Allocentric Memory and Hippocampal Function

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Abstract

The hippocampus plays a pivotal role in human memory. Previous research has showed that the hippocampus is particularly important in providing the spatial memory representations necessary for flexible navigation. The present project aimed to extend this evidence base by investigating the contribution of the hippocampus in such environmentally grounded and thereby allocentric memory representations when no navigation is required.

The Northumberland Gallery Task (NGT) was developed to separate between allocentric memory and its egocentric equivalent without imposing any navigational demands. The task was subject to extensive piloting work, which confirmed the overall reliability of the task and reduced the difficulty discrepancy between the allocentric and egocentric conditions. The role of the hippocampus in non-navigational allocentric memory was then assessed using functional magnetic resonance imaging (fMRI). The results revealed a differential hippocampal involvement when the allocentric and egocentric conditions were contrasted, which was characterised by a negative blood-oxygen-level-dependent (BOLD) signal in the allocentric condition. Although the precise neural basis for this finding could not be determined from the data, likely accounts were evaluated and multimodal imaging was recommended for future investigations.

The demonstration of differential hippocampal engagement in the NGT indicated its potential value as a measure of hippocampal function in clinical populations. The hippocampus has been proposed to play a central part in the pathophysiology of major depressive disorder. Therefore, in an explorative fMRI study, hippocampal function of a small sample of depressed patients and matched control participants was assessed. No evidence was found in support of task-dependent hippocampal dysfunction in depression. Further to this, the consistently demonstrated reduction of hippocampal volume in depression could not be replicated. Specific characteristics of the patient sample may have accounted for the general absence of hippocampal abnormalities, which will require further study in larger samples.

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List of Abbreviations

ANOVA	Analysis Of Variance
ASL	Arterial Spin Labelling
BDI	Beck Depression Inventory
BDI	Beck Depression Inventory
BDNF	Brain-Derived Neurotrophic Factor
BOLD	Blood-Oxygen-Level-Dependent
CA	Cornu Ammonis
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CMRO2	Cerebral Metabolic Rate of Oxygen
CVLT	California Verbal Learning Test
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
ECT	Electroconvulsive Therapy
EEG	Electroencephalography
EHI	Edinburgh Handedness Inventory
FEW	Family Wise Error
fMRI	Functional magnetic resonance imaging
HAM-D	Hamilton Rating Scale for Depression
HPA	Hypothalamic-Pituitary-Adrenal
HRF	Hemodynamic Response Function
ICV	Intracranial Volume
LED	Light Emitting Diod
MDD	Major Depressive Disorder
MINI	Mini International Neuropsychiatric Interview
MR	Magnetic Resonance
MWM	Morris Water Maze

NART	National Adult Reading Test
NGT	Northumberland Gallery Task
NGT-R	Northumberland Gallery Task Revised
NSWM	Newcastle Spatial Working Memory task
OLM	Object Location Memory
PET	Positron Emission Tomography
PPA	Parahippocampal Place Area
RAM	Radial Arm Maze
RAVLT	Rey Auditory Verbal Learning Test
ROI	Region Of Interest
RSC	Retrosplenial Cortex
SBSOD	Santa Barbara Sense of Direction Scale
SSRI	Selective Serotonin Re-uptake Inhibitor
STAI	State-Trait Anxiety Inventory for Adults
TL	Temporal Lobectomy
VPT	Visual Patterns Test
VS	Viewpoint-Shift
WAIS-R	Wechsler Adult Intelligence Scale Revised
WMS	Weschler Memory Scale

Chapter 1 General introduction

The representation of spatial locations in memory is a vital cognitive function that underlies our understanding of and subsequent behaviour in the environment that surrounds us. A particularly important challenge for the representation of space in the brain follows from the inherently relative nature of location, which necessitates a contextualisation relative to a spatial reference frame (Levinson, 1996; Klatzky, 1998). Ever since the discovery of environmentally tuned cells in the hippocampus of the freely moving rat, the hippocampus has been proposed to represent location relative to a spatial reference frame that is grounded in an absolute framework of environmental landmarks (O'Keefe & Dostrovsky, 1971; O'Keefe, 1978).Distinguishable from such an allocentric system, the posterior parietal lobe has been proposed to provide a complementary egocentric reference frame, in which locations are defined relative to receptor surfaces of the body (Burgess, 2008). Although a close interaction between the two systems is likely to underlie much of our spatial behaviour, the stable environmental framework provided by the hippocampal allocentric subsystem has been proposed to be particularly beneficial for goal-directed navigation (O'Keefe, 1978; Maguire *et al.*, 1998a).

A variety of different tasks have been used to assess the contribution of the hippocampus in human allocentric spatial memory. Whilst some studies have used tasks inspired by classical rodent paradigms, such as the Morris Water Maze (Morris, 1981; Parslow *et al.*, 2004), others have developed and relied on human-specific navigation tasks to test allocentric spatial memory (Maguire *et al.*, 1998a). Consistent with the importance of the allocentric subsystem in goal-directed navigation, such tasks have provided general support for a hippocampal contribution (Astur *et al.*, 2000; Goodrich-Hunsaker *et al.*, 2010). A more specific role has been postulated for the hippocampus in the cognitive processes that underlie the very initial stage of goal-directed navigation, including self- and target-localisation and route planning (Spiers and Maguire, 2006; Cornwell *et al.*, 2008; Xu *et al.*, 2010). Consequently, it can be proposed that the hippocampus provides allocentric spatial memory representations even when such representations do not form the basis for navigation. Consistent with this, hippocampal damage has been found to affect allocentric spatial memory in tasks that do not involve navigation (King *et al.*, 2002; Hartley *et al.*, 2007). However, there has been little evidence from neuroimaging investigations to support this

conclusion (Schmidt *et al.*, 2007). Part I of the present project therefore aims to develop a task that can reliably distinguish allocentric memory from its egocentric equivalent both at a behavioural and at a neural level, without implementing any navigational demands. By the use of such a task in a functional neuroimaging context, the first part of the thesis aims to empirically test the following hypothesis:

Hypothesis 1: The hippocampus provides allocentric memory representations, independently of navigational demands.

In Chapter 2, I provide a detailed background to support the theoretical and empirical context of the aims of Part I of the project. After a closer definition of spatial reference frames, I provide an overview of current theoretical models of how locations are represented in human memory. It will become evident that a two-system model, comprising a transient egocentric system and a more enduring allocentric system, provides a good account for the empirical data and thereby represents a useful theoretical framework for the present project (Shelton and McNamara, 2001; Zhang *et al.*, 2011).

In the subsequent section of Chapter 2, a thorough review of the empirical evidence relating to the role of the hippocampus in allocentric spatial memory will aim to specify the circumstances under which a hippocampal contribution can be expected. An overview of the firing properties of place cells provides a starting point for this review, after which the relevant neuropsychological and neuroimaging evidence is covered. Considering the substantial task development component of the project, the presentation of such evidence is organised to emphasise the experimental paradigm used. As such, the review starts with an evaluation of the hippocampal contribution in human analogues of the classic Morris Water Maze and the Radial Arm Maze (Olton and Samuelson, 1976; Morris, 1981), after which focus is turned to human-specific tasks that exhibit a similar navigational element to assess allocentric spatial memory. In direct relevance to the above hypothesis, evidence derived from tasks that utilise a shift in viewpoint, as opposed to navigation, to engage the allocentric subsystem is subsequently reviewed. As indicated above, it will become clear that whilst neuropsychological evidence has provided support for a hippocampal role in such tasks, the corresponding neuroimaging evidence has been limited and without a definite conclusion. To gain further indications of the precise role of the hippocampus in allocentric spatial memory, the responsiveness of the hippocampus to specific environmental features is then summarised

(e.g. Doeller *et al.*, 2008). In the final section of the review, I briefly comment on the role of the hippocampus beyond allocentric spatial memory.

An important outcome of the review in Chapter 2 is the identification of the need to develop a new task. In Chapter 3, the principles of the Northumberland Gallery Task (NGT) are introduced in the context of previous evidence and models of spatial reference frames. The results derived from the task, as performed by a young sample of healthy volunteers, are subsequently presented and interpreted. In Chapter 4, a set of five experiments aims to further develop the NGT. Whilst the first three experiments focus on making the allocentric and egocentric conditions of the task more equivalent in terms of difficulty, Experiment 5 and 6 focus on ensuring that the task would produce consistent results in a middle-aged sample and that it can be administered as a short version, which was important for the use of the NGT in a clinical population in Part II of the project. In Chapter 5, functional magnetic resonance imaging (fMRI) was used to explore the neural underpinnings of the NGT as performed by young participants. As such, this chapter was primarily concerned with explicitly testing the hypothesis of a role for the hippocampus in a viewpoint-shift task, in which the process of self- and target-localisation depended on the position of environmental landmarks. A secondary aim of this fMRI study was to investigate the role of the parieto-medial temporal pathway, which has been proposed to underlie navigation in humans (Burgess, 2008; Kravitz *et al.*, 2011), in non-navigational allocentric spatial memory. Therefore, a brief background of the proposed function of regions in this pathway is provided as part of the introduction to Chapter 5.

In Part II of the present project, the potential use of the NGT in clinical populations as a measure of hippocampal function was evaluated. In particular, major depressive disorder (MDD) represented the population of interest following proposals that the hippocampus plays a pivotal role in the pathophysiology of this disorder (Sapolsky *et al.*, 1986; Sahay and Hen, 2007; Palazidou, 2012). A substantial evidence base shows that patients with depression exhibit structural abnormalities of the hippocampus and memory impairments that can be considered consistent with hippocampal dysfunction (Porter *et al.*, 2003; Hinkelmann *et al.*, 2009; Koolschijn *et al.*, 2009). Despite such evidence, neuroimaging studies of hippocampal function in depression have been rare and have provided mixed findings (Cornwell *et al.*, 2008; Werner *et al.*, 2009). To expand on such evidence, Part II of the present project therefore aimed to pilot the use the NGT as a measure of hippocampal function in depression.

Following the structural abnormalities of the hippocampus in this disorder, the following working hypothesis was proposed:

Hypothesis 2: Depression is associated with functional abnormalities of the hippocampus

In Chapter 6, a detailed background provides a context for Part II of the project. Following a brief introduction of MDD as a disorder, the change in hippocampal volume in depression is reviewed with a particular focus on its role as the disorder progresses. Subsequently, the occurrence of the arguably hippocampus-relevant memory deficits in depression is explored in a similar way, after which the handful of imaging studies that have investigated hippocampal function directly in depression are described. In Chapter 7, the behavioural and neuroimaging results derived from the NGT in a small sample of depressed patients and age- and sex-matched healthy controls are reported. Such results are evaluated in the context of additional cognitive measures included in the test protocol.

In Chapter 8, a summary of the contributions derived from Part I and Part II of the project is provided. Subsequently, the more significant limitations of the project are reiterated and suggestions are made for future research. In the final section of Chapter 8 and the thesis as a whole, conclusions in regards to the role of the hippocampus in non-navigational allocentric short-term memory and the potential use of the NGT in clinical populations are offered.

Part I

The Northumberland Gallery Task and the Hippocampus

Chapter 2 Background (Part I)

2.1 Spatial reference frames

2.1.1 Spatial reference frames defined

Spatial reference systems can be thought of as coordinate systems that can be used to specify locations (Klatzky, 1998; Carlson *et al.*, 2010). Such spatial reference systems can be mathematically defined based on its origin and orientation of the primary axes. In terms of the origin, a location can be represented in relation to the position of the observer (self-object vector) or in relation to the external environment (object-object vector; Figure 2-1) (Wang, 2012). In other words, the origin is either centred on receptor surfaces of the body, such as the retina or the midline of the body, or, on the environment or objects within that environment (Burgess *et al.*, 2002). The self-object vectors are commonly referred to as egocentric whilst the object-object vectors are referred to as allocentric (Wang, 2012). A further distinction can be made along the dimension of the orientation of the primary axes of the reference frame, which will be referred to as the reference direction. The reference direction can be aligned with a number of different axes, including the viewpoint of the observer, the orientation of an external object or cardinal directions. Similarly to the origin dimension, the reference direction therefore also varies in terms of its dependence on the position of the observer. As a consequence of the combination of the origin and orientation of the primary axes, it is possible to have mixed reference frames. For example, a reference frame may have an egocentric origin but an allocentric reference direction (i.e. self-object vectors defined relative to a reference direction that is independent of the observer).

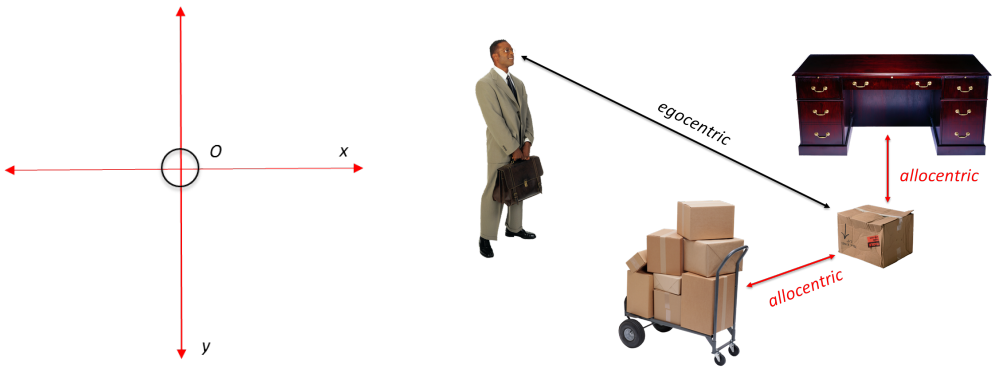


Figure 2-1: Illustration of the origin (*O*) and axes (*x*,*y*) of a Cartesian coordinate system (left) and of the basic distinction between reference frames with an allocentric origin and an egocentric origin (right). Images on the right are from Microsoft PowerPoint for Mac Clip Art (14.2.1).

2.1.2 The egocentric updating model

The topic of spatial reference frames has received considerable attention in the last decade and the debate concerning the existence and relative importance of different types of reference frames is on-going (Li *et al.*, 2012; Wang, 2012). Different theoretical approaches have tended to use different research paradigms, which in turn have relied on different definitions and assumptions of the reference frames of interest, making an integration of the available evidence challenging. To aid clarity, I will therefore start by summarising the research paradigms used and evidence put forward in support of an earlier model, the egocentric updating model, which will provide a basis against which more recent models can be evaluated.

Wang and Spelke (2000) proposed the egocentric updating model, in which spatial memory and navigation rely mainly on dynamic egocentric representations, making it distinct from the orientation-free and enduring cognitive maps previously proposed (Tolman, 1948). Early evidence for the egocentric updating model was derived from the spatial updating paradigm. In one such study, Simons and Wang (1998) asked participants to learn the location of five objects placed on a table. During a brief delay a curtain occluded the table and one of the objects was shifted to a different location. At test, participants had to detect this location change after either walking around the table or after an equivalent rotation of the table. Whilst viewpoint changes were found to have little effect on change-detection performance, an equivalent rotation of the table impaired performance. The results were interpreted as evidence that egocentric representations were indeed dynamically updated, but only if sufficient information about self-movement was available. Since such information was lacking in the table rotation condition, this updating mechanism was proposed to be unavailable.

A later influential study by Wang and Spelke (2000) implemented a disorientation paradigm to further investigate the validity of the egocentric updating model. The study was based on the assumption that an allocentric representation, defined as being independent of observer position both in terms of the origin and the reference direction, should be unaffected by changes in observer position. In contrast, since egocentric self-object vectors were thought to be updated one by one as the observer moves through the environment, an accumulation of error was predicted for more substantial locomotion. Participants learned the locations of six objects randomly placed in a room by walking around. In a chamber inside of the room,

participants were then asked to point to the objects with their eyes open, after physically turning a small amount blindfolded and after being disoriented blindfolded. The pointing errors were separated into the errors that stemmed from a misperception of heading and errors that stemmed from a deterioration of the represented inter-target vectors. Critically, only an egocentric updating process was proposed to predict an increase of configuration errors as a result of observer movement. In line with this, configuration error was found to be greater following complete disorientation compared to a smaller turn, indicating that the updating process could proceed without much error for a smaller turn but not for more substantial locomotion. This disorientation effect remained even when participants were reoriented by a directional cue, which was interpreted as discounting an explanation involving the uncertainty of self-orientation. Interestingly, configuration error did not increase following disorientation when participants were asked to point to the corners of the room instead of the objects. Based on such evidence, Wang and Spelke (2002) suggested that people depend on dynamic egocentric representations for spatial memory and navigation but use an encapsulated geocentric module to reorient after disorientation.

Another source of evidence put forward for the egocentric updating model was derived from the so-called alignment effect, which entails the finding that it takes longer to recognise a scene from a viewpoint that is different from the original study view (Diwadkar and McNamara, 1997). In a typical procedure, participants learn the location of several objects from a particular viewpoint and are then asked to make spatial judgments from various different perspectives. In one such study, Shelton and McNamara (1997) asked participants to learn the locations of seven objects in a room, after which they were taken into a different room and tested on a computer. Participants were asked to imagine a certain heading, as defined by two of the object locations (e.g. “imagine that you are standing at the shoe facing the lamp”), and to indicate the direction of one of the remaining objects by positioning a line on the computer screen (judgement of relative direction). By varying the two objects that defined the heading direction, the imagined perspective at test could be either aligned or misaligned with the learning perspective. The results showed that headings aligned with the learning perspective resulted in smaller pointing errors compared to misaligned headings. As such, the alignment effect was interpreted as a reflection of a representation with an egocentric origin, which needed to be aligned with the test perspective by an error-prone updating process.

2.1.3 Two-system models

The sole emphasis on egocentric representations in the egocentric updating model was opposed in subsequent studies. In a review, Burgess (2006) synthesised the evidence present at the time and by doing so re-evaluated some of the findings presented in support of the egocentric updating model. Although the presence of an automatic egocentric updating process during self-motion was not opposed, it was highlighted that the effect of environmental cues could not always be discounted.

In a revised spatial updating experiment, Burgess *et al.* (2004) manipulated not only the position of the observer around the table and the orientation of the table but also the position of a single external cue. To exclude the influence of any additional external cues, the room was completely dark except for the array of objects and the external cue, which were painted in fluorescent paint. It was proposed that when the table was rotated alone, both object-object vectors and subject-object vectors would be disrupted (automatic egocentric updating only occurs in the presence of self-motion information), whilst the object-object vectors would be maintained when the table was rotated along with the external cue. Improved performance was found when the vector between the external cue and the object array was maintained, which suggested that allocentric representations are likely to play a role alongside the dynamic egocentric representations suggested by Wang and Spelke (2000).

In response to the alignment effect (Diwadkar and McNamara, 1997), Burgess (2006) highlighted that performance is not only improved when the heading is aligned with the original learning view but also when it is aligned with a salient environmental axis. Similar to the methodology used by Shelton and McNamara (1997), Mou and McNamara (2002) asked participants to make judgments of relative direction based on the memory of seven object locations. By organising the target objects along salient intrinsic axes, the authors were able to demonstrate an improved performance for imagined test headings aligned with such environmental axes. Consequently, it was clear that locations could be represented in respect to other objects (Burgess *et al.*, 2004) and to a reference direction defined by the intrinsic structure of the environment (Mou and McNamara, 2002). Although Wang and Spelke (2000) acknowledged the influence of the surface geometry of the environment in disorientation, this allocentric representation was not considered to contribute directly to object location memory. To accommodate findings of the influence of environmental cues on

the organisation of object location memory, later models therefore had to incorporate parallel egocentric and allocentric representations.

In the reference direction model (Shelton and McNamara, 2001; Mou and McNamara, 2002; Mou *et al.*, 2004), it was proposed that whilst an egocentric subsystem is important for the computation and representation of the transient self-object vectors required for locomotion, an environmental subsystem is responsible for representing the object-object vectors of spatial layouts in familiar environments. An integral element of the environmental subsystem is that the environment is represented in terms of a reference direction or a conceptual 'north' (Shelton and McNamara, 2001). Importantly, this reference direction is assumed to be fixed and independent of changes of the observer position (i.e. allocentric). The reference direction can be selected based on a range of cues, including a salient intrinsic axis in the environment or an egocentric viewing perspective (McNamara *et al.*, 2003). In this model, the reference direction is therefore assumed to be independent of observer position even in cases where it is was originally aligned with an egocentric viewing perspective. In the last study of a series of experiments conducted by Shelton and McNamara (2001), participants learned the locations of objects from three different viewpoints in counterbalanced order after which they were tested in a judgment of relative direction task. A random placement of objects and a cylindrical room ensured that the initial study view represented the only salient cue on which to base the reference direction. In the case of egocentric updating, the reference direction would be dependent on the position of the observer and so would be updated as the study view changed, predicting improved performance from the last study view or equal performance across study views. In contrast to such predictions, improved performance was found to be limited to the first view, indicating that once the reference direction was acquired at the original viewpoint it remained fixed and independent of changes in the position of the observer. Shelton and McNamara (2001) furthermore proposed that the reference direction would only change if a later study view provided a much more salient reference direction.

In a recent development of the reference direction model, Zhang *et al.* (2011) proposed that both object-object and self-object vectors are represented with respect to a fixed allocentric reference direction. Following a change in observer position, the individual needs to update his/her orientation with respect to this reference direction in order to gain access to the relevant object-object and self-object vectors. In the spatial updating paradigm, there are two sources of information that could be used to recover the reference direction: by updating the

allocentric heading based on information about self-motion or by using the visual input of the interobject vectors in the scene. Whilst both sources of information are available when participants are required to walk around the table, only the latter is available in the table rotation condition. When Zhang *et al.* (2011) made the reference direction explicit in the array, the typical facilitative effect in the self-locomotion condition was eliminated, indicating that the challenge of the spatial updating paradigm was indeed the recovery of the reference direction. Importantly, since the reference direction was not aligned with the egocentric view during learning in this study, the results could not be attributed to updating relative to the egocentric orientation (Wang and Spelke, 2000). The allocentric updating model therefore not only proposes that both self-object and object-object vectors are represented in relation to a fixed allocentric reference direction, but also that the orientation of the observer is represented and updated in relation to the same reference direction.

The allocentric updating model has recently been used to provide an explanation for the disorientation effect. Li *et al.* (2012) summarised the evidence and concluded that the disorientation effect was limited to situations in which participants learned an irregular layout from the middle of the layout. Considering that an egocentric updating process would not predict differences according to situation, the authors took the view of Zhang *et al.* (2011) and proposed that the challenge in the disorientation paradigm was to recover the allocentric reference direction. Specifically, whilst the turn condition allows for updating of the observer position relative to the reference direction, the disorientation condition requires a complete recovery of the reference direction. It was proposed that learning an irregular array from a central learning position would result in a reliance on self-object vectors that are represented relative to a fixed reference direction aligned with the original learning viewpoint. It was revealed that by informing participants about the learning direction after disorientation, the disorientation effect could be eliminated in the consequent pointing task (i.e. configuration error was equivalent in the disorientation and turn conditions). This was interpreted as indicating that disorientation did not disrupt the self-object vectors but instead interfered with the ability to recover the reference direction. Similar evidence has been reported for much briefer presentations in the spatial updating paradigm, where informing participants about the study view in the table rotation condition was found to eliminate the relative facilitative effect in the self-locomotion condition (Mou *et al.*, 2009). In relation to the remaining disorientation effect when a directional cue was used in a previous study (Wang and Spelke,

2000), Li *et al.* (2012) argued that since the directional cue was unlikely to have determined the reference direction, using it after disorientation would not help recovery of the reference direction. Following this, Li *et al.* (2012) proposed the uncertainty hypothesis, in which the disorientation effect is accounted for by a greater uncertainty in identifying the fixed reference direction and not by disruptions in memory.

