stroke without posterior parietal involvement) mixed ANOVA was performed to examine whether there is an interaction between types of errors, hemisphere, and posterior parietal lobe involvement. The types of trials were the within-subjects variable, and the lesion group was the between-subjects variable. Because the data (percentage correct scores in the recognition phase) were not normally distributed (Shapiro-Wilk test, $p < 0.002$ in the angle shift trials for each lesion group) even after using multiple different transformations (log, ln, arcsine square root, Box-Cox, exponential, or rank-based inverse transformation), a non-parametric mixed ANOVA was performed using the Aligned Rank Transform procedure in ARTool (Higgins et al. 1990; Wobbrock et al. 2011). There was no significant main effect of lesion location (right posterior parietal, left posterior parietal, right hemisphere stroke without posterior parietal involvement, left hemisphere stroke without posterior parietal involvement) on recognition task scores overall ($F(3, 39) = 0.212, p = 0.888$) and there was no significant interaction between trial types and lesion location (right posterior parietal, left posterior parietal, right hemisphere stroke without posterior parietal involvement, left hemisphere stroke without posterior parietal involvement) in terms of recognition scores ($F(6, 78) = 0.227, p = 0.967$). Pairwise comparisons were performed for the percentage correct in the temporal order condition to confirm that performance did not differ between the four groups (as Figure 5.6 suggests that patients with right posterior parietal lobe involvement made numerically more errors in this condition, compared to the other groups). A Mann-Whitney U test showed that the right posterior parietal lobe group did not perform significantly worse than the other three groups in this condition (all p 's > 0.5).

Although no significant differences were found between the lesion groups, the non-parametric mixed ANOVA did find a significant main effect of trial type on the overall recognition task score ($F(2, 78) = 14.284, p < 0.001$). The Sign test was performed for pairwise

comparisons using the original data (untransformed). This was chosen because of the asymmetrical distribution of the differences between the paired data. There was a significantly higher percentage of correct responses in the object position shift trials compared to the temporal order shift trials ($Z = -2.028$, $p = 0.043$, Cohen's $d = 0.444$), a significantly higher percentage of correct responses in the angle shift trials compared to the temporal order shift trials ($Z = -3.849$, $p < 0.001$, Cohen's $d = 0.911$), and a significantly higher percentage of correct responses in the angle shift trials compared to the object position shift trials ($Z = -3.079$, $p = 0.002$, Cohen's $d = 0.703$). When examining each of the four lesion groups separately, significant differences in correct responses between conditions were found only in the left posterior parietal group (Friedman test: $\chi^2(2) = 6.741$, $p = 0.034$) and the left non-posterior parietal group (Friedman test: $\chi^2(2) = 6.727$, $p = 0.035$). A paired t-test, a Wilcoxon signed-rank test, or a Sign test was then performed depending on whether the assumptions were met. These left hemisphere stroke groups had a significantly higher percentage of correct responses in the angle shift trials compared to the temporal order shift trials (left posterior parietal: $t(8) = -3.137$, $p = 0.014$, Cohen's $d = 1.06$; left non-posterior parietal: $Z = -2.213$, $p = 0.027$, Cohen's $d = 1.661$).

Across the whole group of patients, performance in the encoding check differed depending on the type of information, i.e., object identity, object position, and temporal order (Friedman test: $\chi^2(2) = 19.52$, $p < 0.001$). Post hoc tests revealed that patients were better able to recall the position ($Z = -3.84$, $p < 0.001$, Cohen's $d = 0.908$; Sign test) and temporal order ($Z = -2.43$, $p = 0.015$, Cohen's $d = 0.540$; Sign test) of the objects than the identity of the objects. Performance did not significantly differ between the four lesion groups (all p 's > 0.31 and all $\eta_p^2 < 0.027$ using a Kruskal-Wallis H Test; Table 5.2). Also, performance in the encoding check (overall, object position, and temporal order) was significantly positively correlated with performance in the respective conditions of the recognition phase of the spatio-

temporal task ($r_s = 0.559$, $p < 0.001$ for overall performance; $r_s = 0.412$, $p = 0.006$ for object position; $r_s = 0.348$, $p = 0.022$ for temporal order).

Table 5.2. Percentage correct in the encoding check of the spatio-temporal task

Mean and SEM.

	Right posterior parietal lobe involvement	Left posterior parietal lobe involvement	Right without posterior parietal lobe involvement	Left without posterior parietal lobe involvement
Temporal Order	0.88 (0.04)	0.86 (0.03)	0.91 (0.02)	0.91 (0.02)
Object identity	0.84 (0.05)	0.85 (0.01)	0.90 (0.03)	0.86 (0.03)
Object Position	0.91 (0.05)	0.94 (0.01)	0.92 (0.02)	0.92 (0.02)
Overall	0.88 (0.05)	0.89 (0.01)	0.91 (0.02)	0.89 (0.02)

5.3.2.1 Lesion overlap of patients with the worst performance

As many patients were at, or close to, ceiling on the spatio-temporal task, I looked separately at the lesion characteristics of the few patients who showed most impaired performance (overall or in each condition; Figure 5.7).

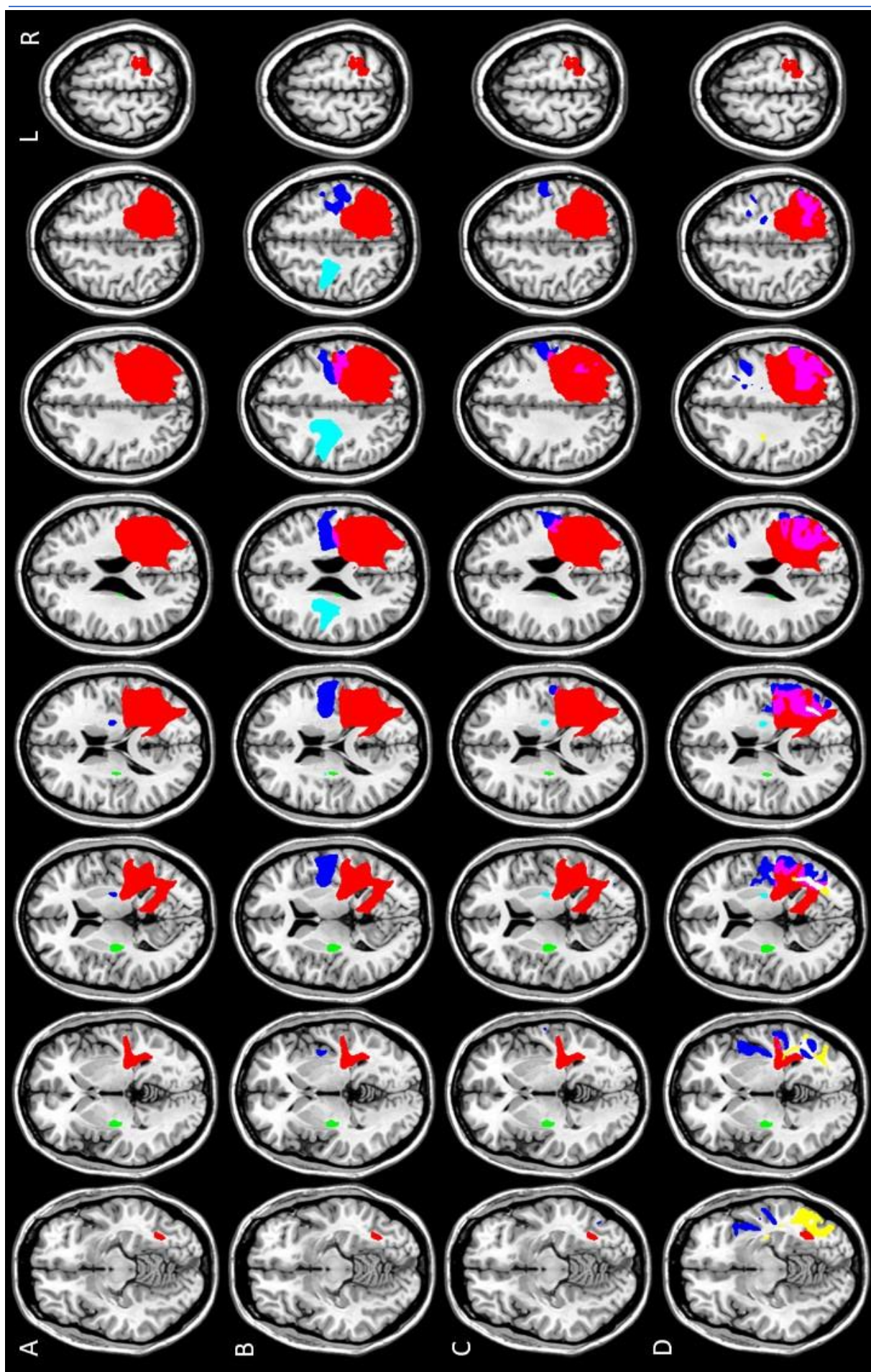


Figure 5.7. Lesions of the worst performers in the recognition phase of the spatio-temporal task

A) 3 patients with the worst OVERALL performance: Red: 10 errors, Green: 10 errors, Blue: 7 errors; B) 4 patients with the worst performance in the ANGLE shift condition: Red: 2 errors, Blue: 2 errors, Turquoise: 3 errors, Green: 3 errors; the region of overlap shown in pink (2 patients) is in the right supramarginal gyrus (MNI x, y, z coordinates: 52, -22, 34, respectively), right postcentral sulcus (46, -26, 44), and right posterior insula (40, -18, 24); C) 4 patients with the worst performance in the OBJECT POSITION shift condition: Red: 3 errors, Blue: 3 errors, Turquoise: 3 errors, Green: 4 errors; the region of overlap shown in pink (2 patients) is in the right supramarginal gyrus (54, -22, 32), right angular gyrus (40, -62, 36), right inferior parietal gyrus (42, -48, 38), right intraparietal sulcus (36, -48, 44), right postcentral sulcus (52, -16, 40), and right posterior insula (48, -16, 24); D) 6 patients with the worst performance in the TEMPORAL ORDER shift condition: Red: 5 errors, Blue: 3 errors, Yellow in the right hemisphere: 3 errors, Turquoise: 3 errors, Green: 3 errors, Yellow in the left hemisphere: 3 errors; the region of overlap of 2 patients is shown in pink; the region of overlap of 3 patients is in the right angular gyrus (38, -58, 18), right middle occipital gyrus (38, -62, 18), and right superior temporal sulcus (40, -56, 16)

5.3.2.2 Voxelwise statistical analyses examining accuracy in the recognition phase of the spatio-temporal task

The neural correlates of memory for egocentric, allocentric, and temporal order information were also examined using voxelwise statistical analyses (method described in section 3.3.3.1). Below, I report the regions that were found to be significantly associated with the behavioural scores in the spatio-temporal task (percentage correct), the atlas in which they were found to be significant, and whether the correlation was positive or negative. A positive z means that the more damage in that ROI the higher the behavioural score, whereas a negative z means that the more damage in that ROI the lower the behavioural score.

5.3.2.2.1 Right hemisphere stroke group

Because the General Linear Model assumes that the data are normally distributed, an arcsine transform for proportional data was performed for the following scores: percentage correct in the angle shift condition, percentage correct in the object position shift condition, percentage

correct in the temporal order shift condition, and percentage correct in total. The transformed scores were inputted into NiiStat and NPM and the following settings were used: 5,000 permutations in NiiStat; 8,000 permutations in NPM; ROI-based analyses using the AICHA (Joliot et al. 2015), the FOX (Fox et al. 2005), and the JHU (Faria et al. 2012) atlas, and voxel-based analyses; threshold: 0.05; in the voxel-based analyses: only include voxels damaged in at least 2 patients; modality: lesion; option: only right hemisphere. The voxel-based analyses (NiiStat and the NPM Brunner-Munzel test) did not identify any significant voxels for any of the above scores. The ROI-based analyses showed that the only significant associations when not regressing for lesion volume were:

- Percentage correct in the temporal order shift condition: lateral parietal cortex (FOX atlas; negative z), intraparietal sulcus (FOX atlas; negative z)
- Percentage correct in total: intraparietal sulcus (FOX atlas; negative z)

When regressing for lesion volume, the only significant association was:

- Percentage correct in the temporal order shift condition: intraparietal sulcus (FOX atlas; negative z)

5.3.2.2.2 Left hemisphere stroke group

As with the right hemisphere group, an arcsine transform for proportional data was performed for the following scores: percentage correct in the angle shift condition, percentage correct in the object position shift condition, percentage correct in the temporal order shift condition, and percentage correct in total. The transformed scores were inputted into NiiStat and NPM and the following settings were used: 5,000 permutations in NiiStat; 8,000 permutations in NPM; ROI-based analyses using the AICHA (Joliot et al. 2015), the FOX (Fox et al. 2005), and the JHU (Faria et al. 2012) atlas, and voxel-based analyses; threshold: 0.05; in the voxel-based

analyses: only include voxels damaged in at least 2 patients; modality: lesion; option: only left hemisphere.

The voxel-based analyses (NiiStat and the NPM Brunner-Munzel test) did not identify any significant voxels for any of the above scores. In the ROI-based analyses, the only significant association was between the percentage correct in the object position shift condition and the intraparietal sulcus (FOX atlas; positive z). This was found both when and when not regressing for lesion volume.

5.3.3 Confidence ratings in the spatio-temporal task

I examined the confidence ratings of each lesion group (Figure 5.8), as previous literature has shown that patients with posterior parietal lobe lesions appear to have impairments in the subjective experience of remembering even when accuracy is intact (Ciaramelli et al. 2017; Davidson et al. 2008; Hower et al. 2014; Simons et al. 2010). Data on confidence for temporal order trials were not collected from 3 patients in the right posterior parietal lobe group.

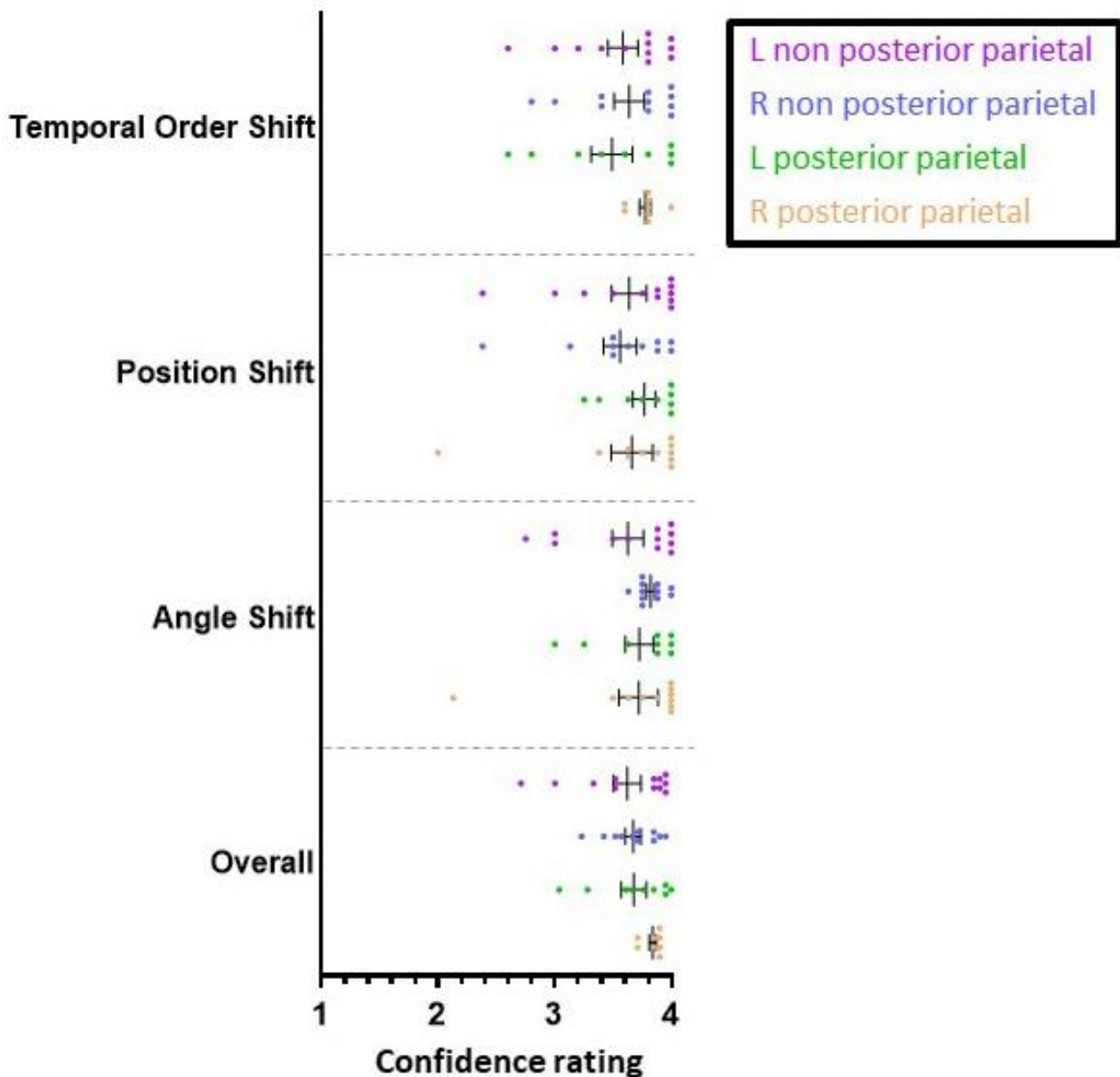


Figure 5.8. Confidence ratings in the recognition task in each condition and each lesion group

The black lines represent the mean and SEM.

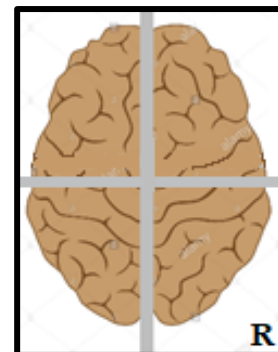
Although it seems that in the angle shift trials, the right posterior parietal group rated their correct responses with slightly lower confidence than the right hemisphere stroke group without posterior parietal lobe involvement, whereas the opposite seems to have occurred in the object position shift trials (Table 5.3), the Kruskal-Wallis H Test showed that there was no

significant difference between the four lesion groups in the confidence ratings given for the correct or wrong responses in each condition (all p 's > 0.098 and all $\eta_p^2 < 0.085$).

Table 5.3. Confidence ratings depending on the condition and on whether their answer was correct or wrong in the four lesion groups

Right hemisphere stroke without posterior parietal lobe involvement (top right of each square); left hemisphere stroke without posterior parietal lobe involvement (top left of each square); left posterior parietal lobe group (bottom left of each square); right posterior parietal lobe group (bottom right of each square).

		Mean Confidence in each lesion group	
Object position shift trials	Correct responses	3.72	3.68
		3.77	3.72
	Wrong responses	2.90	2.43
		3.66	2.73
Angle shift trials	Correct responses	3.67	3.82
		3.74	3.76
	Wrong responses	2.33	3.5
		2	2.9
Temporal order shift trials	Correct responses	3.15	3.58
		3.24	3.89
	Wrong responses	2.85	3.35
		2.41	3.26



Correlation analyses between confidence and percentage correct (Table 5.4), showed that only the right posterior parietal group made accurate judgments about their performance in the object position shift trials, and only the left hemisphere stroke group without posterior parietal involvement seemed to make accurate judgments about their performance in the temporal order condition, angle shift condition, and overall.

Table 5.4. Spearman correlations between the confidence ratings and percentage correct in the recognition phase of the spatio-temporal task in the four lesion groups

The significant correlations are shown in orange. OP: object position shift condition, A: angle shift condition, TO: temporal order shift condition. Right hemisphere stroke group without posterior parietal lobe involvement (top right of each square); left hemisphere stroke group without posterior parietal lobe involvement (top left of each square); left posterior parietal lobe group (bottom left of each square); right posterior parietal lobe group (bottom right of each square).

		Confidence			
		OP	A	TO	overall
% correct	OP	0.514	0.465		
		-0.605	.690*		
	A		0.632*	0.554	
			0.420	0.477	
TO			0.577*	0.094	
			0.531	0.384	
overall				0.741**	0.461
				0.005	-0.013

5.3.3.1 Voxelwise statistical analyses on confidence ratings

Voxelwise statistical analyses were performed in each hemispheric group, to examine whether damage to particular regions or voxels was significantly associated with reduced confidence for correct trials in the spatio-temporal task. Confidence ratings for incorrect trials were not analysed because most patients made no, or very few, errors on this task. The confidence ratings for correct trials (per condition and overall) were not normally distributed when analysed separately for each hemispheric group, and thus the de-skew option was chosen in NiiStat and all other settings were the same as in the voxelwise statistical analyses for memory accuracy.

The voxel- and ROI-based analyses in the right hemisphere stroke group did not find any regions whose damage was significantly associated with reduced confidence in correct trials, neither when or when not regressing for lesion volume. This was also the case in the ROI-based analyses in the left hemisphere stroke group. In contrast, in the voxel-based analyses in the left hemisphere group, damage to the left putamen and left internal and external capsule was significantly associated with lower confidence ratings for correct trials in the: a) angle shift condition (when and when not regressing for lesion volume; Figure 5.9B and Figure 5.9A, respectively), b) object position shift condition (when and when not regressing for lesion volume; Figure 5.9D and Figure 5.9C, respectively), and c) overall (when and when not regressing for lesion volume; Figure 5.9F and Figure 5.9E, respectively).

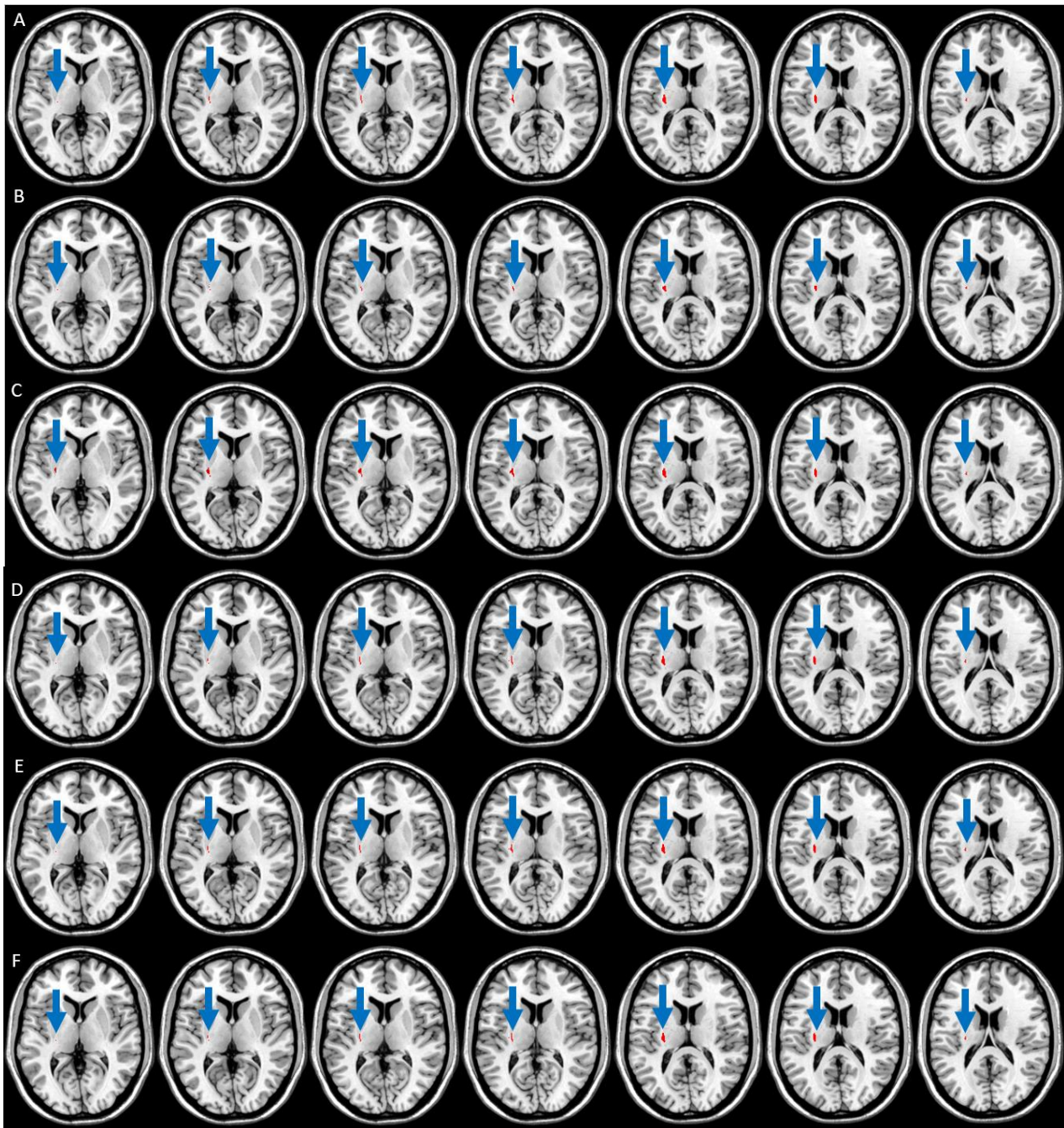


Figure 5.9. Voxels that were significantly associated with confidence for correct trials in the left hemisphere stroke group analysis, shown on axial slices of a ch2 brain template

A) angle shift condition (when not regressing for lesion volume); **B)** angle shift condition (when regressing for lesion volume); **C)** object position shift condition (when not regressing for lesion volume); **D)** object position shift condition (when regressing for lesion volume); **E)** overall (when not regressing for lesion volume); **F)** overall (when regressing for lesion volume)

5.3.4 ACE-III

A Kruskal-Wallis H Test showed that there was no statistically significant difference between the four lesion groups in the ACE-III total score ($\chi^2(3) = 4.281$, $p = 0.233$, $\eta_p^2 = 0.033$).

Performance on the different ACE-III domains is shown in Figure 5.10.