The above models share several features with the model proposed by Waller and Hodgson (2006), which also made a distinction between a transient egocentric system and a more enduring system. In this model, it was proposed that transient egocentric representations of individual objects existed in parallel with an enduring representation of the array configuration. The former system was proposed to dominate performance when an individual is fully oriented in the environment and that a switch to an offline enduring system occurs when online information about the environment becomes unreliable. In this framework, a switch from the detailed but transient egocentric system to the enduring but spatially coarse system is considered the cause of the disorientation effect. To support their model, Waller and Hodgson first replicated the increase in configuration error following disorientation in the egocentric pointing task (Wang and Spelke, 2000) and consequently demonstrated *reduced* configuration error following disorientation in the arguably more allocentric judgment of relative direction task. Although the enduring system was never specified in terms of whether it represented object location allocentrically or egocentrically, the double dissociation in the two tasks was interpreted as a shift from a transient egocentric system to a more enduring system.

2.1.4 Summary

From the background provided above, it is evident that spatial reference frames play an invaluable role in allowing locations to be represented in memory. Although the precise nature of such reference frames is still being debated (Li *et al.*, 2012; Wang, 2012), it appears as if a two-system model can best account for the empirical findings. The three two-system models described above all include a transient egocentric subsystem to support locomotion and a more enduring subsystem to supports goal-directed navigation (Shelton and McNamara, 2001; Waller and Hodgson, 2006; Mou *et al.*, 2009; Zhang *et al.*, 2011). In the reference direction model and the allocetrinc updating model, the enduring subsystem is specified to represent locations relative to an allocentric reference direction, which is selected based on

the initial egocentric viewpoint if the environment does not provide a salient environmental axis (McNamara *et al.*, 2003). Importantly, following the disruption caused in the disorientation paradigm or in the table condition of the spatial updating paradigm, the reference direction needs to be recovered before the represented vectors can be accessed (Zhang *et al.*, 2011; Li *et al.*, 2012). When no information about self-movement is available, this process will necessarily rely on the inter-object vectors of the visual scene (Zhang *et al.*, 2011). I will return to these theoretical principles in order to contextualise the NGT in Chapter 3. Such principles also provide a context to the subsequent section, which concerns the hippocampal contribution to allocentric spatial memory.

2.2 Hippocampal spatial memory

2.2.1 Introduction

The effect of medial temporal lobe damage on memory has been known since the first report of patient H.M. and the anterograde amnesia that resulted from the removal of his medial temporal lobe as a treatment for medically intractable epilepsy (Scoville and Milner, 1957). H.M.'s resection included the anterior hippocampus bilaterally, the amygdala and the majority of the parahippocampal-entorhinal cortex, which resulted in a global inability to form new long-term memories whilst short-term memory, working memory, and other cognitive abilities such as reading and writing were spared. Consistent with the amnesic syndrome, H.M.'s memory impairment was also reflected in tasks of spatial memory, including learning a stylus maze and remembering object locations (Milner, 1965; Smith and Milner, 1981). In a review of 147 cases of amnesia, Spiers *et al.* (2001b) concluded that damage to the hippocampus consistently resulted in an inability to form new episodic long-term memories with spared procedural and working memory. Although no conclusion could be drawn in relation to spatial memory specifically in this particular review, Kessels *et al.* (2001) concluded in a meta-analysis of 27 studies that hippocampal damage consistently results in significant impairment in a range of different spatial domains, including maze learning, object-location memory, spatial working memory and positional memory. The role of the hippocampus in spatial memory in healthy individuals was recently confirmed in a meta-analysis of 72 fMRI studies (Kim, 2011). The study concluded that the anterior hippocampus was consistently more active for stimuli that were subsequently remembered. Importantly, such subsequent memory effects in the hippocampus were strongly modulated

by the nature of the material, with robust effects during pictorial material encoding but relatively weak and left-lateralised effects during verbal encoding. Taken together, both neuropsychological and neuroimaging investigations appear to support the view that the hippocampus is critical for spatial memory.

From the brief introduction above, it is evident that the hippocampus plays an important part in spatial memory. However, the important discovery of place cells in the rodent hippocampus (O'Keefe and Dostrovsky, 1971) allowed more specific predictions to be made in regards to the effect of hippocampal damage (for more detail about place cells, see section 2.2.2.). In the influential cognitive map theory, O'Keefe (1978) proposed that hippocampal place cells provided the mechanism for a "locale" neural system, which organizes perceptual stimuli in an interconnected mental framework rather than as isolated components connected by pair-wise associations. In other words, the locale system was argued to consolidate and store allocentric representations, in which spatial vectors were represented in an absolute framework of spatial landmarks, independently of the orientation of the observer. In contrast, egocentric representations, in which spatial vectors were dependent on the orientation of the observer, were proposed not to require the hippocampal locale system. As such, the cognitive map theory predicted that the hippocampus would be particularly useful in navigation from novel start positions and when novel short cuts are required.

In the following sections, evidence relevant to a hippocampal contribution to allocentric spatial memory will be reviewed. A closer description of the firing properties of place cells will provide the starting point, after which the extensive and variable evidence base of neuropsychological and neuroimaging investigations will be considered. As a consequence of the influence of the cognitive map theory, the vast majority of such investigations have involved an element of navigation to test the hippocampal contribution to allocentric representations of space. Whilst some studies have used tasks inspired by classical paradigms used to assess the effect of hippocampal damage in rodents (e.g. the MWM; (Morris, 1981; Parslow *et al.*, 2004), others have developed and relied on human-specific navigation tasks to test allocentric spatial memory (Maguire *et al.*, 1998a). In a minority of studies, which lacks the navigational element, memory is tested by a shift in viewpoint between presentation and recall, which, similarly to navigation from novel starts positions, is assumed to require an allocentric representation (King *et al.*, 2002). In the following review, neuropsychological and neuroimaging evidence relevant for each task category will be considered in turn. In this

way, the rationale and design of the tasks will be emphasised, which will be important for the purposes of the task development component of the present project. Although it is acknowledged that a range of regions outside of the medial temporal lobe contribute to spatial memory, evidence implicating the hippocampus will be the focus of the review.

It is important to highlight that neuropsychological and neuroimaging investigations should be seen as complementary techniques in the investigation of the role of the hippocampus in allocentric spatial memory. Although neuropsychological investigations are critical for determining the *necessity* of the hippocampus and the medial temporal lobe in spatial memory, such investigations come with important limitations. First, the neuropsychological approach assumes that the brain functions normally with the exception of the damaged region. Second, the nature, localisation and extent of the damage depend on whether it was produced by neurological disease or surgical ablation. Third, even if the damage is surgically imposed, it tends to vary widely between patients. As a result of such limitations, evidence from neuropsychological studies can be difficult to evaluate. Since neuroimaging can be applied in healthy individuals, such limitations can be overcome. However, it is worth emphasising that the correlational nature of neuroimaging means that it can only provide information about the *involvement* of a region in a particular cognitive process. In other words, an activated region could play a causal role or could be activated in an optional or even epiphenomenal way. Thus, neuropsychological and neuroimaging investigations both provide important clues to the role of the hippocampus in allocentric spatial memory.

2.2.2 Place cells

A critical evidence base for the role of the hippocampus in allocentric spatial memory comes from demonstrations of the firing properties of the cells in hippocampus proper and nearby structures. In a seminal study, O'Keefe and Dostrovsky (1971) recorded from units of hippocampal pyramidal cells in a freely moving rat and discovered that some cells demonstrated location-specific firing. The place cells fired intensely only when the rat's head was is in a certain part of the environment, referred to as the place field of the cell, and remained virtually silent when the head was outside that field. This indicated that the cells fired in response to the position *per se* and not in response to the particular stimuli available from a specific viewpoint. Based on such viewpoint-independence, place cells can therefore be considered to represent space allocentrically, even if the location to be represented is of

the animal itself. Bird *et al.* (2012) summarised the encoded material of place cells as "a mental representation of where the rat thinks it is" (p. 3).

Consistent with a representation centred on the environment, the place fields of place cells appear to change as a result of changes to the environment. Muller and Kubie (1987) used a cylindrical apparatus, which was uniform in colour except for a salient white cue card. A rotation of the cue card resulted in an equivalent rotation of the place fields, supporting that place cells represent space in relation to distal landmarks. In contrast to such distal cues, it has been proposed that intramaze landmarks do not exert the same control over place cell firing. In line with this, Cressant *et al.* (1997) found that objects placed within a cylinder did not exert control over place cell firing. However, when the same objects were placed against the wall, the objects showed virtually ideal control over the position of place fields.

The importance of local cues and environmental boundaries for place cell firing has come under closer attention more recently (Knierim and Hamilton, 2011). Shapiro *et al.* (1997) used local and distal cues of similar salience and demonstrated that some place fields were controlled by the distal cues, other by the local cues, whilst others showed evidence of remapping. Although a greater number of the place fields were controlled by distal cues than by local cues, the study provided important evidence of the importance of local cues in the presence of a salient distal cue. Further to the influence of distal cues, boundaries appear to be of particular importance for place cell firing. This was demonstrated elegantly by O'Keefe and Burgess (1996), who showed that changing the walls of rectangular box appeared to cause an equivalent stretch or compression of the place fields. In summary, the firing fields of place cells in the hippocampus appear to be controlled by various environmental features, indicating an integral role of such cells in representing space in an allocentric manner (O'Keefe, 1978).

An important feature of place cells is that their place fields are specific for each environment and remain stable across sessions separated by several days (Muller and Kubie, 1987; Muller *et al.*, 1987). Such evidence indicates that the representation is recalled rather than re-created every time the animal encounters the environment, supporting that place cells can represent space in memory. In line with this, when the distal cue was removed in the study by Muller and Kubie (1987) the place fields were maintained, with the exception of a rotation to an unexpected angular position. This shows that the distal cue was represented even when it had been removed from the environment. O'Keefe and Speakman (1987) provided further

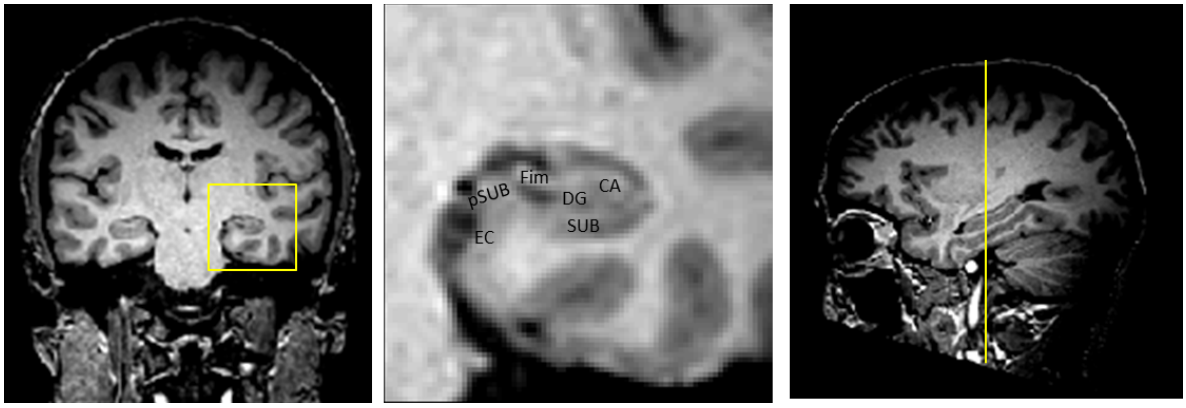


Figure 2-2: Subfields of the hippocampal complex. CA= Cornu Ammonis , DG = dentate gyrus , SUB= subiculum, Fim=fimbria, EC = entorhinal cortex, pSUB=parasubiculum. Structural MR image from an adult male tested in Experiment 7.

evidence of the mnemonic function of place cells. In this study, rats were taught to retrieve food in one of the arms of a 4-arm maze by referring to distal cues. Consistent with the findings of Muller *et al.* (1987), when the distal cues were removed before the rat entered the maze, the place fields remained the same in terms of the distance to the centre but not in terms of the angular position of the arms. However, when the distal cues were not removed until the rat had already spent some time in the maze, the place fields remained completely unchanged. Critically, the behavioural choice of the rat in the maze was highly correlated with the location of the place field. Therefore, place cells appear to support stored representations of the environment that not only can be recalled as a whole even if some elements are missing but that can be used to guide behaviour. Considering the location-specific response pattern of place cells, they represent a prime candidate for the mechanism that underlies allocentric spatial representations (O'Keefe, 1978).

Importantly, the place cells in the hippocampus receive important inputs from neighbouring regions. Specifically, the hippocampus proper, i.e. the Cornu Ammonis (CA) regions, is in close proximity to the dentate gyrus, subiculum and entorhinal cortex (Figure 2-2). The entorhinal cortex in particular provides a major gateway to the hippocampal formation from the perihinal cortex and the ventral "what" stream and from the parahippocampal cortex and the dorsal "where" stream, including the retrosplenial cortex and the posterior parietal cortex (Goodale and Milner, 1992; Suzuki and Clayton, 2000). It is therefore worth noting that spatially tuned cell types complementary to the place cells in the hippocampus have been discovered in such neighbouring regions. One example is head direction cells, which are found along the Papez circuit (mammillary bodies, anterior thalamus, presubiculum,

retrosplenial cortex, entorhinal cortex) and appear to code for the animal's current head direction (Taube, 1998). These cells fire selectively when the head of the animal points in a certain allocentric direction, regardless of the orientation of the head relative to the body, providing a compass-like signal based on the integration of self-motion cues. Head direction cells can therefore be said to be view-specific and location-independent, which can be seen as complementary to the location-specific and view-independent firing of place cells. Grid cells can be found in the medial entorhinal cortex and in the pre- and para-subiculum and fire whenever the location of the animal coincides with any vertex of a regular grid, indicating an updating of the firing pattern in response to self-motion (Hafting *et al.*, 2005). Place cells, head direction cells and grid cells are thought to be coordinated by distal cues, as evidenced by a coherent change of their place fields when the location of a distal cue is changed (Bird *et al.*, 2012). Finally, boundary cells have been discovered in the subiculum and exhibit firing fields that appear to reflect the allocentric vector to a boundary (Lever *et al.*, 2009). Border cells, which are found in the medial entorhinal cortex, have similar properties to the boundary cells but appear to only fire when the animal is close to or at the boundary (Solstad *et al.*, 2008). In summary, it appears as if the place cells in the hippocampus receive inputs from a range of different cell types with distinct spatial tunings. Such evidence supports proposals that the hippocampus represents a central component in a memory system that allows environment-centred spatial representations to be encoded and used (Becker and Burgess, 2001; Byrne *et al.*, 2007; Knierim and Hamilton, 2011).

2.2.3 Human analogues of rodent spatial memory tasks

2.2.3.1 Morris Water Maze

Neuropsychological evidence

Following early evidence of the effect of hippocampal lesions in rats on navigation ability in the infamous Morris Water Maze (MWM; (Morris, 1981; Eichenbaum *et al.*, 1990)) several investigations have implemented human analogues of this task to assess the effect of temporal lobe and hippocampal damage in humans. As in the original task, Astur *et al.* (2000) asked participants to learn the location of a hidden platform relative to environmental landmarks over successive trials (Morris, 1981). Using desktop virtual reality, participants used a joystick to 'swim' in a circular pool to find the platform from different start positions.

The variation in start positions is critical for the rationale behind the MWM as such variation is assumed to prevent subjects from using their start position to remember the platform location and to instead remember it in relation to surrounding environmental landmarks (i.e. allocentrically). As in the original task, a fixed set of training trials were followed by a probe trial, in which the platform was removed without warning. In a sensory-motor control condition, participants had to 'swim' to a visible platform both in the training trials and in the probe trials. Ten patients with unilateral hippocampal removals (five right-sided, five left-sided), either following a selective amygdalohippocampectomy or anterior temporal lobectomy (TL), were tested in the task. Relative to control participants and patients who had undergone surgery in areas outside the temporal lobe, both patient groups with temporal lobe lesions were slower to find the platform in the training trials and spent less of their swim distance in the correct quadrant on the probe trials. Patients showed no impairment in the control condition or in a complex visual memory task, which highlighted the specificity of the demonstrated impairment.

In a similar study, Feigenbaum and Morris (2004) used a touch sensitive screen fitted into a wooden cabinet in the horizontal plane to display the virtual pool from a bird's eye perspective. Sixteen left TL patients, 16 right TL patients and 16 matched control participants were asked to 'swim' with their finger until they found the hidden platform. In an allocentric condition, participants were instructed to move to different locations around the monitor between trials, simulating the different start locations in the original task. In an egocentric condition, start positions remained the same but the locations of the virtual objects surrounding the pool were changed. In a final place learning condition, both start positions and object locations remained the same. The results showed that only patients with right-sided damage were impaired and only in the allocentric condition, supporting the link between allocentric learning and long-term memory and the integrity of the hippocampus. It is worth mentioning that despite the similarities with the study by Astur *et al.* (2000), the cabinet version of the MWM differs in one important aspect. Specifically, the physical movement around the monitor in this task could have provided sufficient self-motion information to update an egocentric representation of the target location (Simons and Wang, 1998), which may have undermined the use of an allocentric representation to solve the task.

In a more selective sample, Goodrich-Hunsaker *et al.* (2010) studied the performance of five amnesic patients with atrophy limited to the hippocampus bilaterally in a desktop virtual

version of the MWM. Consequently, one condition involved navigation to a hidden platform from four different start positions whilst another involved navigation to a visible platform. In an additional condition, a proximate intramaze landmark consistently indicated the location of the hidden platform, which changed on each trial, whilst the start position remained the same. Thus, a simple cue-response strategy was sufficient to solve this condition. Relative to control participants, patients with hippocampal atrophy were impaired only when the platform location had to be represented in terms of the surrounding environment. Furthermore, in a room reconstruction test performed immediately after the navigation task, patients were unable to reconstruct the basic layout of the test environment. Therefore, although patients were able to associate the platform location with a single 'beacon' landmark, they were unable to represent and use the layout of the environment to remember the platform location.

In contrast to such consistent findings, Bohbot *et al.* (1998) did not find evidence for an effect of hippocampal damage in a human analogue of the MWM. In this version of the task, patients searched for a sensor, which had been hidden under the carpet, from two different entrances. After a 30-minute delay, patients were asked to return to the sensor from the first encountered entrance. Four patients with left-sided hippocampal damage and six patients with right-sided hippocampal damage were unimpaired in this task. However, all three patients with right-sided parahippocampal damage were found to be impaired, indicating that the parahippocampus and not the hippocampus were critical for solving the task. Compared to the studies by Astur *et al.* (2000) and Feigenbaum and Morris (2004), the limited number of start positions in the study by Bohbot *et al.* (2004) may not have been sufficient to encourage the use of the surrounding environment to remember the target location. Since memory for the sensor position was tested from the same view as it was first presented, a visual snapshot of the scene would have been sufficient to solve the task.

Taken together, damage affecting the right or bilateral hippocampus appears to result in an inability to learn the location of a target relative to environmental landmarks in the MWM (Astur *et al.*, 2000; Feigenbaum and Morris, 2004; Goodrich-Hunsaker *et al.*, 2010). Conversely, the hippocampus does not appear to be necessary when a proximal landmark consistently indicates the target location (Goodrich-Hunsaker *et al.*, 2010) or when a visual snapshot strategy is sufficient to remember the target location (Bohbot *et al.*, 1998).

Neuroimaging evidence

Following the promising results provided by the neuropsychological studies, several neuroimaging studies have opted for human analogues of the MWM. A great advantage of such studies is that they allow assessment of the contribution of the intact hippocampus in different phases of the MWM task, although variability between the different task versions used occasionally make a direct comparison difficult.

Cornwell *et al.* (2008) used a magnetoencephalographic (MEG) system to measure theta oscillations in the hippocampus, which have been proposed to provide a critical timing mechanism for synaptic plasticity and thereby learning and memory (O'Keefe and Recce, 1993). Participants performed a virtual version of the MWM, which included the typical hidden-platform condition but used aimless movement as a control condition. Two early peaks of left hippocampal and parahippocampal theta activity were observed during navigation trials relative to control trials, consistent with an early hippocampal involvement in navigation relative to environmental landmarks. Furthermore, a between-subject analysis of performance effects showed a robust inverse correlation between average path length and theta activity during the first second of navigation in the left posterior hippocampus, indicating a particularly rapid engagement of the hippocampus and parahippocampus in the best navigators.

In the MWM task used by Shipman and Astur (2008), participants were required to search for a hidden platform below one out of four floating balls from different start positions. In a control condition, all surrounding landmarks were obscured by high stonewalls and participants simply navigated to a visible platform. The absence of landmarks was implemented in this condition to minimise the occurrence of incidental encoding. Furthermore, a fixation condition simply required participants to gaze at a crosshairs on the screen. The blocked analysis revealed that relative to the fixation condition, both hidden and visible trials were associated with *decreased* hippocampal activity in the right hemisphere, more so for the hidden trials. Although the direct contrast between the visible and hidden trials was not reported, a significant decrease in hippocampal activity was demonstrated for the hidden trials relative to the fixation trials. Although the interpretation of such apparent deactivations remains elusive (Buxton *et al.*, 2004), this result appeared to contradict the recruitment of the hippocampus in the spatial condition of the MWM. However, in a post-hoc event-related analysis, the right hippocampus was found to be more active in the hidden

compared to the visible condition, which was interpreted as evidence of a specific and time limited role for the hippocampus in the initial phase of navigation.

Whilst the above studies adopted the classical feature of learning the location of a hidden target location over successive trials through trial and error, other studies have used a visible target location at presentation to allow for a new target location to be presented on each trial. The representation of each target location therefore needs to be maintained for just a limited period of time. In a virtual circular arena with random patterns rendered on the walls, Parslow *et al.* (2004) used fMRI to investigate allocentric location memory. At presentation, participants navigated to the visible target location and, after a 30-second long unfilled delay, returned to the target location based on the memory acquired at presentation. In a viewpoint-independent condition, the start position was different at presentation and test, similar to the hidden platform condition in the MWM. In a viewpoint-dependent condition, the arena walls had been rotated and participants navigated from the same start position, encouraging the use their own location to guide navigation. Participants were explicitly instructed to use the walls to remember the pole location in the former condition and to use their own location in the latter. Whilst no hippocampal activation was found when the viewpoint-independent and the viewpoint-dependent conditions were contrasted directly, increased activity was found in the hippocampus and parahippocampus bilaterally when the viewpoint-independent condition was contrasted with rest but only at encoding. No such effect was observed for the viewpoint-dependent condition, indicating a specific involvement of the hippocampus when the target had to be encoded in relation to the patterns on the walls. In a later study, Antonova *et al.* (2009) used the same task in young and older adults. No viewpoint-dependent condition was included in this study, however, which meant that all contrasts were between the viewpoint-independent condition and rest periods. At encoding, increased bilateral hippocampal and left parahippocampal activation was revealed in young but not in older adults. Similarly, at retrieval, increased activation was found in the right hippocampus and the left parahippocampal gyrus in young adults only.

In the study by Baumann *et al.* (2010) the experimental principle was the same as in the above studies but instead of the traditional circular pool there were no environmental boundaries. In this infinite plane, participants had to remember the location of a single target relative to three landmarks. At encoding, participants navigated to the visible target and after a brief delay had to navigate to the remembered location from a different position in 75% of

the trials and from the same position on 25% of the trials. In the control condition, the target location remained visible at retrieval. Encoding of the target relative to the landmarks in the control condition was minimised by informing participants of what type of trial they were about to perform. Relative to the control condition, there was significant activation of the bilateral hippocampus and the right parahippocampus but only at encoding. Furthermore, greater activity in the right hippocampus at encoding predicted more accurate performance as did increased activity in the left hippocampus at retrieval.