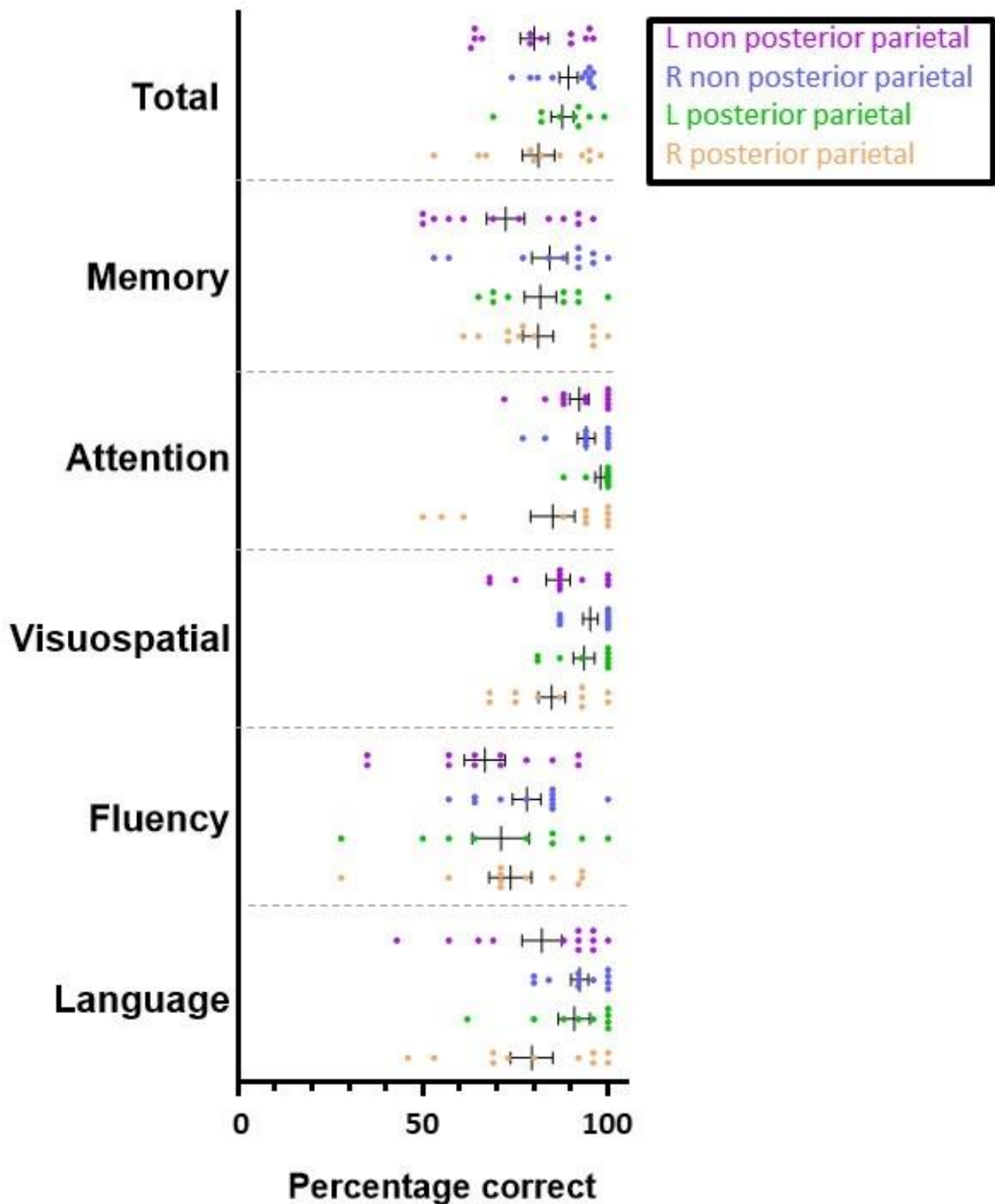


Figure 5.10. Performance of each lesion group on the ACE-III

The black lines represent the mean and SEM.

I also examined whether score differences in the spatio-temporal task were related to differences in any of the ACE-III domains, with the main prediction being that performance on the ACE-III visuospatial and memory domains would be most strongly correlated with performance in the angle shift condition and position shift condition as these conditions were developed to assess visuospatial aspects of episodic memory. As can be seen in Table 5.5, the percentage correct only in these two conditions was significantly correlated with the ACE-III memory or ACE-III visuospatial domain. However, these significant correlations were only found in patient groups with posterior parietal lobe involvement.

Table 5.5. Spearman correlations between the ACE-III and percentage correct in the recognition phase of the spatio-temporal task in the four lesion groups

The significant correlations are shown in orange: $|r_s| = 0.5–0.79$, and red: $|r_s| = 0.8–1$. OP: object position shift condition, A: angle shift condition, TO: temporal order shift condition. Right hemisphere stroke group without posterior parietal lobe involvement (top right of each square); left hemisphere stroke group without posterior parietal lobe involvement (top left of each square); left posterior parietal (bottom left of each square); right posterior parietal (bottom right of each square).

	ACE											
	total		attention		memory		fluency		language		visuospatial	
% correct OP	0.448	0.289	0.415	0.216	0.499	0.368	.630*	-0.032	0.456	0.138	0.333	0.066
	0.476	0.151	-0.317	0.036	.699*	0.231	0.166	0.129	0.214	0.149	0.343	0.069
% correct A	0.326	-0.038	0.170	-0.120	0.065	0.226	0.261	0.000	0.460	0.077	0.373	-0.356
	-0.207	.749**	-0.188	.843**	0.139	0.571	-0.413	0.481	-0.358	.608*	-0.302	.829**
% correct TO	0.369	-0.022	0.324	-0.118	0.316	-0.304	.601*	-0.095	0.270	0.413	0.390	-0.482
	-0.075	0.532	-0.179	0.375	-0.189	0.483	0.000	.716*	-0.039	0.558	0.123	0.255
% correct overall	0.472	0.062	0.328	0.101	0.390	0.088	.677*	-0.183	0.449	0.105	0.403	-0.124
	0.212	.602*	-0.338	0.541	0.374	.603*	-0.005	0.571	0.043	0.515	0.191	0.456

5.3.5 Other control tasks

Performance on the Rey-Osterrieth Complex Figure Test was not statistically different between the four lesion groups ($p > 0.426$ and $\eta_p^2 < 0.058$ for all Rey figure scores shown in Table 5.6; Kruskal-Wallis H). Correlation analyses were performed between percentage of correct responses in the spatio-temporal task and performance on the Rey-Osterrieth Complex Figure Test (placement, presence, accuracy, immediate retention, and delayed retention). Significant correlations were found only in some lesion groups and only between some scores. First, in the right posterior parietal group ($r_s = 0.627$, $p = 0.039$) and left non-posterior parietal group ($r_s = 0.591$, $p = 0.043$), performance in the angle shift condition was significantly correlated with the ability to correctly place the clusters (not the details) of the figure when copying it. When examining the clusters inside the figure separately from those outside the figure, in the right posterior parietal group this correlation was significant for the clusters outside the figure ($r_s = 0.731$, $p = 0.011$) but not those inside the figure ($r_s = 0.253$, $p = 0.454$), whereas the opposite occurred in the left non-posterior parietal group ($r_s = 0.729$, $p = 0.007$ for clusters inside the figure; $r_s = 0.137$, $p = 0.671$ for clusters outside the figure). Second, in the right non-posterior parietal group, performance in the angle shift condition was significantly correlated with immediate presence and accuracy ($r_s = 0.671$, $p = 0.024$), and immediate retention ($r_s = 0.672$, $p = 0.023$). Third, in the left posterior parietal group, overall performance in the spatio-temporal task was significantly correlated with the ability to correctly place the details (not the clusters) of the figure when copying it ($r_s = 0.699$, $p = 0.036$).

According to normative data (Kessels et al. 2000), the Corsi forward total score of the stroke patients as a group was within the 17th percentile. There was no statistically significant difference between the four lesion groups either in this score ($\chi^2(3) = 3.663$, $p = 0.300$, $\eta_p^2 = 0.017$; Kruskal-Wallis H Test), or in the Corsi backward total score ($F(3,39) = 1.49$, $p = 0.232$, $\eta_p^2 = 0.103$; one-way ANOVA; Table 5.6). Across the whole group of patients, correlation

analyses between percentage correct in the recognition phase of the spatio-temporal task and performance on the Corsi block task (total scores) showed that the Corsi forward total score was significantly correlated with percentage correct in the angle shift condition ($r_s = 0.340$, $p = 0.026$), temporal order shift condition ($r_s = 0.334$, $p = 0.028$), and overall ($r_s = 0.366$, $p = 0.016$), while the Corsi backward total score was significantly correlated with percentage correct in the temporal order shift condition ($r_s = 0.327$, $p = 0.033$) and overall ($r_s = 0.359$, $p = 0.018$).

Table 5.6. Performance on the Corsi block task and Rey-Osterrieth Complex Figure Test

All Rey figure scores are T-scores apart from the placement scores which are raw scores. T-score ≤ 39 indicates below average or impaired performance. Mean and SEM.

	Right posterior parietal lobe involvement	Left posterior parietal lobe involvement	Right without posterior parietal lobe involvement	Left without posterior parietal lobe involvement
Corsi block task				
Forward span	4.63 (0.24)	4.55 (0.29)	5.27 (0.19)	4.91 (0.35)
Backward span	4.54 (0.47)	4.88 (0.42)	5.54 (0.20)	4.75 (0.35)
Forward total score	29.1 (3.17)	30.3 (3.71)	38.8 (3.1)	37.5 (4.9)
Backward total score	29.7 (5.39)	33.8 (5.46)	42.6 (3.82)	31.4 (4.43)
Rey-Osterrieth Complex Figure Test				
Copy presence and accuracy	43.45 (4.14)	45.11 (4.88)	46.72 (3.26)	40.58 (2.45)
Immediate presence and accuracy	48.18 (2.84)	46 (3.64)	48.45 (2.85)	45.5 (2.99)
Delayed presence and accuracy	51.18 (2.95)	49.22 (4.41)	49.18 (3.71)	48.33 (3.36)
Immediate retention	51.9 (1.86)	48 (3.2)	49.9 (3.05)	48.41 (2.95)
Delayed retention	52.72 (2.21)	53.33 (1.96)	49.72 (2.68)	53.5 (3.96)
Copy placement	5.9 (0.45)	5.88 (0.48)	6.63 (0.33)	6 (0.27)
Immediate placement	3.9 (0.7)	3.22 (0.9)	4.54 (0.65)	4 (0.59)
Delayed placement	4.27 (0.63)	2.77 (0.64)	4.18 (0.68)	4 (0.66)

5.3.6 Analysis of specific regions of interest

As previous literature has suggested that the angular gyrus and supramarginal gyrus may be the areas in the parietal lobe that are particularly important in episodic memory, egocentric representations and the subjective experience of remembering (Bonnici et al. 2018; Bréchet et al. 2018; Davidson et al. 2008; Hassabis et al. 2007; Humphreys et al. 2020; Irish and Vatansever 2020; St. Jacques, Conway, Lowder, et al. 2011; Russell et al. 2019), I examined whether performance on the spatio-temporal task (percentage correct and confidence ratings) and the control tasks differed between patients with and patients without damage to these regions. The number of patients with supramarginal or angular gyrus involvement was 15 (11 in right hemisphere, 4 in left hemisphere). When looking at this group (patients with unilateral damage to the supramarginal or angular gyrus) compared to patients whose lesion did not involve damage to these regions, performance did not significantly differ on any tasks. When comparing right hemisphere stroke patients with, to those without, supramarginal or angular gyrus involvement, the only significant difference in performance across all tasks was found for the ACE-III visuospatial score (worse score in those with involvement; $U = 29$, $p = 0.031$, Cohen's $d = 0.981$; Mann-Whitney U test; Figure 5.11). When comparing left hemisphere stroke patients with, to those without, supramarginal or angular gyrus involvement the only significant difference in performance across all tasks was found for the ACE-III memory score (worse score in those without involvement; $t(19) = -2.588$, $p < 0.001$, Cohen's $d = 1.438$; parametric t-test; Figure 5.11).

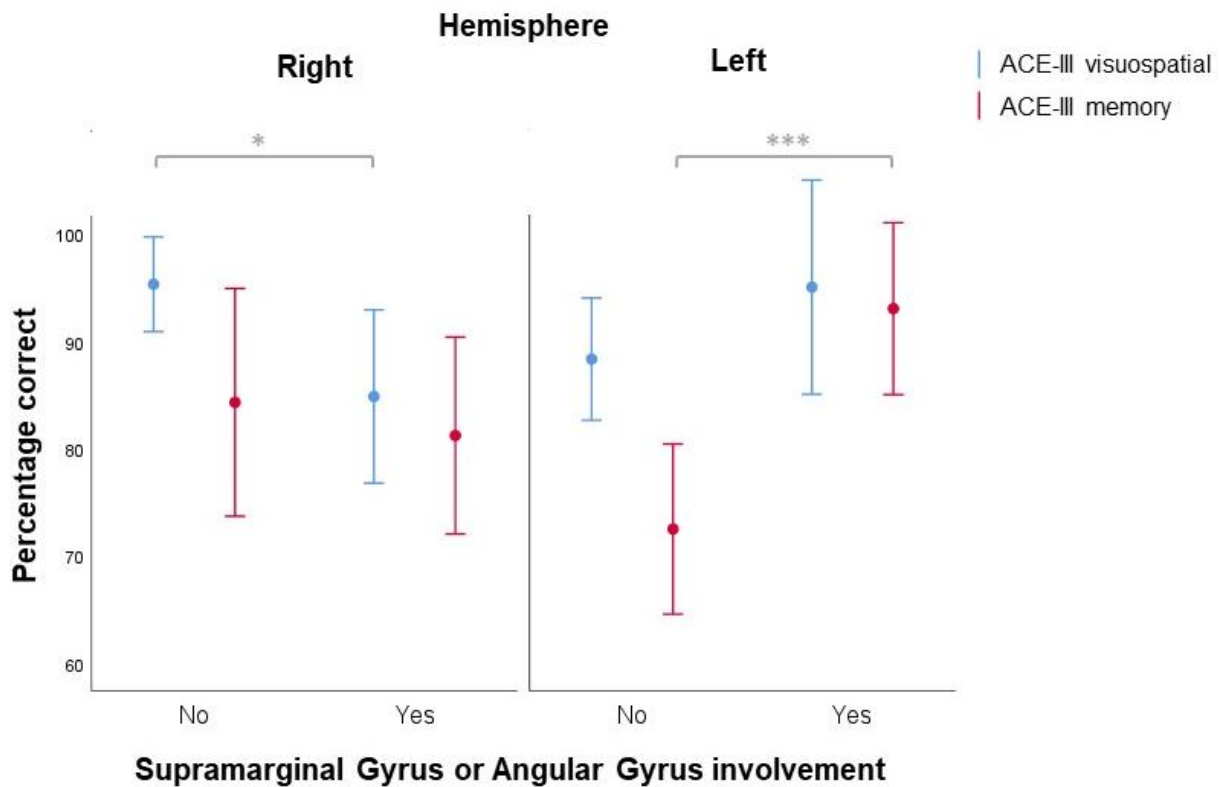


Figure 5.11. Performance on the ACE-III visuospatial and memory domain depending on the presence of damage to the (left or right) supramarginal or angular gyrus

Only the comparisons shown with asterisks were significant. The coloured lines represent the mean and 95% CI.

*: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$.

5.4 Discussion

In this study, a paradigm was developed to assess three contextual elements of episodic memory (egocentric, allocentric and temporal order) using objective and subjective measures in stroke patients, in order to determine the neural correlates of these functions. Most patients made no or a very small number of errors in this paradigm, with the possible reasons being that: a) the use of 21 scenes and a two-alternative forced-choice recognition paradigm may not have been difficult enough (although this was purposefully made more difficult than the version used in the pilot phase), and b) patients were tested quite a long time after their stroke

(median = 312 days) and thus they may have initially had memory problems, but these completely or partly recovered by the time they participated in the experiment.

The relatively small variability in patients' accuracy in the spatio-temporal task is likely one of the main reasons why the results of the voxelwise statistical analyses failed to support most predictions of the current study. The analyses did not show posterior parietal lobe damage to be associated with lower accuracy in the angle shift condition of the spatio-temporal task and with lower confidence in one's memory judgments, or that medial temporal lobe damage is associated with lower accuracy in the object position shift condition. Contrarily, when regressing for lesion volume, damage to the right intraparietal sulcus was associated with poorer accuracy in the temporal order shift condition, and damage to the left intraparietal sulcus was associated with better accuracy in the object position shift condition. Furthermore, damage to the left putamen and left internal and external capsule was associated with lower confidence for the correct trials in the object position shift condition, angle shift condition, and overall. This is consistent with a recent study showing that the integrity of the left external capsule and the posterior limb of the left internal capsule improved after individuals with subjective memory complaints had completed a training program which involved judging their own memory performance (Youn et al. 2019).

The finding that the posterior parietal lobe group did not make significantly more angle shift errors compared to the group without damage to this lobe (even though the first group had significantly larger lesion volume than the latter group), and that no posterior parietal lobe region was significantly associated with the amount of angle shift errors in the voxelwise statistical analyses, is inconsistent with the findings of Russell and colleagues (2019). By using a very similar task, they found that the angular gyrus bilaterally could discriminate whether the perspective from which healthy elderly subjects were viewing a scene, was the same or different to that at encoding (using multi-voxel pattern analysis; MVPA), and in 6 stroke

patients whose lesion involved the right supramarginal gyrus the objective score (but not the subjective score) in the angle shift condition was significantly lower than healthy controls.

Apart from the lack of sensitivity of the task, there are other possible reasons why the right posterior parietal lobe stroke group here did not have such a low objective score in the angle shift condition compared to the right posterior parietal lobe stroke group of Russell and colleagues (2019). Compared to the right posterior parietal lobe group in the current study, their group of patients were on average seven years older and seemed to be more severely affected by the stroke (seven out of the eleven right posterior parietal lobe stroke patients in my study had previously suffered from spatial neglect, whereas in that study all patients had previously suffered from spatial neglect). An additional reason could be that the egocentric condition in their task involved encoding more features, i.e., in their task there were numbers outside the grid and participants changed seating position. Although in both my and their task patients were given the same instructions (i.e., try to remember what the scenes look like to you), by changing seating position they may have intuitively thought that they needed to remember both their position in relation to the objects and the position of the objects in relation to the grid (position 1, 2, 3, or 4). In contrast, in the experiment presented here, participants may have intuitively thought that they would need to remember only the object position in relation to themselves (not relative to the grid) because (a) they did not change seating position and (b) without the numbers, the grid looked the same from whichever 90 degrees angle it was shown. Thus, in Russell and colleagues' (2019) study, participants may have been more likely to form two bindings (object-to-external-space and object-to-self; even though they were not explicitly asked to do this), whereas in my study participants were more likely to form only an object-to-self binding. This suggests that a key role of the right posterior parietal lobe may be the ability to remember the integration of more than two features after a long interval. Specifically, when one is required to remember the object position in relation to the external world, the right posterior parietal lobe seems to be necessary for integrating this

combination with memory for the object position in relation to the self (Russell et al. 2019) and with the “what-when” combination (Berryhill et al. 2007); it does not seem to be essential for remembering the object position in relation to the self when this is the only binding that needs to be remembered (as was shown in my experiment).

A previous study found that during encoding, greater activations in the angular and supramarginal gyrus were related to subsequent recall (objective score) in a task involving object-sound pairs than a task involving object-object pairs (Tibon et al. 2019). This means that the role of these regions may be in the integration of information from different modalities. However, another interpretation of these findings would be that these regions are involved in remembering different types of information (not necessarily different modalities). Functional MRI studies have shown that the angular gyrus is involved in recalling with high precision word-picture pairs (Trelle et al. 2019) and multiple object-related features (Dobbins and Wagner 2005; Richter et al. 2016). Also, angular gyrus disruption or damage can affect visuo-auditory integration (Yazar et al. 2017), and the ability to retrieve multi-featural context (Ciaramelli et al. 2017) and the internal details of autobiographical events (Bonnici et al. 2018). If indeed these regions are involved in remembering different types of information, then the results of Tibon and colleagues (2019) are in line with the following two findings. First, they are in keeping with the fact that I did not find an association between angular or supramarginal gyrus damage and the objective score in the angle shift condition (because this condition did not require the integration of many different types of information). Second, they conform with the finding of Russell and colleagues (2019) who reported that in 6 patients whose lesion involved the right supramarginal gyrus this score was significantly lower than healthy controls (as their angle shift condition involved integrating different types of information, for example, numbers, objects, and viewpoint).

Furthermore, the fact that damage to the left intraparietal sulcus was associated with better performance in the object position shift condition, is in line with the study by Russell and colleagues (2019) who found that damage to posterior parietal lobe regions did not impair performance in this condition.

5.4.1 Temporal order aspects of episodic memory

My finding that the right intraparietal sulcus is important in memory for temporal order is in line with other studies. For example, Berryhill and colleagues (2007) assessed two patients with infarcts involving the posterior parietal lobe bilaterally and found that during recall of autobiographical events, these patients reported significantly fewer “when” internal details (but not significantly fewer “where” internal details). The parietal lobe seems to be involved in sequence processing in many domains. Specifically, the intraparietal sulcus has been found to be involved in processing numerical order, alphabetical order, and horizontal positional order (Attout et al. 2014). The involvement of the parietal lobe in both number processing (Benavides-Varela et al. 2017; Chochon et al. 1999; Dehaene 1996; Kiefer and Dehaene 1997; Pinel et al. 1999) and memory for temporal order reflects the phenomenon that humans have, for many centuries, represented time with numbers (Bruton 1979).

My finding that there was no significant difference between left and right hemisphere groups in their ability to remember the temporal order in which the objects were presented (objective or subjective score), is in line with studies that examined stroke patients, and found that the two hemispheric groups did not significantly differ in their ability to remember the temporal order of the tests of a neuropsychological test battery (Schoo et al. 2014) or in recalling the absolute or relative temporal order of scenes from a route they had watched on a video (Claessen, Visser-Meily, Jagersma, et al. 2016). In contrast, another study showed that left hemisphere stroke patients were impaired in remembering the order of 2D items

immediately after they had been presented on a screen, but patients with right hemisphere stroke were unimpaired (Kant et al. 2017). However, their study did not report whether left hemisphere stroke patients had aphasia. These patients might have been less able (than the right hemisphere stroke patients) to implement a verbal strategy to perform the task successfully.

In the recognition phase of the spatio-temporal task, participants (both healthy subjects and patients, in both the pilot phase and in the experimental study) were more capable of noticing the difference between the original and changed video in the angle shift and object position shift trials, than in the temporal order shift trials, which indicates that spatial (rather than temporal order) information seems to be particularly salient to our perceptual systems. This difference in salience may have been one reason why participants (both healthy subjects and patients, in both the pilot phase and in the experimental study) were better able to remember spatial information (location and viewpoint) than temporal order information in the recognition phase of the spatio-temporal task. The second reason may be that spatial information was available for a longer duration when they encoded each event compared to temporal order information (it took about eight seconds to position the two objects on the grid compared to about twenty seconds which was the duration for which they were left on the grid). The third reason may be that increased temporal order errors may actually reflect impaired ability to remember accurately a high number of details about an event, i.e., independent of what type of information it is. In fact, this may be the reason why damage to the posterior parietal lobe was significantly associated with the percentage of correct responses in the temporal order shift trials, i.e., it may be required to integrate many different details about an event; in the current experiment it happened to be the temporal order details but in a different experiment it may be another type of extra detail about the event.

5.4.2 Control tasks

Many participants seem to have adopted a verbal strategy for remembering the temporal order of the objects in the spatio-temporal task, as indicated by participants' self-reports during the debrief session and the fact that there was a significant positive correlation between some patients' ability to remember the temporal order of the objects and the ACE-III fluency scores. This was likely facilitated by the fact that they were told the name of each object when it was placed on the grid.

The fact that some of the questions in the ACE-III memory domain were assessing semantic memory, could explain why the ACE-III memory domain was strongly correlated with accuracy in the allocentric but not the egocentric condition of the spatio-temporal task. As discussed in Chapter 1 (Figure 1.2), a cognitive map involves allocentric representations and may be related more to semantic than episodic memory. Also, the ACE-III visuospatial domain was very strongly correlated with accuracy in the angle shift but not in the object position shift trials. This suggests that the angle shift condition was tapping more into the ability to make a visuospatial representation of the event, and the object position shift condition more into memory processes. The reason that the significant correlation between the ACE-III visuospatial domain and accuracy in the angle shift condition was driven only by the right posterior parietal lobe group may be because this group showed larger variability in the ACE-III visuospatial domain, as some patients with right posterior parietal lobe involvement may have had constructional apraxia (the number of patients who made more than 2 errors in the visuospatial domain was: 5 in the right posterior parietal lobe group, 0 in the right hemisphere stroke group without posterior parietal lobe involvement, 2 in the left posterior parietal lobe group, 3 in the left hemisphere stroke group without posterior parietal lobe involvement).

Among the three conditions of the spatio-temporal task, only the angle shift condition was significantly correlated with performance on the Rey-Osterrieth Complex Figure Test.

Specifically, the more errors in the angle shift condition, the more information was lost from copy to immediate recall in the Rey-Osterrieth Complex Figure Test and the poorer the ability to draw clusters of the figure in the correct place relative to (a) the overall structure of the figure or (b) oneself, depending on the strategy used. Importantly, the correlation was significant only for clusters (i.e., groups of short lines that form certain shapes), but not for small single line segments. This indicates that poor performance in the angle shift condition may have occurred due to poor ability to remember from one fixation to the next, the position of the 3D items relative to (a) the overall layout of the scene (the grid) or (b) oneself.

In the encoding check, the superior performance in recalling the position and temporal order of the objects (compared to the identity of the objects) may have occurred because for object identity they were asked to *recall* the objects (not a recognition task), for temporal order just by guessing they could be 50% correct, and for object position just by guessing they had a 25% chance of being correct for the first object and 33% for the second object of each scene.

5.4.3 Limitations and future directions

5.4.3.1 Spatio-temporal task

One important limitation of the spatio-temporal task is that it seemed to be too easy, as most patients made very few errors. Furthermore, I cannot be absolutely sure that the different conditions of the task reliably probed the purposed functions (allocentric memory, egocentric memory, and memory for temporal order). As in the previous chapter, in the recognition phase of the task some participants mentioned that they could not remember seeing some objects, which means that their response did not indicate memory for object location or for the viewpoint from which they saw these scenes or for the temporal order in which objects had appeared. It is challenging to create a task that examines purely the egocentric or purely the

allocentric viewpoint, because they are not mutually exclusive processes (Burgess 2006; Neggers et al. 2005, 2006). For example, based on the reports of some participants, it seems that in the object position shift condition participants may have adopted an egocentric strategy, i.e., they may have remembered the objects relative to their own body (the object was on my right or left, close or far from me) and thus this condition may have not examined allocentric aspects of memory. Thus, future studies could adopt an alternative approach (see Figure 5.12) which may be able to more clearly distinguish between egocentric and allocentric memory processes, and would be more difficult e.g. by (a) increasing the total number of scenes, (b) not telling participants to encode the scenes or that they will be tested (thus memories would be incidental and more real-life-like), (c) increasing the duration of the interval, and (d) presenting just one video per trial in the recognition phase.

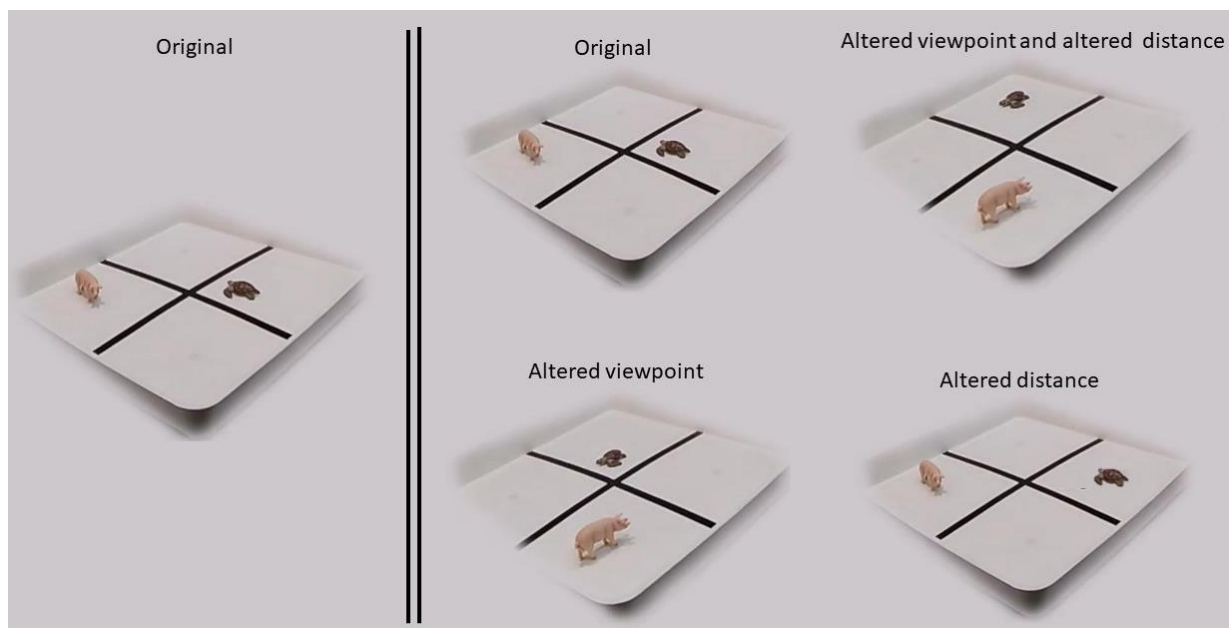


Figure 5.12. Example of a trial from an adapted version of the task that may be more accurate in assessing egocentric and allocentric aspects of memory and may be more difficult

At encoding, participants would be presented with the left image (original) and in the recognition phase they would see one of the four images shown on the right. They would be asked the same questions as a previous study (3D experiment in Kapsetaki et al., under review): “Was this the scene you saw previously irrespective of the viewpoint? If yes, was this scene from your own viewpoint?”

5.4.3.2 Recruitment

One of the limitations of conducting a non-portable and relatively lengthy experiment is that participation is limited. The fact that the spatio-temporal task was set up in the laboratory and the whole experiment lasted about 3 hours (compared to Chapter 6 in which all tasks were portable and lasted in total less than an hour), restricted participation. Patients were less likely to consent if they lived too far and patients in a wheelchair were less willing to come because of difficulties travelling. Due to the low number of participants, some brain regions were not damaged in any patients and other regions were only damaged in very few patients. Thus, the lesion analysis may not have been able to fully explore what is the role of every relevant brain region in memory for egocentric, allocentric, and temporal order information. For example, none of the lesion analyses detected a significant association between task performance and damage to the hippocampus, left angular gyrus, or left supramarginal gyrus, which is probably because very few patients had damage to these regions and most of them had only a few voxels damaged. Only 5 patients had damage involving the left hippocampus (the number of hippocampal voxels damaged in each patient was: 1, 4, 9, 18, 163), 7 patients had damage involving the right hippocampus (the number of hippocampal voxels damaged in each patient was: 1, 3, 3, 23, 46, 69, 106), 1 patient had damage involving the left supramarginal gyrus, and out of the 4 patients who had damage involving the left angular gyrus 3 of them had damage in fewer than 33 angular gyrus voxels. In contrast, 11 of the right hemisphere stroke patients had a lesion involving the angular gyrus and/or supramarginal gyrus, and only 2 of these patients had damage in fewer than 33 voxels in this combined ROI. Although my screening database included 430 patients, it did not include any patients with focal left or right posterior parietal lobe damage who were eligible and willing to participate and thus I was not able to examine what effect would a lesion restricted only to the posterior parietal lobe have on task performance.

In addition, due to time constraints and the likelihood that healthy subjects would be at ceiling, I did not recruit a separate large group of healthy elderly subjects, and thus I was not able to classify patients into impaired and unimpaired groups based on a cut-off value. Thus, future studies should include such a control group.

5.4.3.3 Standard neuropsychological tasks

Some degree of proactive and retroactive interference may have occurred between the spatio-temporal task and the standard neuropsychological tasks. For example, in both the Corsi block task and the spatio-temporal task one needs to encode the position and the temporal order of stimuli. Previously, it has been shown that a memory test in which a pattern was sequentially tapped interfered with performance on the Corsi block task but not with a memory task in which the location of objects was shown simultaneously rather than sequentially (Zimmer et al. 2003). However, in my experiment there may have been only a small degree of interference because the stimuli were very different between these two tasks (2D squares compared to 3D objects). Also, performance on the ACE-III fluency and language domains (specifically in object naming and in the task in which participants are required to name as many animals as possible) may have been facilitated by the fact that 6 animals were presented in the spatio-temporal task and 3 out of the 9 objects shown in the ACE-III were previously presented in the spatio-temporal task.

5.5 Conclusion

To my knowledge, this is the first study to examine memory for egocentric and allocentric representations and for temporal order with objective and subjective measures in stroke patients via a single paradigm approach. I found that damage to the right intraparietal sulcus was associated with poorer ability to remember the temporal order in which the objects had been presented. The voxelwise statistical analyses did not detect any association between

posterior parietal lobe damage and accuracy in the egocentric condition of the spatio-temporal task, or between medial temporal lobe regions and accuracy in the allocentric condition. The small variation in the number of errors in the egocentric and allocentric condition (possibly because the task was not sensitive enough) and the limited number of patients who had lesions involving some of the regions that I had predicted to be associated with these processes (e.g. hippocampus, left angular gyrus, and left supramarginal gyrus), may have been key reasons for not detecting the potentially important role of these regions in these processes. Future studies should recruit a larger number of patients with damage involving these regions and adapt the task to make it more sensitive to deficits in egocentric and allocentric aspects of memory.

6 Spatial Memory following Stroke

6.1 Introduction

Despite the plethora of studies examining memory for spatial information, it is not yet clear which regions in the human brain are critical for this function. Some reasons for this include the fact that the tasks varied in the type of stimuli, the duration of the retention interval, and whether a correct response required only memory for the location of the stimuli or memory for both the location and temporal order of the stimuli. This chapter describes a study employing a validated task, the Four Mountains Test (4MT; Hartley et al. 2007), to examine memory for spatial information in a relatively large group of patients with focal lesions, allowing a more robust neuroanatomical evaluation of this cognitive domain.

6.1.1 Four Mountains Test

The 4MT is a four-alternative forced choice recognition task which tests spatial memory (primarily allocentric memory) for unknown visual scenes (Figure 6.2). Participants are required to encode a scene which includes four mountains of different size and shape, and after a short delay they observe four scenes with four mountains each. These four scenes are shown from a changed viewpoint compared to the scene at encoding. Participants are required to recognize which one has the exact same mountains, in the exact same order around a high mountain, and the distance between these four mountains is exactly the same as the scene at encoding.

There are many reasons why this task may be more suitable, compared to previously used paradigms, for testing memory for spatial information in stroke patients. First, it is more

ecological compared, for example, to the Corsi block task. Second, it is a purely spatial task; that is, a correct response does not require the ability to also remember the temporal order of stimuli, which is the case for the Corsi block task. Third, it is portable (which means that it can be used at the bed-side) and is easy to administer, allowing a large proportion of patients to be tested. Fourth, it is relatively brief; this is important in stroke patients because 31–46% of these patients tend to have deficits in sustained attention (Hyndman and Ashburn 2003; Hyndman et al. 2008; Stapleton et al. 2001), specifically to spatial locations if the damage involves the right posterior parietal cortex (Malhotra et al. 2009), one of the areas that are of particular interest in the current thesis. Fifth, it does not require complex instructions. Sixth, it does not require a manual response, which is required in the Corsi block task, and is therefore not subject to the same confounds relating to mispointing and localization. One further advantage of using this task is that it has been validated in a number of patient populations and there are also available performance data from groups of healthy individuals.

Most stroke studies on spatial memory have not examined item recognition and spatial memory within one paradigm. Stroke studies that have examined each of these separately using one paradigm (e.g. Duarte et al. 2010; van Geldorp, Kessels, and Hendriks 2013; Parkin et al. 1994; Russell et al. 2019; Tu et al. 2014), asked participants to retrieve the stimulus (recall or old/new recognition) and then asked them to retrieve its position (recall or recognition). In the 4MT, the analysis of the types of errors can provide information on whether impaired performance is due to impaired memory for the items, impaired memory for their location, or both (Hartley et al. 2007).

The 4MT was initially developed to detect early spatial memory deficits in Alzheimer's disease (Bird et al. 2010; Hartley et al. 2007). Patients with prodromal Alzheimer's disease tend to have deficits in both egocentric and allocentric navigation, as well as the translation between them (Serino and Riva 2013), and have been found to be impaired in the memory

(but not in the perception) trials of the 4MT (Bird et al. 2010; Moodley et al. 2015). The brain regions that tend to be most affected in prodromal Alzheimer's disease are the hippocampus, parahippocampal gyrus, retrosplenial cortex/posterior cingulate gyrus, precuneus, and parietal cortex (Coughlan et al. 2018; Serra et al. 2010), and these patients seem to have involvement of white matter tracts including the fornix, parahippocampal cingulum, and uncinate fasciculus (O'Dwyer et al. 2011; Sachdev et al. 2013; Zhuang et al. 2013). Thus, results from Alzheimer's disease patients carrying out the 4MT support the account that a network, rather than just one or two specific brain regions, is likely involved in spatial memory. Byrne, Becker and Burgess (2007) have proposed a model of how such a network may function, although this was based mainly on non-human animal literature.

Although the 4MT has already been employed in patients with neurodegenerative diseases, it has rarely been used in individuals with focal lesions, such as stroke patients. To my knowledge, its use has previously been reported in only five stroke patients: two patients with an infarct in the left basal ganglia, two patients with a lacunar infarct in the right basal ganglia (these four patients were tested at least two years post-stroke; Harris et al. 2019) and one patient with a right posterior cerebral artery infarct (Hartley et al. 2007). These patients were examined because they had damage to brain areas that were of particular interest to the researchers carrying out those studies. Specifically, Hartley and colleagues (2007) wanted to assess a small group of patients whose brain damage (due to different aetiologies) involved the hippocampus, in order to examine the role of this region in short-term retention of allocentric topographical information. Harris and colleagues (2019) aimed to examine hippocampal function in Huntington's disease, and the reason that they included stroke patients with damage to the basal ganglia is that control subjects were needed to ensure that impaired performance in patients with Huntington's disease was not due to basal ganglia damage. However, a larger scale study of the 4MT across a heterogeneous group of patients has not previously been carried out.

6.1.2 Potential impact on activities of daily living

Many activities in our daily life appear to rely on our ability to remember the location of stimuli and/or the distance between them. These include the ability to know our location, remember where food, water, and our home are located, and how to navigate to them and imagine future scenarios. Therefore, if stroke patients do have spatial memory deficits, these may greatly impact upon their daily activities, productivity, and quality of life, and would be an added hurdle to the recovery process after stroke.

6.1.3 Lesion laterality

Unlike most previous studies examining spatial memory in stroke patients, this study aimed to assess a large sample of both left and right cerebral hemispheric stroke patients, and ensured that they did not have spatial neglect, visual field defects, or aphasia. Patients with lesions in either hemisphere were assessed because it has been repeatedly shown, mainly in functional neuroimaging studies, that regions in both cerebral hemispheres are involved during spatial memory tasks (Aguirre et al. 1996; Maguire et al. 1998; Moscovitch et al. 1995; Owen et al. 1996), e.g. when participants perform an allocentric spatial memory task (Galati et al. 2010; Rosenbaum et al. 2004; Schmidt et al. 2007; Sulpizio et al. 2013), an egocentric spatial memory task (Russell et al. 2019), or in studies that have assessed both egocentric and allocentric spatial memory (Agarwal et al. 2017; Chen et al. 2014, 2018; Dhindsa et al. 2014; Gomez et al. 2014; Parslow et al. 2004; Postle and D'Esposito 2003; Wallentin et al. 2008), e.g. using the 4MT (Sormaz et al. 2017). There have been some studies examining spatial memory in left hemisphere stroke patients (van Asselen, Kessels, Kappelle, et al. 2006; Kessels, de Haan, et al. 2002; Kessels, Kappelle, et al. 2002; Tu et al. 2014), but usually the sample size in these studies was relatively small and they mostly used the Corsi block task and/or a 2D object-location task. As stated above, the Corsi block task is not a purely spatial task as it requires intact memory for both the location of items and their temporal order.

6.1.4 Methodology used in the current study to examine functional neuroanatomy

Examining functional neuroanatomy by assessing stroke patients is not without its pitfalls. As discussed in Chapter 3, diaschisis, which is not detectable with conventional imaging methods, can occur in the early stages, and neural plasticity is likely to be occurring in the more chronic stage, potentially distorting the link between lesion location and behavioural performance. However, it does have advantages over other conditions such as traumatic brain injury, neurodegenerative diseases, and tumours. Compared to these conditions, stroke tends to cause relatively more focal damage. Also, compared to tumours and neurodegenerative diseases, a stroke causes sudden (rather than progressive) change in brain function, which suggests that relatively less plasticity may be present in stroke patients.

The inclusion of a large number of patients allows the use of voxelwise statistical lesion analyses and lesion network mapping. These neuroanatomical methods use a voxelwise approach, allow the use of continuous behavioural variables, and are free of *a priori* assumptions about lesion-behaviour relationships. Thus, they are potentially more powerful and accurate compared to methods that tend to be used in smaller patient samples, such as lesion subtraction analysis.

6.2 Aims, hypotheses, and predictions

The aims of this study are to:

- use the 4MT to examine whether stroke patients have impaired spatial memory
- examine whether performance on the 4MT is associated with daily function
- compare spatial memory between stroke patients and data from other patient groups who are known to have spatial memory deficits, specifically patients with Alzheimer's disease

- use the 4MT to examine which brain regions are critical for memory for spatial information (egocentric and allocentric) using voxelwise lesion analyses (descriptive and statistical) and lesion network mapping

The hypotheses are that:

- a network of brain regions including the hippocampus, parahippocampal gyrus, retrosplenial cortex, and posterior parietal cortex plays a crucial role in spatial memory
- because many human functions rely on these brain regions, intact spatial memory is essential for performing many of our daily life activities

The predictions are that:

- compared to healthy age-matched controls, both a group of right hemisphere stroke patients and a group of left hemisphere stroke patients will show impaired performance on the 4MT
- stroke patients whose lesion involves damage to the hippocampus, parahippocampal gyrus, retrosplenial cortex, or posterior parietal cortex will be impaired on the 4MT
- Alzheimer's disease patients as a group will perform worse than stroke patients on the 4MT, because a patient with Alzheimer's disease is more likely than a stroke patient to have damage to at least one of the four above-mentioned brain regions
- accuracy on the 4MT will be strongly negatively correlated with the modified Rankin Scale (a measure of activities of daily living)

6.3 Methods

6.3.1 Subjects

A total of 112 patients with a first unilateral cerebral hemispheric stroke passed screening and completed the experiment. The recruitment of this large sample was possible due to the

portability of the equipment used (as many patients could be tested on the ward or at their home) and the short duration of the tasks in this study. Of these patients, 59 had a stroke in the right hemisphere (23 females) and 53 had a stroke in the left hemisphere (20 females). The behavioural analyses included all 112 stroke patients, whereas the lesion analyses included 100 stroke patients (50 patients in each hemispheric group). The reasons why 12 patients were excluded from the lesion analyses are that: in 7 patients a lesion was described on the scan report but was not clearly visible for mapping, 3 patients had symptoms suggestive of stroke but no lesion was found on CT (no MRI was performed), 1 patient had symptoms suggestive of stroke but did not have clear evidence of stroke on MRI, 1 patient did not have an acute stroke but a possible stroke many years ago.

This sample size was chosen because I wanted to examine two patient groups with damage to each hemisphere and to maximize power in the analyses. Lesion network mapping is a relatively new technique and the sample sizes used have varied vastly. In previous lesion network mapping studies examining different conditions, the total number of patients with and without the condition of interest was fewer than 50 patients (Boes et al. 2015; Darby et al. 2017; Fischer et al. 2016; Klingbeil et al. 2020; Laganriere et al. 2016; Philippi et al. 2020; Sutterer et al. 2016) or ranged between 73 and 625 patients (Cohen et al. 2019; Corp et al. 2019; Cotovio et al. 2020; Darby, Horn, et al. 2018; Darby, Joutsa, et al. 2018; Fasano et al. 2017; Ferguson et al. 2019; Joutsa et al. 2018, 2019; Padmanabhan et al. 2019; Snider et al. 2020).

All right hemisphere stroke patients were pre-morbidly right-handed apart from three patients who were left-handed and two patients who were ambidextrous. All left hemisphere stroke patients were pre-morbidly right-handed apart from three patients who were left-handed and two patients who were ambidextrous. Further details regarding inclusion criteria are described in section 2.5.1. A Mann-Whitney U test showed that there was a significant

difference in the days since stroke between the left and right hemisphere stroke group ($U = 882$, $p < 0.001$, Cohen's $d = 0.810$; Figure 6.1 and Table 6.1), but no significant difference in age between the two hemispheric groups ($U = 1352$, $p = 0.22$, Cohen's $d = 0.238$; Table 6.1). Further demographic details are shown in Table 6.1.

Comparative data for other groups, including healthy participants, were obtained from previously published studies (Bird et al. 2010; Moodley et al. 2015; Pengas et al. 2010; Wood et al. 2016). A consideration that ought to be made when performing these comparisons is that those four studies used a paper version rather than an electronic version of the 4MT. Although these two versions have not been directly compared previously, comparisons of healthy subjects' results from Moodley and colleagues (2015) and Hartley and Harlow (2012), as well as results of subjects with mild cognitive impairment from Moodley and colleagues (2015) and Power and colleagues (2020) shows that these versions yield similar results.

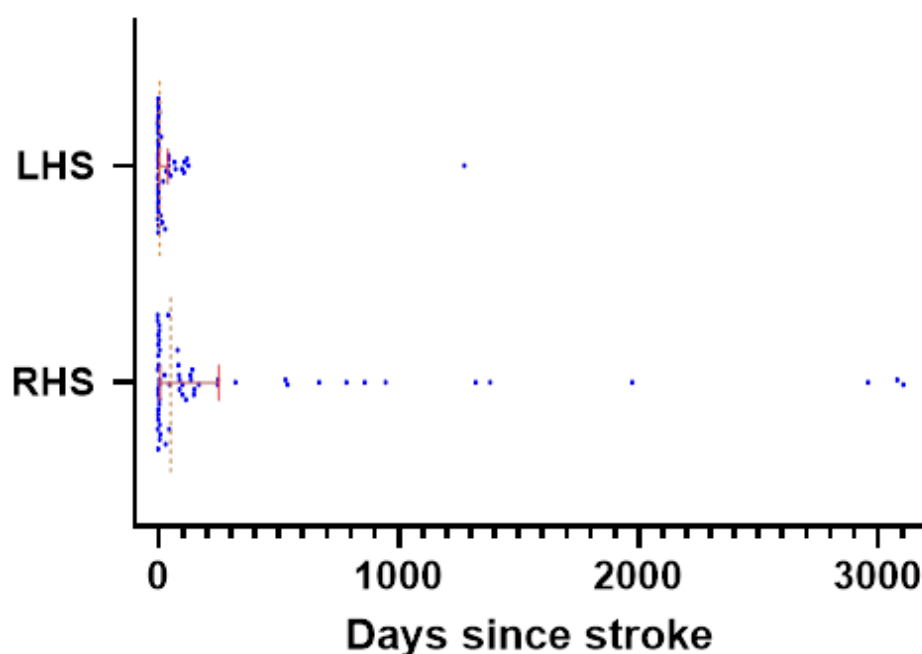


Figure 6.1. Number of days between stroke onset and 4MT assessment in the left and right hemisphere stroke patients

Each blue dot represents one patient. The red lines represent the median and IQR.

Table 6.1. Demographics

Mean and SEM except those with * for which median and IQR are shown because the data were not normally distributed. R: right hemisphere stroke, L: left hemisphere stroke.

	Stroke group	Mean	SEM	Minimum	Maximum
Age (years)	R	69*	23*	18	91
	L	62.09	1.91	30	84
Age left education (years)	R	18*	5.5*	0	30
	L	18*	5*	13	35
Days since stroke	R	50*	245*	0	3109
	L	3*	38*	0	1277

6.3.2 Screening, control, and activities of daily living tasks

Before performing the spatial memory tasks, subjects underwent a screening procedure on the day of testing. This included a visual field test (to exclude hemianopia), a visual acuity test (Jaeger chart; Runge 2000), a visual extinction test, the Sheffield screening test for acquired language disorders (Syder et al. 1993) to exclude aphasia in left hemisphere stroke patients, and 3 tests to exclude spatial neglect: the star cancellation task from the Behavioural Inattention Test (Wilson et al. 1987), the line bisection task (a total of 6 lines of 3 different lengths), and the Mesulam shape cancellation task (Mesulam 1985). These tests (and their specific cut-off scores) are described in section 2.3. It should be noted that individuals who had previously been found to have spatial neglect could still be included in the current study if they showed no evidence of lateralized bias when screened for the current study.

The 4MT was administered via an iPad immediately after the screening tests if the patient fulfilled the criteria described in section 2.5.1. After performing the 4MT, participants also completed the forward Corsi block task (Corsi 1972) using Inquisit 5 software (Draine 2016) on the same iPad on which they had performed the 4MT. Also, representational neglect was assessed using a paradigm similar to the one described by Kaski and colleagues (2016). If patients had representational neglect, they were not excluded. The measure of

representational neglect was the index $\ln \frac{\text{total details reported on the right}}{\text{total details reported on the left}}$ which has been described in a previous study (Bartolomeo et al. 1994). More details about the Corsi block task and the representational neglect task, and the rationale for using them are discussed in sections 2.4.2 and 2.4.3, respectively.

Clinically available modified Rankin Scale scores were used to examine whether there was any correlation between performance on the 4MT and activities of daily living. The modified Rankin Scale score (Farrell et al. 1991) ranges from 0 to 6, where 0 indicates that the patient has no symptoms at all and 6 indicates that the patient is deceased.

6.3.3 Four Mountains Test

The 4MT was presented on a 9.7-inch iPad touchscreen which was placed in front of the participant at a distance of approximately 38 centimetres. Firstly, participants read the instructions and performed a practice session with written and verbal feedback to ensure that they fully understood the task. The practice session included 2 spatial perception trials and then 3 spatial memory trials. In the perception trials, participants were required to look at the top image on the screen and select which of the two bottom images showed the same scene as the top image but from a different angle. The experimental task included 15 trials examining spatial memory. In each trial, an image of a computer-generated landscape with four mountains (left panel in Figure 6.2) was presented for 8 seconds and then a fixation cross was shown for 2 seconds. Then participants were shown four images (the initially viewed landscape but from a rotated viewpoint, which was the correct response, and three “foil” images; right panel in Figure 6.2), and were required to select which of these showed the same place as the previous image they had seen. Participants could respond within a maximum of 30 seconds and received a verbal neutral prompt after 20 seconds. If they had not provided their response within 30 seconds, the next image was shown, and their response

was recorded as “not selected” (it was not inputted as an error). No feedback was provided during the experimental task. All 15 trials were shown within 1 block. The position of the correct image and “foil” images on the iPad screen was randomized from trial to trial. The task was not randomized between participants, that is, each participant performed the exact same task (the trials were in the same order, and the position of the correct and foil images on the screen in each trial were the same from participant to participant).

Note that the weather conditions, lighting, shadows, and colours of the images changed between the image at encoding and the four images at recognition. Thus, subjects could not use any information regarding these features to solve the task. That is, they needed to rely only on the spatial features including the layout, shape, height, and distances between the mountains. In all the images across all trials, there was one mountain that never changed height or shape (this was the tallest mountain among all four mountains) and thus acted as a reference landmark. Spatial and ordinal foils included the exact same four mountains as the sample image (shape and size), but their position was different. In contrast, elemental foils included mountains that were not present in the sample scene (different height or shape; Table 6.2 summarises the differences between these images).

All four images presented at recognition were shown from a different viewpoint compared to the image at encoding, none of them were shown from the exact same angle, and these angle changes differed across trials (the rotation could be up to 90 degrees; Figure 6.3). Although participants could potentially use either an egocentric reference frame or an allocentric reference frame to solve the 4MT, it is more likely that they would use an allocentric reference frame, because the 4MT requires the estimation and memory for distances between the mountains, as all four images at recognition are shown from a different angle compared to the image at encoding. An allocentric frame would require fewer computations, especially in the trials in which the angle change between the image at encoding and the images at

recognition is very large. Although to some extent one could detect an egocentric deficit on the 4MT by examining the degrees of angle change in each foil, one would need many foils with many different degrees of rotation to successfully detect such a deficit.

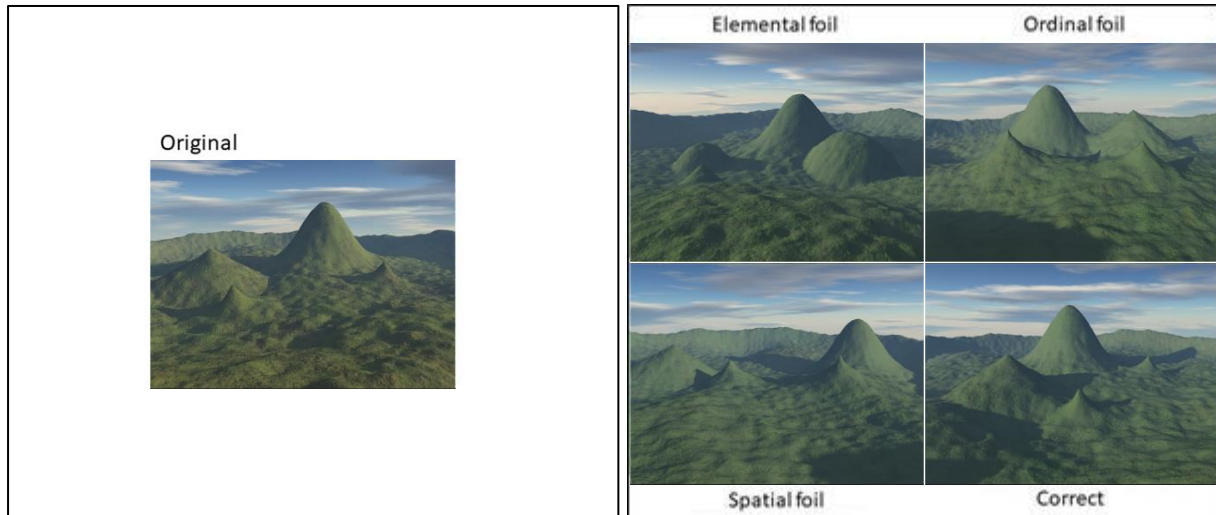


Figure 6.2. Example of a trial in the 4MT (Hartley et al. 2007)

This example was not used in the actual test. Note that no words were shown with the stimuli; these are displayed here solely for illustration purposes.