Rodriguez (2010) used a sparse virtual version of the MWM to investigate the use of heading vectors. In the encoding phase, participants navigated to a visible target location in a circular arena, after which a brief delay passed before participants had to navigate to the remembered position from novel start positions. In an allocentric condition, a red square on the wall represented the single available landmark. In a cue-place condition, one out of eight wall cues acted as a proximate landmark by always indicating the target location. A shuffle of the wall cues on each trial ensured that participants were using a simple cue-place association to solve the task. Thus, whilst both conditions involved navigation to a remembered target location relative to a cue on the wall, the heading direction was directly given in the cue-place condition but needed to be calculated in the allocentric condition. When the encoding and test phases were collapsed, increased activity was demonstrated in the right posterior hippocampus when the allocentric condition was contrasted with the cue-place condition. Furthermore, when the analysis was limited to the encoding phase, increased activity was found in the right anterior hippocampus in the *cue-place condition* relative to the allocentric condition. Such results were interpreted as an involvement of the right posterior hippocampus in calculating heading vectors and of the right anterior hippocampus in the encoding of a cue-place association.

In summary, although all the above studies were analogues of the MWM they have been far from identical. Whilst some studies implicated successive learning across trials (Cornwell *et al.*, 2008; Shipman and Astur, 2008) others used a new target location in every trial by simply making it visible at encoding (Parslow *et al.*, 2004; Antonova *et al.*, 2009; Baumann *et al.*, 2010; Rodriguez, 2010). Furthermore, whilst two studies used a visible target condition as a control condition (Shipman and Astur, 2008; Baumann *et al.*, 2010), others used rest periods (Parslow *et al.*, 2004; Antonova *et al.*, 2009), aimless navigation (Cornwell *et al.*, 2008) and cue-place learning (Rodriguez, 2010) as the control condition. Despite such

differences, all of the above studies provided at least some evidence in support of a hippocampal contribution in environment-centred representations in the MWM. Furthermore, there are indications that the hippocampus is particularly important in the initial phase of navigation (Cornwell *et al.*, 2008; Shipman and Astur, 2008), suggesting a potential role in re-orientation and calculation of a heading vector (Rodriguez, 2010). The relative role of the hippocampus at encoding and retrieval in the MWM, however, is not clear from the studies that allowed such a comparison to be made (Parslow *et al.*, 2004; Antonova *et al.*, 2009; Baumann *et al.*, 2010; Rodriguez, 2010).

2.2.3.2 Radial Arm Maze

Neuropsychological evidence

Another task that has been used extensively in rodent research and that has been adapted to human participants is the Radial Arm Maze (RAM; (Olton and Samuelson, 1976)). Goodrich-Hunsaker and Hopkins (2010) used such a human analogue of the RAM in a sample of five amnesic patients with selective hippocampal atrophy. As in the rodent version of the task, the virtual maze consisted of a central platform with eight identical arms radiating outward, four of which were randomly rewarded in different trials and four of which were never rewarded. Through trial and error, participants learned to retrieve the reward without entering the non-rewarded arms or re-entering rewarded arms. Although there is no explicit control of strategies in a typical RAM, the identical arms of the maze are thought to encourage use of the surrounding distal landmarks for accurate performance. Relative to control participants, patients were found to spend more time on longer paths to find the rewards and to make significantly more errors.

In a similar but real-life analogue of the RAM, Abrahams *et al.* (1997) tested 30 patients with temporal lobe damage as a consequence of temporal lobe epilepsy and 47 patients who had undergone unilateral temporal lobectomy. In this task, nine bins were arranged in a circle on a table to represent the arms of the maze. Once the experimenter had hid objects in four of the bins, patients were required to walk slowly around the table to a specified location, after which a simple filler task was performed for one minute. As a result of such observer movement between presentation and recall, the task was proposed to require patients to use the cues available in the surrounding room to solve the task, minimising the use of an egocentric memory. At test, memory for the identity of the hidden objects was tested

separately from the memory for the object locations. Consistent with previous studies (Smith and Milner, 1981), patients with right-sided temporal lobe damage demonstrated a selective deficit on the location memory test, independently of the cause of their damage. It is worth mentioning that although patients were asked to look away during the rotation around the table, the physical movement could have provided sufficient self-motion information to update the egocentric position in relation to the array. Similarly, since the filler task occurred after the rotation around the table, it is unlikely to have disrupted egocentric updating if it did occur. However, the authors argued that because of the processing demands of the task, an allocentric strategy would have been more efficient.

Taken together, it appears as if selective hippocampal atrophy alone (Goodrich-Hunsaker and Hopkins, 2010) is sufficient to produce a similar impairment of right-sided temporal lobectomy in analogues of the RAM (Abrahams *et al.*, 1997). Findings derived from human analogues of the RAM therefore provide further support for the necessity of the hippocampus when spatial learning based on environmental cues is encouraged.

Neuroimaging evidence

As in neuropsychological investigations, several neuroimaging studies have adopted human analogues of the RAM to assess spatial memory. In the study by Iaria *et al.* (2003), participants retrieved hidden objects at the end of the arms of a virtual eight-arm radial maze, which was surrounded by environmental landmarks. In a subsequent probe trial, in which participants were required to avoid re-entering previously rewarded arms, the walls were raised to conceal the environmental landmarks. In conjunction with verbal reports, this probe trial allowed the experimenters to categorise participants who exhibited worse performance following the removal of landmarks as using a spatial strategy whilst categorising the remaining participants as using a non-spatial strategy. In a control condition, the rewards in the arms were visible from the centre of the maze. Relative to the control condition, goal-directed navigation resulted in increased activity in the right hippocampus but only when participants who had used a spatial strategy were considered separately. When all participants were considered, no increase in hippocampal activity could be detected. In a similar RAM, Bohbot *et al.* (2004) categorised participants as using a non-spatial strategy or a spatial strategy by the self-report of participants. Consistent with the findings of Iaria *et al.* (2003), the contrast revealed an increase in the right hippocampus only in participants who

had used a spatial strategy, indicating that topographical learning specifically involved the hippocampus. Interestingly, participants who initially used a spatial strategy and then shifted to a non-spatial strategy showed a corresponding disappearance of hippocampal activation. As such, it is also evident that the RAM does not explicitly ensure that a hippocampus-dependent memory strategy is used.

Marsh *et al.* (2010) similarly required participants to use surrounding landmarks when retrieving rewards in an eight arm radial maze but implemented a different protocol to control the strategies used in the task. By varying the initial viewing perspective from the start position at the central platform, a non-spatial strategy was arguably prevented. In the control condition, the surrounding landmarks were shuffled and participants were asked to search the arms randomly for the hidden rewards, preventing the use of environmental landmarks in this condition. When the conditions were contrasted, activations were found in the parahippocampus rather than in the hippocampus, indicating that the parahippocampal cortex may play a greater role in processing spatial information. Although the authors did not make any reference to the studies described above, it is worth noting that although the variation of viewpoint from the start position would have required the use of the landmarks for orientation, participants may have opted for a non-spatial strategy for the remainder of the trial. If participants used a non-spatial strategy for the majority of the trial, the lack of hippocampal involvement would arguably be less surprising.

In the study by Astur *et al.* (2005), the importance of accounting for or controlling for the strategy choice of participants in the RAM was further highlighted. In this study, activity during the retrieval of hidden rewards and visible rewards in the maze were contrasted whilst no experimental control was asserted over the spatial strategies used by participants. Consequently, the finding of a significant hippocampal deactivation during search for the hidden rewards was difficult to interpret. It is also worth noting that the hippocampal clusters reported in this study may be more accurately referred to as originating in the parahippocampal gyrus.

In summary, it appears that when a spatial strategy is ensured, the hippocampus is involved during spatial learning in the RAM. However, it is also evident that when no experimental control is asserted, participants will spontaneously adopt a strategy that may or may not involve the recruitment of the hippocampus.

2.2.4 Human-Specific Tasks

2.2.4.1 Navigation tasks

Neuropsychological evidence

The evidence derived from human analogues of classic rodent spatial memory tasks has been complemented by evidence derived from tasks developed specifically for humans. Such tasks commonly involve environments typical of the world in which humans live and navigate in, including virtual neighbourhoods, towns and office buildings. Although there is great variability between task designs, neuropsychological studies have generally involved a training phase, in which patients learn about the environment through a first-person perspective, and a later test phase, which requires participants to use the acquired topographical knowledge to solve a task. The continuous navigation through a large-scale environment, which cannot be seen in its entirety from a single position, is assumed to encourage the formation of an allocentric representation.

In an early study, Maguire *et al.* (1996a) showed video footage of navigation along two overlapping routes through an urban area to test the topographical memory of eleven left TL patients and nine right TL patients. Patients watched the footage a minimum of four times and were tested to criterion in a scene recognition task, after which they were tested on a number of different measures, including proximity judgments, route knowledge and a sketch map. Results showed that both patient groups were impaired on all of the tasks, except for proximity judgments, for which only the right TL group differed significantly from controls.

Spiers *et al.* (2001a) opted for a virtual town environment, in which the topographical memory of a sample of 13 left TL patients and 17 right TL patients was tested. Patients first explored the town (15-60min), after which they were asked to navigate to ten different locations using the most direct route. In addition, patients' knowledge of the environment was tested in a scene recognition task and a map drawing task. Right TL patients were found to be impaired relative to left TL patients and control participants in the navigation task and in the scene recognition task, whilst both patient groups were impaired in the map-drawing task. Interestingly, left TL patients were found to be more impaired in a context-dependent episodic memory task, including the retrieval of the spatial context in which a particular target object was received. Such evidence indicated that the left temporal lobe might be more

important for episodic memory of spatial context, which may explain the equivalent impairment in left TL and right TL groups for some topographical memory tasks.

In a recent study, Weniger *et al.* (2012) investigated spatial learning in two different virtual environments, a park and a maze. The goal in both environments was to find a target location, which remained in the same position across trials, from a single start position. The critical difference between the two environments was that the virtual park allowed environmental landmarks to be used to guide performance whilst the high walls of the maze prevented this. 44 patients with drug refractory temporal lobe epilepsy, 22 of who showed evidence of hippocampal sclerosis, and 42 control participants completed the study. Patients with hippocampal sclerosis were found to be impaired in both environments, more so in the maze environment, whilst patients without hippocampal sclerosis were unimpaired in both environments, evidencing a specific role of the hippocampus in both environments. Given its egocentric nature, the impairment in the maze environment was not predicted and it was proposed that further damage to the bilateral postcentral gyrus in the group with hippocampal sclerosis could have accounted for this finding. Furthermore, it is worth noting that control participants may have been able to use path integration to acquire some allocentric knowledge about the maze environment. If patients were unable to acquire such knowledge, an impairment would have been predicted in both environments.

In summary, temporal lobe damage appears to have an effect on the ability to use a spatial representation acquired through navigation in tests of topographical knowledge (Maguire *et al.*, 1996a; Spiers *et al.*, 2001a). Similarly, damage to the hippocampus specifically appears to result in an inability to acquire a spatial representation from navigation in a virtual environment (Weniger *et al.*, 2012).

Neuroimaging evidence

Human-specific tasks have arguably been used more extensively in the neuroimaging literature and have generally focused on encoding or retrieval of landmark-centred spatial information. In encoding studies, participants are scanned as they are learning about an environment whilst in retrieval studies extensive experience of the environment is acquired outside of the scanner prior to testing phase.

In terms of encoding of allocentric representations, human analogues of classic rodent tasks have already provided evidence in support of a hippocampal contribution (section 2.2.3).

Neuroimaging studies using human-specific tasks have generally been able to extend such support. In an early positron emission tomography (PET) study, participants were scanned whilst acquiring topographical knowledge by watching video footage of navigation through an urban environment or whilst simply remembering events in the same environment from a stationary viewpoint (Maguire *et al.*, 1996b). When the former condition was contrasted with the latter, activation was demonstrated in the right hippocampus and the parahippocampus bilaterally, indicating a role for the hippocampus in encoding. In a different study, Moffat *et al.* (2006) scanned young and older adults whilst they explored and learned the locations of objects and interconnecting hallways and whilst they simply followed a designated path in an indoor virtual environment. Participants were instructed to remember the environment in order to construct an accurate map and describe routes between landmarks in the subsequent testing session. When the two conditions were contrasted, clusters of differential activation were demonstrated in the right hippocampus and the parahippocampus bilaterally, but only in the young adults.

Suthana *et al.* (2009) scanned participants whilst they passively viewed navigation to target locations either from a single starting point or from multiple starting points in a virtual town. Participants were explicitly instructed to learn a particular target location relative to the initial starting point in the former condition and relative to environmental landmarks in the latter. In a control condition, participants pressed a button each time the direction of navigation changed in the same environment but without the landmarks present. Whilst several medial temporal lobe regions, including the parahippocampal gyrus, were active in both encoding conditions relative to the control condition, encoding from multiple start positions further recruited the hippocampus. Computational unfolding allowed such recruitment to be specified to activity in the right posterior CA1 region, which furthermore was found to correlate with performance.

Based on the evidence described above, the hippocampus appears to play an important role when participants encode viewpoint-independent representations of the environment through navigation. It is worth noting, however, that two early studies did not support a role of the hippocampus in spatial learning during navigation. Aguirre *et al.* (1996) used fMRI to investigate the neural underpinnings of learning the topography of a simple maze, which was empty from objects with the exception of objects in the cul-de-sacs. The results evidenced no hippocampal activation during learning or recall of the maze, whilst the parahippocampus

was active in both circumstances. Similarly, a PET investigation revealed parahippocampal activation but no hippocampal activation when participants were acquiring topographical knowledge through navigation in two environments, one which contained salient objects and textures and one that only varied geometrically (Maguire *et al.*, 1998b). Maguire *et al.* (1999) argued that the discrepancy between such early studies could be explained by a lack of realism and environmental detail in the environments used. It is also possible that the lack of explicit instructions to encode the representation in a viewpoint-independent manner may account for some of the discrepant findings. Overall, the variation between studies using human-specific tasks and the general lack of control of learning strategies make it difficult to arrive at a definite conclusion. However, combined with the results derived from analogues of rodent spatial memory tasks, which provide better experimental control of memory strategies, it is reasonable to conclude that the hippocampus does contribute to encoding of allocentric information from navigation.

Further to the neuroimaging studies that have investigated encoding, other studies have scanned participants whilst they are retrieving topographical knowledge in order to solve a goal-directed navigation task. In this type of study, familiarity with the test environment is ensured either by incidental but extensive experience with a particular environment or by an explicit training protocol. In an early PET study, London taxi drivers were scanned whilst they recalled complex routes around the city that they had been familiar with for several years (Maguire *et al.*, 1997). Compared to retrieval of non-topographical information (e.g. the plots of familiar films), retrieval of the routes was found to increase activation in the right hippocampus. An interesting side to this result is that navigation expertise in taxi drivers appears to affect hippocampal structure, namely increase posterior hippocampal volume and reduce anterior hippocampal volume relative to matched control participants and bus drivers (Maguire *et al.*, 2000; Maguire *et al.*, 2006a).

In a later study by Maguire *et al.* (1998a), the involvement of the right hippocampus in topographical retrieval was confirmed in a sample drawn from the normal population. Participants explored and familiarised themselves with a virtual town, after which they were scanned whilst they navigated to specified goals or simply followed a trail of arrows in the virtual town. A contrast between the two conditions revealed significant activation in the hippocampus bilaterally during goal-directed way finding and, additionally, activation in the right hippocampus was found to correlate positively with navigation accuracy. In a similar

study, participants were familiarised with two similar but distinct environments prior to scanning (Hartley *et al.*, 2003). Participants explored the first environment freely for 15 minutes whilst they walked back and forth a prescribed route in the second. During scanning, participants navigated between specified target locations in the first environment and followed the learned route in the second environment. In a control condition, participants simply followed a trail of markers. In contrast to the study by Maguire *et al.* (1998a), no hippocampal activation was found when the way-finding condition was contrasted with the route following or trail following conditions. However, activation in the right posterior hippocampus was found to correlate with performance in the way-finding condition. Furthermore, whilst good navigators exhibited the predicted increase in activation in the right hippocampus, poor navigators showed decreased hippocampal activation. Consequently, it was argued that between-subject variation might have explained the null finding in the categorical analysis. Furthermore, such between-subject variation in hippocampal engagement indicates that the loose experimental control may have resulted in the use of different strategies, some of which involved the hippocampus and some of which did not.

In the study by Burgess *et al.* (2001), participants explored a virtual town until they felt confident that they could find their way around it (20-40min). Participants then navigated through and out of visually similar rooms in the virtual town, in which they received objects from particular characters. Scanning was performed at test when participants were cued with a particular place or character and asked which one of two objects that was received in that particular place or from that particular character. In a control condition, participants were asked which of the two objects was the widest. Relative to the control condition, only the retrieval of the spatial context of the objects resulted in increased activation of the parahippocampus bilaterally and the left hippocampus. Relative to the neuropsychological study conducted by Spiers *et al.* (2001a), such evidence is consistent with a role for the left hippocampus episodic memory of spatial context.

In a more recent study, Xu *et al.* (2010) administered extensive training of a virtual office building prior to scanning. Participants were subsequently scanned whilst they navigated to target locations in three different conditions, in which the environment either stayed the same, all landmarks were removed or a blockade restricted direct access to the target. In a control condition, participants followed a line through the environment. Consistent with the study conducted by Maguire *et al.* (1998a), increased activity was found in the right posterior

hippocampus when normal way finding was contrasted with line following and activity in the right anterior hippocampus was found to correlate with performance. Furthermore, hippocampal activity was demonstrated when normal way finding was contrasted with navigation in the other two experimental conditions. Interestingly, increased activation was found in the anterior bilateral hippocampus when the initial and the execution phases of normal way finding were contrasted. Such an early recruitment of the hippocampus in goal-directed way finding has been demonstrated in previous studies using virtual versions of classic spatial memory tasks (Iaria *et al.*, 2003; Cornwell *et al.*, 2008; Shipman and Astur, 2008). Further support for this was found in a study of London taxi drivers (Spiers and Maguire, 2006). In this study, based on their pre-existing extensive knowledge of the road network of London, taxi drivers navigated in a virtual version of the city in response to 'customer' requests. Immediately after the scan, participants watched a video of their own navigation and gave verbal reports of what they remembered thinking, which were then categorised and associated with the brain activity data. Hippocampal engagement was found to be brief and to only occur when the drivers were planning a route to a new destination, providing further support for an early engagement of the hippocampus in allocentric navigation.

From the studies above, it appears as if the hippocampus is involved when participants are required to retrieve topographical knowledge to guide task performance. Although studies have not been entirely consistent in showing increased hippocampal activity in the categorical analysis, hippocampal involvement has nevertheless been indicated in participants who perform well in the task (Hartley *et al.*, 2003). Based on findings in the RAM, it is clear that participants spontaneously choose to use a particular strategy when they learn about an environment and that this choice has direct consequences for the involvement of the hippocampus (Iaria *et al.*, 2003; Bohbot *et al.*, 2004). Thus, if memory strategies cannot be controlled, the recruitment of the hippocampus across participants is likely to be diluted. Since the studies above asserted no explicit control over strategies used during learning, it is difficult to determine the exact nature of the representation used to guide performance at retrieval. Nevertheless, the implication of the hippocampus in navigation-based memory tasks appears to be consistent, with indications of a right lateralisation (Maguire *et al.*, 1996b; Maguire *et al.*, 1998a; Moffat *et al.*, 2006; Suthana *et al.*, 2009), which in turn appears to be distinct from an apparent left lateralisation for episodic memory

for spatial context (Burgess *et al.*, 2001). Another important aspect of the studies focusing on retrieval of topographical knowledge is the potentially brief engagement of the hippocampus in the very initial phase of navigation (Spiers and Maguire, 2006; Xu *et al.*, 2010), which is consistent with a pervious indications (Cornwell *et al.*, 2008; Shipman and Astur, 2008).

2.2.4.2 Viewpoint-shift tasks

Neuropsychological evidence

Another category of tasks that has been used to assess allocentric spatial memory in humans is what will be referred to as viewpoint-shift tasks. In this type of task, navigation is not the means by which the use of an allocentric representation is encouraged. Instead, such a representation is encouraged by a shift in viewpoint between the encoding and the recall of the spatial material. The rationale behind this type of task is that by making the observer-position unstable, target locations need to be represented relative to environmental cues. Relative to other tasks described in this review, the design of viewpoint-shift tasks overlap substantially with that of the MWM, particularly versions that use a new target location on each trial (Parslow *et al.*, 2004). Specifically, both tasks require participants to learn a location from a particular viewpoint and to remember it from a different viewpoint. In viewpoint-shift tasks, however, participants are not required to navigate to the target location at encoding or at recall. The task is therefore only suitable for humans, who can indicate their memory to the experimenter by other means than actual navigation behaviour (e.g. by pressing buttons). More importantly, the absence of navigation allows for an improved isolation of the cognitive processes likely to underlie the brief recruitment of the hippocampus in navigation-based tasks (e.g. Cornwell *et al.,* 2008; Spiers and Maguire, 2006).

Holdstock *et al.* (2000) used a viewpoint-shift task in a single patient with selective hippocampal damage. The task implicated a light board, on which a single LED light was lit for two seconds. In the allocentric condition, the presentation of the light was followed by a filled delay of 5, 20 or 60 seconds. Before the end of the delay period, participants were asked to move around the board to a location indicated by the experimenter, whilst looking away. Memory for the single location was then tested from the new location, before the next trial started. In the egocentric condition, the lights in the room were turned off so that the participant's own location represented the only available cue. In a control condition, the

lights in the room were left on and no movement was required from participants, presumably allowing the use of environmental and self-position cues. Whilst the patient did not differ from control participants in the egocentric and control conditions for any of the delays, she was significantly impaired for the 20s and the 60s delay in the allocentric version of the task. Thus, even in the absence of navigation and learning over successive trials, allocentric spatial memory appeared to be affected by selective hippocampal damage at longer delays. However, it is important to emphasise that the gradual movement around the light board may have allowed for an updating of an egocentric representation.

A number of insights into the effect of selective hippocampal damage in viewpoint-shift tasks have come from a task, which took place in a virtual courtyard (King *et al.*, 2002). In this task, participants were asked to remember the locations of a number of target objects, which were presented sequentially over placeholders on the ground of the courtyard. After a five second unfilled delay, during which time the placeholders were visible, participants were required to distinguish the target locations from a number of foil locations from the same viewpoint or from a different viewpoint. An important feature of the task was that in the shifted-view condition, participants did not experience a gradual shift in viewpoint, but simply appeared in the new location. Such an immediate viewpoint-shift provides no information about self-motion, which greatly reduces the likelihood of a strategy of egocentric updating (Simons and Wang, 1998).