Table 6.2. Characteristics of the images in the 4MT

	Correct	Elemental foil	Ordinal foil	Spatial foil
Compared to the sample image:				
after changing viewpoint, the distances between the 4 mountains were	same	same	same	different
after changing viewpoint, the position of 3 mountains was	same	same	exchanged (different order around the high mountain)	≥1 of the mountains moved to a new position (but all were shown in the same order around the high mountain)
the shape and/or size of 3 mountains were	same	different	same	same

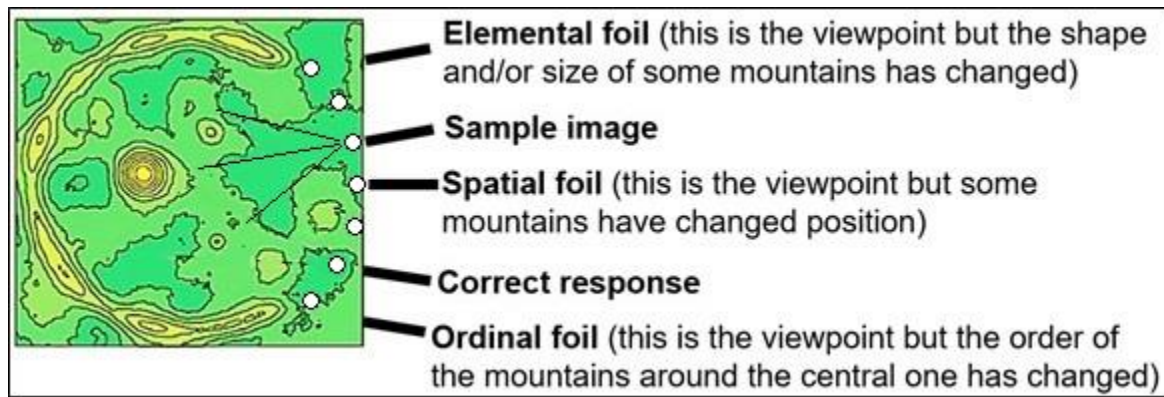


Figure 6.3. A bird's-eye view of the landscape from which the images were taken showing the different viewpoints (white circles)

On the right is an example of the viewpoint of each image in one trial. Each type of foil was not always shown from the same angle across trials. For example, the ordinal foil was not always taken from the bottom viewpoint. Compared to the sample image, the test images can be shown from a clockwise or anti-clockwise rotation. Note that participants did not see this illustration. Illustration adapted from Hartley and colleagues (2007) and Chan and colleagues (2016).

6.3.4 Voxelwise statistical and descriptive analyses

Voxelwise statistical (voxel- and ROI-based) and descriptive analyses were performed for the whole group of patients, but also separately for each hemispheric group. The statistical analyses were performed for the scores listed in Table 6.3, whereas the descriptive analyses were performed only for the total errors on the 4MT (impaired compared to unimpaired group). Five atlases were used in the ROI-based analyses. Four of these atlases include grey matter regions: the Harvard-Oxford atlas (Desikan et al. 2006) and the JHU atlas (Faria et al. 2012) which have quite broad parcellations of the grey matter, the AICHA atlas (Joliot et al. 2015) which has more granular grey matter parcellations, and the FOX atlas (Fox et al. 2005) which contains areas of the default mode network which is potentially relevant to the current study. Atlases that contain white matter ROIs, the JHU atlas (Faria et al. 2012) and the Julich atlas (Zhang et al. 2010), were used to also examine the potential role of white matter tracts on task performance. These atlases and voxelwise analyses are discussed in more detail in section 3.3.3.

Table 6.3. The 4MT scores that were used in the voxelwise statistical analyses and what type of deficit each score may reflect

	Type of memory deficit that the scores may reflect
Total errors	spatial memory and item recognition
Elemental errors, $\frac{\text{Elemental errors}}{\text{Total errors}}$	item recognition
Ordinal errors, $\frac{\text{Ordinal errors}}{\text{Total errors}}$	allocentric memory (specifically remembering the spatial order of the stimuli)
Spatial errors, $\frac{\text{Spatial errors}}{\text{Total errors}}$	allocentric memory (specifically remembering the distances between stimuli)
Spatial+Ordinal errors, $\frac{\text{Spatial+Ordinal errors}}{\text{Total errors}}$	allocentric memory
$\frac{\text{Elemental errors}}{(\text{Ordinal errors}+\text{Spatial errors})}$	item recognition compared to allocentric memory

6.3.5 Lesion network mapping

Next, in collaboration with Dr Paul Bentley, I examined whether the regions found as significant in the 4MT are part of a wider spatial memory network, by relating the lesion-behaviour data of the 4MT to resting-state and task-based fMRI data from previous studies.

Although Ferguson and colleagues (2019) used lesion network mapping to reveal an episodic memory network and its key node, there are a number of key differences between the current study and their study (as discussed in section 3.3.4). First, I ensured the absence of neurological impairments unrelated to memory per se, such as aphasia, spatial neglect, and hemianopia, that may affect performance. Second, lesion delineation was performed directly on each patient's native scan, rather than using a limited number of slices from each patient's scan to draw on a template brain. Third, rather than including patients who each performed very diverse memory tasks (verbal, visual, autobiographical, semantic, and/or temporal order), memory was assessed using the same task across all patients. This allowed me to carry out

a focused evaluation of the neuroanatomy specifically relating to spatial memory. It should be noted that, although the fMRI datasets I used included subjects who were younger than the patients tested here, it has been shown that age differences do not affect the results (Boes et al. 2015; Horn et al. 2017).

6.3.5.1 Using previously published task-based fMRI data

In order to examine whether a network of regions (which are not *a priori* defined by the researcher) is necessary for remembering spatial information, task-based fMRI data from a previous study were related to lesion-behaviour data from the 4MT. Specifically, I assessed whether the total number of errors on the 4MT was significantly higher in patients whose lesions involved (compared to patients whose lesions did not involve) damage to a particular brain network. This network comprises brain regions that in healthy subjects are more activated when performing a similar task to the 4MT (compared to when performing a control task).

To determine which would be the most appropriate fMRI study to use, I searched Web of Science (all databases) for studies that: a) performed fMRI in healthy subjects, b) used tasks that probe the same cognitive domain as the 4MT, c) reported egocentric and allocentric activations, and d) the coordinates were available within the article or in the Neurosynth database (discussed in section 3.3.4). This review of studies led to the shortlisting of six studies (Table 6.4).

Table 6.4. Relevant fMRI studies which could be used in the current analysis

Study	Availability of coordinates	Number of subjects	Delay interval	Do they report egocentric and allocentric activations?
Gomez et al. 2014	http://neurosynth.org/studies/24688464/	18	Did not report any delay between encoding and testing phase	Yes
Dhindsa et al. 2014	http://neurosynth.org/studies/25278860/	15	3 seconds	Yes, but there is no clear distinction between egocentric and allocentric memory in the tasks.
Sulpizio et al. 2013	http://neurosynth.org/studies/23274842/	15	Either a short (2 seconds) or a longer (6 seconds) delay	Yes, but the Neurosynth table only reports areas selective for spatial memory across viewpoint changes; it does not differentiate egocentric and allocentric memory. The differentiation is only presented in a few brain images in the article.
Agarwal et al. 2017	Available in table in full-text article	8	Did not report any delay between the encoding and testing phase	Yes, but comparisons were made between an egocentric and an allocentric task, not each one compared to a control task.
Wallentin et al. 2008	http://neurosynth.org/studies/17915262/	21	2 seconds	Yes, but the coordinates for all the comparisons between the viewpoint conditions and the control tasks are not reported.
Schmidt et al. 2007	Available in table in full-text article	13	5 seconds	Yes, but there is no clear distinction between egocentric and allocentric memory in the tasks.

After evaluation of each of these studies, I chose the coordinates from the study by Gomez and colleagues (2014) as being most relevant. They used a task in which participants were required to encode the position of four to six 3D-like furniture items which they sequentially saw within a virtual reality room. This task contained four conditions and the location of the objects within the room differed across these conditions. In the allocentric condition the room and the furniture were seen from a bird's eye view, in the ERO condition (Egocentric with Rotation Only) these were seen as if the participant was standing at a fixed location in the room and was rotating their head, in the EU condition (Egocentric Updating) these were seen as if the participant was walking in the room, and the control condition

contained a random mixture of very short clips from the above three conditions. The following are some of the comparisons that were made in that study: a) egocentric versus control, b) egocentric versus allocentric, c) allocentric (ALLO) versus control, and d) “egocentric plus allocentric” versus control. In the first two comparisons, I used coordinates from their ERO condition rather than their EU condition, because the latter is more like a navigation task than the 4MT.

Firstly, I converted the Talairach coordinates reported in Gomez and colleagues' (2014) study into MNI coordinates by using the Lancaster transform (icbm2tal; Lancaster et al. 2007) as recommended by Laird and colleagues (2010). This was performed on GingerALE version 2.3.6 (<http://www.brainmap.org/ale/>) which is part of the BrainMap software.

Then, these MNI coordinates were transformed into spheres which could be used as ROIs for the lesion network analysis. The radius of each sphere was 5 millimetres, a standard size that has been used across many studies (Bastiaansen et al. 2011; Calamante et al. 2013; Chaminade et al. 2010; Cools et al. 2005; Gandour et al. 2004; Grabowski et al. 1998; Roberts and Humphreys 2010). To construct the spheres, I used MarsBaR (Brett et al. 2002) which is available in the SPM8 toolbox in MATLAB (http://jpeelle.net/mri/misc/marsbar_roi.html). I then combined the sphere ROIs of each comparison, e.g. one file with sphere ROIs for the “egocentric > allocentric” comparison and another file of sphere ROIs for the “egocentric > control” comparison. This was performed on MarsBaR by following the guidelines provided by <http://marsbar.sourceforge.net/tutorial/define.html>. Then I exported these combined sphere ROIs into NIfTI files (again using MarsBar and following the instructions in the link above) so they could be used as a single file of ROIs. The sphere ROIs that were created are shown in Figure 6.4 and the coordinates on which they are based are shown in Table 6.5.

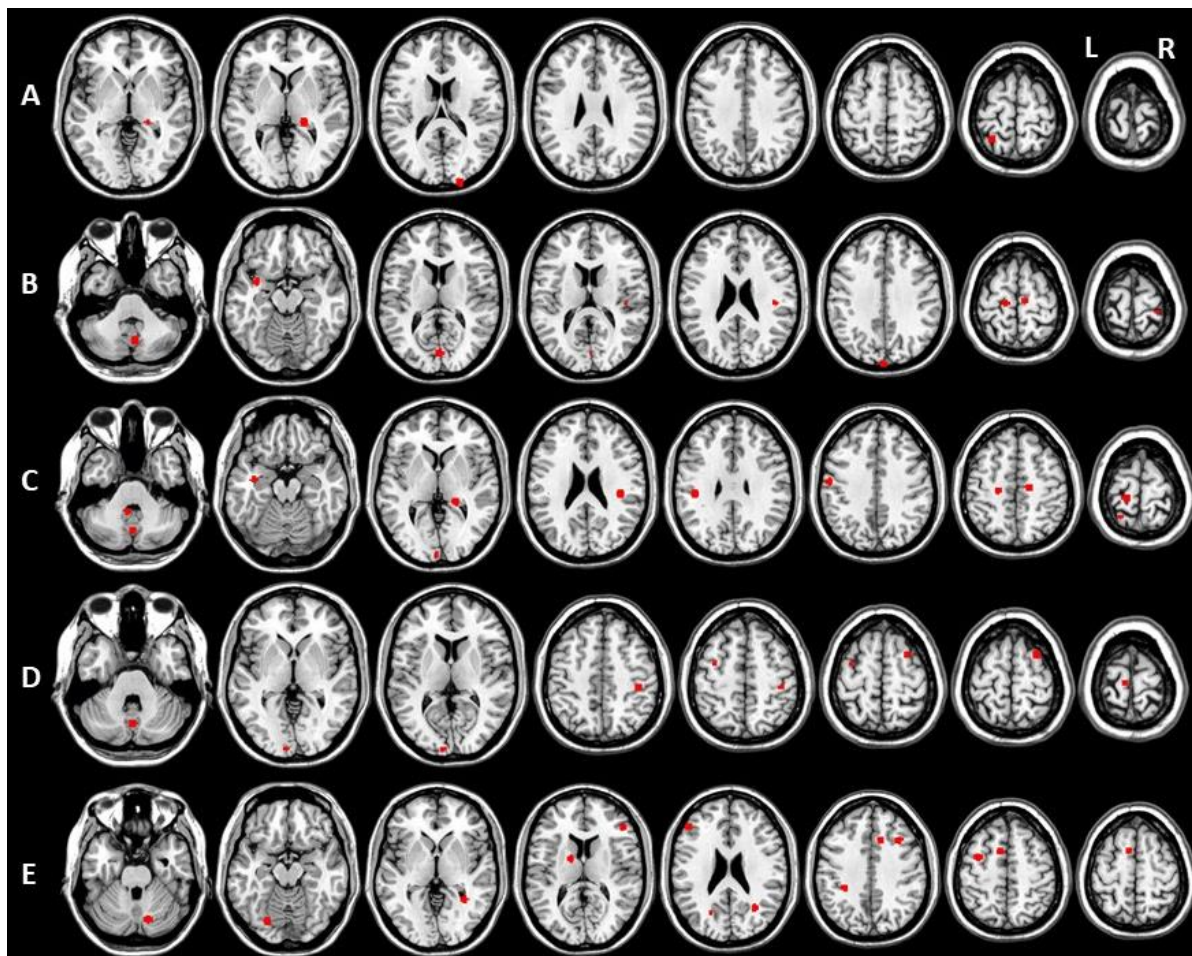


Figure 6.4. Spheres based on the study by Gomez and colleagues (2014)

A) Voxels that showed more activation in the “ERO+EU+allocentric” conditions compared to the control condition; B) Voxels that showed more activation in the allocentric condition compared to the egocentric condition; C) Voxels that showed more activation in the allocentric condition compared to the control condition; D) Voxels that showed more activation in the egocentric condition compared to the control condition; E) Voxels that showed more activation in the egocentric condition compared to the allocentric condition.

These are presented on axial slices of a ch2 brain template available in MRICron.

Table 6.5. The x, y, z coordinates of the spheres shown in Figure 6.4

The sign ">" indicates that these regions were more activated during the condition on the left of ">" than during the condition on the right of ">". R: right; L: left.

Condition	MNI Coordinates			Region
	x	y	z	
"ERO+EU+allocentric" > control	21.03	- 99.4	17.22	R lateral occipital gyrus
	20.69	- 31.99	3.83	R hippocampus
	- 27.1	- 51.12	65.93	L superior parietal gyrus
Egocentric > control	- 8.32	- 97.59	4.09	L calcarine gyrus
	- 33.81	- 2.53	57.87	L precentral sulcus
	40.72	- 28.62	50.22	R postcentral gyrus
	- 7.54	- 23.97	79.72	L paracentral lobule
	27.86	8.2	65.85	R superior frontal gyrus
	0.85	- 68.87	- 33.64	R vermis VIII
Egocentric > allocentric	33.68	- 50.33	2.06	R posterior temporal lobe
	30.72	- 60.28	22.15	R inferior lateral parietal lobe
	- 21.06	- 66.43	28.12	L precuneus cortex
	- 30.74	- 36.6	37.66	L postcentral gyrus
	- 33.87	0.35	54.23	L middle frontal gyrus
	33.96	20.72	38.73	R middle frontal gyrus
	- 47.33	37.06	22.81	L middle frontal gyrus
	11.32	20.95	42.45	R paracingulate gyrus
	- 7.92	7.14	56.47	L superior frontal gyrus
	46.58	35.71	14.62	R inferior frontal sulcus
	13.92	- 73.52	- 26.68	R cerebellar crus I
	- 24.84	- 75.91	- 15.7	L cerebellar area VI
	- 14.92	- 2.26	13.82	L thalamus
Allocentric > egocentric	- 1.41	- 93.29	38.29	L occipital pole
	1.46	- 80.77	11.23	R intracalcarine cortex
	- 34.79	2.21	- 17.66	L anterior temporal lobe
	28.15	- 33.41	80.04	R superior parietal lobule
	43.57	- 22.8	20.46	R inferior parietal lobule
	8.45	- 20.04	63.37	R precentral gyrus
	- 14.17	- 22.9	68.52	L precentral gyrus
	4	- 66.29	- 40.68	R cerebellar area VIII
Allocentric > control	- 1.79	- 97.26	7.31	L calcarine gyrus
	20.7	- 35.18	4.15	R posterior hippocampus
	- 37.97	- 9.39	- 15.34	L insula
	- 23.72	- 53.36	76.18	L superior parietal lobule
	- 43.85	- 25.68	28.96	L inferior parietal lobule
	40.38	- 25.69	24.16	R inferior parietal lobule
	- 55.66	- 12.02	37.89	L central sulcus
	- 17.34	- 31.11	72.75	L paracentral lobule
	- 20.9	- 22.56	49.55	L precentral gyrus
	14.8	- 18.83	53.05	R precentral gyrus
	0.85	- 68.87	- 33.64	R vermis VIII
	- 5.69	- 46.35	- 33.52	L cerebellar area IX

6.3.5.2 Using previously published resting-state fMRI data

Next, I examined whether the areas that were found as significant in the 4MT study are part of a spatial memory network by using a resting-state functional network from a previous study (Yeo et al. 2011). This approach of using resting-state fMRI data has been used in many other lesion network mapping studies (Boes et al. 2015; Fasano et al. 2017; Fischer et al. 2016; Laganiere et al. 2016).

I firstly identified the network of brain regions that are functionally connected to the seed voxel (the mass centre coordinates of whichever ROIs were found to be most significantly associated with the total number of errors on the 4MT in the voxel-lesion symptom mapping analyses) using a publicly available connectome dataset on Neurosynth. This dataset contains resting-state fMRI data from 1,000 healthy right-handed subjects (42.7% males, age range 18–35 years, mean age = 21.3 years; Holmes et al. 2015; Yeo et al. 2011). I downloaded this functional connectivity map (also called network map) from Neurosynth and created a brain mask of it using the SPM8 toolbox in MATLAB (<http://www0.cs.ucl.ac.uk/staff/g.ridgway/masking/>; Ridgway et al. 2009). This was thresholded and an analysis was performed to examine which lesion maps (out of the 100 stroke patients in the current study) did and which did not overlap with this thresholded network map. Hence, I could examine whether lesions that overlap with this network map are associated with more total errors on the 4MT compared to lesions that do not overlap it.

6.4 Results

6.4.1 Behavioural analyses

6.4.1.1 Performance on the 4MT and comparison to previous studies

Impaired performance on the 4MT was defined as having 6 or more total errors. This cut-off was found by calculating the 95% CI of the raw data from three previous studies that examined healthy elderly subjects using the 4MT (87 subjects in total; Bird et al. 2010; Moodley et al. 2015; Pengas et al. 2010; Figure 6.5), which was 4.3–5.16. A parametric t-test showed that there was no significant difference in the number of total errors made between the left and right hemisphere stroke group ($t(110) = 1.353$, $p = 0.179$, Cohen's $d = 0.256$). Compared to healthy age- and education-matched controls from previous studies, both the left and right hemisphere stroke group performed significantly worse. This difference was significant both when the healthy elderly subjects from the three previous studies (Bird et al. 2010; Moodley et al. 2015; Pengas et al. 2010) were combined into one group ($U = 1218$, $p < 0.001$, Cohen's $d = 0.859$ for the comparison with the left hemisphere stroke group; $U = 956$, $p < 0.001$, Cohen's $d = 1.256$ for the comparison with the right hemisphere stroke group; using a Mann-Whitney U test; Figure 6.5) and when they were examined individually (with the exception being the comparison between the healthy elderly Italian group in Moodley and colleagues' 2015 study and the left hemisphere stroke group; blue bars in Figure 6.6). In the left hemisphere stroke group 36 out of 53 patients (67.9%) were impaired, whereas in the right hemisphere stroke group 48 out of 59 patients (81.3%) were impaired (Figure 6.5).

The mean (\pm SEM) number of trials for which no response was provided within the allotted 30 seconds was 0.13 (\pm 0.05) in the right hemisphere stroke group and 0.20 (\pm 0.07) in the left hemisphere stroke group. A Mann-Whitney U test showed that, among the trials for

which a response was provided within the time limit, response times were not significantly different between the two hemispheric groups (in the right hemisphere stroke group the median and IQR was 7.9 and 3.75 seconds, respectively; in the left hemisphere stroke group the median and IQR was 9.28 and 4.85 seconds, respectively; $U = 1239$, $p = 0.059$, Cohen's $d = 0.363$).

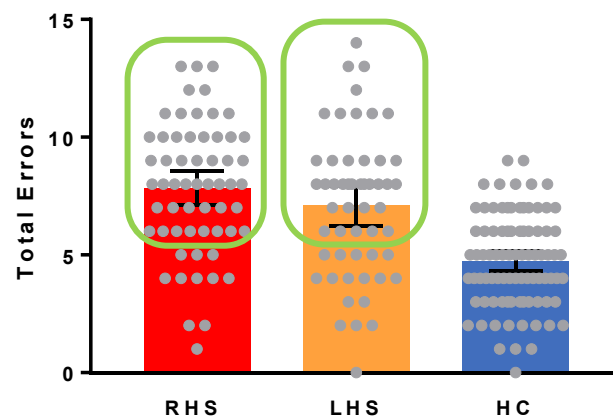


Figure 6.5. Performance of right hemisphere stroke patients (RHS), left hemisphere stroke patients (LHS) and healthy age- and education-matched controls (HC) on the 4MT

The green circles enclose patients who were impaired on the 4MT. Each column and error bar represents the mean and 95% CI, respectively.

Statistical comparisons were performed between the stroke patients from the current study and groups of patients from previous studies that have used the 4MT (Bird et al. 2010; Moodley et al. 2015; Pengas et al. 2010; Wood et al. 2016; raw data from each study; Figure 6.6; Table 6.6), using a two sample t-test or its non-parametric equivalent, a Mann-Whitney U test, if the assumptions of the parametric test were not met. Homogeneity of variance and normality were assessed using Levene's test and the Shapiro-Wilk test, respectively.

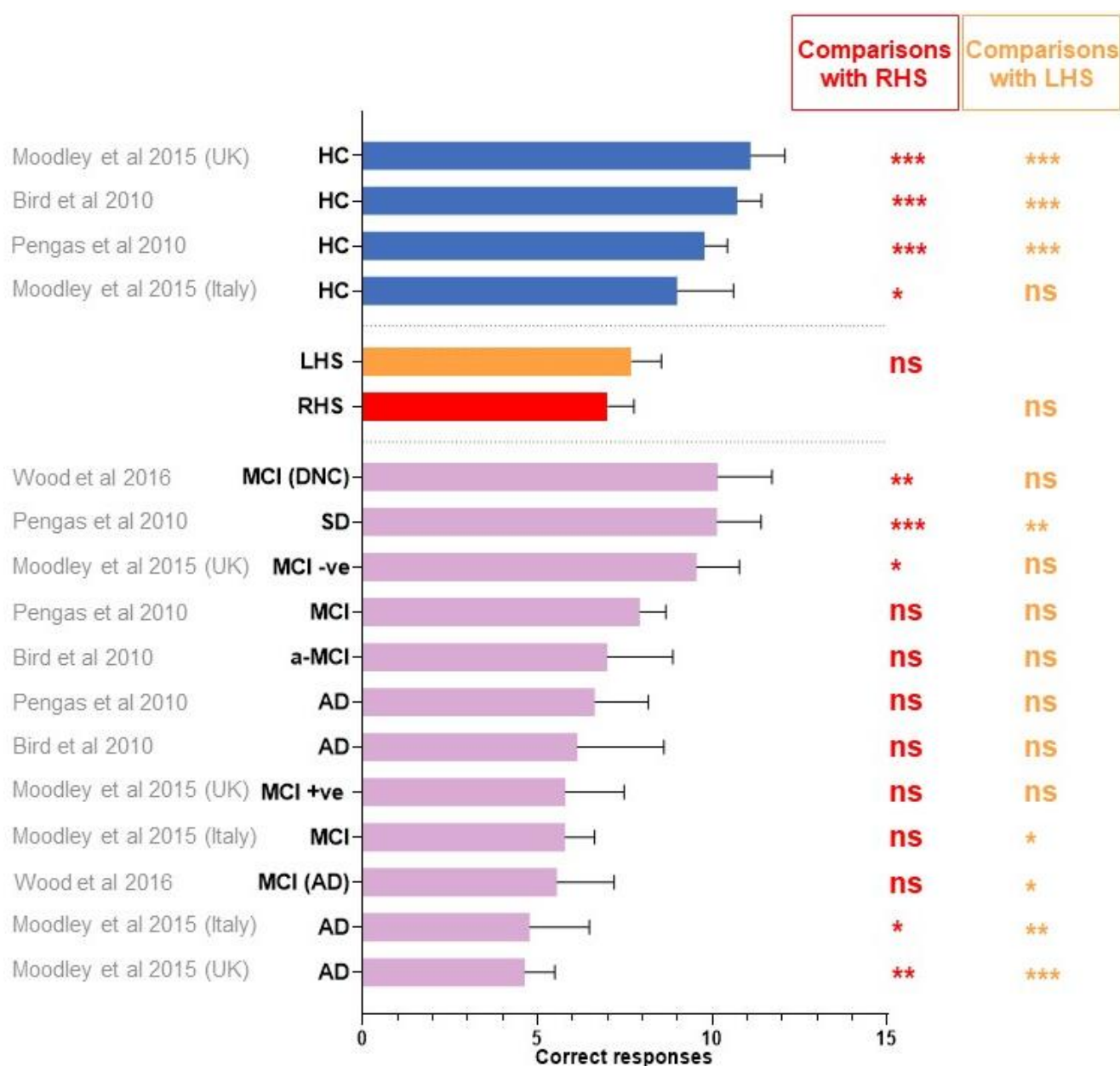


Figure 6.6. Comparisons of 4MT results between stroke patients that took part in the current study (red and orange bars) and subjects from previous studies (age- and education-matched healthy controls in blue; other patient groups in purple).

The red column on the right shows the comparisons between the right hemisphere stroke group and each other individual group. The orange column on the right shows the comparisons between the left hemisphere stroke group and each other individual group. Mean and 95% CI; ns: $p > 0.05$; *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$. HC: age- and education-matched healthy controls; LHS: left hemisphere stroke patients; RHS: right hemisphere stroke patients; MCI: mild cognitive impairment; AD: Alzheimer's disease; MCI (DNC): MCI who did not convert to AD; MCI (AD): MCI who converted to AD; a-MCI: amnesic MCI; MCI +ve: MCI with abnormal levels of amyloid and tau in the cerebrospinal fluid; MCI -ve: MCI with normal levels of amyloid and tau in the cerebrospinal fluid; SD: semantic dementia.

Table 6.6. Characteristics of the studies included in Figure 6.6

The 4MT version that Pengas and colleagues (2010) used has some slight differences to the version I used: a) the delay interval was 3 seconds instead of 2 seconds, and b) the original image was shown for 12 seconds instead of 8 seconds.