The viewpoint-shift task was used to study spatial memory of patient Jon, who exhibits a 50% bilateral reduction of the hippocampus with no other damage within the temporal lobes (Gadian *et al.*, 2000), and a sample of matched control participants. Jon was found to be impaired in both conditions of the task. However, whilst he performed well above chance in the same-view trials, he performed worse for viewpoint-shifts of 55 degrees and at chance for viewpoint-shifts of 85 and 140 degrees. To test the specificity of Jon's impairment in the shifted-view condition, another experiment was run in which Jon's same-view performance was matched with that of control participants by varying the number of foils used for the two groups. Consequently, whilst Jon did not differ from the control groups in the same-view condition he showed a disproportionate impairment in the shifted-view condition, in which his performance was at chance for all list lengths exceeding one object. To investigate the processes involved in the shifted-view condition, the relationship between response times and different degrees of viewpoint-shift was assessed in a separate control group. The resulting

linear relationship indicated that a process of mental alignment was used to solve the shifted-view condition. Although the interpretation of such an alignment effect depends on the favoured theoretical framework (see section 2.1), King *et al.* (2002) argued for an allocentric explanation. Specifically, as list length increased, it was proposed that compared to storing and manipulating self-object vectors individually, it would be more efficient to incorporate the target locations in a single enduring representation orientated along the study viewpoint. This interpretation of the alignment effect is therefore comparable to that offered by the reference direction model, in which locations are thought to be represented relative to a fixed reference direction (Shelton and McNamara, 2001). Consequently, Jon's impairment in the shifted-view condition was interpreted as an inability to form or store the type of representation that would normally support allocentric behaviour. This conclusion was strengthened by Jon's normal performance on a mental rotation task, which indicated that the impairment was unlikely to reflect an impairment of the manipulation process itself.

In a separate study, Jon's performance in the same-view condition was investigated further (King *et al.*, 2004). In a variation of the same-view condition, the background scene was changed between two visually distinct towns between presentation and recall. Relative to the impairment caused by shifting the viewpoint in the previous study (King *et al.*, 2002), the impairment caused by changing the background was of comparable size. Consequently, it was proposed that Jon was relying on a mechanism of visual matching rather than stored egocentric vectors to solve the same-view condition. Based on such findings, Jon's hippocampal damage appeared to have spared transient sensory-bound representations whilst impairing the ability to represent subject-object vectors in an enduring way. Alternatively, it could be proposed that Jon had difficulty representing both self-object and object-object relative to a stable allocentric reference direction (Zhang *et al.*, 2011).

In a later study, Shrager *et al.* (2007) provided an interesting contrast to the studies described above. In this study, six memory-impaired patients with bilateral lesions limited to the hippocampus were tested in a task that was almost identical to the task used by King *et al.* (2002). Relative to controls, patients were found to perform normally in both the same-view and the shifted-view conditions for short list lengths and to show the typical decline in performance for increasing list lengths in both conditions. The results were interpreted as evidence against an allocentric deficit as a result of selective hippocampal damage, which was in stark contrast to the disproportionate allocentric impairment previously reported (King

et al., 2002). However, a close examination of the exact procedures used in the two studies reveals an important difference, namely the nature of the viewpoint-shift. Whilst the viewpoint-shift in the original task was immediate and occurred out of view of participants, Shrager *et al.* (2007) used a viewpoint-shift that was gradual and visible to participants. Critically, the visible viewpoint-shift would have provided sufficient self-motion information to allow for moment-by-moment egocentric updating. Thus, only when egocentric updating is not a viable option does the hippocampus appear to be necessary for the retrieval of object locations following a viewpoint-shift.

To summarise the results derived from the viewpoint-shift task introduced by King *et al.* (2002), patients with selective hippocampal damage appear to show impaired performance in the shifted-view condition but only when an egocentric updating process is not possible (Shrager *et al.*, 2007). As such, whilst patients appear to be able to represent and update transient egocentric representations when sufficient self-motion information is available, they do not seem able to represent object-object vectors in a way that allows the effects of a viewpoint-shift to be calculated. In the context of the reference direction model, it can therefore be proposed that patients with hippocampal damage were unable to represent the targets relative to a fixed reference direction aligned with the study perspective (Shelton and McNamara, 2001).

More recently, viewpoint-shift tasks have been used to investigate the contribution of the hippocampus over shorter delays. Hartley *et al.* (2007) investigated hippocampal recruitment in perception of and short-term memory for topographical and non-spatial information in four patients with focal hippocampal damage and one patient with damage extending to the right parahippocampus. Perception was tested in a match-to-sample task and short-term memory was tested in a delayed-match to sample task, in which the latter involved a delay of two seconds. For both the topographical and the non-spatial tasks, complex mountain configurations served as the stimuli. In the topographical tasks, the sample scene had to be matched to a target scene with the same topography seen from a different viewpoint whilst in the non-spatial task the sample had to be matched in accordance to the prevailing weather conditions. Whilst none of the patients were found to be impaired in either of the non-spatial tasks, all patients exhibited impaired short-term memory for the topographical information. Such evidence suggested that the hippocampus was necessary for allocentric topographical memory even at short delays. In regards to the perception of topographical layouts, three of

the patients were found to be impaired, which indicated a possible effect of hippocampal damage on viewpoint-independent perception.

Lee *et al.* (2005) used an oddity paradigm to investigate the role of the hippocampus in viewpoint-independent perception. In this task, participants were required to select the odd one out from an array of stimuli with no requirement to maintain any material in memory. In one of a series of experiments, the stimuli consisted of irregularly shaped virtual scenes or faces, seen from the same view or a different view. Four patients with focal hippocampal damage and three patients with more extensive medial temporal lobe damage were tested. Whilst both patient groups were found to be unimpaired for both types of face stimuli, they all showed impairment for the scene stimuli when view-independent perception was required. Consistent with the indications provided in the study by Hartley *et al.* (2007), the hippocampus therefore appeared to play a role in viewpoint-independent perception for spatial material.

Although the controversy surrounding the role of the hippocampus in perception and working memory is on-going (Jeneson and Squire, 2012; Lee *et al.*, 2012a), it appears from the evidence above that hippocampal damage has a detrimental effect for performance in viewpoint-shift tasks, regardless of whether the task implements a long delay (Holdstock *et al.*, 2000; King *et al.*, 2002), a short delay (Hartley *et al.*, 2007) or no delay at all (Lee *et al.*, 2005). Consequently, it can be proposed that viewpoint-shift tasks capture the process of landmark-based self- and target-localisation that has previously been implicated in the initial phase of goal-directed navigation (Spiers and Maguire, 2006; Cornwell *et al.*, 2008; Xu *et al.*, 2010).

Neuroimaging evidence

Compared to neuropsychological investigations, the use of viewpoint-shift tasks has been much more limited. To my knowledge, there has only been one neuroimaging study that has used a task that can be considered equivalent in design to the viewpoint-shift task introduced by King *et al.*, 2002 (Schmidt *et al.*, 2007). On the other hand, there have been a few neuroimaging studies investigating perspective taking (Lambrey *et al.*, 2012), which tend to overlap somewhat with viewpoint-shift studies in terms of task design. In addition, there have been studies assessing landmark-based referencing without a memory component, in which viewpoint-shifts between each trial have ensured that distance judgments are made

relative to environmental landmarks. Therefore, before turning to the study by Schmidt *et al.* (2007), I will consider results derived from these alternative tasks.

Committeri *et al.* (2004) introduced a task in which participants judged which of two target objects that was closer to either the observer, a reference object or to a fixed environmental landmark in the same environment. Despite requiring participants to reference a stable environmental landmark, no evidence was found of a hippocampal contribution. Although this can be considered contradictory to a role of the hippocampus in the allocentric reference frame, it should be emphasised that the task did not require any form of topographical learning. Furthermore, since the task only required the consideration of a single viewpoint per trial, it also did not require viewpoint-independent perception. Therefore, whilst the hippocampus appears to play a role in topographical learning (Maguire *et al.*, 1996b) and potentially even viewpoint-independent perception (Lee *et al.*, 2005), it does not appear to be involved when participants are required to make a simple distance judgment relative to an environmental landmark.

Studies investigating perspective taking commonly involve imagining seeing an array of target locations from different perspective. However, since viewpoint-shifts between different perspectives tend to be imagined, they are likely to be both 'visible' and gradual in nature without a disorientating element. As has been highlighted previously, such a gradual shift in viewpoint theoretically allows for updating of the transient self-object vectors governed by the egocentric subsystem (Shelton and McNamara, 2001). Conversely, the allocentric subsystem would arguably provide a more efficient strategy following more substantial imagined viewpoint-shifts, supporting the consideration of perspective-taking studies here. In the study by Hannula and Ranganath (2008), participants viewed a three-dimensional 3x3 grid with four objects positioned in different locations. During a 11s long delay, participants were instructed to form and maintain a mental image of the scene rotated 90 degrees from the original viewpoint. At test, the scene was presented from the new viewpoint and participants were required to detect different changes of the object positions. Hippocampal activation was found to predict accuracy at encoding and test but not during the delay, which was interpreted as a role for the hippocampus in short-term relational memory. It also suggested that the actual imagination of the shift in viewpoint during the delay did not involve the hippocampus. In a similar task, Lambrey *et al.* (2012) investigated the neural basis of perspective taking and object rotation. Four objects were presented on a virtual table

situated in a room with numerous environmental cues. During the presentation phase, participants had to imagine a rotation of viewpoint or a rotation of the table to an extent specified by an arrow, after which they performed a change-detection task. The left hippocampus was found to be more active in the self-rotation condition compared to the table rotation condition at test and during the delay. Since the rotations were imagined at presentation, this contradicted a role for the hippocampus in the viewpoint-shift *per se*, supporting the findings of Hannula and Ranganath (2008). However, in both of the perspective-taking studies, a hippocampal contribution appeared to be important for performance in the task, which indicates that this region is indeed important for the type of representation that can sustain the effects of viewpoint-shifts (King *et al.*, 2002).

In contrast to using an imagined and pre-determined viewpoint-shift, Schmidt *et al.* (2007) implemented an instantaneous and unpredictable viewpoint-shift equivalent to that of King *et al.* (2002). In this task, a single target object was presented in a virtual roof garden, after which a five second delay passed before participants were required to decide whether the location of the target object had changed or not. Importantly, a viewpoint-shift of 0°, 45°, 90°, 135° or 180° was implemented between encoding and recall. In a control task, participants indicated whether a separate object was present in the scene or not. The response time data showed evidence of an alignment effect, which was consistent with previous studies assessing the effect of viewpoint-shifts on location memory (Diwadkar and McNamara, 1997; King *et al.*, 2002). Similarly to the study by Hartley *et al.* (2003), a hippocampal involvement was indicated by a positive correlation between hippocampal activity and performance. However, when the experimental condition was simply contrasted with the control condition, no hippocampal activity was detected. The hippocampus was also not sensitive to increasing viewpoint-shifts, which supports previous indications that this region is not involved in the manipulation process *per se* (Hannula and Ranganath, 2008; Lambrey *et al.*, 2012). Instead, the left lingual gyrus and parahippocampal gyrus were identified as regions that were sensitive to an increasing shift in viewpoint. The authors explained the lack of hippocampal activation in the contrast analysis by a lack of task complexity, particularly the use of a single target location. An alternative account is the lack of specificity of the control condition, which did not require any spatial material to be represented. If the aim were to detect neural activation that is specific to the workings of the allocentric memory subsystem, an ideal control condition would arguably engage the egocentric memory

subsystem. The importance of selecting an appropriate control condition when investigating hippocampal function has been emphasised previously (Stark and Squire, 2001), which suggests that the use of a general no-memory control condition in the study by Schmidt *et al.* (2007) may not have been sufficient. Consequently, it can be proposed that a hippocampal contribution would be detectable if the sensitivity of the contrast could be increased by the inclusion of an egocentric control condition.

Taken together, the evidence suggests that the hippocampus is not involved when participants are required to simply reference an environmental landmark, at least not when there are no demands on memory or viewpoint-independence (Committeri *et al.*, 2004). The remaining studies all appear to indicate that the hippocampus is not implicated in the process of imagining a viewpoint-shift *per se* (Hannula and Ranganath, 2008; Lambrey *et al.*, 2012). However, hippocampal activation appears to support the accuracy of the allocentric memory representations that can sustain such imagined viewpoint-shifts (Hannula and Ranganath, 2008). In the only viewpoint-shift task to use the typical instantaneous viewpoint-shift, however, the hippocampus could not be implicated in the contrast analysis (Schmidt *et al.*, 2007). I propose that by using a more precise control condition, which recruits the egocentric subsystem, the sensitivity of the contrast analysis can be increased sufficiently to implement the hippocampus in a viewpoint-shift task in a neuroimaging context.

2.2.4.3 Environmental modulation of hippocampal involvement

Whilst neuropsychological studies can only determine whether a brain region is necessary for a particular function, neuroimaging allows for the assessment of the *relative* involvement of the hippocampus for different kinds of material. Several recent neuroimaging studies have utilised this advantage to increase knowledge about what spatial features that are represented in the hippocampus.

Consistent with the firing fields of place cells (Muller and Kubie, 1987), the hippocampus appears to be particularly sensitive to the presence of boundaries. In the study by Doeller *et al.* (2008), participants gradually learned the location of target locations relative to an intramaze landmark or a boundary. The more participants' responses were influenced by the boundary, the more activity was found in the right posterior hippocampus. In contrast, greater influence of the intramaze landmarks resulted in increased activity in the dorsal striatum. More recently, Bird *et al.* (2010) asked participants to imagine standing in the midst of a

simple 3D scene consisting of towers and boundaries and to visualise a full rotation of their own viewpoint. Hippocampal activity was found to increase with increasing numbers of environmental boundaries, particularly for well-imagined scenes. In contrast, hippocampal activity did not vary with colour complexity or with the level of accuracy by which participants were able to match the imagined scene matched with a later screen shot.

Lee and Rudebeck (2010) investigated the effect of spatial processing demand (2D shapes versus complex 3D rooms) and working memory demand (one-back versus two-back matching task) on hippocampal activity. Activity in the posterior hippocampus and the parahippocampal cortex was found to increase with increased spatial processing demand, irrespective of working memory load. Furthermore, within complex spatial processing, such activity increased further as a result of increased working memory load. This latter finding is consistent with the results of Axmacher *et al.* (2007), who showed an increase in medial temporal lobe activation during encoding and maintenance of multiple compared with single face stimuli. Taken together, it appears as if the hippocampus is sensitive to increasing memory load but only if the stimulus is visually complex.

The hippocampus has also been demonstrated to be sensitive to the metric distances in an environment. In a spatial route planning task, Viard *et al.* (2011) showed a robust increase in anterior hippocampal activity with increasing proximity to a goal, which is consistent with its role in route planning (Spiers and Maguire, 2006). A similar sensitivity to metric distances was demonstrated when participants viewed photographs of familiar campus landmarks (Morgan *et al.*, 2011). The hippocampal response to each landmark was dependent on the distance between that landmark and the landmark shown on the preceding trial, evidencing a distance-related adaptation effect in the hippocampus, in which closer landmarks are considered more representationally similar than more distant landmarks. Such evidence suggests that the hippocampus represents space in an absolute coordinate system, supporting its role in allocentric spatial memory.

The above evidence demonstrates that the hippocampus is sensitive to several spatial features, including the presence and number of boundaries, the complexity of spatial stimuli, memory load and the metric distance to a goal and between familiar landmarks. Such sensitivity strengthens the idea that the hippocampus provides the mechanism necessary to represent space allocentrically. Furthermore, it could potentially provide an explanation for some of the discrepancies in the neuroimaging literature. For example, it supports the argument that the

spatial detail of the environment is important for the detection of hippocampal activity (Maguire *et al.*, 1999) and that the hippocampus may become increasingly important as the representation of individual self-object vectors becomes inefficient for greater number of target locations (King *et al.*, 2002).

2.2.4.4 Beyond allocentric spatial memory

It is important to state explicitly that the review above has focused solely on the role of the hippocampus in allocentric spatial representations and has therefore not considered any of the other likely functions of the hippocampus. In this section I intend to provide a brief overview of the role of the hippocampus beyond the specific function of supporting allocentric memory.

In addition to studies linking the hippocampus to allocentric processing, several studies have demonstrated a role for the hippocampus in spatial and relational memory more generally. For example, Olson *et al.* (2006) demonstrated a relational memory impairment in a sample of nine patients with bilateral medial temporal lobe damage, four of who had damage limited to the hippocampus. In a 9x9 grid, participants were required to remember three sequentially presented objects, locations or object-location conjunctions, over an eight second delay period and then make a recognition judgment. It was found that whilst patients were able to remember objects and locations, they were impaired in the object-location conjunction condition. Similarly, Braun *et al.* (2011) found that damage to the right hippocampus resulted in a memory impairment for colour-location associations but not for colour-shape or colour-letter associations after a delay of five seconds. Taken together, this evidence therefore highlights that the hippocampus is involved in memory for object-place relations even if they are not required to be represented allocentrically. Adding to this, it has been well established that hippocampal damage can impair performance on tasks that require participants to learn associations *without* any obvious spatial properties (Mayes *et al.*, 2007). For example, in the study of Hannula *et al.* (2006) patients with hippocampal damage were found to be impaired for the memory of face-scene pairs, evidencing a general impairment to relational memory. As a further example, Kumaran *et al.* (2007) found that patients with selective hippocampal damage were impaired in a task of relational learning independently of whether the material was spatial or non-spatial. It is therefore acknowledged that the function of the hippocampus is likely to cover a variety of different associations, spatial and non-spatial.

2.2.5 Summary

From the background provided above, it is evident that the majority of evidence derived from neuropsychological studies of patients with hippocampal damage and neuroimaging studies of healthy individuals appear to support an integral role for the hippocampus, particularly in the right hemisphere, in the provision of allocentric spatial memory representations (for an overview of studies covered, see Table 2-1). In addition, neuroimaging studies have revealed that the hippocampus is sensitive to a number of environmental features, which is consistent with the firing properties of the place cells that reside in this region. Although the vast majority of neuropsychological and neuroimaging evidence has been derived from tasks that make navigational demands, there is evidence to suggest that the hippocampus is particularly important for the cognitive processes that underlie the initial phase of navigation (Spiers and Maguire, 2006; Cornwell *et al.*, 2008; Shipman and Astur, 2008; Xu *et al.*, 2010). Consequently, it can be proposed that the hippocampus plays a role in providing the allocentric representations that are necessary for the initial self- and target-localisation that precedes actual navigation execution. Consistent with this, neuropsychological investigations that have used viewpoint-shift tasks have supported a role for the hippocampus in providing allocentric memory representations even when no navigation is required (King *et al.*, 2002; Hartley *et al.*, 2007). However, corresponding neuroimaging evidence has been limited and has yet to provide a convincing conclusion (Schmidt *et al.*, 2007).

As has been highlighted previously, the use of a general control condition in the study by Schmidt *et al.* (2007) is likely to have limited the sensitivity of the contrast analysis. An arguably more informative control condition has been included in a number of navigation-based studies, in which the landmarks are made unavailable or unreliable to encourage the use of an egocentric reference frame (Table 2-1). In contrast, only one viewpoint-shift study has included an egocentric control condition to provide a comparison of the workings of the allocentric and egocentric subsystems (King *et al.*, 2004). However, if this particular task was to be taken from a neuropsychological to a neuroimaging context, the complete change of the background scene in the egocentric condition could be a limiting factor. Specifically, since the allocentric condition does not involve an equivalent visual change, any differences in brain activity could be due to a more dramatic change in the visual scene in the egocentric condition. Therefore, the current review has also identified the need for a new task. For the purposes of the present project, an ideal task would include a visually similar egocentric

condition, in addition to a viewpoint-shift condition. Such a task would be expected to increase the sensitivity of a categorical contrast in a neuroimaging context, which in turn would provide an improved measure of the hippocampal contribution to allocentric representations when no navigation is required.

Table 2-1: Overview of tasks that have been used in neuropsychological and *neuroimaging* studies. * studies that have not supported a hippocampal involvement. VS=Viewpoint-Shift tasks. WMW=Morris Water Maze. RAM=Radial Arm Maze.

Reference	Task Type	Navig-ation	Allocentric condition	Egocentric condition
Parslow et al. (2004)	*MWM*	*Yes*	*Novel start position*	*Landmarks moved*
Shipman and Astur (2008)	*MWM*	*Yes*	*Novel start position*	*None*
Rodriguez (2010)	*MWM*	*Yes*	*Novel start position*	*None*
Goodrich-Hunsaker *et al.* (2010)	MWM	Yes	Novel start position	None
Cornwell et al. (2008)	*MWM*	*Yes*	*Novel start position*	*None*
Baumann et al. (2010)	*MWM*	*Yes*	*Novel start position*	*None*
Astur *et al.* (2000)	MWM	Yes	Novel start position	None
Antonova et al. (2009)	*MWM*	*Yes*	*Novel start position*	*None*
Feigenbaum and Morris (2004)	MWM	Yes	Gradual move to new start position	Landmarks moved
Bohbot *et al.* (2004)*	MWM	Yes	Novel start position	None
Moffat et al. (2006)	*Other*	*Yes*	*Encoding by navigation*	*None*
*Maguire et al. (1998b)**	*Other*	*Yes*	*Encoding by navigation*	*None*
*Aguirre et al. (1996)**	*Other*	*Yes*	*Encoding by navigation*	*None*
Suthana et al. (2009)	*Other*	*Yes*	*Encoding from footage of navigation*	*None*
Maguire et al. (1996b)	*Other*	*Yes*	*Encoding from footage of navigation*	*None*
Maguire *et al.* (1996a)	Other	Yes	Encoding from footage of navigation	None
Spiers *et al.* (2001a)	Other	Yes	Goal-directed navigation	None
Maguire et al. (1998a)	*Other*	*Yes*	*Goal-directed navigation*	*None*
Hartley *et al.* (2003)	Other	Yes	Goal-directed navigation	None
Spiers and Maguire (2006)	*Other*	*Yes*	*Goal-directed navigation*	*None*
Xu et al. (2010)	*Other*	*Yes*	*Goal-directed navigation*	*Landmarks removed*
Weniger *et al.* (2012)	Other	Yes	Goal-directed navigation	Landmarks obscured
*Marsh et al. (2010)**	*RAM*	*Yes*	*Novel start orientation*	*None*
Iaria et al. (2003)	*RAM*	*Yes*	*None*	*None*
Bohbot et al. (2004)	*RAM*	*Yes*	*None*	*None*
Astur et al. (2005)	*RAM*	*Yes*	*None*	*None*
Goodrich-Hunsaker and Hopkins, 2010	RAM	Yes	None	None
Burgess et al. (2001)	*Other*	*Yes*	*Recall of spatial context*	*None*
Maguire et al. (1997)	*Other*	*Yes*	*Recall of complex routes*	*None*
Abrahams *et al.* (1997)	RAM	No	Gradual move to new position	None
Holdstock *et al.* (2000)	VS	No	Gradual viewpoint-shift	Room darkened
Shrager *et al.* (2007)*	VS	No	Gradual viewpoint-shift	None
Lee *et al.* (2005)	VS	No	Instantaneous viewpoint-shift	None
Hartley *et al.* (2007)	VS	No	Instantaneous viewpoint-shift	None
Schmidt et al. (2007)	*VS*	*No*	*Instantaneous viewpoint-shift*	*None*
King *et al.* (2002)	VS	No	Instantaneous viewpoint-shift	None
King *et al.* (2004)	VS	No	Instantaneous viewpoint-shift	Background changed