Study	Population
Bird et al. 2010	<ul style="list-style-type: none"> • Healthy elderly (N = 25; mean age = 65.3 years, SD = 7.6; the level of education was not reported) • Alzheimer's disease (N = 7) • Amnesic mild cognitive impairment (N = 6)
Moodley et al. 2015	<p>Italy</p> <ul style="list-style-type: none"> • Healthy elderly (N = 10; mean age: 71.3 years, SD = 4.0; mean years of education: 12, SD = 2.8) • Mild cognitive impairment (N = 14) • Alzheimer's disease (N = 9; mean age: 74.3 years, SD = 5.1) <p>UK</p> <ul style="list-style-type: none"> • Mild cognitive impairment (N = 21; 9 biomarker negative, 10 biomarker positive) • Alzheimer's disease (N = 11) • Healthy elderly (N = 20; mean age: 62.6 years, SD = 6.1; mean years of education: 12.1, SD = 1.7)
Pengas et al. 2010	<ul style="list-style-type: none"> • Mild cognitive impairment (N = 28) • Alzheimer's disease (N = 14) • Semantic dementia (N = 14) • Healthy elderly (N = 32; mean age = 68.7 years, SD = 5.6; mean years of education: 13.5, SD = 2.5)
Wood et al. 2016	<ul style="list-style-type: none"> • Mild cognitive impairment who did not convert to Alzheimer's disease (N = 6; mean age: 65.2 years) • Mild cognitive impairment who converted to Alzheimer's disease (N = 9; mean age: 71.7 years)

Critically, only two patients were incorrect on both trials of the spatial perception task of the 4MT (which was included as part of the practice session). There were seven patients who

were incorrect in the first trial of the perception task (the lure in this trial was an elemental foil) but were correct on the second trial of the perception task. All of these seven patients were impaired on the 4MT and three of them had hippocampal damage.

One possible explanation for patients' impaired performance is fatigue and/or reduced sustained attention towards the later trials of the 4MT, rather than a "pure" memory deficit. Conversely, they may have performed better towards the end due to a learning or practice effect (getting better at adopting different viewpoints and spotting the differences between the foils and the correct image). Thus, I compared performance between the first and last seven trials of the 4MT. In the right hemisphere stroke group, there was no significant difference in the number of errors between the first and last seven trials ($Z = -1.268$, $p = 0.205$, Cohen's $d = 0.235$; using a Wilcoxon signed-rank test). On the other hand, in the left hemisphere stroke group there were significantly more errors in the last compared to the first seven trials ($Z = -2.821$, $p = 0.005$, Cohen's $d = 0.57$; using a Wilcoxon signed-rank test). Overall (across the 112 patients), stroke patients made more errors in the last compared to the first seven trials ($Z = -2.866$, $p = 0.004$, Cohen's $d = 0.39$; using a Wilcoxon signed-rank test).

In the right hemisphere stroke group, there were two patients who had visual extinction and another two who had quadrantanopia, but they did not perform significantly worse compared to the other right hemisphere stroke patients. Similarly, although two left hemisphere stroke patients had quadrantanopia, they did not perform significantly worse compared to the other left hemisphere stroke patients.

6.4.1.1.1 Types of errors

There was no significant difference between the number of spatial errors and the number of ordinal errors in either the right or the left hemisphere stroke group ($p > 0.149$ and Cohen's $d < 0.264$ in all comparisons; using a Wilcoxon signed-rank test for the right hemisphere group

and a paired t-test for the left hemisphere group). However, in both the left and right hemispheric group, patients made fewer elemental versus ordinal errors, and fewer elemental versus spatial errors ($p < 0.002$ and Cohen's $d > 0.661$ in all comparisons; using a Wilcoxon signed-rank test; Figure 6.7). A Mann-Whitney U test was used to examine whether there was any significant difference in the types of errors between left and right hemisphere stroke patients (Figure 6.7). Between these two groups there was no significant difference in the number of ordinal errors ($U = 1401.5$, $p = 0.33$, Cohen's $d = 0.179$), spatial errors ($U = 1535.5$, $p = 0.86$, Cohen's $d = 0$), or elemental errors ($U = 1249$, $p = 0.059$, Cohen's $d = 0.351$).

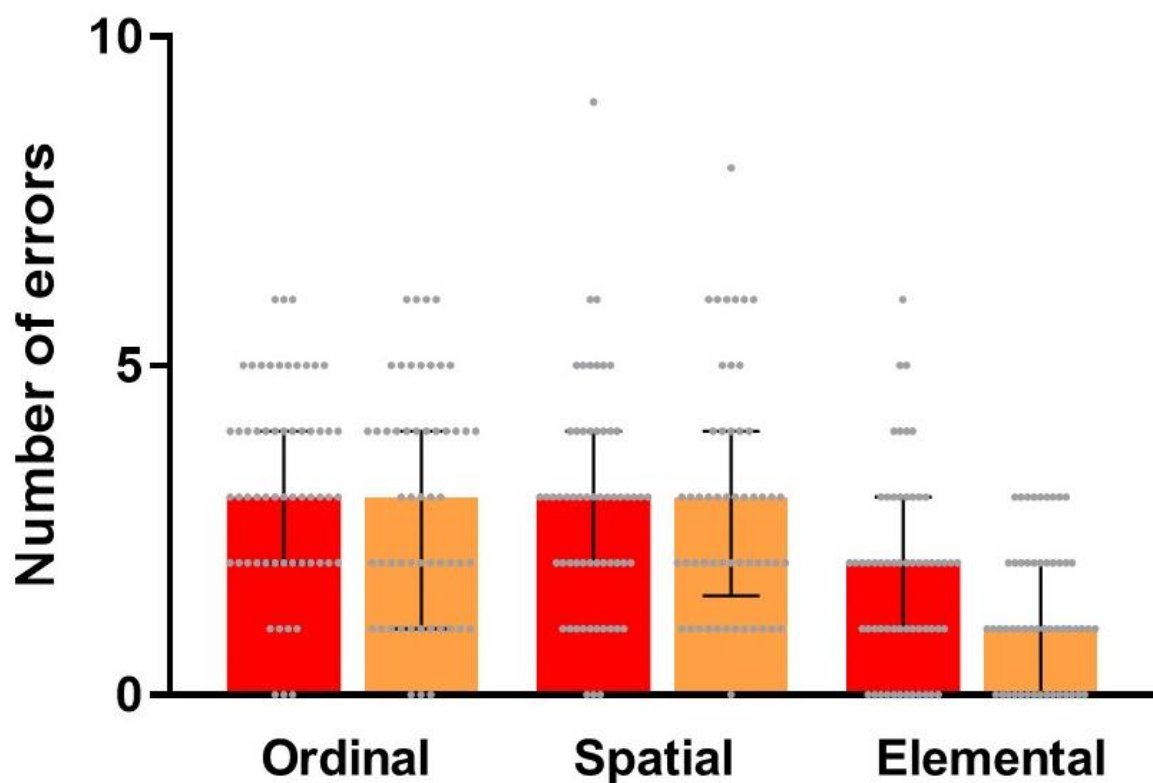


Figure 6.7. Number of different types of errors made by each stroke group (red: right hemisphere stroke patients; orange: left hemisphere stroke patients)

Each column and error bar represents the median and IQR, respectively.

I also analysed the types of errors as percentages of the total errors (Table 6.7). Raw data or means regarding the types of errors were not reported in previous studies. Thus, comparisons could not be made between stroke patients in the current study and healthy subjects or patients with neurodegenerative conditions.

Table 6.7. Percentage of types of errors out of the total number of errors that each patient made

Mean and SEM except those with * for which median and IQR are shown because the data were not normally distributed. R: right hemisphere stroke, L: left hemisphere stroke.

	% Elemental / Total Errors		% Ordinal / Total Errors		% Spatial / Total Errors	
	R	L	R	L	R	L
Mean	20*	16.66 *	42.64	40.29	33.33*	41.09
SEM	22.22*	25*	2.69	2.75	25*	2.74

6.4.1.2 Performance on control tasks and activities of daily living

Of the 112 stroke patients, 4 did not perform the Corsi block task because they felt too fatigued and/or could not understand the task instructions. In the right hemisphere stroke group the Corsi forward span was 4.63 ± 0.15 and the Corsi forward total score was 30.84 ± 2.16 , whereas in the left hemisphere stroke group the Corsi forward span was 4.9 ± 0.14 and the Corsi forward total score was 33.48 ± 2.26 (all these are mean \pm SEM). Performance did not significantly differ between the two groups (for Corsi forward span: $U = 1309.5$, $p = 0.364$, Cohen's $d = 0.167$; for Corsi forward total score: $U = 1330.5$, $p = 0.458$, Cohen's $d = 0.141$; using a Mann-Whitney U test), which is consistent with a previous study (Kessels, Kappelle, et al. 2002). Three previous studies examining healthy subjects have analysed the Corsi total score the same way as the current study (van Asselen et al. 2009; van Asselen, Kessels, Kappelle, et al. 2006; Kessels et al. 2000). According to normative data (Kessels et al. 2000), a total score between 15.1 and 29.3 is defined as borderline, and the stroke patients (both the

left and right hemisphere group) scored within the 15th percentile of age-matched healthy controls. The mean Corsi forward span was found to be between 4.4 and 5.2 in five different groups of healthy elderly subjects (Brunetti et al. 2014; Guariglia 2007; Jaillard et al. 2009; De Nigris et al. 2013; Nys et al. 2006). Thus, both the left and right hemisphere stroke group performed as well as some groups of healthy age-matched subjects.

In the whole group analysis (all 108 patients) and when each hemispheric group was analysed separately, there was a significant positive correlation between the Corsi forward span score and the number of correct responses on the 4MT ($r_s = 0.499$, $p < 0.001$ in whole group analysis; $r_s = 0.583$, $p < 0.001$ in the right hemisphere stroke group; $r_s = 0.405$, $p = 0.004$ in the left hemisphere stroke group), and a significant positive correlation between the Corsi forward total score and the number of correct responses on the 4MT ($r_s = 0.543$, $p < 0.001$ in the whole group analysis; $r_s = 0.615$, $p < 0.001$ in the right hemisphere stroke group; $r_s = 0.472$, $p = 0.001$ in the left hemisphere stroke group).

The mean representational neglect index ($\ln \frac{\text{total details reported on the right}}{\text{total details reported on the left}}$) was -0.033 in the right hemisphere stroke group and -0.05 in the left hemisphere stroke group, which is within the range of healthy subjects who performed a similar task (Bartolomeo et al. 1994). In both stroke groups the median was 0. Across all patients there was no significant correlation between this index and the number of correct responses on the 4MT ($r_s = -0.018$, $p = 0.848$).

The modified Rankin Scale score (post-stroke score) was available for 91 out of the 112 stroke patients, but was obtained within one week of the 4MT assessment in only 57 of them. In this subset of 57 patients, there was a significant correlation between the modified Rankin Scale score and the total errors on the 4MT ($r_s = 0.458$, $p < 0.001$).

6.4.1.3 Comparisons with demographic factors

Overall (across the 112 patients), the number of correct responses on the 4MT was significantly correlated with: a) age at experiment ($r_s = -0.480$, $p < 0.001$), and b) years of education ($r_s = 0.276$, $p = 0.003$). These correlations were significant when examining each hemispheric group separately (apart from the correlation with years of education which was not significant in the right hemisphere group). A Mann-Whitney U test showed that the impaired group ($N = 84$ patients) were significantly older than the unimpaired group ($N = 28$ patients; $U = 533$, $p < 0.001$, Cohen's $d = 0.895$).

6.4.2 Lesion analyses

Lesion analyses were performed to examine whether lesion characteristics such as location and volume, contributed to patients' variability in performance on the 4MT and the Corsi block task.

6.4.2.1 Right hemisphere stroke

6.4.2.1.1 Lesion type and volume

Of the 50 right hemisphere stroke patients, 8 had haemorrhagic and 42 had ischaemic stroke. The median lesion volume (of all 50 right hemisphere stroke patients) was 6372 voxels (IQR = 39102.5 voxels). There was no significant difference in lesion volume between the impaired and the unimpaired patients ($U = 114$, $p = 0.16$, Cohen's $d = 0.413$; using a Mann-Whitney U test).

6.4.2.1.2 Lesion subtraction analysis

Initially, a lesion overlap of all right hemisphere stroke patients was created in order to examine the lesion distribution (Figure 6.8A). The lesions covered almost the entire right hemisphere and most patients had a middle cerebral artery territory infarct (32 out of the 50 patients). Figures 6.8B and 6.8C show the lesion overlaps of patients who were impaired and patients who were unimpaired on the 4MT, respectively. The lesion subtraction analysis (Figure 6.8D) shows that the insula was damaged about 30% more frequently in patients who were impaired than in patients who were unimpaired on the 4MT.

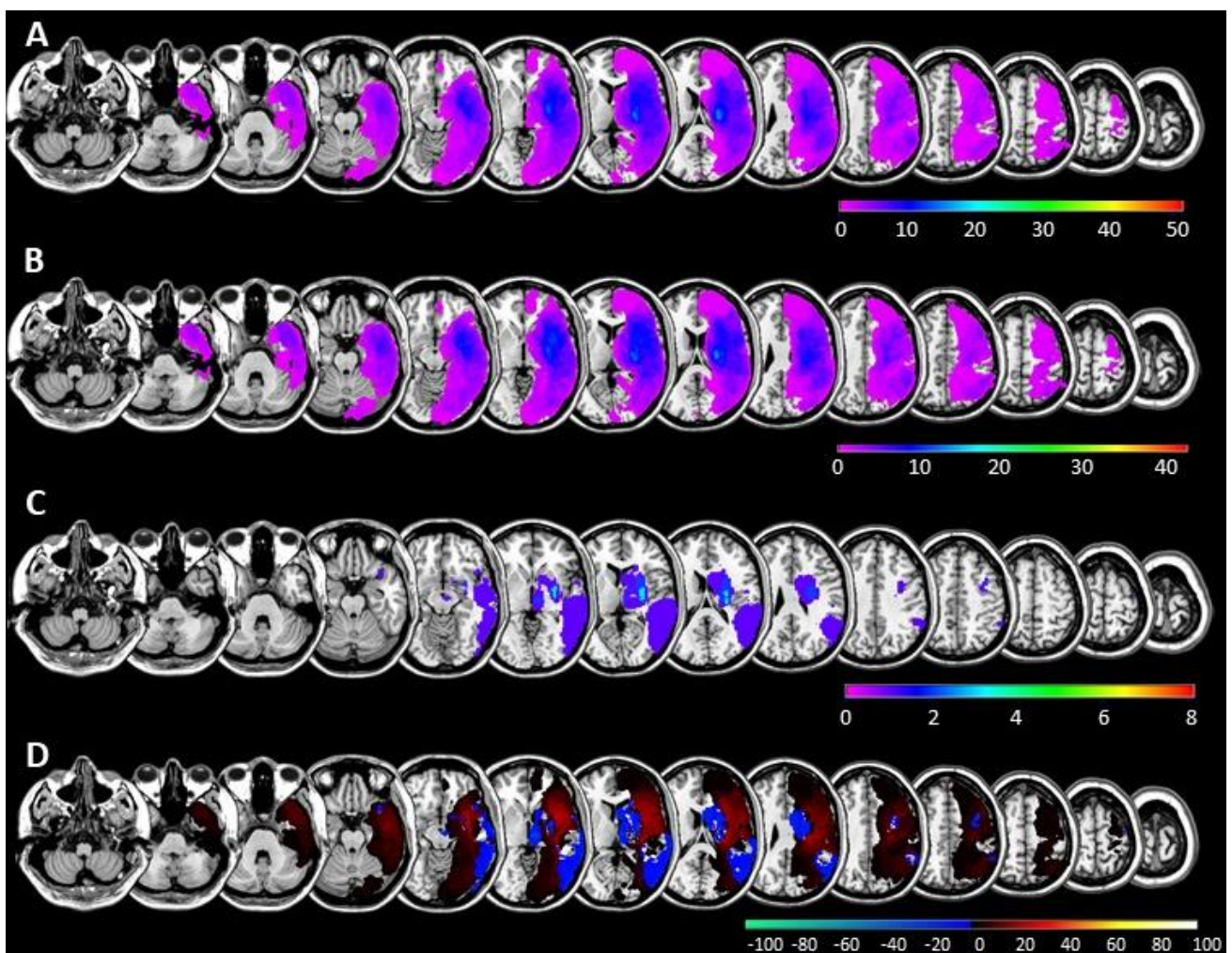


Figure 6.8. Lesion overlap and lesion subtraction analysis of right hemisphere stroke patients on axial slices of a ch2 brain template

A) Lesion overlap of all right hemisphere stroke patients (N = 50); B) Lesion overlap of impaired patients (N = 42); C) Lesion overlap of unimpaired patients (N = 8); D) Lesion subtraction analysis (impaired group minus unimpaired group)

In the lesion overlaps, the colour scale indicates how many individuals had damage to each voxel. In the lesion subtraction analysis, the colour scale indicates increasing frequencies from dark red (difference 1% to 10%) to white (difference 90% to 100%), showing areas damaged more often in patients who were impaired than in patients who were unimpaired, whereas colours from dark blue (difference -1% to -10%) to green (difference -90% to -100%) show areas damaged more often in patients who were unimpaired compared to patients who were impaired.

6.4.2.1.3 Voxelwise statistical analyses

Voxel-lesion symptom mapping analyses were performed examining each of the behavioural scores of Table 6.3 in all 50 right hemisphere stroke patients using the following settings: 5,000 permutations in NiiStat; 8,000 permutations in NPM; ROI-based analyses using the AICHA (Joliot et al. 2015), the FOX (Fox et al. 2005), and the JHU (Faria et al. 2012) atlas, and voxel-based analyses; threshold: 0.05; in the voxel-based analyses: only include voxels damaged in at least 5 patients; modality: lesion; option: only right hemisphere. The voxel-based analyses (NiiStat and the NPM Brunner-Munzel test) did not identify any significant voxels for any of the above scores. In the ROI-based analyses in NiiStat, the only regions that were found to be significantly associated with performance on the 4MT when not regressing for lesion volume, were the lateral parietal cortex and intraparietal sulcus (these ROIs were significantly associated with the number of ordinal errors on the 4MT; FOX atlas; positive z) and the parahippocampal gyrus area 4 (this ROI was significantly associated with the number of total errors on the 4MT; AICHA atlas; positive z). Importantly only the parahippocampal gyrus area 4 remained significant when regressing for lesion volume. This area is located in the posterior part of the parahippocampal gyrus, its size is 2568 mm³, and its mass centre MNI x, y, z coordinates are 17, -27, -10, respectively. Note that the results were the same when

using: a) a higher number of permutations (10,000) or b) a lower threshold (only including voxels damaged in at least 2 patients).

Of the 50 right hemisphere stroke patients, 9 had damage to the parahippocampal gyrus and all 9 of them were impaired on the 4MT. Patients whose lesions included damage to the right parahippocampal gyrus (region 1 and/or 2 and/or 3 and/or 4 and/or 5 according to the AICHA atlas) made significantly more total errors on the 4MT compared to patients who did not have damage to this gyrus ($p = 0.018$; using Welch's t-test because of a large difference in the number of patients per group). It is important to note though that these two groups were not lesion volume matched; the lesion volume of the group with right parahippocampal gyrus damage was significantly larger than the right hemisphere stroke group without parahippocampal gyrus damage ($U = 30$, $p < 0.001$, Cohen's $d = 1.321$; using a Mann-Whitney U test rather than the Welch's t-test because the assumptions of the latter were violated).

An additional analysis was performed in order to examine whether the number of total errors was significantly associated with the amount (volume) of damage to any particular brain region. This was performed in collaboration with Dr Paul Bentley, by using the Harvard-Oxford grey matter atlas and the Julich white matter atlas (Desikan et al. 2006; Zhang et al. 2010). This analysis showed that the more extensive the damage to a number of regions, the more errors were made on the 4MT. These regions were the hippocampal part of the right cingulum bundle, the posterior part of the right cingulate gyrus, the posterior part of the right parahippocampal gyrus, and the right hippocampus (Table 6.8).

Table 6.8. Correlations between total errors and lesion volume within each ROI (threshold $p < 0.05$ uncorrected)

ROI	r_s	p	r_s	p
	Uncorrected for lesion volume		Corrected for lesion volume	
Right hemisphere stroke lesions: Most significant ROIs shown				
Hippocampal part of the right cingulum	0.41677	0.002606	0.355899	0.012081
Posterior division of the right cingulate gyrus	0.369006	0.008363	0.279617	0.051679
Posterior division of the right parahippocampal gyrus	0.367834	0.008588	0.278458	0.052697
Right hippocampus	0.347041	0.013543	0.242574	0.09308
Right intracalcarine cortex	0.315734	0.02551	0.262377	0.068564
Corpus callosum_ superior parietal gyrus	0.305169	0.031163	0.22105	0.126921
Corpus callosum_ superior occipital gyrus	0.282753	0.046635	0.209804	0.147932
Corpus callosum_ middle occipital gyrus	0.280684	0.048334	0.221983	0.125284
Right thalamus-3-occipital	0.280296	0.048658	0.173899	0.232089
Right inferior longitudinal fasciculus	0.280294	0.048659	0.122288	0.402557

6.4.2.1.4 Corsi block task

Next, I examined which regions were significantly associated with performance on the Corsi block task, and whether they were the same as those found in the 4MT analyses. Voxel-lesion symptom mapping analyses were performed in NiiStat, in which I examined the total score on the Corsi block task in 49 right hemisphere stroke patients (1 out of the 50 patients did not perform the Corsi block task) using the following settings: 5,000 permutations; ROI-based analyses using the AICHA (Joliot et al. 2015), the FOX (Fox et al. 2005), and the JHU (Faria et al. 2012) atlas, and voxel-based analyses; 0.05 threshold; in the voxel-based analyses: only include voxels damaged in at least 5 patients; modality: lesion. The de-skew option was chosen in NiiStat because the Corsi forward total score was not normally distributed. When not regressing for lesion volume, the only region that was found to be significantly associated with the Corsi forward total score was the intraparietal sulcus (FOX atlas; negative z), but no region or voxel was found to be significant when regressing for lesion volume. Note that the

results were the same when using: a) a higher number of permutations (10,000) or b) a lower threshold (only including voxels damaged in at least 2 patients).

6.4.2.2 Left hemisphere stroke

6.4.2.2.1 Lesion type and volume

Of the 50 left hemisphere stroke patients, 11 had haemorrhagic and 39 had ischaemic stroke. In the left hemisphere stroke group, the median lesion volume was 3333 voxels (IQR = 19849 voxels). There was no significant difference in lesion volume between the impaired and the unimpaired patients ($U = 237$, $p = 0.597$, Cohen's $d = 0.155$; using a Mann-Whitney U test).

6.4.2.2.2 Lesion subtraction analysis

A lesion overlap of all left hemisphere stroke patients was created in order to examine the lesion distribution (Figure 6.9A). Many patients had a middle cerebral artery territory infarct and the lesion coverage was less compared to the right hemisphere stroke group. For example, there was less coverage of medial temporal lobe areas such as the hippocampus and parahippocampal gyrus. Figure 6.9B and Figure 6.9C show the lesion overlaps of patients who were impaired and patients who were unimpaired on the 4MT, respectively. From the lesion subtraction analysis in Figure 6.9D, it seems that the superior longitudinal fasciculus is damaged about 30% more frequently in patients who are impaired than in patients who are unimpaired on the 4MT.

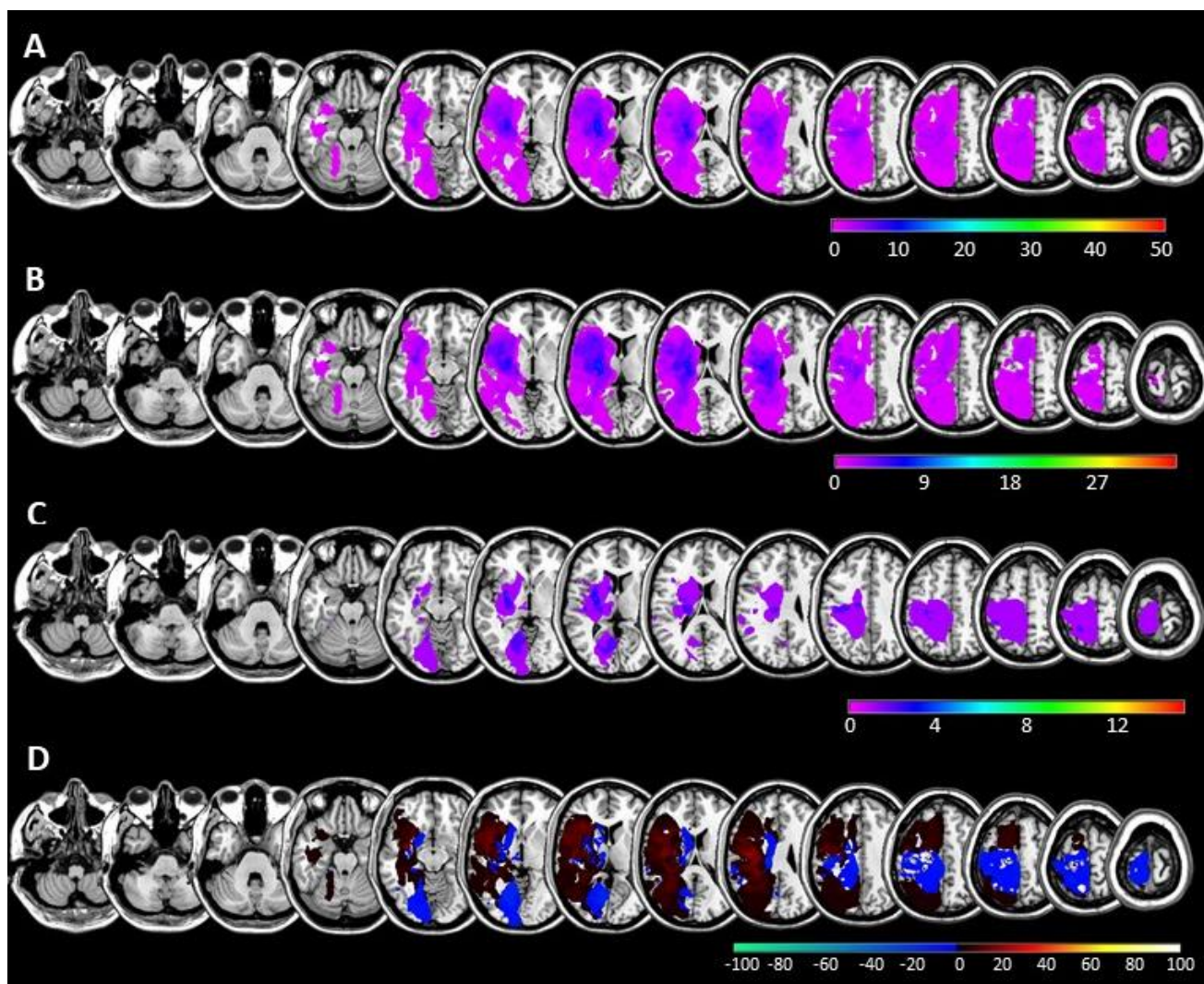


Figure 6.9. Lesion overlap and lesion subtraction analysis of left hemisphere stroke patients on axial slices of a ch2 brain template

A) Lesion overlap of all left hemisphere stroke patients (N = 50); B) Lesion overlap of impaired patients (N = 35); C) Lesion overlap of unimpaired patients (N = 15); D) Lesion subtraction analysis (impaired group minus unimpaired group).