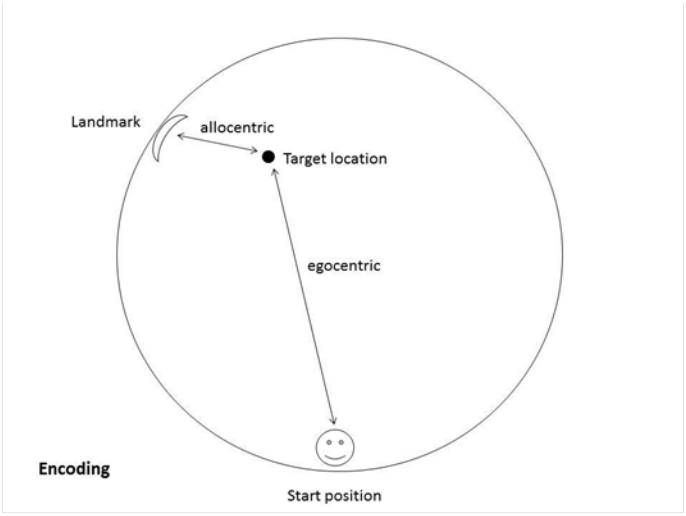
Chapter 3 Experiment 1: Introducing the Northumberland Gallery Task

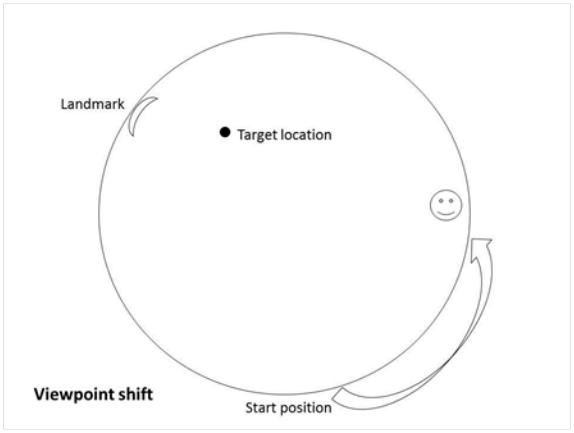
3.1 Introduction

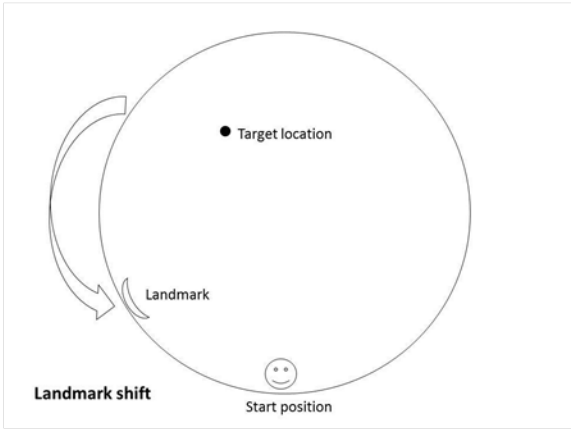
3.1.1 Principles of the NGT

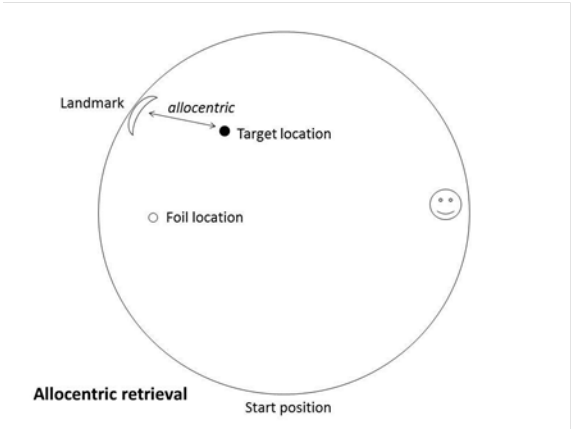
The Northumberland Gallery Task (NGT) was designed by myself, programmed by Andre Bester (Cognition and Communication Research Centre, Northumbria University) and further developed for Experiment 3 by Andreas Finkelmeyer (Institute of Neuroscience, Newcastle University). The NGT was developed to provide a measure of allocentric short-term memory, without imposing any navigational demands, in a neuroimaging context. As was identified in section 2.2.5, an ideal task would include an instantaneous viewpoint-shift to assess allocentric spatial memory and also a visually comparable egocentric condition to allow a tight contrast between the working of an allocentric and an egocentric subsystem. For the purposes of Part II of the present project, it was also important that the task remained straightforward and without any excessive demands on executive function and motivation. Below, I provide a description of the theoretical principles of the NGT.

The visual context for the NGT is a virtual cylindrical room with a number of equally salient landmarks on the walls. At presentation, the observer sees a single target location appear on the floor of the room from a peripheral viewing position (Figure 3-1). In this phase, the target location can be represented both in relation to the environmental landmarks and in relation to the observer position (Figure 3-1, top). However, during the subsequent delay, participants are informed about an out-of-view manipulation of either their own position or the position of the landmarks (Figure 3-1, middle). At test, the manipulation has already occurred and participants are required to distinguish the target location from a single foil location. The shift in viewpoint is assumed to require retrieval of the vectors between the target location and the surrounding environmental landmarks (object-object vectors), reflecting the use of a reference frame with an allocentric origin (Figure 3-1, bottom left). In contrast, the shift of landmark locations is assumed to instead encourage the retrieval of the vector between the target location and the observer position (self-object vector), reflecting the use of a reference frame with an egocentric origin (Figure 3-1, bottom right).









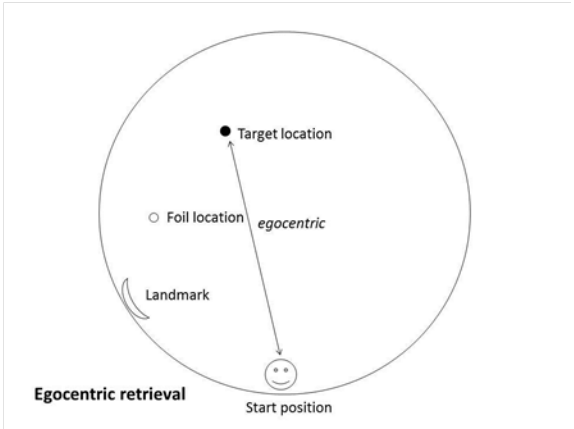


Figure 3-1: Schematic of the principles of the NGT. At encoding (top), the target location can be represented in terms of vectors with an allocentric or egocentric origin. An out-of-view manipulation of the observer viewpoint or the landmarks during the delay period (middle) means that participants have to use the landmarks or their own position, respectively, to distinguish the target from the foil at test (bottom).

As was indicated above, the allocentric condition of the NGT can be considered to be equivalent to a viewpoint-shift task (King, 2002; Schmidt, 2007). It therefore shares an important principle with the classic MWM in that it requires participants to remember the target location from a position that is different from the study position (Morris, 1982). However, as in several other analogues of the MWM (e.g. Parslow, 2009), the NGT does not require participants to learn the location of a hidden target over several successive trials. Instead, the target location is always visible at presentation, which means that a new target location can be used on each trial and that each target location only has to be represented in memory for a short period of time.

Importantly, the viewpoint-shift in the NGT is immediate and occurs out of view, which leaves no information about self-motion available for a moment-by-moment egocentric updating strategy. In the context of two-system models of spatial reference frames, the allocentric condition cannot be solved based on transient self-object vectors provided by the egocentric subsystem (Shelton and McNamara, 2001; Mou *et al.*, 2009; Zhang *et al.*, 2011). Instead, the allocentric condition is proposed to rely on an allocentric subsystem, in which the target location is represented relative to a fixed reference direction (Shelton and McNamara, 2001). Given the cylindrical shape of the NGT environment and the resulting lack of salient environmental axes, the initial study view is likely to represent the most dominant cue for selection of the reference direction (McNamara *et al.*, 2003). The disruption caused by the viewpoint-shift can therefore be expected to require a recovery of such a reference direction to access the spatial vectors that are relevant to the target location. Importantly, in the absence of self-motion information, this recovery process will need to rely on the visual input of the interobject vectors in the scene (Zhang *et al.*, 2011). Consequently, it can be proposed that the allocentric condition of the NGT requires participants to use the environmental landmarks to recover the fixed reference direction, as aligned with the study perspective, in order to retrieve the object-object vectors defining the target location. Although the allocentric updating model postulates that both self-object and object-object vectors can be represented relative to the reference direction (Zhang *et al,* 2011), the instability of the observer position in the allocentric condition of the NGT is thought to favour the use of object-object vectors over self-object vectors to retrieve the target location.

Although the two-system models have been favoured over a one-system egocentric updating model (Wang and Spelke, 2000; Burgess, 2006), it is worth mentioning that the allocentric condition of the NGT does not provide an absolute distinction between the two models. Specifically, it is possible that an encapsulated geocentric module support the process of reorientation to the initial study view following the viewpoint-shift, after which purely egocentric self-object vectors are accessed to retrieve the target location. Since a reorientation to the initial study view *per se* would be indistinguishable from a recovery of an allocentric reference direction that is aligned with the very same initial study view, the two accounts cannot be separated in the NGT. However, both processes would necessarily involve an element of self-localisation based on the surrounding environment, which in turn would require an allocentric representation of the position of the observer at study. Consequently, I argue that a dynamic representation of self-object vectors, as proposed by the egocentric updating model, would be insufficient to support performance in the allocentric condition of the NGT. Instead, as proposed above, the allocentric condition will be assumed to require the engagement of an allocentric subsystem. Even so, it is important to acknowledge that the allocentric condition will require appraisal of the NGT environment through egocentrically defined sensory systems (e.g. the retina, body orientation). Therefore, although the term allocentric is used to refer to the use of a memory representation that is grounded in the NGT environment, it does not imply independence from egocentric sensory systems.

As an important extension of previous viewpoint-shift tasks (King *et al.*, 2002; King *et al.*, 2004; Schmidt *et al.*, 2007), the NGT also includes a visually similar egocentric condition. In this condition, the landmarks are shifted in an equivalent manner to the shift of viewpoint. As a result of such instability of environmental landmarks, participants are encouraged to use their own stable position to represent the target location (Parslow *et al.*, 2004). This is in contrast to a mere absence of a viewpoint-shift, which would allow participants to represent the target location both in terms of their own position and in terms of environmental landmarks. In the context of two-system models of spatial reference frames, the egocentric condition is therefore proposed to rely on the self-object vectors provided by the egocentric subsystem (Shelton and McNamara, 2001). The inclusion of the egocentric condition is particularly important in a neuroimaging context where it provides a tight control condition to the allocentric condition.

In regards to the egocentric condition of the NGT, it is important to emphasise that even when the positions of landmarks are shifted, alternative sources of environmental cues remain available. For example, the virtual room boundaries and the physical edges of the computer screen are not disrupted by the landmark shift and can therefore be used. Although this can be a limiting factor of the egocentric condition, it is worth mentioning that it is virtually impossible to completely eliminate the availability of environmental cues. For example, although the room boundaries could be removed and the edges of the screen could be made invisible by darkening the room, the salient axis of the direction of gravity would remain available as an environmental cue. In this context, it was therefore considered more beneficial to keep the egocentric condition visually indistinguishable from the allocentric condition in all phases of the task. Therefore, the primary difference between the allocentric and egocentric conditions of the NGT is that performance in the former condition depends on the use of discrete landmarks whilst the latter does not.

Finally, the NGT also implements a control condition, in which no manipulation occurs during the delay. Considering that both the observer position and the environmental landmarks remain stable, allocentric and egocentric subsystems are assumed to be equally efficient in solving this condition. Although different participants may prefer to rely on one system to the other (Bohbot *et al.*, 2004), both sources of spatial cues can be used in parallel to solve the task in this condition.

In summary, the primary principle of the allocentric condition of the NGT is that the viewpoint-shift makes the observer position unstable as a cue to location, which requires the target location to be retrieved from a representation that is grounded in the stable external environment, which would be provided by an allocentric subsystem. Conversely, the principle of the egocentric condition is that the manipulation of the landmark positions encourages the use the stable observer position to retrieve the target location, which is thought to result in a relative independence from the allocentric subsystem. Critically, the NGT also does not impose any navigational demands, which is thought to provide an improved isolation of the cognitive process of interest relative to navigation-based tasks.

3.1.2 Predictions

Based on evidence that healthy participants are able to represent a target location both relative to their own position and relative to environmental landmarks (Burgess, 2006),

above-chance performance was predicted in all conditions of the NGT. In the context of two-system models of spatial reference frames, the allocentric condition was expected to engage the allocentric subsystem to recover the reference direction established during study (Shelton and McNamara, 2001; Zhang *et al.*, 2011). In addition, the allocentric condition was expected to require a coordination of the allocentric representation with the current egocentric perspective. In contrast, an egocentric subsystem was expected to be sufficient to solve the egocentric condition. Considering that the self-object vectors provided by the egocentric subsystem can be accessed directly, without a recovery of the relevant reference frame or any coordination processes, the egocentric condition was expected to impose a lesser cognitive cost compared to the allocentric condition. A further reduction of the cognitive cost was predicted for the control condition, in which information sources for both subsystems were available and stable.

In line with the uncertainty hypothesis proposed by (Li *et al.*, 2012), the challenge of the allocentric condition was expected to involve the recovery of the reference direction, which in the NGT would be aligned with the initial study view. As such, a greater viewpoint-shift was expected to result in a greater uncertainty in the identification of the reference direction, imposing a greater cognitive cost as the discrepancy between the study viewpoint and the test viewpoint increases. Consequently, an alignment effect, as reflected by increasing response times for greater viewpoint-shifts, was predicted in the allocentric condition of the NGT.

3.2 Methodology

3.2.1 Participants

41 students completed the study. As part of a participation credit system, students received credits for completing the study, which subsequently supported their own use of the system for recruitment. A technical problem relating to the recording of responses meant that data from two participants could not be included in the analysis. Three participants had a mean accuracy in the control condition that were more than three times the interquartile range and were excluded from the analysis (see section 3.2.5). The remaining 36 participants (26 females) had a mean age of 19.4 years (*SD*=1.66; range=18-26).

3.2.2 Apparatus and materials

3.2.2.1 Task environment

The Northumberland Gallery Task (NGT) was developed by Andre Bester (Cognition and Communication Research Centre, Northumbria University) using the game development tool Unity (2.6.1 for Windows; Unity Technologies). It was presented to participants on a standard 19 inch monitor at a screen resolution of 1024x768 pixels. Participants made their responses by pressing keys on the keyboard, which were colour coded in accordance to the response options.

The task took place in a virtual apparatus consisting of a circular room with a diameter of 10 arbitrary units. The room had a textured grey floor, a uniform grey ceiling and red brick walls. There were seven pictures frames on the walls, within which seven animal drawings were rendered (Figure 3-2). The animal drawings were obtained from a 2D-object databank of drawings of common objects (Rossion and Pourtois, 2004), which had been based on the original set produced by Snodgrass and Vanderwart (Snodgrass and Vanderwart, 1980). The selected animal drawings consisted of a fox, an owl, a bear, a dear, a rabbit, a squirrel and a raccoon, and were easily nameable (Rossion and Pourtois, 2004) and exhibited similar colouring (Figure 3-3). The picture frames were equally sized and placed at equidistance. The seven pictures represented the only landmarks in the environment, with the exception of the wall itself, and will be referred to as such. The nature and placement of the landmarks was important to avoid any memory bias resulting from any large differences in salience between different parts of the environment. Throughout the task, the room was viewed from a stationary peripheral position at a height consistent with the line of sight of a person of average height. This position will be referred to as the observer position. The field of view was set to 100°, which meant that between four and five landmarks were visible from any of the positions used in the task (Figure 3-2).

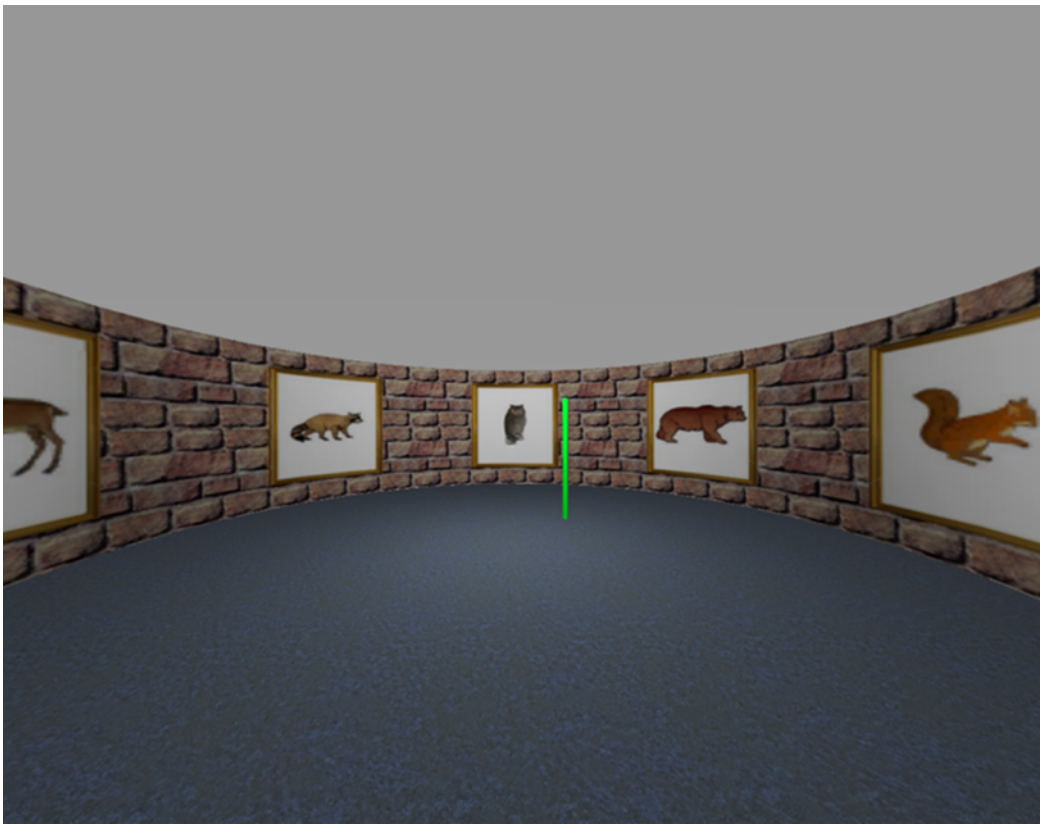


Figure 3-2: Screen shot of the virtual environment providing the context for the NGT.

Figure 3-3: The full set of images used as landmarks in the NGT (Rossion & Pourtois, 2004).

3.2.2.2 Training models

To familiarise participants with the relationships between the landmarks in the NGT environment, a training procedure was implemented prior to the NGT itself (for more detail, see section 3.2.4). For this training procedure, which consisted of a study phase and a testing phase, two small-scale cardboard models of the virtual room were used. The first model was an exact replica of the virtual room and was used for the study phase (Figure 3-4). The second model was used in the testing phase and was identical to the study model with the exception that the picture frames were empty. The test model was used together with seven cards on which each of the animals had been printed.

Figure 3-4: The cardboard model used for the study phase of the familiarization procedure prior to the NGT task. Note that the model used for the test phase was identical but with empty picture frames.

3.2.2.3 Questionnaires

Two questionnaires were included in the procedure of Experiment 1. The first questionnaire, which will be referred to as the NGT Experience Questionnaire, was developed specifically for use in conjunction with the NGT and acted as a measure of participants' experience of the task. The questionnaire consisted of two parts, one that related to difficulty and one that related to memory strategies. In the first part, participants were asked if they had experienced any of the conditions as more difficult and, if this was the case, to specify the condition and to describe why they thought it was particularly difficult. In the second part, participants were asked to describe the strategies used in the three conditions of the NGT in their own words. The outcome of the questionnaires was not used in any formal analyses in the present project. See Appendix A for the full questionnaire.

The second questionnaire was the Santa Barbara Sense of Direction Scale (SBSOD; (Hegarty *et al.*, 2002), which was used as a self-report measure of participants' sense of direction. In this questionnaire, participants rated their own abilities on navigation and way-finding tasks. The scale consisted of 15 self-referential statements (e.g. "I very easily get lost in a new city"), which were rated on a 7-point Likert scale ranging from strongly disagree to strongly agree. The inclusion of this questionnaire was important to ensure that

the cognitive abilities that were measured in the NGT were relevant to real-life spatial behaviour. See Appendix B for the full questionnaire.

3.2.3 Design

As introduced in section 3.1.1, the NGT required participants to remember a single location and to demonstrate the accuracy of this memory by selecting the target location over a foil location after a short delay. All trials exhibited the same structure: a presentation phase, a delay phase and a response phase (Figure 3-5). There were three conditions, which differed in terms of the manipulation between the presentation phase and the response phase. In the allocentric condition, the observer position was shifted to a different peripheral position whilst the landmarks remained stationary. In the egocentric condition, the landmark positions were shifted whilst the observer position remained stationary. The landmarks shift constituted a coherent rotation of the wall, with the ground remaining stationary. The manipulation was not visible to participants but occurred during the delay, and participants were informed about the type of manipulation via a one-word instruction during the delay. In a control condition, both the observer position and the landmark positions remained the same in the presentation phase and in the response phase.

In the presentation phase of the NGT, there were four possible start positions. The start positions were located at the periphery of the room, at 90° intervals, and none were positioned immediately in front of a landmark. The room remained empty for 0.5 second before a green pole appeared at a target location. Target locations were pre-generated at random under two restrictions. First, both the target location and the foil location had to be visible from all start position and from the positions resulting from the change of observer position in the allocentric condition. Second, the target location could not be closer to the wall than 1.0 unit. Seventy-two unique target locations were generated, which were repeated for each of the three conditions, resulting in a total of 216 trials. The pole was presented for 3.0 seconds, after which the delay phase started.

The unfilled delay lasted for 4.5 seconds and consisted of a black screen with a white one-word instruction on the upper half of the screen. The placement of the instruction was intentional and aimed to displace the retinal representation by forcing participants to direct their gaze away from the floor of the NGT environment. There were three instructions: “None”, “You” and “Walls”, which informed participants of the absence of manipulation

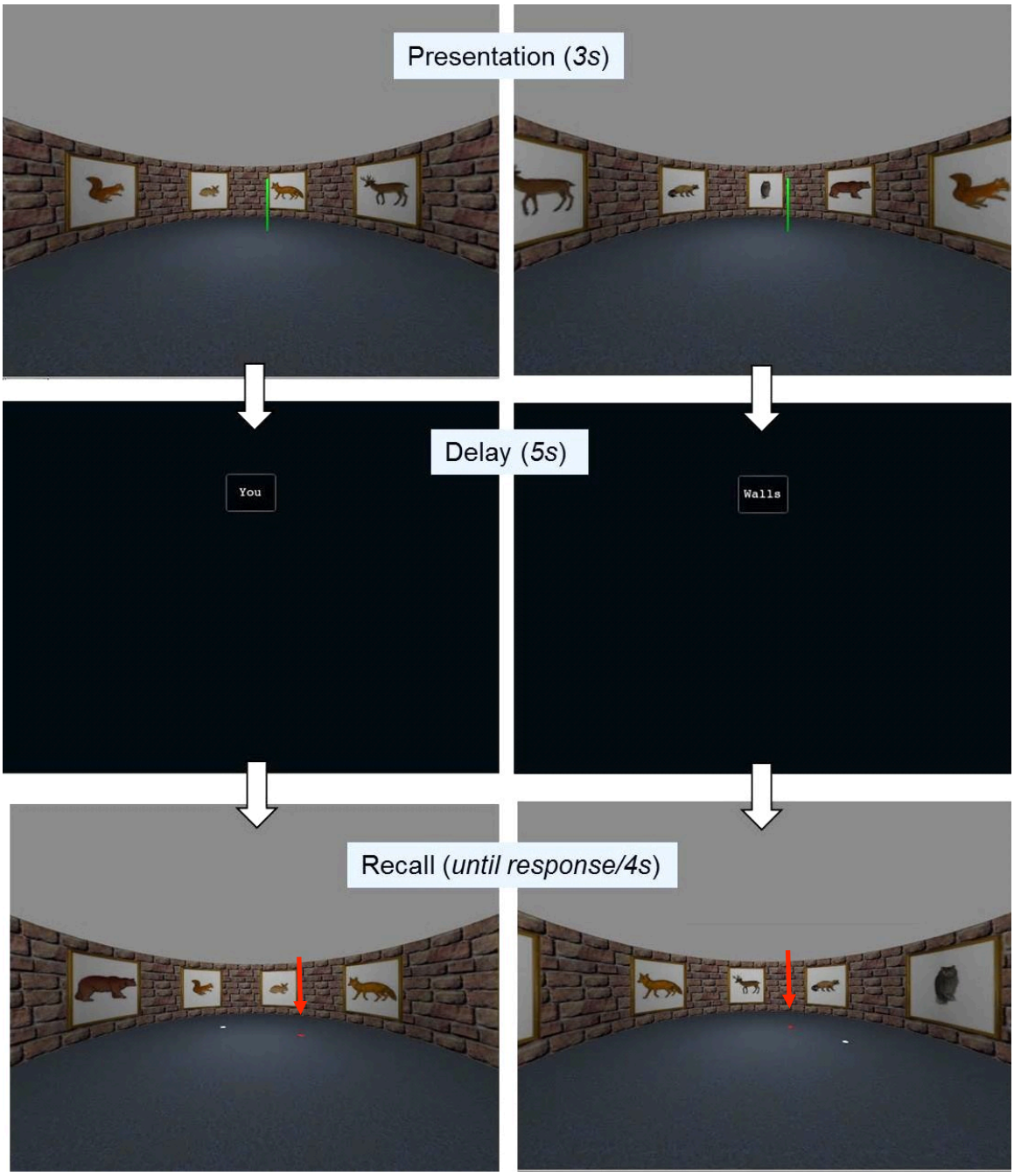


Figure 3-5: Overview of the sequence of events in the allocentric condition (left) and the egocentric condition (right) of the NGT. Note that the 'You' instruction informs about the shift in viewpoint whilst the 'Walls' instruction informs about a shift of the landmarks. Note also that the red response option, as indicated by a red arrow, represents the correct response in both example trials.

(control condition), the manipulation of observer position along the periphery of the wall (allocentric condition) and the manipulation of landmark positions by a rotation of the wall (egocentric condition), respectively. Both manipulations occurred in clockwise and anticlockwise directions at magnitudes of 45°, 90° and 135°. There were an equal number

of trials for each rotation type, resulting in 36 trials for each rotation magnitude with 12 trials in each direction.

After the delay phase, the room was presented again either from the start position, as in the egocentric and control conditions, or from a different position, as in the allocentric condition. The arena remained empty for 0.5 seconds before the response options appeared, resulting in a total delay of 5.0 seconds. The response options constituted a red and a white circular mark at the floor of the arena, of which one represented the target location and one represented the foil location. The target location was represented by the red mark on half of the trials and by the white mark on half of the trials. The size of the marks was kept constant to prevent participants from using variability in size as a cue to location. The distance between the target and the foil was 1, 2 or 3 units (diameter of the arena was 10 units), with 36 trials for each target-foil distance. The foil locations were randomly generated from the target locations under the same restrictions as described above. Participants made their responses by pressing a red key (‘z’ key) with their left hand and a white key (‘m’ key) with their right hand. The trial ended as soon as the participant responded or 4.0 seconds after the response options appeared, after which the next trial started immediately. The Unity software recorded the response time, defined as the time between the onset of the response options and the button press, and the accuracy of the response.

All participants completed the same 216 trials. The trials were divided into two blocks, with a self-paced break in the middle. The two blocks were always completed in the same order but the trial order within each block was randomized for each participant. Trials were fully counterbalanced for manipulation magnitude (45°, 90°, 135°), manipulation direction (clockwise, anticlockwise), target-foil distance (1, 2, 3) and the colour of the response option (red, white).

3.2.4 Procedure

Participants were tested one by one in a dedicated testing room. After completing the SBSOD participants were informed that they were going to perform a location memory task on the computer but that they would first complete a brief training procedure. In this procedure, participants were first asked to study a cardboard model of the NGT environment for two minutes (see 3.2.2). Moving and turning the model during the study

phase was not encouraged nor prohibited. After the study phase, the study model was removed and the second model, in which the picture frames were empty, was placed in front of the participant. The experimenter placed one of the seven animal cards in one of the empty picture frames. The remaining cards were then turned face down and the participant had to randomly select a second card and place it in the correct picture frame, in relation to the first card. This was repeated seven times with each of the seven cards being placed by the experimenter in a fixed order. Participants were not given any feedback during the testing session. If participants did not make any errors, they were allowed to proceed to the NGT. In the case of one or more errors, the study phase was repeated. If the criterion was not reached by the third study phase, the experimenter allowed the participant to have a final look at the study model before proceeding to the NGT.

After the training phase, participants were given close instructions about the NGT and watched an animation on the computer. The animation involved a demonstration of the two manipulations. First, the participant viewed movement along the periphery of the wall, whilst being reminded about the allocentric condition. Second, the participant viewed a rotation of the walls, whilst being reminded about the egocentric condition. Finally, the participant had the opportunity to complete six practice trials. In the first three practice trials, the green pole remained in the room in the response phase to indicate the correct response option whilst the last three practice trials were identical to the actual trials. The six practice trials were repeated until the participant reported feeling confident about the instructions.

Before commencing the actual trials, participants were encouraged to sit as close as possible to the computer screen and to keep their index fingers on the response buttons throughout the task. Participants were told to make their responses as quickly and as accurately as possible. They were informed that each block of the task would take approximately 20 minutes to complete and that there would be a break between the blocks. After the task had been completed, participants were asked to fill in the NGT Experience Questionnaire. The testing session took approximately 60 minutes to complete in total.

3.2.5 Data analysis

The present section relates to all behavioural analyses involving the NGT in the present and in upcoming experiments. Participants with a mean accuracy in the control condition that

was more than three times the interquartile range were excluded from all analyses. Non-response trials were excluded from all analyses and only correct trials were used for analyses of response times. Significant main effects revealed by analyses of variance (ANOVAs) were followed up post-hoc with pairwise comparisons with Bonferroni correction for multiple comparisons. Significant interaction effects were followed up with paired and independent t-tests (two-tailed) without correction for multiple comparisons. For brevity, full ANOVA tables were only presented when the effects and interactions reported were of central importance. One-sample t-tests were used to test whether average performance was significantly above chance in each of the conditions. At-chance performance was indicated by § in figures. Relationships were tested with Pearson's correlation coefficients (two-tailed). In all figures, error bars reflected the standard error of the mean. In all tables, significant effects were highlighted in **bold** and trends towards significant effects were highlighted in *italics*. A significant effect was defined as $p<.05$ whilst a trend towards a significant effect was defined as $.05\leq p<.10$ for all analyses.

3.3 Results

3.3.1 Main analyses

For Experiment 1, 1.9% of the total number of trials was non-response trials, of which 68% were allocentric trials, 20% were egocentric trials and 12% were control trials. As described in the previous section, such trials were excluded from all analyses.

A one-way ANOVA with condition (allocentric, egocentric, control) as a within-subject factor revealed a significant main effect of condition on accuracy ($F(2,70)= 414.76$, $p=<.001$; Figure 3-6) and on response times ($F(2,70)= 265.54$, $p=<.001$; Figure 3-6).

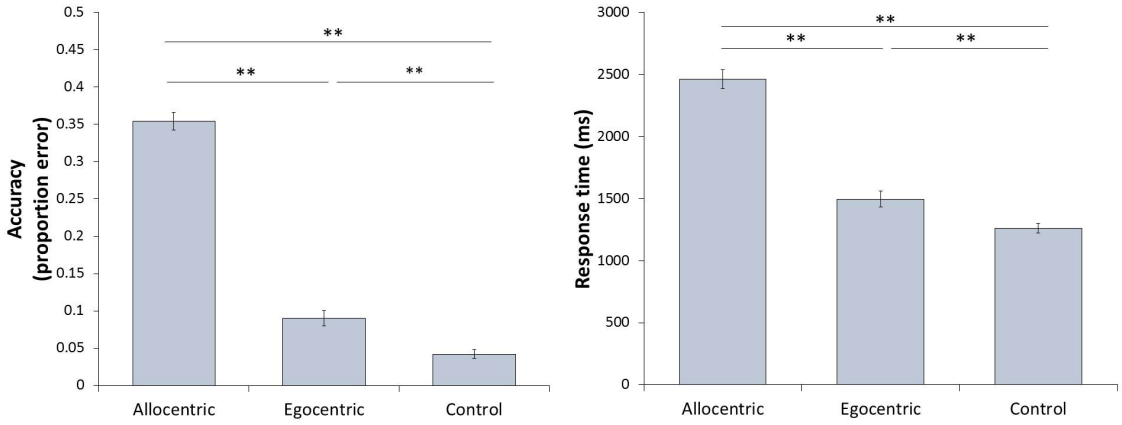


Figure 3-6: Main effect of condition on accuracy and response times and outcome of pairwise comparisons (* p<.05; ** p<.01).

A more detailed 2x3x3 repeated measures ANOVA followed, with condition (allocentric, egocentric), angle of rotation (45°, 90°, 135°) and target-foil distance (1 unit, 2 units, 3 units) as within-subject factors (Table 3-1, Table 3-2). In addition to the already demonstrated effect of condition, there was a significant main effect of angle of rotation and target-foil distance on accuracy and response times (Figure 3-7, Figure 3-8). There were also several significant interaction effects. For accuracy and response times, there was a significant interaction between condition and angle of rotation (Figure 3-9, Figure 3-10), which appeared to be a reflection of a greater effect of angle of rotation in the allocentric relative to the egocentric condition. There was also a significant three-way interaction between condition, angle of rotation and target-foil-distance (Figure 3-11, Figure 3-12). For accuracy, the interaction between condition and target-foil distance was significant, which appeared to reflect a greater effect of distance in the allocentric condition (Figure 3-13). The interaction between rotation and target-foil distance also had a significant effect on accuracy (Figure 3-14), which appeared to constitute a more variable effect of rotation angle for target-foil distances of 1 unit. Note that the exclusion of response times for incorrect trials meant that one participant did not have data for all cells, which meant that the detailed ANOVA for response times was based on 35 instead of 36 participants.

Table 3-1: Repeated measures ANOVA for the effect of condition, angle of rotation and target-to-foil distance on accuracy.

Source	MS	df	*F*	*p*
Condition	10.709	1	364.665	**>.001**
error (condition)	0.029	35		
Rotation	0.564	3	26.332	**>.001**
error (rotation)	0.021	70		
Distance	0.977	2	33.475	**>.001**
error (distance)	0.029	70		
Condition X Rotation	0.055	2	3.272	**0.044**
error (condition X rotation)	0.017	70		
Condition X Distance	0.068	2	3.457	**0.037**
error (condition X distance)	0.02	70		
Rotation X Distance	0.094	4	5.633	**>.001**
error (rotation X distance	0.017	140		
Condition X Rotation X Distance	0.041	4	2.530	**0.043**
error (condition X rotation X direction)	0.016	140		

Table 3-2: Repeated measures ANOVA for the effect of condition, angle of rotation and target-to-foil distance on response times.

Source	MS	df	*F*	*p*
Condition	1.56E+08	1	288.337	**>.001**
error (condition)	539821.914	34		
Rotation	5066898.814	2	29.031	**>.001**
error (rotation)	175436.49	68		
Distance	3206577.262	2	25.160	**>.001**
error (distance)	127449.398	68		
Condition X Rotation	2904005.717	2	19.708	**>.001**
error (condition X rotation)	147350.768	68		
Condition X Distance	101999.782	2	0.936	0.397
error (condition X distance)	109013.026	68		
Rotation X Distance	207321.191	4	2.257	*0.066*
error (rotation X distance	91868.812	136		
Condition X Rotation X Distance	398032.301	4	4.134	**0.003**
error (condition X rotation X direction)	96280.005	136		

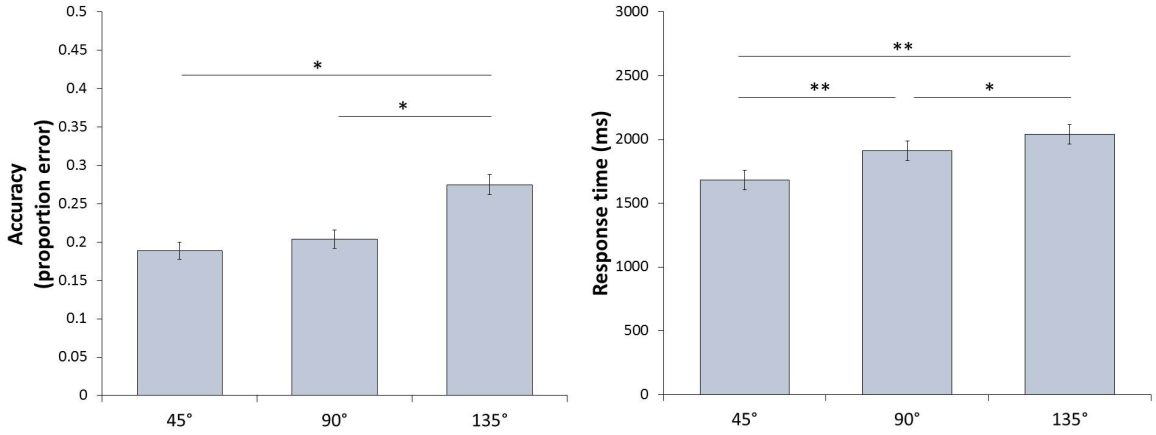


Figure 3-7: Main effect of angle of rotation on accuracy and response times and outcome of pairwise comparisons (* p<.05; ** p<.01).

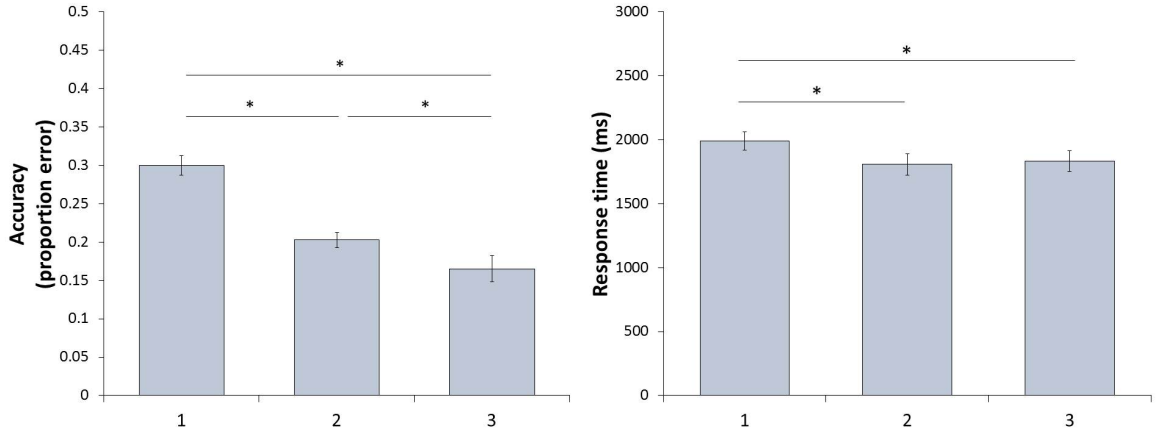


Figure 3-8: Main effect of target-foil distance (units) on accuracy and response times and outcome of pairwise comparisons (* p<.05; ** p<.01).

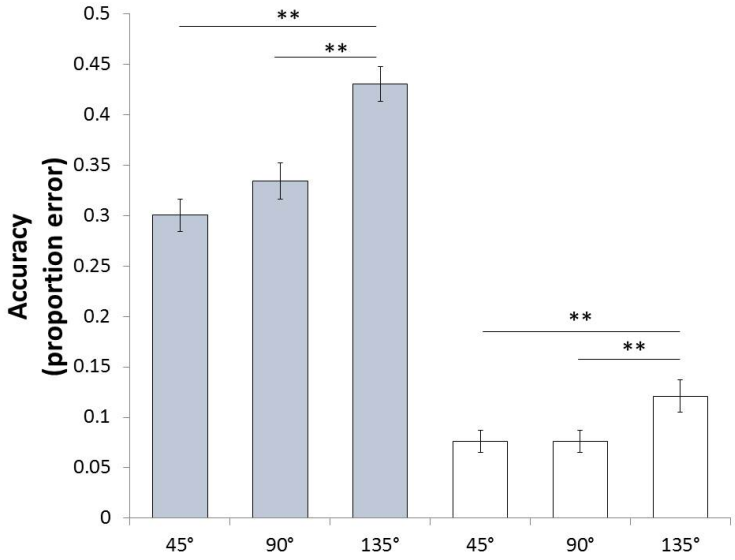


Figure 3-9: Interaction effect between condition and angle of rotation on accuracy and outcome of pairwise comparisons (* p<.05; ** p<.01). Filled bars reflect the allocentric condition. Unfilled bars represent the egocentric condition.

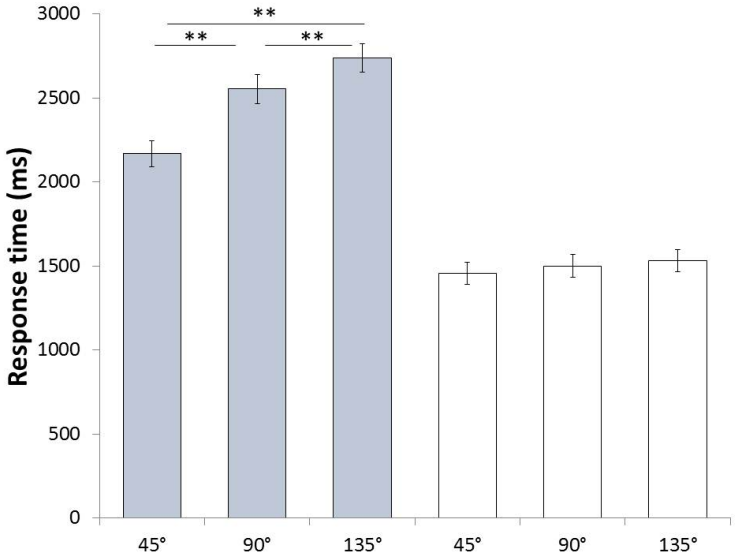


Figure 3-10: Interaction effect between condition and angle of rotation on response times and outcome of pairwise comparisons (* p<.05; ** p<.01). Filled bars represent the allocentric condition. Unfilled bars represent the egocentric condition.

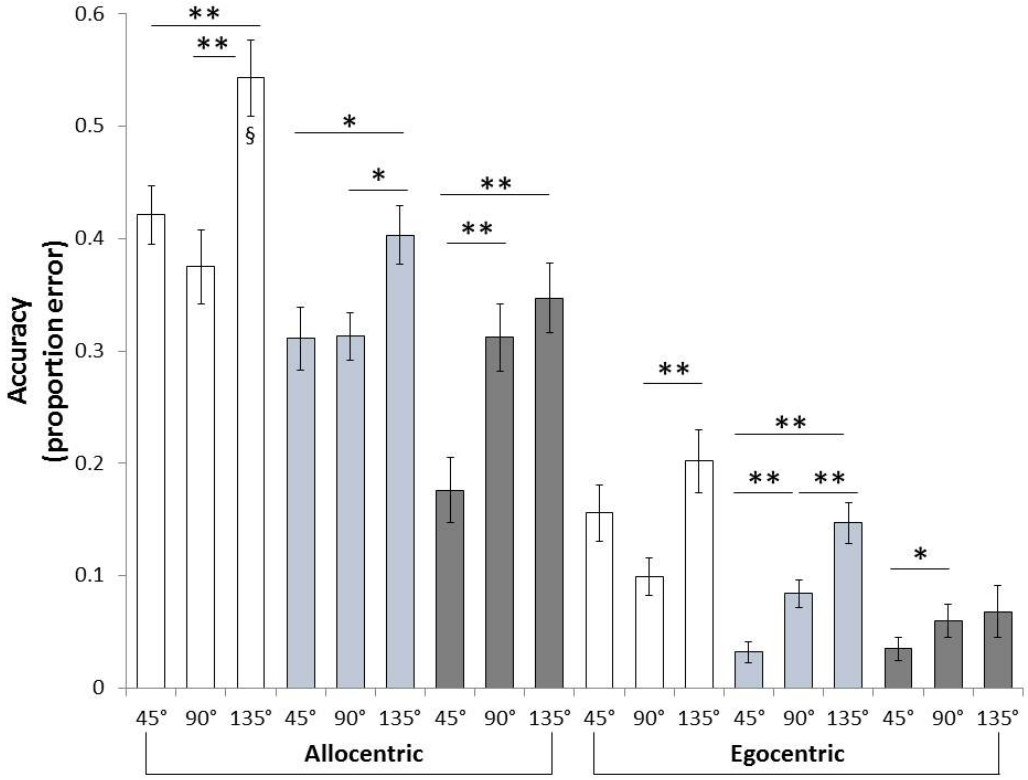


Figure 3-11: Interaction effect between condition, angle of rotation and target-foil distance on accuracy and outcome of pairwise comparisons (* p<.05; ** p<.01). Unfilled bars represent distances of 1 unit, light grey bars represent distances of 2 units and dark grey bars represent distances of 3 units. § reflects chance performance.

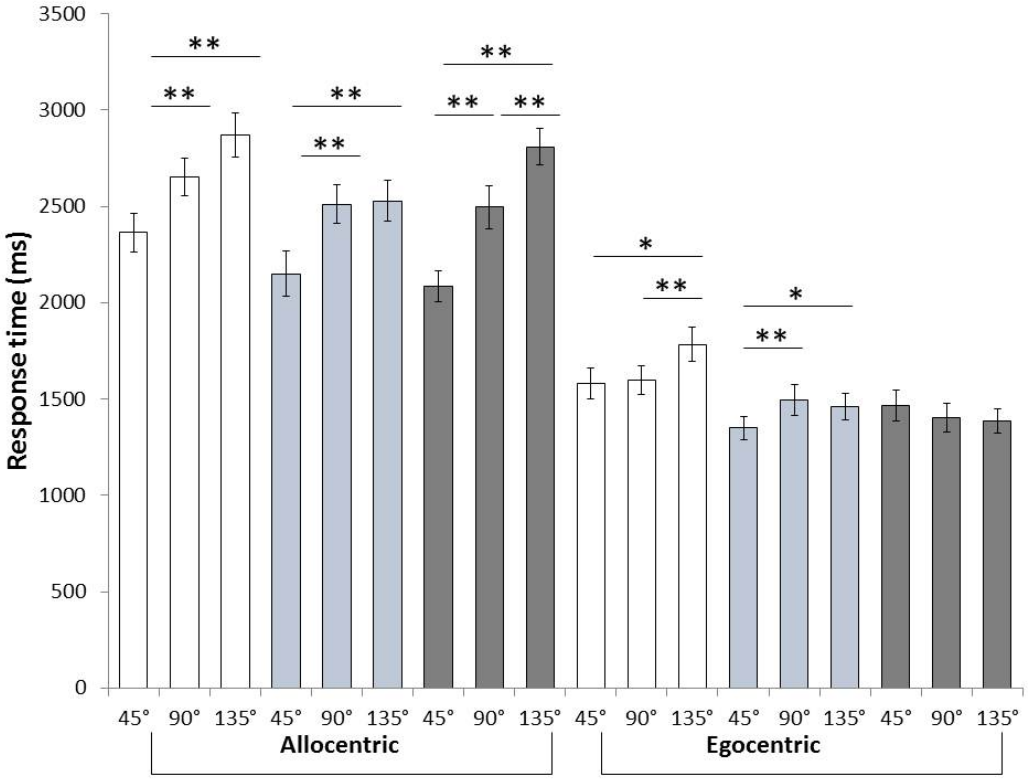


Figure 3-12: Interaction effect between condition, angle of rotation and target-foil distance on response times and outcome of pairwise comparisons (* p<.05; ** p<.01). Unfilled bars represent distances of 1 unit, light grey bars represent distances of 2 units and dark grey bars represent distances of 3 units.