In the lesion overlaps, the colour scale indicates how many individuals had damage to each voxel. In the lesion subtraction analysis, the colour scale indicates increasing frequencies from dark red (difference 1% to 10%) to white (difference 90% to 100%), showing areas damaged more often in patients who were impaired than in patients who were unimpaired, whereas colours from dark blue (difference -1% to -10%) to green (difference -90% to -100%) show areas damaged more often in patients who were unimpaired compared to patients who were impaired.

6.4.2.2.3 Voxelwise statistical analyses

Voxel-lesion symptom mapping analyses were performed in all 50 left hemisphere stroke patients examining the total errors, elemental errors, ordinal errors, spatial errors, and “spatial plus ordinal” errors, using the following settings: 5,000 permutations in NiiStat; 8,000 permutations in NPM; 50 left hemisphere stroke patients; ROI-based analyses using the AICHA (Joliot et al. 2015), the FOX (Fox et al. 2005), and the JHU (Faria et al. 2012) atlas, and voxel-based analyses; 0.05 threshold; in the voxel-based analyses: only include voxels damaged in at least 5 patients; modality: lesion. The de-skew option was chosen in NiiStat for whichever data were not normally distributed, e.g. the types of errors. Of all the analyses on the above scores, no significant regions or voxels were found using NiiStat (either when or when not regressing for lesion volume) or the NPM Brunner-Munzel test. Note that the results were the same when using: a) a higher number of permutations (10,000) or b) a lower threshold (only including voxels damaged in at least 2 patients).

Separate voxel-lesion symptom mapping analyses were performed for the following scores: $\frac{\text{elemental errors}}{\text{total errors}}$, $\frac{\text{ordinal errors}}{\text{total errors}}$, $\frac{\text{spatial errors}}{\text{total errors}}$, $\frac{\text{elemental errors}}{\text{ordinal errors} + \text{spatial errors}}$, $\frac{\text{ordinal errors} + \text{spatial errors}}{\text{total errors}}$, because I needed to exclude one patient who had 0 total errors as these ratios would be invalid in this patient. The following settings were used: 5,000 permutations in NiiStat; 8,000 permutations in NPM; 49 left hemisphere stroke patients; ROI-based analyses using the AICHA (Joliot et al. 2015), the FOX (Fox et al. 2005), and the JHU (Faria et al. 2012) atlas, and voxel-based analyses; 0.05 threshold; in the voxel-based analyses: only include voxels damaged in at least 5 patients; modality: lesion. Of all the analyses on the above scores, no significant regions or voxels were found using NiiStat (having or having not regressed for lesion volume) or the NPM Brunner-Munzel test. The results were the same when using: a) a higher number of permutations (10,000) or b) a lower threshold (only including voxels damaged in at least 2 patients).

An additional analysis was performed in order to examine whether the number of total errors was significantly associated with the amount (volume) of damage to any particular brain region. This was performed in collaboration with Dr Paul Bentley, by using the Harvard-Oxford grey matter atlas and the Julich white matter atlas (Desikan et al. 2006; Zhang et al. 2010). No significant correlations were found (having or having not regressed for lesion volume).

6.4.2.2.4 Corsi block task

Next, I examined which brain regions were significantly associated with performance on the Corsi block task in the left hemisphere stroke group (47 left hemisphere stroke patients were included in this analysis as 3 patients did not perform the Corsi block task). The methodology was the same as that used with the right hemisphere stroke patients (section 6.4.2.1.4). No region or voxel was found to be significantly associated with the Corsi forward total score. The results were the same when using: a) a higher number of permutations (10,000) or b) a lower threshold (only including voxels damaged in at least 2 patients).

6.4.2.3 Lesion analyses in both the left and right hemisphere stroke group

6.4.2.3.1 Lesion volume

There was no significant difference in lesion volume between the left and right hemisphere stroke group ($U = 1096.5$, $p = 0.29$, Cohen's $d = 0.210$; using a Mann-Whitney U test). Also, there was no significant difference in lesion volume between the impaired and the unimpaired patients ($U = 712.5$, $p = 0.158$, Cohen's $d = 0.089$; using a Mann-Whitney U test across the whole group of patients).

I did not perform a Multiple Linear Regression to examine the relative contribution of lesion volume and days since stroke on performance because all the assumptions were met apart from linearity. To test the assumption of linearity I performed a hierarchical multiple regression which showed that there was a curvilinear effect between total errors and lesion volume, and also between total errors and days since stroke. I used the heteroscedasticity test (Daryanto 2013) to examine the assumption of homoscedasticity; both the Breusch-Pagan and the Koenker test showed that there was no violation of this assumption. There was no multicollinearity in the data (variance inflation factor scores < 10, and tolerance scores > 0.2; specifically, the scores were 1.058 and 0.945 respectively). The values of the residuals were independent (the Durbin-Watson score was close to 2, i.e., 2.011). The values of the residuals were normally distributed and there were no outliers (all Cook's Distance values were < 1).

6.4.2.3.2 Voxel-lesion symptom mapping using flipped lesions

Since there was no significant difference in the number of total errors on the 4MT between the left and right hemisphere stroke group, additional voxel-lesion symptom mapping analyses were performed in NiiStat, in which the left hemisphere lesions were flipped to the right side so that all lesions of the 100 patients were localized to one (the right) hemisphere. The following settings were used: 5,000 permutations; 100 stroke patients; ROI-based analyses using the AICHA (Joliot et al. 2015), the FOX (Fox et al. 2005), and the JHU (Faria et al. 2012) atlas, and voxel-based analyses; 0.05 threshold; in the voxel-based analyses: only include voxels damaged in at least 10 patients; modality: lesion. No voxels or regions were found to be significantly associated with total errors on the 4MT (having or having not regressed for lesion volume). The results were the same when using: a) a higher number of permutations (10,000) or b) a lower threshold (only including voxels damaged in at least 4 patients).

6.4.2.3.3 *A priori* anatomical analyses for areas of interest

Additional analyses were performed (in collaboration with Dr Paul Bentley) for the number of total errors on the 4MT, using *a priori* determined combinations of ROIs (shown in Table 6.9 and Figure 6.10). The reason for choosing these particular ROIs was that they form an *a priori* bilateral network involving the parahippocampal gyrus and superior parietal lobule, which may be particularly important for performing the 4MT, as indicated by prior literature examining spatial memory (non-human studies as well as functional neuroimaging and lesion studies in humans, e.g. Aggleton et al. 1995; van Asselen, Kessels, Neggers, et al. 2006; Berryhill and Olson 2008; Fritch, Spets, and Slotnick 2020; Hannula and Ranganath 2008; Hartley et al. 2007; Jonides et al. 1993; Libby et al. 2014; Luzzi et al. 2000; Neave et al. 1996; Neave, Nagle, and Aggleton 1997; Nystrom et al. 2000; Owen et al. 1996; Ricciardi et al. 2006; Schmidt et al. 2007). The atlases that were used are the Harvard-Oxford grey matter atlas and the Julich white matter atlas (Desikan et al. 2006; Zhang et al. 2010).

These analyses showed that the more extensive the damage to the following combination of regions in the right hemisphere: the posterior cingulate gyrus, hippocampal part of the cingulum bundle, parahippocampal gyrus, and superior parietal lobule, the more errors were made on the 4MT (Table 6.9). However, the amount of damage to these regions in the left hemisphere was not significantly associated with the number of errors on the 4MT.

Table 6.9. Correlations between total errors on the 4MT and lesion volume within each ROI combination (threshold $p < 0.05$ uncorrected)

CGH: hippocampal part of the cingulum; postCG: posterior cingulate gyrus; PHG: parahippocampal gyrus; SPL: superior parietal lobule; RH: right hemisphere; LH: left hemisphere.

ROI	r_s	p	r_s	p
	Uncorrected for lesion volume		Corrected for lesion volume	
A PRIORI RH ROIs (Combination)				
Right CGH+postCG+PHG	0.4381	0.0015	0.3605	0.0109
Right CGH+postCG+PHG+SPL	0.4785	0.00044	0.4076	0.0037
A PRIORI LH ROIs (Combination)				
Left CGH+postCG+PHG	0.1480	0.3050	- 0.1582	0.2778
Left CGH+postCG+PHG+SPL	0.1081	0.4548	- 0.0955	0.5138

A Kruskal-Wallis H test was performed to compare the number of total errors on the 4MT between patients with (roi+) compared to those without (roi-) damage to the combination of regions described above. This showed that there was a statistically significant difference in the number of total errors between the four groups shown in Figure 6.10 in the ROI combinations: a) “CGH + postCG + PHG” ($\chi^2(3) = 12.17$, $p = 0.0068$, $\eta_p^2 = 0.096$), and b) “CGH + postCG + PHG + SPL + CallosumSPL” ($\chi^2(3) = 11.85$, $p = 0.0079$, $\eta_p^2 = 0.092$). The significant result arises from right hemisphere lesions. Specifically, right hemisphere stroke patients with damage to the combined ROI “CGH + postCG + PHG” performed significantly worse than right hemisphere stroke patients who did not have damage to this combined ROI ($t(48) = 3.309$, $p = 0.0018$; using a t-test). Also, right hemisphere stroke patients with damage to the combined ROI “CGH + postCG + PHG + SPL + CallosumSPL” performed significantly worse than right hemisphere stroke patients who did not have damage to this combined ROI ($t(48) = 3.595$, $p = 0.000763$; using a t-test). Note that the result was significant both when the CallosumSPL ROI was included in the “CGH + postCG + PHG + SPL” ROI combination and when it was not included in this ROI combination.

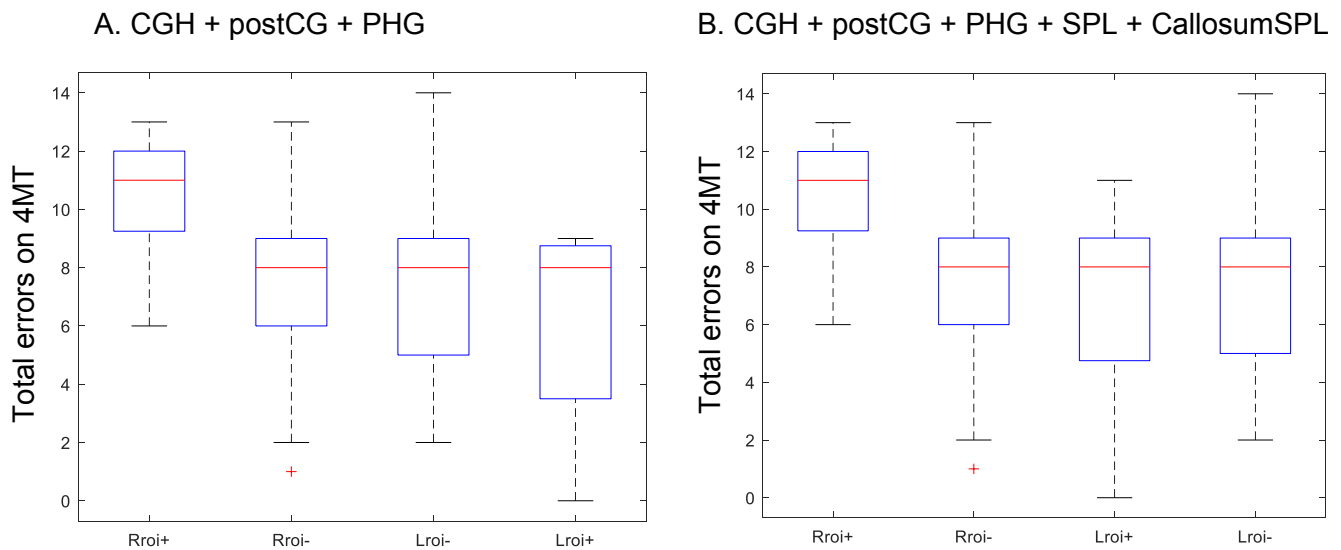


Figure 6.10. Total number of errors in patients with or without damage to a combination of ROIs

Each red line represents the median, and the horizontal edges of each blue box represent the 25th and 75th percentile. The top whiskers are drawn up to the largest point that falls within a distance of 1.5 IQR above the 75th percentile. The bottom whiskers are drawn up to the lowest point that falls within a distance of 1.5 IQR below the 25th percentile. The red cross represents an outlier. R: right hemisphere; L: left hemisphere; postCG: posterior cingulate gyrus; PHG: parahippocampal gyrus; CGH: hippocampal part of the cingulum; SPL: superior parietal lobule; CallosumSPL: splenium of the corpus callosum

6.4.2.3.4 Lesion network mapping

The ROI combinations that were used in the previous section were predefined based on results from previous investigations of episodic memory, spatial representation, and navigation. To more accurately examine whether spatial memory relies on a network of regions, I used a lesion network mapping technique that utilized: a) ROI combinations based on a previous fMRI study which employed a similar task to the 4MT, or b) previous resting-state fMRI data.

6.4.2.3.4.1 Using previously published task-based fMRI data

Significantly more total errors were made on the 4MT by stroke patients who had (compared to those who did not have) damage to the right hemisphere regions that were more activated in healthy subjects during the allocentric condition of Gomez and colleagues' (2014) task (compared to the control condition; Table 6.10; Figure 6.11). That is, patients who had lesions involving the right side of the network shown in Figure 6.4C (i.e., areas listed in Table 6.11), performed worse than patients whose right hemisphere lesion did not involve any of these spheres. However, no significant results were found for the left side of any of the networks shown in Figure 6.4. That is, patients whose lesion involved damage to spheres in the left side of one of these networks did not make more total errors on the 4MT than patients whose left hemisphere lesion did not damage those spheres.

Table 6.10. Bespoke ROI analysis using masks of spheres centred on coordinates

RHS Lesions only:	t-stat (df = 48)	p
'combined spheres_ALLOCENTRIC > CONTROL'	2.097789	0.041213
'combined spheres_ALLOCENTRIC > EGOCENTRIC'	0.255377	0.799523
'combined spheres_EGOCENTRIC > ALLOCENTRIC'	0.927304	0.358408
'combined spheres_EGOCENTRIC > CONTROL'	0.426143	0.671908
'combined spheres_(ERO+EU+ALLO) > CONTROL'	1.874334	0.066977

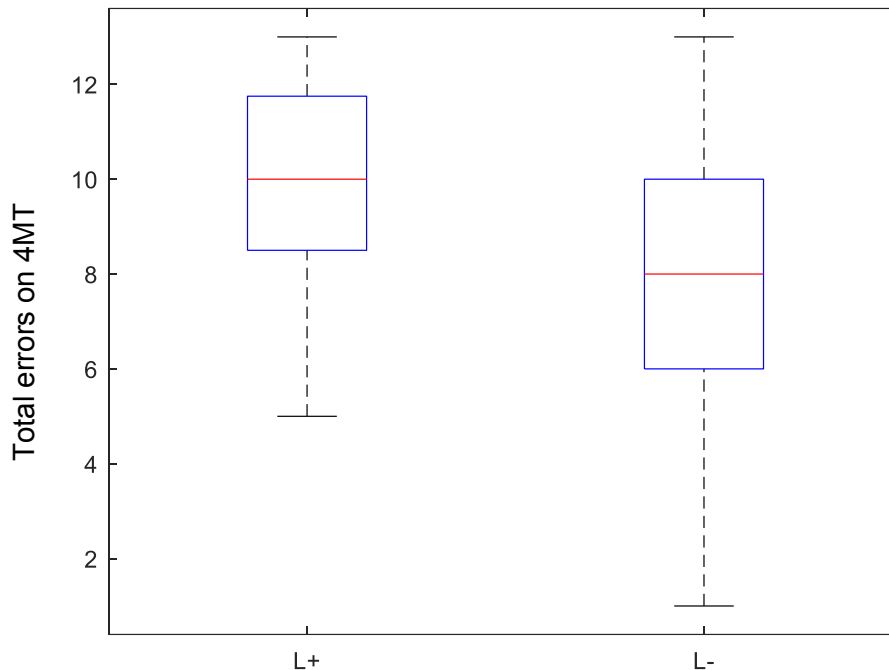


Figure 6.11. The number of total errors in patients who had (L+) compared to those who did not have (L-) damage to the right hemisphere regions of the ALLOCENTRIC > CONTROL sphere ROI combination

Each red line represents the median, and the horizontal edges of each blue box represent the 25th and 75th percentile. The top whiskers are drawn up to the largest point that falls within a distance of 1.5 IQR above the 75th percentile. The bottom whiskers are drawn up to the lowest point that falls within a distance of 1.5 IQR below the 25th percentile.

Table 6.11. Locations of spheres whose damage was associated with worse performance on the 4MT

These locations were found by overlapping the right hemisphere spheres of the “allocentric > control” condition (only the ones that were damaged by at least one patient) on the AICHA atlas in MRICron.

Locations of spheres based on the AICHA atlas	How many voxels of this region does the sphere include
Anterior nuclei of the right thalamus (area 6 in AICHA atlas)	1
Right posterior hippocampus	61
Anteroinferior part of the right supramarginal gyrus (area 1 in AICHA atlas)	7
Right posterior insula	44
Anteroinferior part of the right paracentral lobule (area 1 in AICHA atlas)	6

6.4.2.3.4.2 Using previously published resting-state fMRI data

The second technique used to identify a network of regions critical for task performance utilized freely available resting-state fMRI data. The thresholded network map of brain regions that are functionally connected to the right parahippocampal gyrus seed voxel (the mass centre coordinates of the ROI that was found to be significantly associated with the number of total errors in the voxel-lesion symptom mapping analyses) is shown in Figure 6.12. Patients whose lesion overlapped this thresholded network map had more total errors on the 4MT than patients whose lesion did not overlap this map ($t(98) = 3.39, p < 0.001$; Figure 6.13).

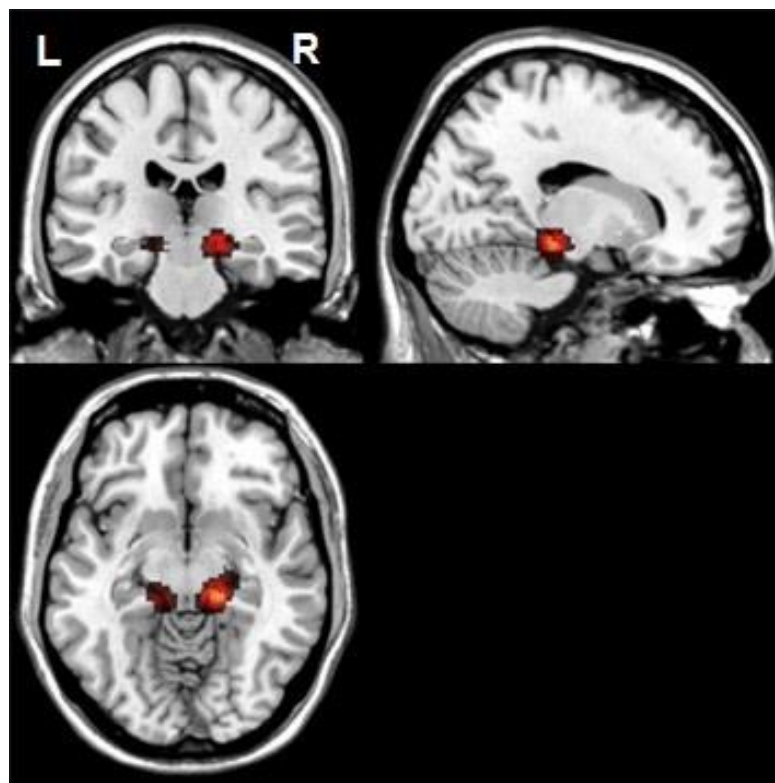


Figure 6.12. Functional connectivity map: High threshold map of the functional network (thresholding at 99.9%ile)

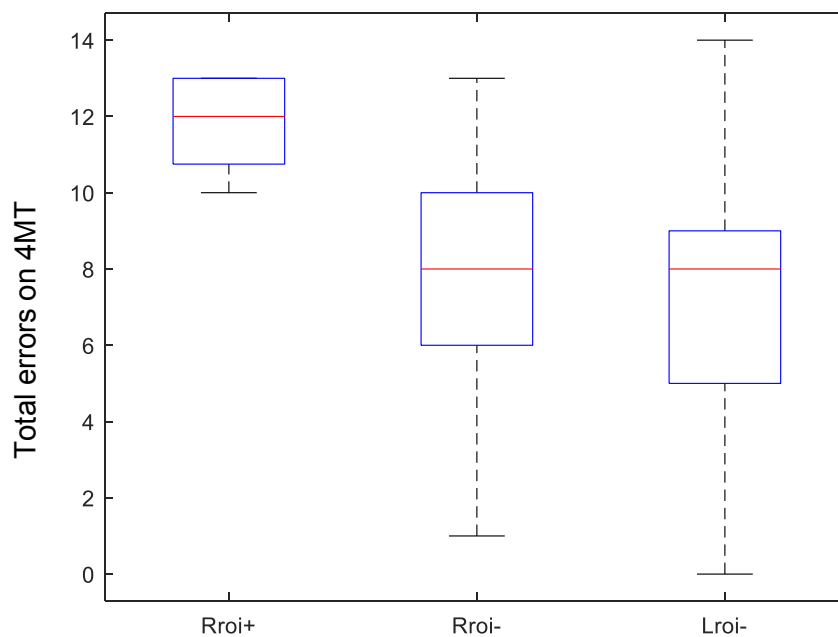


Figure 6.13. Box plot showing the number of total errors on the 4MT in patients whose right hemisphere lesion did (Rroi+) or did not (Rroi-) overlap the thresholded network, and patients whose left hemisphere lesion did not (Lroi-) overlap this network. None of the patients had a lesion overlapping the left side of this network

Each red line represents the median, and the horizontal edges of each blue box represent the 25th and 75th percentile. The top whiskers are drawn up to the largest point that falls within a distance of 1.5 IQR above the 75th percentile. The bottom whiskers are drawn up to the lowest point that falls within a distance of 1.5 IQR below the 25th percentile.

6.5 Discussion

6.5.1 Performance on the 4MT

Both the right and the left hemisphere stroke patient group examined in the current study were significantly impaired at the group level on the 4MT when compared to age-and education-matched healthy controls. In fact, stroke patients performed as poorly as some groups of patients with mild cognitive impairment and Alzheimer's disease, and were significantly worse than semantic dementia patients. Importantly, stroke patients' performance on the 4MT was significantly correlated with their degree of disability in daily activities. These findings show that

stroke patients as a group are as impaired as patients with conditions that are typically associated with particularly poor spatial memory, and suggest that spatial memory deficits should be screened for more frequently following hemispheric stroke. The 4MT could be used to screen for these deficits as it has the advantage that it can be performed on the wards and the patients' home. Therefore, one can assess patients even if they have mobility issues (as was the case with some patients in the current study), which is much more difficult if the task is strictly laboratory-based.

The modified Rankin Scale was significantly correlated with performance on the 4MT, even though this scale is not an assessment of the ability to perform daily activities that are only related to memory for spatial locations (e.g. remembering the location of one's keys). This indicates two important implications. First, spatial memory may be essential for performing many daily activities. Second, interventions aiming at improving stroke patients' spatial memory may have a significant impact on their daily life (as will be discussed in Chapter 7).

The most frequent types of errors made were spatial and ordinal errors rather than elemental errors. This indicates that the stroke groups tested seem to be poorer at remembering the arrangement of the mountains (allocentric information; specifically, the distance between the mountains and their spatial order) than their size and shape (item recognition). A qualitative analysis of the types of errors from a previous study (Hartley et al. 2007) suggests that this pattern seems to also occur in healthy young and healthy elderly subjects.

The fact that there was no significant difference between left and right hemisphere stroke patients in the number of errors on the 4MT is consistent with previous studies which found no significant difference in spatial processing or spatial memory between left and right hemisphere stroke patients, for example, on the Corsi block task (van Asselen et al. 2008,

2009; van Asselen, Kessels, Neggers, et al. 2006; van der Ham et al. 2011, 2012; Kessels, Kappelle, et al. 2002), in self-reports of spatial disorientation (Kraft et al. 2014), on object-location recall tasks with 0-minute (Kant et al. 2017; Kessels, de Haan, et al. 2002), 3-minute (Kessels, de Haan, et al. 2002), or 30-minute interval (Kessels et al. 2006), and on the Knox Cube Test (Martin et al. 1996). However, van Asselen and colleagues (2006) found that right hemisphere (but not left hemisphere) stroke patients performed significantly worse than healthy controls on a spatial working memory 2D search task.

6.5.2 Performance on the Corsi block task

Stroke patients as a group were impaired on the 4MT, but did not seem to be as impaired in comparison to healthy controls on the Corsi block task; their Corsi forward total score was within the 15th percentile of age-matched healthy subjects, and, as indexed by the Corsi span, they performed as well as some groups of healthy elderly subjects from previous studies. This suggests a difference in sensitivity between these two tests, and that the 4MT was able to tap into a more specific cognitive function which seems to be particularly impaired in stroke patients. In both the 4MT and the Corsi block task, stimuli are presented for a few seconds, the delay interval is just 1–2 seconds, and memory for spatial locations is required. These similarities can explain why a significant correlation was found between these tasks. However, the main differences are that the 4MT does not require memory for temporal order, and critically, it requires the ability to adopt different viewpoints. Therefore, stroke patients, particularly those with damage to the spatial memory network described above, may find it markedly difficult to adopt a different viewpoint.

6.5.3 Demographics

The fact that age and years of education were significantly correlated with the amount of correct responses on the 4MT (in the whole group of stroke patients) is in line with studies that

found that performance on various neuropsychological tests tends to be better in younger individuals and in those with higher levels of education (Rosselli and Ardila 2003; Wiederholt et al. 1993). Specifically, studies that have used the 4MT in healthy subjects found that performance was significantly associated with years of education (Ritchie et al. 2018) and age (Hartley et al. 2007; Pengas et al. 2010; Ritchie et al. 2018). By comparing the raw data of previous 4MT studies, I found that Hartley and Harlow's (2012) young group performed significantly better than Moodley and colleagues' (2015) very elderly Italian group ($U = 66$, $p = 0.008$, Cohen's $d = 0.912$; using a Mann-Whitney U test), but not Moodley and colleagues' (2015) elderly UK group or Bird and colleagues' (2010) elderly group (all p 's > 0.108 and all Cohen's d 's < 0.439 using a Mann-Whitney U test). This is in keeping with a relatively weak effect of age on performance, which may be heightened in a patient population.

As was the case in the previous experimental chapters, the current study did not reveal gender differences in task performance. This is consistent with previous studies in healthy subjects that have used the 4MT (Hartley and Harlow 2012; Pengas et al. 2010; Ritchie et al. 2018) or a slightly different computerized version of the Corsi block task that I used (Shah et al. 2013).