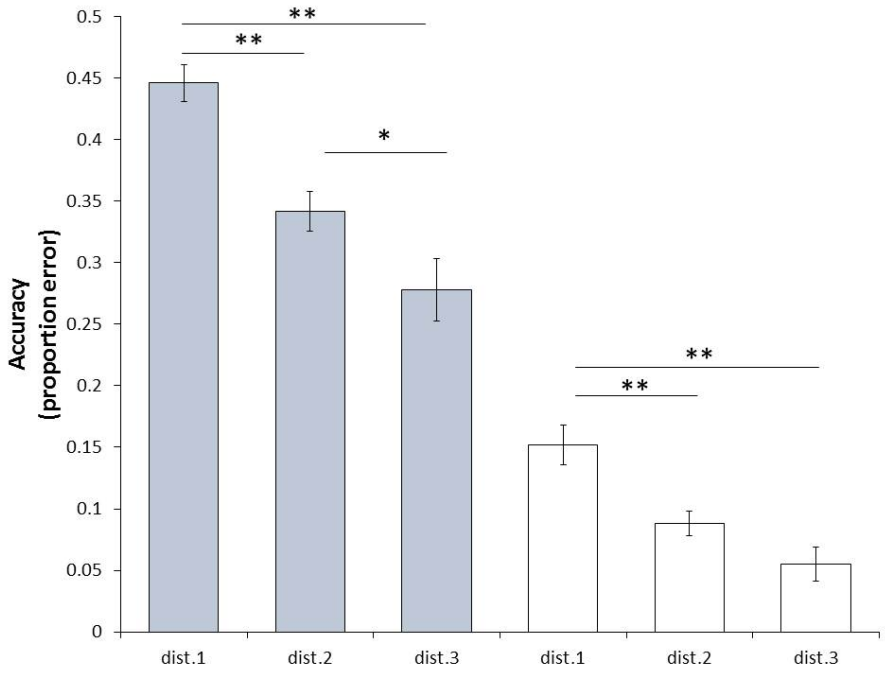


Figure 3-13: Interaction effect between condition and target-foil distance on accuracy and outcome of pairwise comparisons (* p<.05; ** p<.01). Filled bars represent the allocentric condition. Unfilled bars represent the egocentric condition.

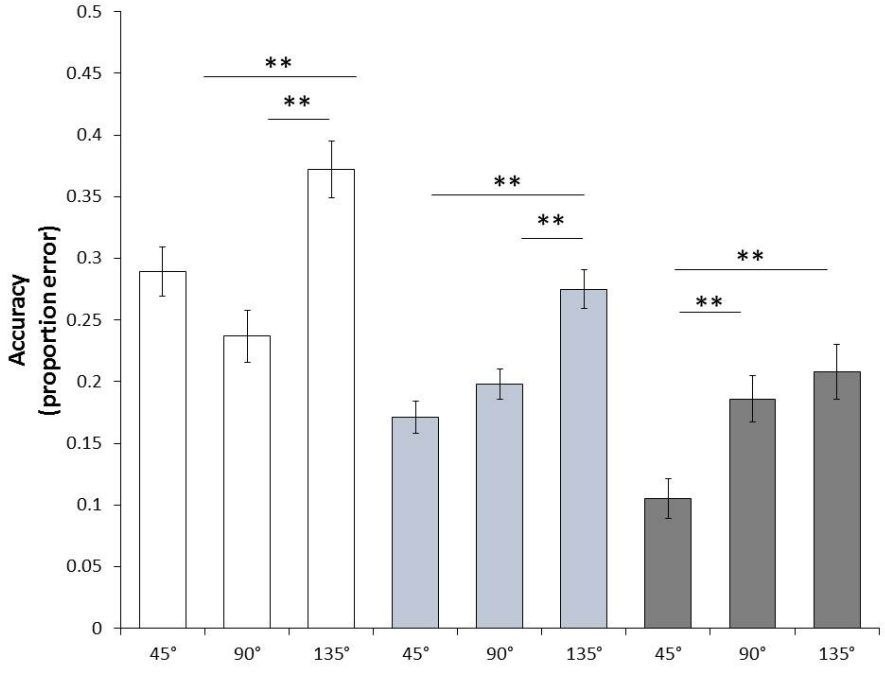


Figure 3-14: Interaction effect between angle of rotation and target-foil distance on accuracy and outcome of pairwise comparisons (* p<.05; ** p<.01). Unfilled bars represent distances of 1 unit, light grey bars represent distances of 2 units and dark grey bars represent distances of 3 units.

3.3.2 Additional analyses

3.3.2.1 Training performance

Participants made an average of 1.5 errors (*SD*=2.82; range=0-15) in the training phase that preceded the NGT. Pearson's correlation coefficient (two-tailed) revealed that training errors did not correlate with accuracy or response times in the allocentric ($r(34)=.27$, $p=.12$; $r(34)=.01$, $p=.96$), egocentric ($r(34)=-.27$, $p=.12$; $r(34)=.06$, $p=.73$) or control condition ($r(34)=.01$, $p=.97$; $r(34)=.06$, $p=.72$).

3.3.2.2 The effect of rotation direction and start position

The effect of rotation direction (clock-wise, anti-clock-wise) and start positions (0°, 90°, 180°, 270°) on accuracy and response times were investigated separately from the main ANOVA. This was because there were no a priori predictions concerning the effect of these two factors and the interactions between these and the experimental variables were not of interest. Paired t-tests revealed that whilst the direction of the rotation (clockwise, anti-clockwise) had no effect on accuracy ($t(35)=.17$, p=.85) it did have a significant effect on response times ($t(35)=-2.66$, p=.012), with longer response times for the clockwise rotations (*M*=1923.86, *SD*=364.08) compared to anti-clockwise rotations (*M*=1857.20, *SD*=361.08). One-way repeated measures ANOVAs furthermore revealed no effect of start position on accuracy ($F(3,105)=.55$, $p=.65$) or response times (F(3,105)=1.67, p=.18).

3.3.2.3 Relationship with the Santa Barbara Sense of Direction Scale

SBSOD score correlated significantly with error rates in the allocentric condition ($r(34)=-.47$, $p=.004$; Figure 3-15) and in the egocentric condition ($r(34)=-.36$, $p=.031$; Figure 3-16) but not in the control condition ($r(34)=-.092$, $p=.59$). Response times correlated significantly with SBSOD score in the egocentric condition ($r(34)=-.34$, $p=.044$) but not in the allocentric condition ($r(34)=-.32$, $p=.059$) and the control condition ($r(34)=-.16$, $p=.35$).

3.3.2.4 Sex differences

A 3x2 mixed ANOVA, with sex entered as a between-subject factor and condition as a within-subject factor, revealed a significant main effect of sex ($F(1,34)=5.59$, $p=.024$) but no interaction with condition ($F(2,68)=.69$, $p=.51$) on accuracy. The main effect constituted

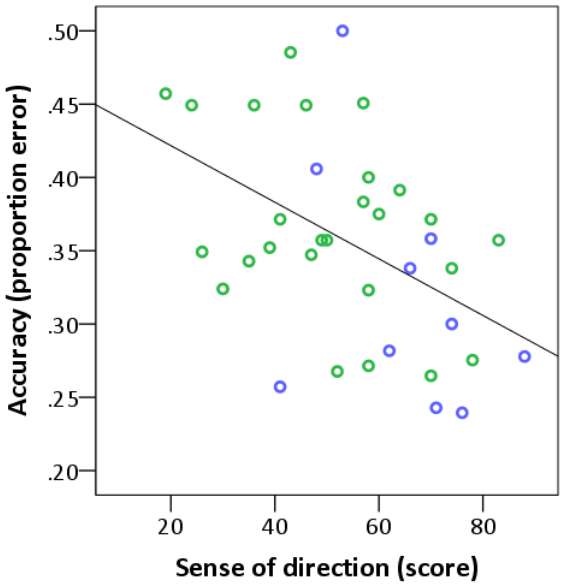


Figure 3-15: Scatterplot demonstrating the relationship between accuracy in the allocentric condition and score on the Santa Barbara Sense of Direction scale (R^2=.22). Green circles represent female participants. Blue circles represent male participants.

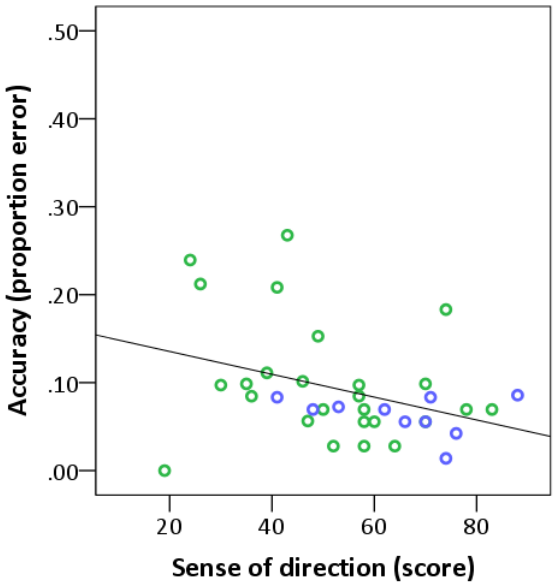


Figure 3-16: Scatterplot demonstrating the relationship between accuracy in the egocentric condition and score on the Santa Barbara Sense of Direction scale (R^2=.13). Green circles represent female participants. Blue circles represent male participants.

a slightly higher error rate in females (*M*=.17, *SD*=.041) compared to males (*M*=.14, *SD*=.029). For response times, there was no significant main effect of sex ($F(1,34)=877.46$, $p=.25$) or interaction between sex and condition ($F(2,68)=2.26$, p=.11).

3.4 Discussion

In line with the predictions, young participants produced above-chance performance in all conditions of the NGT, supporting that a location can be retrieved from short-term memory based on both environmental landmarks and observer position (Burgess, 2006). The allocentric condition was found to produce higher error rates and response times than the egocentric and control conditions, which is likely to reflect, at least in part, the additional cognitive cost associated with the recovery of the reference direction and the coordination between spatial reference systems in the allocentric condition (Zhang *et al.*, 2011). Furthermore, the egocentric condition was found to produce higher error rates and longer response times than the control condition, evidencing the availability of two sources of spatial cues in the latter condition. Consistent with the alignment effect demonstrated in similar investigations (King *et al.*, 2002; Schmidt *et al.*, 2007), response times were found to increase with increasing viewpoint-shifts in the allocentric condition whilst there was no such effect of equivalent shifts of landmark positions in the egocentric condition. As was proposed in the introduction, this effect could be the reflection of the greater uncertainty in identifying the reference direction after more substantial viewpoint-shifts (Li *et al.*, 2012).

An alternative explanation of the alignment effect lies in the visual effect produced by greater viewpoint-shifts. Specifically, for larger viewpoint-shifts, landmarks that are relevant to a particular target location are more likely to disappear out of view. Longer response times may therefore be a reflection of an additional retrieval of out-of-view landmarks in order to access the target location. For example, if the target location was represented based on its vectors to landmark A and B and both landmarks disappear out of view following the viewpoint-shift, the participant may use a visible landmark C to first retrieve the positions of landmarks A and B to infer the target location. Unfortunately, it is not clear how this interpretation could be discounted in any paradigm implementing a peripheral viewpoint-shift (King *et al.*, 2002; Schmidt *et al.*, 2007). Importantly, although the 'disappearance' of relevant landmarks represents a valid account for the alignment effect, it also provides further support that environmental landmarks are indeed used to solve the allocentric condition.

In contrast to the effect of viewpoint-shifts in the allocentric condition, response times were not affected by the extent of landmark shifts in the egocentric condition. Such a pattern of

results was expected since a landmark shift can and should be ignored in the egocentric condition whilst the extent of the viewpoint-shift has to be taken into account in the allocentric condition. However, the extent of the manipulation was unexpectedly found to affect error rates both the allocentric and the egocentric condition. Whilst the increase in error rates with increasing viewpoint-shifts provides further support of an alignment effect in the allocentric condition, it is unclear why error rates should increase with greater landmark shifts in the egocentric condition. One potential explanation is a distraction effect, by which a larger rotation of the walls may direct attention away from the target location of the floor. Similarly, a visual snapshot strategy in the egocentric condition may have been more detrimental to performance when the background scene changed more substantially. Another potential explanation is that the greater demand in the allocentric condition may have biased participants towards favouring object-object vectors at encoding, which would have been more detrimental to performance when landmark shifts were more substantial. Such a bias is unlikely to have been conscious, however, since there were no indications of representing object-object vectors for the egocentric condition section of the NGT Experience Questionnaire.

Although the explanation for the effect of increasing landmark shifts on error rates cannot be determined by the data, it is worth mentioning that increasing viewpoint-shifts appeared to have a greater effect on error rates than increasing landmark shifts, as indicated by a significant interaction between condition and angle of rotation. As an example, the mean increase in error rate from 45° to 135° was twice as high in the allocentric condition (10%) compared to the egocentric condition (5%). Thus, it appears as if different factors are contributing to the effect on error rates in the allocentric and egocentric conditions. Importantly, the response time data indicates that when participants are making a correct response in the egocentric condition there is no effect of the extent of the landmark shift. Thus, whilst factors such as distraction and strategy choice may have increased the probability of error for more substantial manipulations in the egocentric condition, such factors do not appear to have an effect on response times for correct trials. This is in contrast to the allocentric condition, where the extent of the viewpoint-shift increases the probability of making an error *and* increases the response times in correct trials. In brief, the distinct pattern of results for the effect of the extent of the manipulation on performance

in the allocentric and egocentric condition suggests that different cognitive processes are at play in the two conditions.

The main analysis also revealed the expected effect of target-foil distance on response times and error rates in both conditions. The finding that smaller target-foil distances posed a greater challenge supports that distances in the NGT environment are perceived appropriately and in a similar way to real-world distances. The interaction between target-foil distances and condition indicated that target-foil distance may have had a somewhat greater effect in the allocentric condition. Furthermore, target-foil distance was found to interact with angle of rotation. It appears that this interaction is mainly driven by a more variable effect of angle of rotation for small target-foil distances, which may constitute a floor effect. Such a floor effect is supported by the at-chance performance for the largest rotation and the smallest target-foil distance in the allocentric condition (135°, distances of 1 unit). The three-way interactions are difficult to interpret but at least in the case of response times, larger target-foil distances appear to produce a pattern of results that is more consistent with the expected influence of manipulation magnitude in the allocentric condition and its lack of influence in the egocentric condition. Although speculative, this could suggest that factors such as distraction may have had a greater effect when the target is closer to the foil in the egocentric condition.

The additional analyses showed that training performance did not correlate with performance in the NGT task, suggesting that efficient learning of the environment did not affect later use of such environmental knowledge. However, the variability in training errors may not have provided sufficient sensitivity in the correlation analysis. Self-reported sense of direction was found to correlate with performance in both the egocentric and the allocentric condition. This is an important finding as it indicates that the cognitive processes assessed in the NGT task are likely to be relevant for everyday spatial tasks, such as giving directions, judging distances and finding one's way (Hegarty *et al.*, 2002). The sex difference analysis indicated a very slight male advantage in terms of error rates, which can be considered consistent with the general male advantage in spatial tasks (Postma *et al.*, 1998).

Chapter 4 Task Development

4.1 Introduction

An evident issue with the NGT as introduced in the previous chapter is that the allocentric condition is substantially more difficult than the egocentric condition. Such a substantial difference is problematic in two respects. First, although control conditions in imaging studies are commonly less demanding than experimental conditions, for example the visible compared to hidden platform condition in analogues of the MWM (Shipman and Astur, 2008), equal performance in the contrasted conditions is undoubtedly ideal. This follows from the fact that when the two conditions are contrasted in a neuroimaging context, any differences in activity could be attributed to differences in difficulty levels. Second, in the case of testing in clinical populations, patients may show an impairment in the allocentric condition not because of the allocentric nature of the task but because the greater demand of this condition. Consequently, Experiments 2, 3 and 4 focused on improving performance in the allocentric performance. Experiments 5 and 6 subsequently focused on making the NGT more suitable for use in clinical populations in preparation for Part II of the project. As such, the NGT was used in a middle-aged sample in Experiment 5 and an abbreviated version of the NGT was piloted in Experiment 6.

4.2 Experiment 2: The effect of training

4.2.1 Introduction

In Experiment 2, participants' familiarity of the NGT environment was increased by the implementation of a more extensive training paradigm. According to classical theories of the development of spatial knowledge, object-to-object vectors are better represented when the environment has been experienced more frequently (Siegel, 1975). Similarly, in the reference direction model of reference frames, the familiarity of the environment is emphasized in relation to the recruitment of the environmental subsystem to represent object-object vectors (Shelton and McNamara, 2001). It is possible that the brief training paradigm implemented in the previous chapter did not provide participants with sufficient environmental knowledge to make efficient use of the landmarks in the allocentric condition. In the extended training paradigm of Experiment 2, knowledge of the landmarks in the NGT environment was acquired by exposing participants to 'videos' of navigation

from a first-person perspective. Only one landmark was visible at any one time, which encouraged participants to gradually build an enduring topographical representation of the environment over multiple training sessions. Furthermore, the navigation element provided participants with first-hand experience of distances in the NGT environment. Overall, the extended training paradigm was predicted to improve participants' knowledge of the environment and thereby improve performance in the allocentric condition.

4.2.2 Methodology

4.2.2.1 Participants

38 students completed the study for participation credit. Five participants were excluded from the analysis following failure to reach the fixed criterion for the extended training. One participant had a mean accuracy in the control condition that were more than three times the interquartile range and was therefore excluded. The remaining 32 participants (21 females) had a mean age of 23.7 years (*SD*=5.73; range: 18-39).

The results from Experiment 2 were contrasted with the results derived from the sample tested in Experiment 1, who completed a much more limited training paradigm (section 3.2.1). Only one participant failed to reach the training criterion in the limited training paradigm. To make the two samples equivalent in terms of not including participants who failed to reach the criterion, this one participant was excluded, which resulted in a total sample size of 35 and a mean age of 19.5 (*SD*=1.67; range=18-26). As was indicated by the means, the two samples differed significantly in terms of age ($t(65)=.4.15$, $p<.001$) but not in terms of sex proportions ($t(65)=4.15$, $p=.62$) or self-reported sense of direction ($t(65)=.85$, $p=.40$).

4.2.2.2 Apparatus and procedure

The NGT was identical to the one described in section 3.2. The preceding training, however, differed. In contrast to the limited training paradigm in Experiment 1, which involved the use of cardboard-models, Experiment 2 implemented an extended and computerised training paradigm. Relative to the original training paradigm (section 3.2.2), the extended training paradigm constituted a similar 2-minute study phase and a subsequent test phase, in which participants' memory for pairs of landmarks locations was assessed. However, the

nature of knowledge acquisition at study and the response mode at test differed between the two training versions.

In the study phase of the extended training version, participants passively watched navigation from one landmark (i.e. picture frame) to another from a first-person perspective. Whilst watching such navigation, participants were instructed to learn the locations of all the landmarks for an upcoming test. When a landmark was reached, navigation stopped for one second. The view then gradually turned to face the centre of the arena and navigation continued to the next landmark. As was mentioned in the introduction, an important feature of the study phase was that only the picture frame that represented the current target of navigation depicted its animal stimulus (Figure 4-1). Consequently, participants had to integrate each individual landmark to form a complete representation of the NGT environment.

After the study phase, participants completed a test phase, which required participants to actively navigate, by pressing the arrow keys on the keyboard, from one specified landmark to another in the arena with empty picture frames (Figure 4-2). This was repeated seven times in a fixed order with each of the seven animals being used as the start position. Relative to the limited training paradigm, the testing phase was therefore equivalent in that it required participants to remember the landmark locations but was different in that it required participants to respond by navigating to the landmark locations instead of placing cards in a cardboard model. As in the limited training paradigm, participants were allowed to proceed to the NGT as soon as they reached a criterion of zero errors in the seven test trials. In the case of one or more errors, the study phase was repeated, after which participants were given another attempt to reach the criterion in a new testing phase. After each testing phase, a progress bar was displayed indicating how close performance was to criterion level. Given the relatively high demand of the extended training paradigm, such a motivating factor was considered useful. A maximum of ten study sessions were completed.

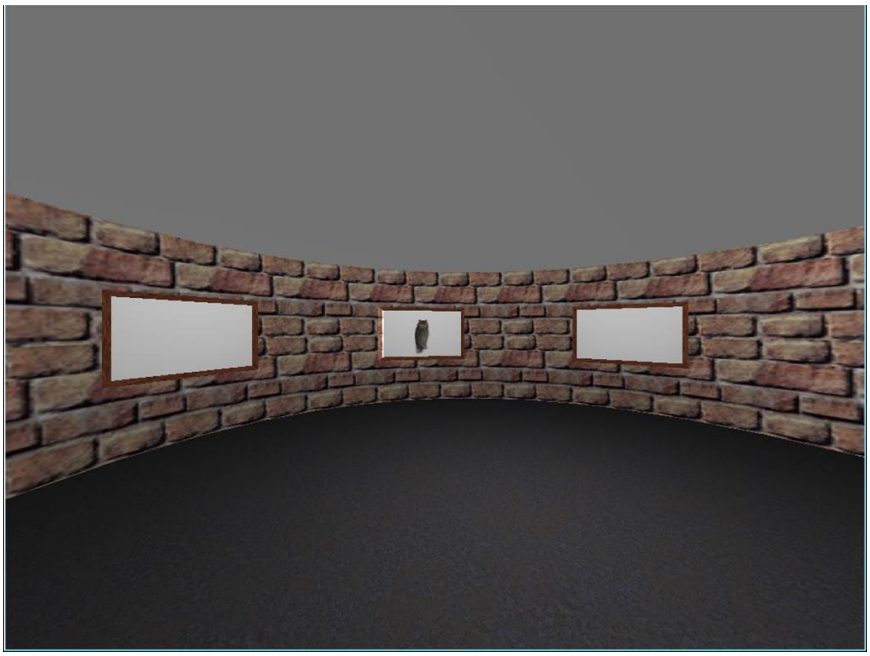


Figure 4-1: Screen shot from the study phase of the extended training paradigm. Note that only the current target of navigation is visible.