6.5.4 The critical brain regions for 4MT performance

The strong points in the lesion analysis of the present study are the inclusion of a relatively large number of both left and right hemisphere stroke patients, many of whom were tested in the acute stage (thus it is unlikely that major plasticity changes would have occurred). This enabled the use of voxelwise statistical analyses (using exclusively lesion data) and lesion network mapping (using lesion data combined with resting-state or task-based fMRI data). The lack of a significant correlation between the number of total errors on the 4MT and lesion volume indicates that performance was more closely linked to the location of the lesion rather

than its size. This is in keeping with the finding that lesion volume accounts for less than 20% variance in a number of cognitive domains including spatial memory (Corbetta et al. 2015). The lesion locations that were most closely linked to performance on the 4MT are discussed below.

In the voxelwise statistical analyses, the only region that was found to be significantly associated with performance on the 4MT (number of total errors) when regressing for lesion volume was the posterior division of the right parahippocampal gyrus (specifically area 4 in the AICHA atlas). Separate analyses showed that the number of total errors on the 4MT was positively correlated with the extent of damage to the hippocampal part of the cingulum bundle in the right hemisphere, and to a network in the right hemisphere which contains the posterior cingulate gyrus, parahippocampal gyrus, superior parietal lobule, hippocampal part of the cingulum bundle, and splenium of the corpus callosum.

The lesion network mapping technique using task-based fMRI data from a previous study, revealed that damage to a network of right hemisphere brain regions that are more active during an allocentric task (compared to a task that examines neither spatial relations between objects nor spatial relations between oneself and objects) led to significantly more total errors on the 4MT, indicating that this is a network of regions that are necessary for spatial memory (allocentric in particular). The critical regions of this network are the anterior nuclei of the right thalamus, the right posterior hippocampus, the anteroinferior part of the right supramarginal gyrus, the right posterior insula, and the anteroinferior part of the right paracentral lobule. The fact that right hemisphere lesions involving the “allocentric > control” spheres led to worse performance on the 4MT (compared to right hemisphere lesions that did not involve damage to these spheres) and that this was not the case for the “egocentric > control” spheres, provides further evidence that the 4MT draws more on allocentric versus egocentric memory resources.

When a high threshold functional connectivity map was used in the lesion network mapping analysis (resting-state fMRI data using a posterior parahippocampal gyrus seed voxel), right hemisphere lesions involving damage to this map were associated with more total errors compared to right hemisphere lesions that did not involve this map. One limitation of this analysis is that only 5 cases overlapped this high threshold functional connectivity map, and if the threshold was decreased (which means that the network map included more areas and included more cases) then it was not as strongly significant ($p \sim 0.04$ in a lower threshold map which included 10 cases instead of $p < 0.001$ in the high threshold map which included 5 cases). In other words, damage to the network of brain regions that are functionally connected to the right posterior parahippocampal gyrus led to significantly more total errors, indicating that this is a network of regions that are critical for spatial memory, but this was found only when the threshold was relatively high (it included very few areas other than the parahippocampal gyrus).

Most of the areas mentioned above are the same as those affected in early Alzheimer's disease (Coughlan et al. 2018). These findings are also consistent with a previous study which found that a patient whose right hemisphere stroke involved the posterior hippocampus, and lingual and parahippocampal cortices, was impaired on the 4MT (Hartley et al. 2007). Previous studies have performed volumetric analyses in subjects (healthy young subjects, and patients with Alzheimer's disease or mild cognitive impairment) and found that performance on the 4MT was related to the volume of the bilateral hippocampus, bilateral lateral parietal cortex, right entorhinal cortex, bilateral precuneus, right angular gyrus, right calcarine sulcus, left superior temporal gyrus, right middle and inferior temporal gyri, bilateral thalamus, bilateral cerebellum, as well as total brain volume (Hartley and Harlow 2012; Moodley et al. 2015). In contrast, Ritchie and colleagues (2018) did not find any significant association between the 4MT score and hippocampal volume or total brain volume in healthy middle-aged subjects. Also, Bird and colleagues (2010) examined patients with Alzheimer's disease, fronto-temporal

dementia, or subjective memory impairment and found that medial temporal lobe atrophy was not significantly correlated with performance on the 4MT. A previous study found that stronger connectivity between the lingual gyrus and the left anterior (but not posterior) hippocampus was linked to better performance on the 4MT (Sormaz et al. 2017). Although these regions were not part of the network identified in the current study, this finding supports the account that a network of regions are necessary for spatial memory.

There are many possible reasons for the lack of significant findings in the lesion symptom mapping and lesion network mapping analyses of the left hemisphere stroke group. Firstly, despite the equally large sample size, the lesion distribution of the left hemisphere stroke group was not as wide as that of the right hemisphere stroke group. For example, no left hemisphere lesion overlapped the high threshold functional connectivity map that was used in the lesion network mapping analysis. Although I screened patients with severe spatial neglect and thus these patients may have been included in the study if they had recovered at a later stage, I did not screen patients with severe aphasia and thus did not include patients who had recovered from severe aphasia. This is likely to have limited the lesion distribution in the left hemisphere stroke group.

A second potential reason for this difference between the groups is that the left hemisphere group was assessed in the more acute stage after stroke onset. This difference in time of participation is because the presence of spatial neglect in many right hemisphere stroke patients prevented them from participating in the very acute stage. Diaschisis (which can cause dysfunction even in the opposite hemisphere) and oedema may have led to more extensive network disruption in the left hemisphere stroke patients. These phenomena occur mainly in the acute stage after stroke onset, and thus would not have been present as often in the right hemisphere stroke group.

Although the right hippocampus was found to be significant in the voxelwise lesion analysis, this did not remain significant when regressing for lesion volume, unlike the right parahippocampal gyrus which did remain significant. This is in keeping with evidence that parahippocampal gyrus volume seems to be better able to differentiate between healthy, amnesic mild cognitive impairment, and Alzheimer's disease subjects as compared to hippocampal volume (Echávarri et al. 2011). Below, I discuss studies that have examined the function of the parahippocampal gyrus. All these are functional neuroimaging studies in humans (unless otherwise stated). To my knowledge, there have not been any studies of patients with lesions involving only the parahippocampal gyrus.

Neuroimaging studies have shown parahippocampal gyrus activity when remembering object locations after an angle shift (which seems to be proportional to how much the angle has changed; Schmidt et al. 2007; Sulpizio et al. 2013), when processing allocentric representations (Committeri et al. 2004; Galati et al. 2010), during topographical learning (Aguirre et al. 1996), and during maze navigation in a virtual environment (Grön et al. 2000). This region shows greater activity when viewing navigation footage of events compared to non-navigational footage (Maguire et al. 1996), and when learning in an environment containing objects and textures compared to a plain empty environment (Maguire et al. 1998). The right parahippocampal gyrus has been found to be more active when performing a mental navigation task compared to a verbal task (Rosenbaum et al. 2004), and when retrieving the location of objects than (a) from whom they had been received, (b) whether the objects were old/new, or (c) temporal order information (Burgess et al. 2001; Hayes et al. 2004).

The finding that the parahippocampal gyrus was significantly associated with total errors on the 4MT even when regressing for lesion volume indicates that the parahippocampal gyrus may be particularly important for spatial memory involving scenes rather than plain 2D objects. Evidence for this comes from a study by Mormann and colleagues (2017) who recorded

directly from cells in the parahippocampal gyrus of epileptic patients and found that parahippocampal gyrus neurons responded to pictures of scenes with a spatial layout but not pictures without a spatial layout. For example, a face or animal in which the background behind these stimuli was monochromatic did not elicit a response, whereas if the background or the whole picture showed a spatial layout it did elicit a parahippocampal gyrus response. Also, the integrity of the right parahippocampal gyrus in behavioural variant frontotemporal dementia patients seems to correlate with performance on a scene construction task assessing the ability to imagine and describe scenes in rich detail (Wilson et al. 2020).

In the current study the posterior division of the right parahippocampal gyrus was most linked with performance on the 4MT. The posterior division of the parahippocampal gyrus is known as the parahippocampal cortex (Raslau et al. 2015), a region that seems to be more active for spatial (compared to nonspatial) information when retrieving general knowledge or personal events (Gilmore et al. 2020; Hoscheidt et al. 2010), and its activity appears to be related to how well spatial information is remembered. Activity in the posterior parahippocampal gyrus during encoding was greater for scenes that participants subsequently retrieved compared to those they had subsequently forgotten (Staresina et al. 2011; Stark and Okado 2003), whereas there was no difference for objects they had subsequently retrieved compared to objects they had subsequently forgotten (Staresina et al. 2011). In contrast, the anterior parahippocampal gyrus showed the opposite pattern; it showed a difference for objects but not for scenes (Staresina et al. 2011). In line with this, in another study, activity in the parahippocampal cortex during scene encoding was greater for scenes that were subsequently "remembered", less for those that participants subsequently "knew", and even less for those that they had subsequently forgotten (Brewer et al. 1998). Similarly, Sommer and colleagues (2005) found that the greater the activity of the posterior parahippocampal gyrus during encoding, the better participants were in remembering the location of 2D objects. Parahippocampal cortex activity was greater for pictures (showing different objects at different

locations paired with faces) that participants recognized as old compared to those that they correctly rejected as new (Düzel et al. 2003). In addition, the parahippocampal cortex seems to be more active when encoding a route that participants virtually navigated from a first-person (compared to an aerial) view (Shelton and Gabrieli 2002). Kunz and colleagues (2020) performed single-neuron recordings in epileptic patients and found that anchor cells, which are cells that seem to process egocentric spatial information and may be involved in the egocentric-to-allothetic transformation, were located mainly in the parahippocampal cortex. Therefore, a possible reason why the right posterior parahippocampal gyrus was found to be significantly associated with performance on the 4MT is that this region appears to be involved in encoding stimuli locations from a first-person view with high accuracy.

Interestingly, the parahippocampal cortex includes the parahippocampal place area (Epstein 2014; Weiner et al. 2018), an area that seems to be involved in processing visual scenes depicting places (Epstein and Kanwisher 1998), both familiar and unfamiliar, and its activity does not increase if there is a sense of motion in the scene (Epstein et al. 1999). The parahippocampal place area seems to be more active when viewing scenes compared to non-scene objects (Epstein and Higgins 2007), when a spatial layout is present compared to the absence of a spatial layout, for example, single objects shown on a monochromatic background (Harel et al. 2013; Henderson et al. 2008), and when viewing familiar compared to unfamiliar scenes (Epstein, Higgins, et al. 2007). Also, the parahippocampal place area seems to code the expanse of the environment (open compared to closed space; Kravitz, Peng, and Baker 2011).

Another region that was linked to successful performance on the 4MT, even when regressing for lesion volume, was the hippocampal part of the right cingulum. This is consistent with work in rodents that has shown that the cingulum seems to be important in allocentric spatial memory (Aggleton et al. 1995; Neave et al. 1996, 1997; Owen et al. 1996).

In humans, the hippocampal and parahippocampal parts of the cingulum, which connect the hippocampus and parahippocampal gyrus to the retrosplenial and posterior cingulate cortices (Bennett et al. 2015), seem to be involved in verbal episodic memory (Alm et al. 2020; Ezzati et al. 2016).

There are two potential reasons why the right parietal cortex and right hippocampus were not found to be as strongly linked to 4MT performance as was the right parahippocampal gyrus. First, the 4MT is not exclusively an allocentric or exclusively an egocentric memory task. Patients with right hippocampal damage may have somewhat compensated for their potential allocentric memory deficit by relying more on egocentric representations to solve the task, whereas patients with right parietal cortex damage may have somewhat compensated for their potential egocentric memory deficit by relying more on allocentric representations to solve the task. Second, although spatially tuned cells are abundant in both the hippocampus and the parahippocampal gyrus, the ones that are located in the hippocampus appear to be mainly allocentrically tuned, whereas the parahippocampal gyrus contains cells that appear to be allocentrically or egocentrically tuned and can perform transformations between egocentric and allocentric representations (as discussed in section 1.6.2). Thus, the intact function of cells in the latter region may be of particular importance for successful performance on the 4MT.

One may argue that the right parahippocampal gyrus area 4 was found to have a stronger link with performance on the 4MT (than the right hippocampus, right parietal cortex, and other areas of the right parahippocampal gyrus) because by chance there may not have been many patients with damage to the right hippocampus, right parietal cortex, and other areas of the right parahippocampal gyrus in the group that I assessed. However, this is unlikely to be the case. There were many patients whose lesion involved the right hippocampus (either or both the anterior and posterior part) and/or the right parietal cortex, and the number of

patients with damage to the right parahippocampal regions as defined by the AICHA atlas were: four patients in area 1, seven patients in area 2, one patient in area 3, six patients in area 4, and seven patients in area 5.

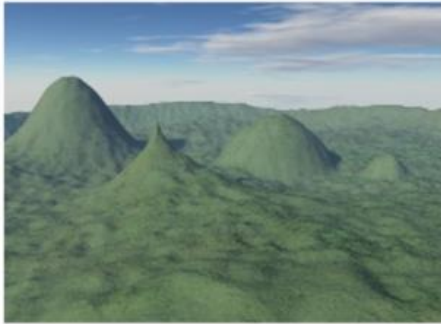
6.5.5 Limitations and future directions

Although the healthy subjects from the previous studies from which I gathered the 4MT raw data were age- and education-matched to the stroke patients in the current study, I could not compare the presence and severity of small vessel disease, and the volume of different brain regions between these groups, because of the unavailability of these data. It has been shown that higher stroke risk is associated with lower right hippocampal volume and more white matter hyperintensities (Zsoldos et al. 2020). Thus, I cannot exclude the possibility that more severe small vessel disease and lower hippocampal volume were the reasons that stroke patients performed poorer than those healthy individuals.

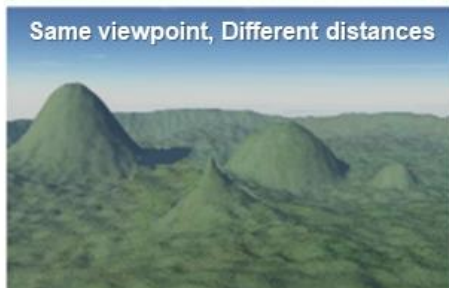
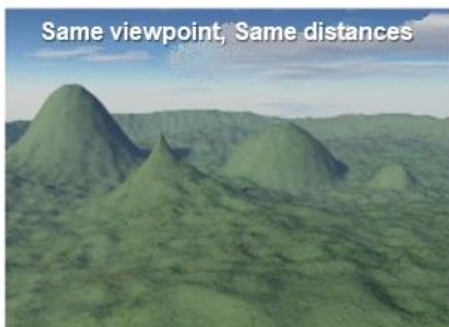
There are some features that could be modified in future versions of the 4MT, so that it can provide a clearer understanding of spatial memory deficits following stroke. First, to facilitate participants' understanding of the landscape and the possible viewpoints from which the mountains could be seen, a bird's eye view of the landscape (Figure 6.3) could be shown in the practice session of the 4MT. Second, the 4MT is unable to disentangle whether a memory deficit is due to problems in encoding, storage, or retrieval. Future studies could address this by including two testing sessions: one session immediately after the scene was shown (in which they could be asked to describe the scene from memory) and one session after a delay interval. Third, patients' deficits could be in egocentric memory, allocentric memory, or both, but the 4MT does not clearly differentiate between these deficits. Future studies could use a slightly altered version of the 4MT, in which there is a much clearer distinction between the allocentric and egocentric conditions. Fourth, the angle change

between the sample and correct image are not always the same across trials; it can range from about 15 degrees to about 90 degrees. The different levels of angle change may reveal differences in the severity of egocentric memory deficits. Fifth, to examine whether patients' impaired performance was because there was a deficit in changing viewpoint or a deficit in the ability to remember a spatial layout (the distances between the mountains and their order without there being a change of viewpoint), future studies could use an adapted version of the 4MT in which there is no change of viewpoint (similar to the no-rotation task used by Urgolites and colleagues 2017). Sixth, many people tend to perform at the same level. Thus, increasing the number of trials may increase interindividual variability in task performance. Finally, in the 4MT, the scenery is very similar across trials, so there may have been some degree of proactive interference. Therefore, any error may have been due to a deficit in inhibiting images of previous trials and encoding the image of the next trial, rather than impaired retrieval, or it could be due to a deficit in a combination of these processes. Future studies using the 4MT could use an adapted version in which each trial would involve different types of scenery, so that proactive interference is reduced. For example, one trial could include sand dunes, and another could be mountains with snow. An alternative version of the 4MT which may be able to surpass most of these limitations is shown in Figure 6.14. However, it should be acknowledged that the current version, as used here, allowed the testing of a large patient group and subsequent comparison with other patient populations.

Encoding



Recognition



Irrespective of viewpoint, is this the same scene as before?

Is this the exact viewpoint from which you saw the scene previously?

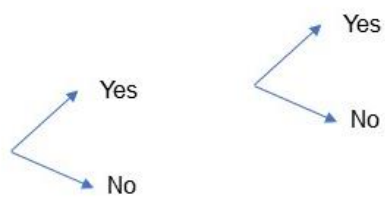
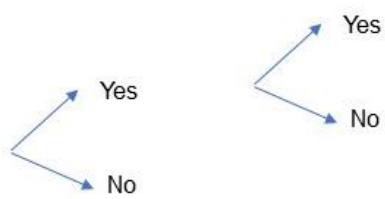
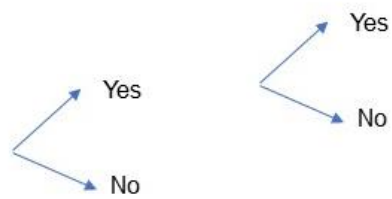
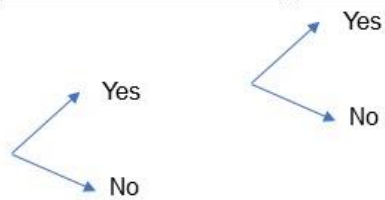


Figure 6.14. Example of a trial from an adapted version of the 4MT

At the start of the experiment, participants would be shown the landscape from which the pictures are taken (for example see Figure 6.3). In the encoding session, participants would be presented with the top image and in the recognition session they would see one of the four images shown at the bottom of this figure. The grey boxes show the questions they would be asked for each image. The second question would be asked only if the participant answers “yes” in the first question. These questions would likely enable a clearer differentiation between allocentric and egocentric aspects of memory. Participants would be told to pay attention only to the mountains, not the weather conditions, because the latter would be different across these images. The amount of distance and viewpoint change could differ across trials so that differences in the severity of egocentric and allocentric memory deficits could be detected. The type of scenery, for example, green hills, sand dunes, and mountains with snow, would differ from one trial to the next. Note that no words would be shown with the stimuli; these are displayed here solely for illustration purposes.

It has recently been shown that interindividual differences in the ability to perceptually discriminate between very similar scenes and objects, can contribute to interindividual differences in the ability to discriminate old from new objects (which differed in very few details) in a forced-choice memory paradigm (Gellersen et al. 2020). In the current experiment, I was unable to perform a quantitative analysis of the patients’ performance on the perception trials of the 4MT, to examine whether they also had a deficit in *perceiving* complex visual scenes and whether the parahippocampal gyrus is also significantly associated with performance on these trials. The reason is that these were only two perception trials and they were part of the practice session in which I guided participants through what they needed to do. Thus, future studies could use the full version of the perception subtask of the 4MT as has been used in previous studies (Bird et al. 2010; Moodley et al. 2015).

6.6 Conclusion

To my knowledge, this is the largest to date study examining spatial memory in stroke patients using lesion network mapping and voxelwise lesion analyses. Both right and left hemisphere stroke patients performed significantly worse than healthy elderly subjects at a group level (even though none of the patients had spatial neglect, aphasia, or hemianopia), and in fact

performed as poorly as some groups of mild cognitive impairment and Alzheimer's disease patients. Importantly, stroke patients' performance was correlated with activities of daily living. This indicates that spatial memory deficits should be screened for more frequently following stroke, and the 4MT may be an appropriate test to examine these deficits. Future studies using the 4MT should also analyse the types of errors (not only the total number of errors), given the importance of this analysis as has been documented in this study.

Because some patients were more impaired than others, I examined which regions were associated with the poorest performance on the 4MT and whether these regions were part of a spatial memory network. Lesion symptom mapping and lesion network mapping showed that the most important areas for spatial memory seem to be in the right hemisphere, specifically the posterior parahippocampal gyrus, the hippocampal part of the cingulum bundle, and the following two networks: a) posterior cingulate gyrus, parahippocampal gyrus, superior parietal lobule, hippocampal part of the cingulum bundle, and splenium of the corpus callosum, and b) anterior nuclei of the thalamus, posterior hippocampus, anteroinferior part of the supramarginal gyrus, posterior insula, and the anteroinferior part of the paracentral lobule. In the left hemisphere stroke group, there were no clear anatomical findings, possibly due to diaschisis and less widespread lesions.

7 General Discussion

7.1 Introduction

This final chapter summarizes the main results of the experimental chapters, how they relate to previous literature, potential general limitations of the work presented in this thesis, as well as directions for future research.

7.2 Summary of Main Results

The studies discussed in this thesis examined different aspects of memory in healthy ageing and in stroke patients, as well as their neural correlates. In Chapter 2, I described the various screening tests and standard neuropsychological tests that were used in the studies presented in this thesis, the rationale for performing these tests, and the results from the screening procedure. In Chapter 3, the methods used for lesion analysis and the advantages and disadvantages of each method were explained.

The study described in Chapter 4 was designed to explore the importance of self-perspective features of episodic memory, by assessing whether there is any correlation in performance between a laboratory-based task that examines egocentric features of memory of 2D scenes and a task that examines memory for autobiographical events. No strong correlation was found between episodic memory for 2D scenes and episodic memory for real-life autobiographical events in either young or elderly subjects, and healthy ageing did not affect discrimination ability in the object position shift or viewpoint shift condition of the episodic picture task. Previous studies have used a similar laboratory-based task, but rather than presenting the objects as pictures on a screen, they were real objects shown in a 3D environment (Kapsetaki et al., under review; Russell et al. 2019). Compared to the experiment

in Chapter 4, the first study (Kapsetaki et al., under review) found a positive and more significant relationship between performance on the autobiographical memory interview and on the laboratory-based task, and the second study (Russell et al. 2019) found more deficits in memory for egocentric perspective in healthy elderly subjects. The results from the chapter highlight the disparity between memory for events experienced in a 2D compared to a 3D environment.

However, even when the encoded scenes in the laboratory-based task were 3D (Kapsetaki et al., under review), only a weak correlation was found between performance on that task and performance on an autobiographical memory interview. This suggests that some other features may be lacking from events as presented in laboratory-based tasks which differentiate them from real-life events. One of these features is temporal order information. According to Tulving (1972, 1983, 2002), episodic memory does not only involve remembering spatial information, but also temporal information. Therefore, in the study described in Chapter 5, a laboratory-based episodic memory task was developed which, apart from memory for egocentric and allocentric spatial representations, also assessed memory for temporal order. Further, the events were presented in a real 3D rather than a 2D environment. This task was used to examine which brain regions are critical for memory for egocentric, allocentric, and temporal order information by assessing a group of patients with a first unilateral stroke who did not have spatial neglect, hemianopia, or aphasia at time of testing. Voxelwise statistical analyses showed that damage to the right intraparietal sulcus was associated with worse memory for temporal order, but did not show that damage to medial temporal lobe regions was associated with lower accuracy in the allocentric memory condition, or that damage to parietal lobe regions was associated with lower accuracy in the egocentric memory condition and lower confidence ratings.

The primary aim of the experiment in Chapter 5 was to use a novel paradigm to examine different aspects of memory within a relatively small selected group of patients with focal brain lesions, rather than in comparison with control groups. In contrast to this approach, in the study using the 4MT in stroke patients, described in Chapter 6, I was able to test a large group of patients with a paradigm that has been tested in other populations. The 4MT primarily tests allocentric memory for visual scenes and was developed to detect early spatial memory deficits in Alzheimer's disease (Bird et al. 2010; Hartley et al. 2007). Both a large group of patients who suffered a first right hemisphere cerebral stroke and a large group of patients who suffered a first left hemisphere cerebral stroke performed worse than age- and education-matched healthy control subjects, and in fact performed as poorly as some groups of mild cognitive impairment and Alzheimer's disease patients. Critically, none of the stroke patients had spatial neglect, hemianopia, or aphasia at the time of testing—ruling out the possibility that these other cognitive deficits might be contributing to poor performance. Importantly, stroke patients' performance on the 4MT was correlated with activities of daily living, highlighting the potential functional relevance of spatial memory impairment following stroke.

The second aim of the final experimental chapter was to use the 4MT in stroke patients to examine which brain regions are critical for memory for spatial information by using voxelwise descriptive and statistical analyses, as well as lesion network mapping. I was able to identify a network of right (but not left) hemisphere regions, specifically the posterior parahippocampal gyrus, the hippocampal part of the cingulum bundle, and the following two combinations: a) posterior cingulate gyrus, parahippocampal gyrus, superior parietal lobule, hippocampal part of the cingulum bundle, and splenium of the corpus callosum, and b) anterior nuclei of the thalamus, posterior hippocampus, anteroinferior part of the supramarginal gyrus, posterior insula, and the anteroinferior part of the paracentral lobule.

Together, these studies provide additional insights into: a) how memory for events can differ depending on the type of environment in which they are experienced, b) which brain regions are important for memory for egocentric, allocentric representations, and temporal order information, and c) whether these aspects of memory are affected following stroke. These are discussed in more detail below.

7.3 Implications

7.3.1 Differences in memory depending on the format in which stimuli are presented

No strong correlation was found between an episodic picture task assessing memory for spatial information and a task assessing memory for autobiographical real-life events. This poses the question as to what is different between these processes. Is the lack of a correlation due to the fact that the events presented in these tasks differ in both the number of sensory stimuli and in their dimensions?

Previous studies have shown that real objects are more attention-capturing than 3D-like images or 2D images of the same objects (Gomez et al. 2018). Furthermore, infants prefer looking at real objects compared to photographs of these objects (Gerhard et al. 2016), and real objects are remembered better than colour photographs or line drawings of these objects (Snow et al. 2014). Also, in another study, objects that had been seen in an immersive virtual reality environment were recognized more vividly compared to the same objects observed in the same environment but on a 2D screen (Kisker et al. 2019).

A number of studies have shown that real objects are processed in somewhat different brain regions to those that process photos of the same objects (Freud et al. 2018; Marini et al.

2019; Perani et al. 2001; Snow et al. 2011), and somewhat different regions underlie memory for real-life events compared to memory for events encoded in a laboratory-based paradigm (involving auditory, olfactory stimuli, words, or pictures of objects, faces, or scenes) as has been shown in neuroimaging studies (Cabeza et al. 2004; Chen et al. 2017; Fink et al. 1996; Gilboa 2004; McDermott et al. 2009; Monge et al. 2018; Nyberg et al. 2002). Conforming to this, patients with agnosia are better able to recognize real objects than line drawings of objects (Chainay and Humphreys 2001; Grossman et al. 1997; Hiraoka et al. 2009; Holler et al. 2019; Humphrey et al. 1994).

The three main paradigms that I employed (Figure 7.1) are clearly more like a real-life event compared to remembering a list of words, but still lack the complexity of a real-life autobiographical event. Although the images in Figures 7.1A and 7.1C include shadows which introduce depth to the scene and thus have some characteristics of 3D scenes, the fact that they are shown on a screen means that they lack additional depth cues that would be present in a real-life environment. The spatio-temporal task (Figure 7.1B) has greater ecological validity compared to the episodic picture task (Figures 7.1A) and the 4MT (Figures 7.1C) because it involves remembering real stimuli in a real environment, which means it may be a more valid representation of memory in a real-life situation. Also, it is important to note that it is easier to recognize novel views of symmetrical as opposed to asymmetrical objects (Vetter et al. 1994). Therefore, object recognition from different viewpoints may have been easier in the 4MT compared to the other two tasks because the mountains are radially symmetrical. The key advantage in using artificial and laboratory-based scenes in experiments is that this allows control and manipulation of every aspect of the task. Moreover, none of the participants would have seen the scenes before, thus avoiding any familiarity effect which might potentially have occurred if they were shown real-life scenes.



Figure 7.1. Examples of scenes shown in the three main tasks of this thesis

A) Example of an image shown in the 1st experiment (scenes in both the encoding and testing session were shown on a computer screen); B) Snapshot of one of the head-camera videos in the 2nd experiment; in the encoding session, participants observed real-life scenes (real objects on a table), whereas in the testing session they saw videos on a computer screen; C) Example of an image shown in the 3rd experiment (scenes in both the encoding and testing session were shown on an iPad screen)

7.3.2 Is spatial memory affected following stroke?

Most studies examining spatial memory in stroke patients have used the Corsi block task or variations of it. However, some important limitations were detected by using this as a control task in my experiments. Importantly, in this thesis, stroke patients' spatial memory abilities were assessed using two tasks that examine memory for spatial locations distinctively from memory for other types of information, for example, temporal order. Also, in previous studies, spatial memory impairment has mainly been examined in the context of spatial neglect where it has been shown to be an important contributor to clinical severity (e.g. Malhotra et al. 2004; Pisella et al. 2004). The study in Chapter 6 specifically excluded patients with spatial neglect and found that in both left and right hemisphere damage groups, spatial memory was affected to the same degree as neurodegenerative conditions such as Alzheimer's disease. Patients' poor performance on the 4MT is in line with previous studies that assessed quite a small number of stroke patients who did not have hemianopia or spatial neglect (the largest of these studies included 61 patients; van Asselen et al. 2009; van Asselen, Kessels, Neggers, et al. 2006; Duffin et al. 2012; van der Ham et al. 2012; Kessels, Kappelle, et al. 2002; Rossit et al. 2011), and found that these patients showed deficits in remembering spatial information. However, most of these studies included patients who had (or had not been screened for) aphasia, which may have contributed to poor performance on the memory tasks. Furthermore, the memory tasks used in most of these studies (remembering black dots or grey-scale 2D objects on a white background) may not be as ecological as the 4MT.

There are many reasons why the stroke group that participated in the study of Chapter 6 performed quite poorly on the 4MT, but the stroke group that participated in the study of Chapter 5 made only a few errors in the spatial memory trials of the spatio-temporal task. First, most of the patients I tested on the 4MT were in the acute post-stroke stage (median days post-stroke = 9), whereas for the spatio-temporal task most patients were in the more chronic

stage (median days post-stroke = 312). Although there is the possibility of maladaptive plasticity in the chronic stage, two other mechanisms are likely to underpin improved cognitive function at a chronic stage. These are: a) diaschisis in the acute stage which can cause dysfunction in anatomically distant regions, and b) positive plasticity in the chronic stage which can lead to recovery of function. Second, the patients who were tested on the 4MT were three years older and had one year less education compared to the patients who were tested on the spatio-temporal task (these were differences in the medians of each group). These factors may have influenced performance on the 4MT.

Third, the 4MT may be a more challenging task. As it is a 4-alternative-forced-choice task (compared to the spatio-temporal task which is a 2-alternative-forced-choice task), the potential for interference is greater and chance performance is lower (Hou et al. 2015; Kingdon and Prins 2016). Compared to the spatio-temporal task, in the 4MT there are more stimuli to remember per scene (four rather than two), the stimuli are not real-life 3D objects (and thus may be less well remembered; Snow et al. 2014), and they are presented for a shorter duration. Other factors that may have facilitated performance on the spatio-temporal task are that in the encoding phase the stimuli are larger and further apart in distance and in depth compared to the scenes encoded in the 4MT. A previous study has shown that separating stimuli in both 2D space and in depth improves visual working memory performance (Chunharas et al. 2019). Another difficulty in performing the 4MT is that there is a lot of overlap across trials. That is, the stimuli in the 4MT are very similar across trials compared to the spatio-temporal task; in the spatio-temporal task the stimuli are completely different, whereas in the 4MT the stimuli are always mountains with slight differences in their shades of green, their width (the horizontal distance of the base of the mountain as measured on the screen can vary between 0.5 and 5 centimetres), and their height (which can vary between 0.5 and 3 centimetres).

Fourth, the two tasks may tap into different processes. The spatio-temporal task involves more episodic memory resources than the 4MT which involves more working memory resources, because the delay interval is much longer in the spatio-temporal task compared to the 4MT. This is supported by the stronger correlation of the Corsi forward total score with performance on the 4MT than with performance on the spatio-temporal task. Lastly, performance on the spatio-temporal task may have been facilitated by another important factor. Unlike the 4MT, in the spatio-temporal task each stimulus was presented at the centre of one of the squares of a salient grid. This postulation is based on previous studies which found that memory for object locations was superior: a) in environments that did versus those that did not contain a square grid (Bestgen et al. 2013; Edler et al. 2014, 2015; Leifert 2011), b) in a square environment compared to a trapezoid environment, possibly because the trapezoid environment distorts grid-cell based computations (Bellmund et al. 2020), and c) when objects were presented at the centre of grid squares compared to being presented chaotically on the grid (Leifert 2011).

A number of lesion studies have explored which brain regions may be important for remembering spatial information. However, many of them have included a relatively small number of patients. Moreover, some patients in these studies had anoxia or traumatic brain injury. The widespread damage that can be present in these conditions is often undetectable or underestimated with conventional imaging methods (Baldursdottir et al. 2010; Choi et al. 2012; Govindaraju et al. 2004; Haber et al. 2018; Jolly et al. 2020; Scheid et al. 2003; Tong et al. 2003). This means that the lesion localization may not have been very precise. Also, some of these patients had conditions that may have affected their performance such as spatial neglect, aphasia, and hemianopia. To my knowledge, the only two previous studies that have used voxelwise statistical analyses to examine spatial memory in a group of stroke patients, included patients with spatial neglect (Rossit et al. 2011) or the task required also intact memory for temporal order (Kraft et al. 2015). By using the approach described in Chapter 6,

I was able to address some of these issues, and found that a network of brain regions seems to be important for remembering spatial locations. Many of the regions in this network are part of the “posterior medial system” and have been previously shown to be associated with spatial processing (egocentric and/or allocentric representations), spatial memory, and navigation (neuroimaging and lesion studies discussed in Chapters 1 and 6).

7.3.3 Is the parietal lobe critical for memory confidence and accuracy for egocentric representations?

Although parietal lobe regions were part of the spatial memory network identified using the 4MT, this task does not clearly differentiate between egocentric and allocentric memory, in contrast to the spatio-temporal task of Chapter 5 which was designed to more clearly distinguish between these two aspects of memory.

The results presented in Chapter 5 did not show differences in egocentric memory accuracy between patient groups with posterior parietal lobe damage and patient groups without damage to this region nor any association between egocentric memory accuracy and parietal lobe regions in the voxelwise statistical analyses. This is in contrast with a number of studies showing that the parietal lobe seems to be involved in egocentric representations in navigation (Ciaramelli, Rosenbaum, et al. 2010; Seubert et al. 2008; Weniger et al. 2009) and autobiographical memory (Bonnici et al. 2018), and with the only previous lesion study examining egocentric representations in spatial memory (without involving navigation), which found that the parietal lobe, in particular the angular gyrus, is involved in this function (Russell et al. 2019). Some studies have reported that patients with posterior parietal lobe involvement may have a more subtle impairment of episodic memory processes than straightforward reduction in memory accuracy. When performing memory tasks involving words or 2D stimuli, these patients seem to have a diminished subjective experience of remembering, despite

intact memory accuracy (Ciaramelli et al. 2017; Davidson et al. 2008; Hower et al. 2014; Simons et al. 2010). However, the results of Chapter 5 do not conform with these findings.

There are a number of potential reasons for these discrepancies with the previous literature. First, performance on the spatio-temporal task was at, or near, ceiling which suggests that this task was not sensitive enough to detect subtle memory impairment for egocentric representations. Due to the (near) ceiling performance, I could not analyse both confidence ratings for correct trials and confidence ratings for incorrect trials to examine whether subjective performance measures accurately reflect objective performance measures in patients with posterior parietal lobe damage. Second, the studies mentioned above did not include systematic lesion analysis (e.g. voxelwise statistical analysis) in an anatomically unselected group of patients. For example, some studies (Ciaramelli et al. 2017; Ciaramelli, Rosenbaum, et al. 2010; Davidson et al. 2008; Hower et al. 2014; Russell et al. 2019; Simons et al. 2010; Weniger et al. 2009) assessed patients with parietal lobe involvement but not patients without parietal lobe involvement, and another study (Seubert et al. 2008) that did examine two groups of patients (parietal and non-parietal involvement) included only four patients in each group; one of these patients had anoxia (possibly widespread damage) and more than half of them had aphasia (likely impeding their performance).

7.3.4 Are medial temporal lobe regions critical for memory for allocentric representations?

Medial temporal lobe regions were linked to memory accuracy in the 4MT. This is in line with previous case studies showing that bilateral hippocampal damage (due to conditions other than stroke) can lead to allocentric spatial memory deficits (Banta Lavenex et al. 2014; Holdstock et al. 2000; King et al. 2002) and that a patient with a stroke involving, among other regions, the right posterior hippocampus and right parahippocampal cortex, performed poorly

on the 4MT (Hartley et al. 2007). However, neither the hippocampus nor the parahippocampal gyrus were associated with memory accuracy in the object position shift condition in the spatio-temporal task of Chapter 5, which may have been because very few of the participants in that experiment had damage to these regions, and of these patients, most had only a few voxels damaged in these regions.

Apart from the difference in the number of patients with medial temporal lobe damage in the experiments of Chapters 5 and 6, another possible reason why the right parahippocampal gyrus was found to be significantly associated with performance on the 4MT but not with performance in the object position shift condition of the spatio-temporal task, is that the parahippocampal gyrus may be involved solely in processing an open spatial layout but not in allocentric representations. The spatio-temporal task shows a less open spatial environment and contains less spatial layout information compared to the 4MT. Previous studies have found that the parahippocampal gyrus is more active for open environments, scenes, and objects within a spatial layout, compared to closed environments and objects that are not shown within a spatial layout (Epstein, Higgins, et al. 2007; Epstein, Parker, et al. 2007; Harel et al. 2013; Henderson et al. 2008; Kravitz et al. 2011).

Therefore, further work is needed to fully address the above-mentioned question, including a larger sample of patients with parahippocampal gyrus and hippocampal involvement. Future studies could also examine whether these regions are critical for perceiving or remembering allocentric representations (or both), by administering the full version of the spatial perception subtask of the 4MT in addition to the subtask that assesses spatial memory.

7.3.5 Are parietal lobe regions critical for memory for order across domains?

Damage to right parietal lobe regions (intraparietal sulcus and lateral parietal cortex) led to worst memory accuracy for temporal order in the spatio-temporal task (only the right intraparietal sulcus remained significant after regressing for lesion volume). This conforms with a study that found that two stroke patients with damage to the right lateral parietal cortex had deficits in remembering temporal details about past autobiographical events (Berryhill et al. 2007). My analyses also showed that damage to the right intraparietal sulcus was associated with: a) worse performance on the Corsi block task (only when not regressing for lesion volume), a task that requires memory for both spatial locations and temporal order, and b) more ordinal errors on the 4MT (suggesting that patients with right intraparietal sulcus damage could not remember the spatial order of the mountains; this was found only when not regressing for lesion volume).

The fact that this region was found to be associated with different types of order information is in line with functional neuroimaging studies showing that the right intraparietal sulcus is activated when retrieving the order in which past autobiographical events had occurred or imagining the order in which future autobiographical events may occur (D'Argembeau et al. 2015), when encoding, maintaining, and retrieving (after a 7-second delay) the spatial order of either words or faces (Majerus et al. 2010), when mentally reversing the temporal order of auditory stimuli of different frequencies (Zatorre et al. 2010), when making judgments about the spatial order of letters (Marshuetz et al. 2000), numerical and alphabetical order judgments (Attout et al. 2014), when observing movies of actions (Manthey et al. 2003), when imagining movement sequences (Munzert et al. 2008), and when executing motor and task sequences (Jubault et al. 2007). Therefore, this region seems to be critical for processing order information across multiple domains.

However, because most of the tasks mentioned above (including my experiments) do not clearly differentiate between temporal order and spatial order, it is difficult to know whether the right intraparietal sulcus is involved in both processes or actually only one of these. As the stimuli for which order was assessed in my experiments were located at different positions (in the Corsi block task, in the ordinal foils in the 4MT, and in the temporal order trials of the spatio-temporal task), each of these tasks may have assessed memory for temporal order or memory for spatial order or both, depending on the strategy used. For example, if participants used a strategy of “navigating” from the left to the right mountains in the 4MT, then they would have seen the mountains on the left first and the mountains on the right last, thus implying that they had used a temporal order strategy. In the spatio-temporal task, if participants had used a strategy in which they encoded the temporal order of objects as, for example, “left to right” or “near to far”, then this would involve memory for spatial order rather than temporal order. Thus, future studies could examine whether the brain regions that support memory for spatial order are separate to those that support memory for temporal order by using tasks that can more clearly differentiate between the two processes. For example, a task that examines purely memory for temporal order could involve stimuli that are all presented only in one location. This approach was not taken in my experiments, because I aimed to test both memory for temporal order and memory for spatial information using one paradigm.

7.3.6 Translation to the clinic and to other clinical populations

Stroke is most frequently linked with deficits in motor skills, language, and attention rather than memory. The fact that stroke patients as a group were impaired on the 4MT and performance on this task correlated with activities of daily living scores indicates that spatial memory deficits should be screened more frequently following stroke, and the 4MT seems to be an appropriate test to examine these deficits. A frequently used tool for screening cognitive deficits in the acute stage post-stroke, the Oxford Cognitive Screen (Demeyere et al. 2015), does not assess

memory for spatial information, and in the latest version of this tool (OCS-Plus; Demeyere et al. 2020) the only test that assesses memory for non-verbal information is a task in which participants are shown a complex 2D figure which they are asked to copy and remember, and then are asked to draw it immediately after it disappears. However, performance on this task can be affected by impaired upper limb motor function, visuospatial praxis, or construction planning. My findings suggest that more “pure” tests of spatial memory need to be incorporated in future screening tools of cognitive deficits following stroke. Clinicians need to be aware that even if stroke patients do not have damage to core memory regions such as the hippocampus or other medial temporal lobe regions, they still may have memory deficits which may be impacting their daily activities, given that many regions (some of which were not in the medial temporal lobe) were found to be related to memory for spatial information or temporal order in my analyses. Also, the fact that certain regions were found to be critical for confidence judgments suggests that stroke patients with damage to these regions may not be able to correctly judge their own memory abilities, may be unaware of their memory deficits, and thus may not report difficulties with memory.

Additionally, an adapted version of the paradigm introduced in Chapter 5 could be used to assess memory for egocentric, allocentric, and temporal order information in other clinical populations, for example, mild cognitive impairment. Although there have been studies assessing these aspects of memory in individuals with mild cognitive impairment (Bellassen et al. 2012; Deipolyi et al. 2007; Gillis et al. 2013; Hort et al. 2007; Kasper et al. 2016; Laczó et al. 2010; Pirogovsky et al. 2013; Plancher et al. 2012; Ruggiero et al. 2018; Rusconi et al. 2015; Schmitter-Edgecombe et al. 2009; Serino et al. 2015; Weniger et al. 2011), they did not use one paradigm to test all three aspects, they mostly used navigation tasks, and the delay interval was often only a few seconds. Using a single paradigm may provide a more accurate estimation of which aspects of memory are mostly affected in these individuals, because the stimuli and the environment in which they are presented are the same across conditions

(egocentric, allocentric, and temporal order). Tasks with longer delay intervals seem to be more sensitive and specific in distinguishing mild cognitive impairment from healthy ageing (Rabin et al. 2009) and in predicting mild cognitive decline over one year in healthy elderly subjects (Wearn et al. 2020).

7.4 Limitations and future directions

7.4.1 Selection of participants and blinding

A minor limitation of the experiments presented in this thesis, is that it was difficult for the assessor to be blinded. For example, in the experiment of Chapter 4, I knew the age of the participants when administering the tests. Also, although the scorers of the interview did not know in which age group each participant was, by reading the events one could sometimes estimate the age, for example, if they were describing an event occurring in World War II. Furthermore, in Chapters 5 and 6, I needed to know whether the participant was healthy or had suffered a stroke and which hemisphere was lesioned, because different tests were administered to each group.

Participants in the experiments of the current thesis may not have been representative of the whole population. The exclusion of patients who, on the day of testing, had hemianopia, spatial neglect, aphasia, or previously diagnosed cognitive impairment, means that the patients included in my studies were not representative of all stroke patients, and thus I am likely to be underestimating the true level of spatial memory deficits. Additionally, it was difficult to recruit patients who were at the very acute stage because this is when they most frequently had spatial neglect, aphasia, and hemianopia.

7.4.2 Potential confounding factors

Factors that may potentially have confounded the results are differences in the time of day that participants were tested, mood on the day of testing, personality, motivation, curiosity, genotype (Barral et al. 2014; Blokland et al. 2011; Heck et al. 2014; Papassotiropoulos et al. 2011; Zhu et al. 2018), the amount of travel, and what kind of environment they had grown-up in, e.g. in cities or outside cities (Coutrot et al. 2020). In Chapters 5 and 6, I could have included a control group such as patients who were hospitalized in the Neurology Department whose brain scan did not confirm a stroke, for example, patients with transient ischaemic attack. The stressors associated with hospitalization, the risk factors, and comorbidities (e.g. small vessel disease) would be very similar to stroke patients, but these patients would not have had a brain lesion.

In the experiments where I assessed stroke patients, it was impossible to determine how individuals would have performed on this same experiment before their stroke. Stroke patients' poor performance on the memory tasks may not have been due to their stroke but due to undiagnosed pre-stroke cognitive impairment. Furthermore, some patients in my experiments reported that "I was never good at geometry" or "I have always found it hard of thinking about scenes or spaces". An ideal situation would be to compare each patient's performance just before and just after the stroke, but clearly this is not feasible. An alternative approach would be to use questionnaires that could: a) detect pre-stroke cognitive impairment, for example, administering the Informant Questionnaire on Cognitive Decline in the Elderly (Jorm and Korten 1988) to a close relative of the patient, and b) ask about patients' pre-stroke ability to perceive spatial information such as geometry, distances, and shapes (administered to the patient and a close relative). The latter questionnaire could have also been administered to healthy participants in Chapter 4 to examine whether interindividual differences in perceiving scenes may have confounded the results.

Stroke patients (especially those with large lesions) often have deficits in many cognitive domains and thus it is difficult to discern whether and how much they contribute to memory impairment (Nys et al. 2005). Although patients in my studies were screened for hemianopia, spatial neglect, and aphasia, they did not undergo extensive neuropsychological screening. Thus, I cannot know whether poor performance on the memory tasks was because they had a “pure” memory deficit for the particular information examined on those tasks or rather because they had a range of other potentially relevant cognitive deficits that were not screened for. For example, impaired temporal order memory may be secondary to deficits in strategic processing, that is, the ability to devise and retain strategies for organizing the information that is being encoded and retrieved (Fuster 1995; Mangels 1997).

7.4.3 Lesion analyses

Apart from the limitations discussed in Chapter 3, the major ones being (a) the lack of very high resolution structural imaging for all stroke patients (such as high resolution MRI scans and perfusion weighted imaging), (b) the inclusion of patients from both the acute and chronic stage, and (c) the bias of stroke lesion location by the vascular architecture, there are further caveats pertaining to the lesion analyses performed in this thesis which are important to consider. I was not able to compare between patients with lesions restricted to particular areas of interest (e.g. only to the angular gyrus or only to the parahippocampal gyrus or only to the hippocampus), although this could be carried out in future studies. However, it is very rare for a stroke to be restricted to only one anatomical region. It is also very rare for a stroke patient to have bilateral lesions affecting one particular region. Thus, I was unable to examine whether, for example, both angular gyri need to be damaged to cause a deficit in egocentric memory accuracy.

By excluding patients with aphasia, hemianopia, and spatial neglect, the lesion analyses may have been biased towards regions that do not cause these deficits. Regions involved in language, vision, or attention are potentially in close anatomical proximity to areas involved in the memory processes I examined, and thus by excluding these patients I would not have been able to include these regions in the lesion analyses. Furthermore, as patients with haemorrhagic stroke tend to have better functional prognosis compared to ischaemic stroke patients (Paolucci et al. 2003), future studies could examine whether performance on memory tasks differs depending on the type of stroke. I did not perform this analysis in my experiments, because my sample included only a few haemorrhagic stroke patients. Apart from the regions damaged by the lesion, it is likely that pre-stroke interindividual differences in the volume of non-lesioned brain regions may have contributed to differences in performance on the memory tasks. Thus, for each patient, future studies could analyse both the brain regions damaged by the stroke and the volume of the non-lesioned regions.

Finally, in order to have a clearer understanding of what role each brain region (that I found as significant) has in each aspect of memory I examined, future studies could use alternative approaches. For example, although I was able to identify which brain regions are significantly associated with the number of total errors on the 4MT, I did not examine what exact process they are important for; using intraoperative single-cell recordings in patients with drug-resistant epilepsy would provide a greater insight on whether these regions are involved in any of these specific processes (which may not be mutually exclusive): a) encoding a new scene which is shown for only 8 sec, b) maintaining it for 2 sec, c) retrieving it, and/or d) manipulating it (change of viewpoint).

7.4.4 Therapeutic avenues

The approach to rehabilitation and treatment of memory deficits may need to be patient-

centred. Lesion characteristics, demographic factors, and co-morbidities may influence the potential for recovery. To examine whether patients' memory for temporal order and spatial information improves or declines in the more chronic stage depending on these interindividual differences, a longitudinal study of these aspects of memory could be conducted in stroke patients. Previous studies have examined the potential contribution of these factors in long-term recovery of cognitive deficits after stroke (Saxena et al. 2007; del Ser et al. 2005). However, they did not examine specifically memory for temporal order and spatial information, and used low-resolution brain scans potentially leading to an inaccurate estimation of the lesion characteristics.

To clearly understand the aetiology underlying the memory deficits present in certain stroke patients is of potential importance for identifying therapeutic targets. Brain stimulation could be a technique for improving these deficits. To date, there is no clear consensus on the effectiveness of brain stimulation in improving memory (Galli et al. 2019; Tan et al. 2020). There have been brain stimulation studies examining memory in healthy elderly subjects (Goldthorpe et al. 2020), epileptic patients (Natu et al. 2019), Alzheimer's disease patients (Boggio et al. 2012), and in rat models of ischaemia (Gondard et al. 2019). Also, there have been studies using brain stimulation in stroke patients assessing its effect on nonspatial aspects of memory, e.g. memory for pictures of objects (Shaker et al. 2018) or faces (Lu et al. 2015), motor learning (Hamoudi et al. 2018), verbal working memory (Jo et al. 2009; Kim et al. 2010), and verbal learning (Kazuta et al. 2017; Kim et al. 2010). But only two brain stimulation studies in stroke patients have used spatial memory tasks: the Corsi block task (Szépfalusi et al. 2017) and a visual learning test for visuospatial memory (Park et al. 2013). Both of these studies did not examine the effect of transcranial direct current stimulation (tDCS) on its own, but the combined effect of a cognitive training program together with tDCS. Szépfalusi and colleagues (2017) found that performance on the Corsi block task had a tendency to improve after the cognitive training program in both the sham and active tDCS

group (anode on the midline anterior frontal cortex). However, they did not report whether there were significant differences in improvement between the two groups. Park and colleagues (2013) found that patients who received anodal tDCS over the bilateral prefrontal cortex combined with a cognitive training program did not perform significantly better on a visual learning test for visuospatial memory compared to patients who received sham tDCS and completed the cognitive training program.

Previous studies may not have found a memory improvement post-stimulation because of targeting the wrong regions. The approach taken in this thesis aimed to identify the key regions in the development of specific memory deficits, which indicates that, if replicated in future studies, this may help determine which network of regions would be best to target depending on the lesion of each patient. Some limitations of conventional, currently used, non-invasive brain stimulation techniques are that: a) they can only target regions that are near the scalp because the current is weak (thus many of the regions that were found in my analyses cannot be directly targeted), and b) the spatial resolution is relatively diffuse due to skull dispersion. However, novel non-invasive techniques (see for example Grossman and colleagues 2017) may be able to focally stimulate regions that are deep in the brain without recruiting superficial brain regions. Thus, further work is needed to examine whether novel brain stimulation techniques that enhance the functionality of a network of brain regions can improve memory for spatial information in stroke patients.

Additionally, a specific sleep, physical exercise, and diet regime (Shaikh and Coulthard 2013), as well as rehabilitation using spatial memory, navigation, or mental imagery tasks (Boccia et al. 2019), may improve stroke patients' spatial memory abilities. The comparative advantage of remembering 3D (compared to 2D) objects and scenes (Gomez et al. 2018; Kisker et al. 2019; Snow et al. 2014) can be applied to developing effective education and re-education strategies (e.g. Bara and Kaminski 2019). Virtual reality navigation training

programs have been piloted in small groups of stroke patients and have shown promising results (Claessen, van der Ham, et al. 2016; Kober et al. 2013; Lam et al. 2006), but these studies did not examine whether the benefits found in those tasks transferred to actual improvement in stroke patients' performance in real-life novel environments. Nevertheless, previous studies have found a moderate to strong correlation between performance on real-world navigation tasks and performance on 3D-like virtual reality navigation tasks (Busigny et al. 2014; Coutrot et al. 2019; Cushman et al. 2008). Even though spaces shown on a computer screen (compared to navigating in a real environment) do not involve vestibular or proprioceptive cues, a previous study found that grid cells do fire when non-human primates are viewing still scenes on a computer screen (Killian et al. 2012).

7.5 Conclusion

The work presented in this thesis explored the importance of self-perspective in episodic memory, which brain regions are essential for remembering temporal order information and spatial information (for example, egocentric and allocentric representations), and whether these aspects of memory are affected following stroke. This was achieved by addressing some of the issues of previous studies that examined memory in stroke patients, such as the presence of aphasia, neglect, or hemianopia in a proportion of their participants. The lack of a strong correlation between memory for 2D scenes and memory for autobiographical real-life 3D events indicates that how we remember information presented in two dimensions in a laboratory is somewhat different to our memory for real-life events. The overall poor performance of stroke patients on a spatial memory task and its association with an activities of daily living scale, highlights the potential functional relevance of these deficits, and suggests that stroke patients should be screened more often for their ability to remember spatial information. The network of brain regions whose damage was associated with these deficits could potentially be a therapeutic target in the future.

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