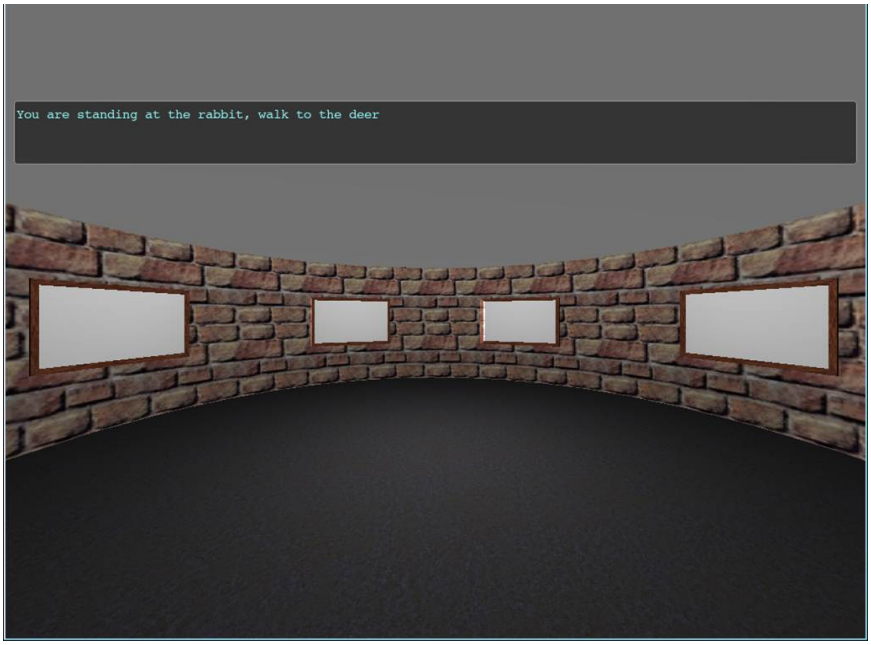


Figure 4-2: Screen shot from the testing phase of the extended training paradigm. The instruction reads: You are standing at the rabbit, walk to the deer.

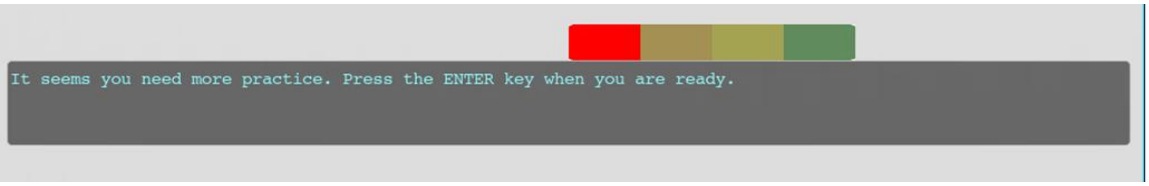


Figure 4-3: Progress bar used to inform participants of their performance in each test phase. This is an example of poor test performance, which is indicated by a red light on the progress bar. The information message reads: It seems you need more practice. Press ENTER when you are ready.

4.2.3 Results

4.2.3.1 Main analysis

For both accuracy and response times, a 2x2x3 mixed ANOVA was conducted with training paradigm (extended, limited) as a between-subject factor and condition (allocentric, egocentric) and angle of rotation (45°, 90°, 135°) as within-subject factors.

There was no significant main effect of training paradigm on accuracy ($F(1,65)=.036$, $p=.849$) or response times ($F(1,65)=.1.316$, $p=.255$). There was also no significant interaction between training paradigm and condition for accuracy ($F(1,65)<.001$, $p=.986$) or response times ($F(1,65)=.203$, $p=.654$). For accuracy and response times there were also no interactions between training paradigm and angle of rotation ($F(2,130)=.273$, $p=.762$; $F(2,130)=1.187$, $p=.309$) or any three-way interactions ($F(2,130)=.212$, $p=.809$; $F(2,130)=2.749$, $p=.068$). The descriptive statistics for accuracy and response time clearly demonstrate the lack of differences between the limited and the extended training paradigms (Figure 4-4, Figure 4-5). Note that adding age as a covariate did not change the outcome of any of the analyses.

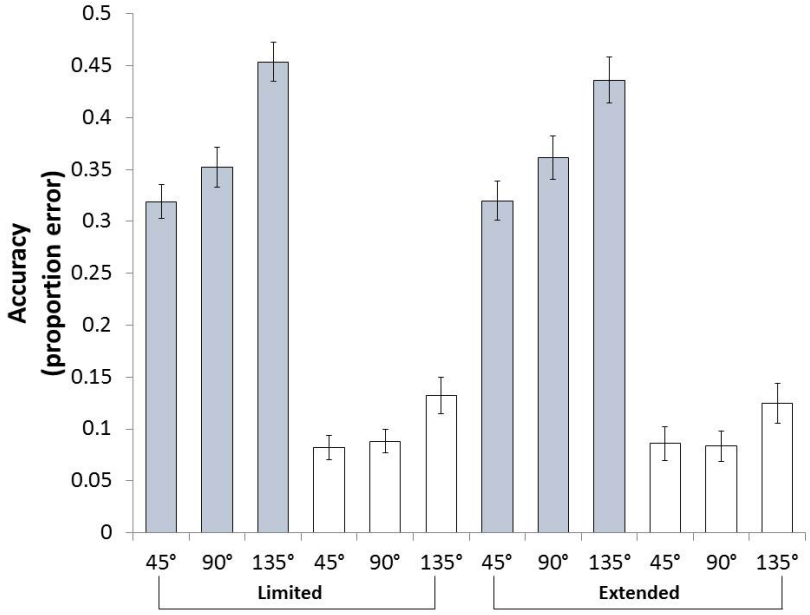


Figure 4-4: Descriptive statistics for accuracy in the allocentric (filled bars) and egocentric (unfilled bars) conditions for all angles of rotation in the NGT, as preceded by the limited training paradigm and the extended training paradigm.

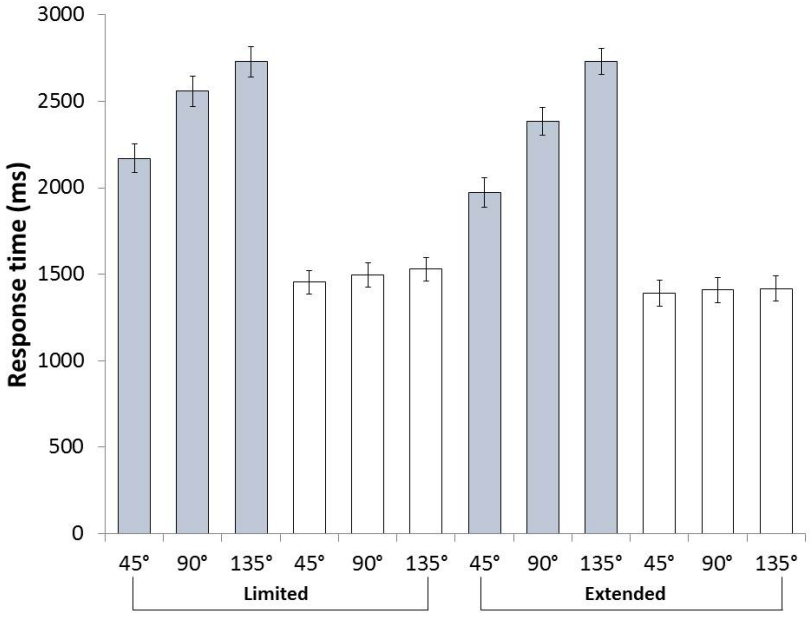


Figure 4-5: Descriptive statistics for response times in the allocentric (filled bars) and egocentric (unfilled bars) conditions for all angles of rotation in the NGT, as preceded by the limited training paradigm and the extended training paradigm.

4.2.3.2 Additional analysis

Compared to the limited training paradigm, in which 97.2% of participants reached the criterion, only 86.5% of participants reached the criterion in the extended training paradigm. Participants also made significantly more errors in the extended training paradigm (M=16.62, SD=6.13) compared to the limited training paradigm (M=1.5, SD=2.82; $t(68)$=13.37, p<.001). Figure 4-6 demonstrates the number of participants who reached the criterion for each subsequent test session. Interestingly, error rates in the allocentric condition correlated positively with the number of sessions required to reach criterion in the extended training paradigm ($r(30)$=.49, p=.004).

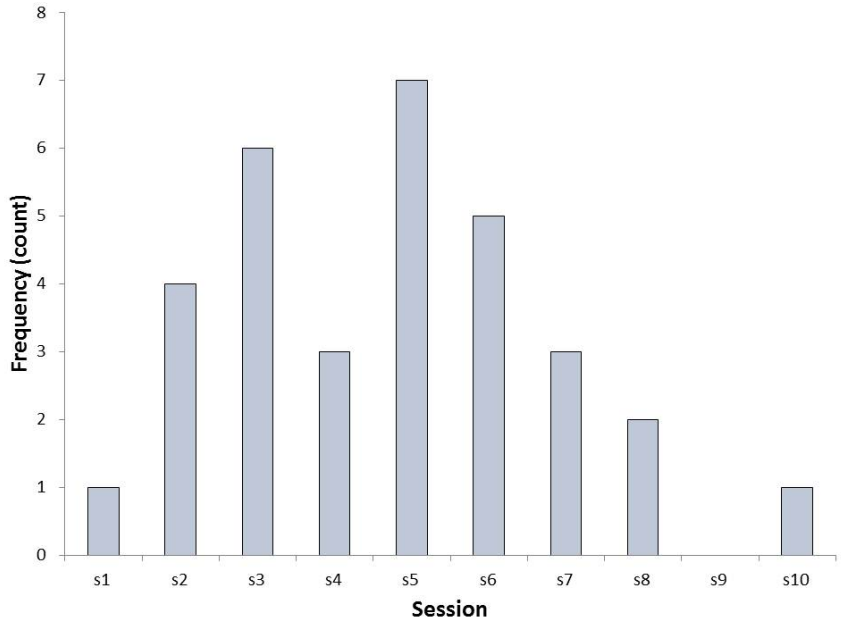


Figure 4-6: Number of participants reaching the criterion of no errors in each test session of the extended training paradigm.

4.2.4 Discussion

The results of Experiment 2 revealed that performance in the NGT did not change as a result of the extended training. A likely explanation for this null finding lies in the identical training criterion implemented in the limited and the extended training paradigm. Specifically, the training criterion of zero errors in both training paradigms meant that participants had complete knowledge of all landmark positions prior to completing the NGT. Therefore, although such knowledge was acquired gradually and from a first-person perspective in the extended training paradigm, this type of knowledge acquisition did not

appear to provide any additional environmental detail to support performance in the allocentric condition. One source of environmental detail that could have been emphasised in the extended training paradigm is the organization of environmental landmarks. However, given the lack of environmental axes provided by the cylindrical shape and landmark placements of the NGT environment, navigation from one landmark to another is unlikely to have provided participants with any additional information. Furthermore, the equal distances between landmarks are likely to have been as easily gaged from a cardboard model as through navigation. Thus, it appears as if the extended training paradigm did not provide participants with any additional information about the NGT environment. Nevertheless, the correlational analysis revealed that participants who reached the criterion early in the extended training paradigm subsequently performed better in the allocentric condition, which indicates that a similar cognitive process was important for the two task requirements. However, once participants had reached the training criterion, the mechanism of knowledge acquisition did not seem to have an overall effect on how efficiently this knowledge was later used in the allocentric condition of the NGT.

4.3 Experiment 3: The effect of subtle environmental axes

4.3.1 Introduction

Experiment 3 aimed to improve performance in the allocentric condition by increasing the efficacy by which the reference direction could be recovered in the allocentric condition. As has been mentioned previously, the lack of environmental axes in the NGT environment means that the initial viewpoint represents the dominant cue for selection of the reference direction (McNamara *et al.*, 2003). Following the instantaneous viewpoint-shift in the allocentric condition, this reference direction needs to be recovered based on inferences from the visual input of the inter-object vectors in the scene (Zhang *et al.*, 2011). It is possible that the lack of environmental axes in the NGT environment make such inter-object vectors ambiguous and difficult to use for reference direction recovery. Experiment 3 therefore aimed to make the reference direction more explicit by introducing subtle environmental axes between opposing landmarks, aligned with the study perspective. This manipulation was predicted to aid the recovery of the reference direction with the result of improved performance in the allocentric condition. In an additional effort to improve

performance in the allocentric condition, larger target-foil distances were used for Experiment 3.

4.3.2 Methodology

4.3.2.1 Participants

36 students completed Experiment 3 for participation credit. One participant had a mean accuracy in the control condition that were more than three times the interquartile range and was therefore excluded. The remaining 35 participants (28 females) had a mean age of 22.8 (*SD*=6.83, range=18-45; note that information about age was missing for one participant). This sample was compared with the sample tested in Experiment 1 (section 3.2.1; *n*=36). The sample tested for Experiment 3 was significantly older than the comparison sample ($t(69)=2.90$, $p=.005$; *M*=19.4 years, *SD*=1.66, range=18-26). The two samples did not differ in terms of sex proportion ($t(69)=-.76$, $p=.45$) or self-reported sense of direction ($t(69)=1.71$, $p=.091$).

4.3.2.2 Apparatus and procedure

A number of changes were made to the NGT itself. First, the number of landmarks was reduced from seven to six. Following the equidistant placement of the landmarks this resulted in three environmental axes being created (Figure 4-7). Second, the number of start positions was increased from four to six and aligned with the landmarks. Third, the magnitude of the viewpoint-shifts and the landmark-shifts was changed from 45°, 90° and 135° in the original version of the task to 60°, 120° and 180° in the modified version. This was to maintain the alignment with the landmarks even after the viewpoint-shift in the modified version. To further accentuate the environmental axes, lines were rendered on the ceiling of the room to connect opposite landmarks (Figure 4-8). The task version used in Experiment 3 will be referred to as 'modified' whilst the task used in Experiment 1 will be referred to as 'original'.

To further maximize the chances of producing improved allocentric performance, the distance between the target and the foil in the recall phase was also increased. Instead of using distances of 1, 2 and 3 units, distances of 2, 3 and 4 units were used for the modified version of the NGT. With the exception of the different number of landmarks in the cardboard model, Experiment 2 used the same training paradigm as the one described in

section 3.2.2. Prior to commencing the NGT task, participants were shown a new animation of the change of observer position and the wall rotation, which were presented along with verbal descriptions from a bird's eye perspective (Figure 4-9).

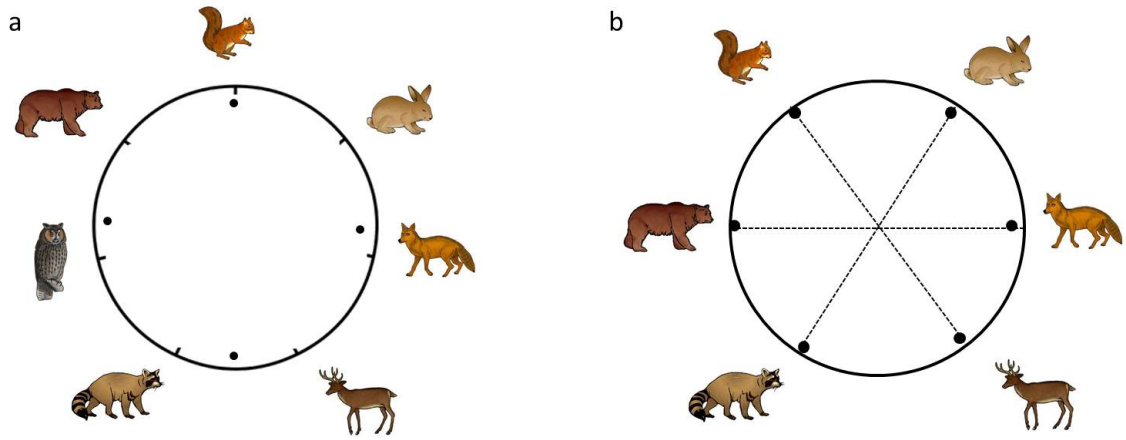


Figure 4-7: Visualization of the original (a) and modified (b) version of the NGT. Animals represent landmarks, black circles represent start positions and the dashed lines represent the subtle environmental axes between landmarks.

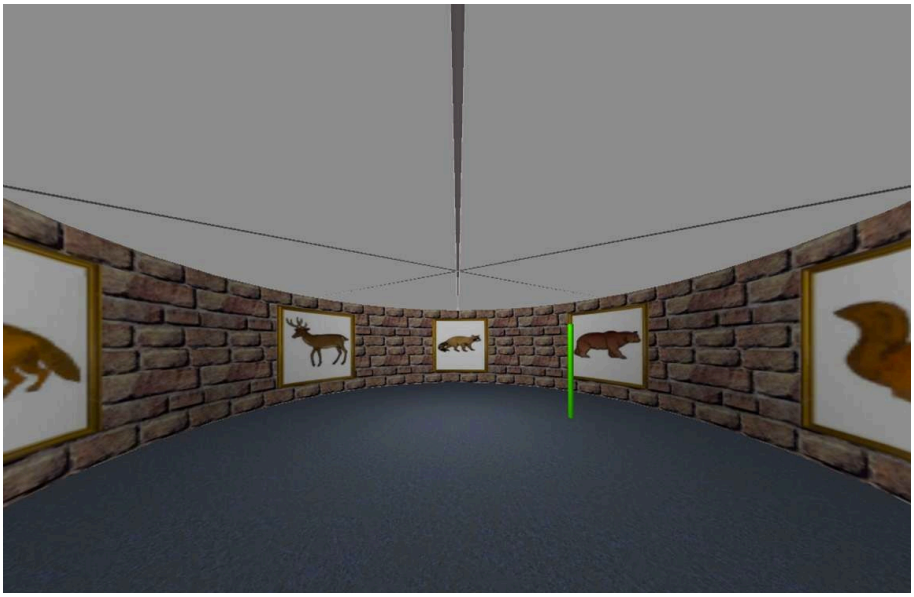


Figure 4-8: Screen shot of the modified version of the NGT. Note that the environment only contains six landmarks and that lines in the ceiling are accentuating the axes produced between such landmarks.

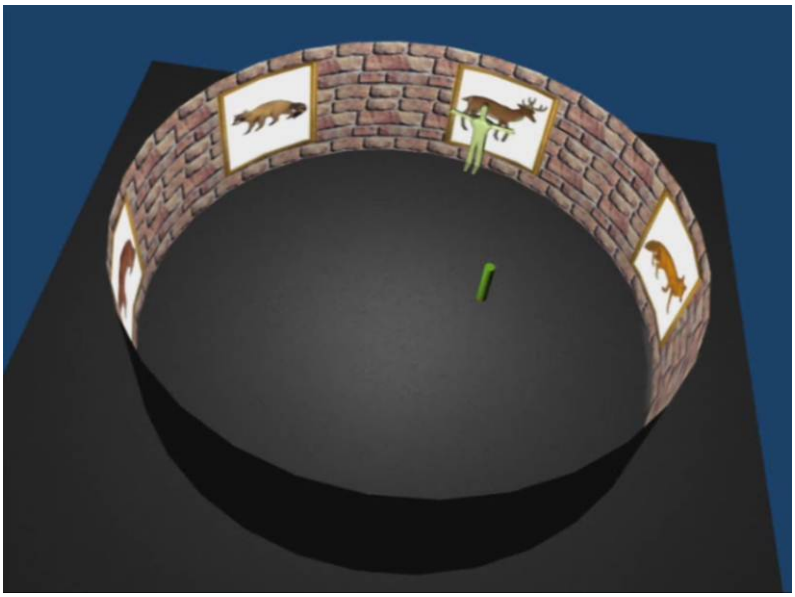


Figure 4-9: Screen shot of animation shown to participants prior to completing the NGT. Note that the position of the avatar and the walls moved in the animation to demonstrate the manipulations in the allocentric and egocentric condition.

4.3.3 Results

4.3.3.1 Main analysis

To test the effect of all task changes implemented in Experiment 3, a 2x3 mixed ANOVA, with task version (original, modified) as a between-subject factor and condition (allocentric, egocentric, control) as a within-subject factor, was conducted. There was no significant main effect of task version for accuracy, although there was a weak trend towards a significant result for response time (Table 4-1, Table 4-2, Table 4-3). For accuracy, there was a strong trend towards a significant interaction between condition and task version. Post-hoc independent tests revealed significantly lower error rates in the modified compared to the original version in the allocentric condition (t(69)=.-2.15, p=.035) but no difference in the egocentric (t(69)=.24, p=.81) and control conditions (t(69)=-1.14, p=.26).

Table 4-1: Mixed ANOVA for the effect of condition and task version (original, modified) on accuracy. * when age was entered as a covariate the interaction between condition and task version remained at trend level (*F*(2,136)=2.619, *p*=.077).

Source	MS	df	*F*	*p*
Condition	1.736	2	439.696	**<.001**
Condition X Task Version	0.012	2	3.062	*0.050**
error (condition)	0.004	138		
Task Version	0.014	1	1.621	0.207
error (task version)	0.009	69		

Table 4-2: Mixed ANOVA for the effect of condition and task version (original, modified) on accuracy. * when age was entered as a covariate the main effect of task version became non-significant (*F*(2,68)=90.595, *p*=.123).

Source	MS	df	*F*	*p*
Condition	28515254.2	2	394.692	**<.001**
Condition X Task Version	3674.512	2	0.051	0.95
error (condition)	72246.796	138		
Task Version	967948.373	1	1773.855	*0.094**
error (task version)	336082.289	69		

Table 4-3: Descriptive statistics for accuracy and response times

Task Version	Condition	mean	s.d.
Original	Allocentric	0.3545	0.07045
(accuracy, error rate)	Egocentric	0.0903	0.0619
	Control	0.0419	0.03541
Modified	Allocentric	0.3090	0.10531
(accuracy, error rate)	Egocentric	0.0953	0.10851
	Control	0.0330	0.02987
Original	Allocentric	2463.781	452.1933
(response time, ms)	Egocentric	1496.836	380.8408
	Control	1261.092	229.4471
Modified	Allocentric	2318.224	483.5803
(response time, ms)	Egocentric	1378.352	512.3087
	Control	1120.621	254.9185

Improved performance in the allocentric condition of the modified version of the task could be due to the larger target-foil distances used in this version of the task. An additional 2x3 ANOVA based on the target-foil distances that the two tasks had in common (i.e. target-foil distances of 2 and 3 units) was therefore conducted. For response times, there was no significant main effect of task version ($F(1,69)=1.248$, $p=.268$) and no interaction between task version and condition ($F(2,138)=.259$, $p=.773$). For accuracy however, there was a strong trend towards a significant main effect of task version, with the modified version producing higher error rates than the original version (Table 4-4, Table 4-5). Thus, when the two task versions are compared for the same target-foil distances, the modified version of the task appears more difficult. A likely explanation for this increase in difficulty is the use of larger angles of rotation in the modified version (60°, 120°, 180°) compared to the

original version (45°, 90°, 135°). This is evident in a qualitative comparison of accuracy and response times for the two task versions (Figure 4-10, Figure 4-11). What is also evident from this figure is that the task versions appear to have been performed similarly, with a similar effect of viewpoint-shifts and landmark-shifts on error rates and response times. This was confirmed in a subsequent analysis of accuracy and response times in the modified version (all target-foil distances), which revealed a significant main effect of condition ($F(1,34)=104.309$, $p<.001$; $F(1,34)=123.436$, $p<.001$) and the typical interaction between condition and angle of rotation ($F(2,68)=15.626$, $p<.001$; $F(2,68)=15.126$, $p<.001$).

Table 4-4: Mixed ANOVA limited to target-distances of 2 and 3 units for the effect of condition and task version (original, modified) on accuracy.

Source	MS	df	*F*	*p*
Condition	1.798	2	451.534	**<.001**
Condition X Task Version	0.003	2	0.642	0.528
error (condition)	0.004	138		
Task Version	0.035	1	3.820	*.055**
error (task version)	0.009	69		

Table 4-5: Descriptive statistics for accuracy and response times based on trials with target-foil distances of 2 and 3 units.

Task Version	Condition	mean	s.d.
Original	Allocentric	0.3088	0.09649
(accuracy, error rate)	Egocentric	0.0595	0.06484
	Control	0.0222	0.02412
Modified	Allocentric	0.3405	0.09711
(accuracy, error rate)	Egocentric	0.0930	0.10021
	Control	0.0340	0.0287

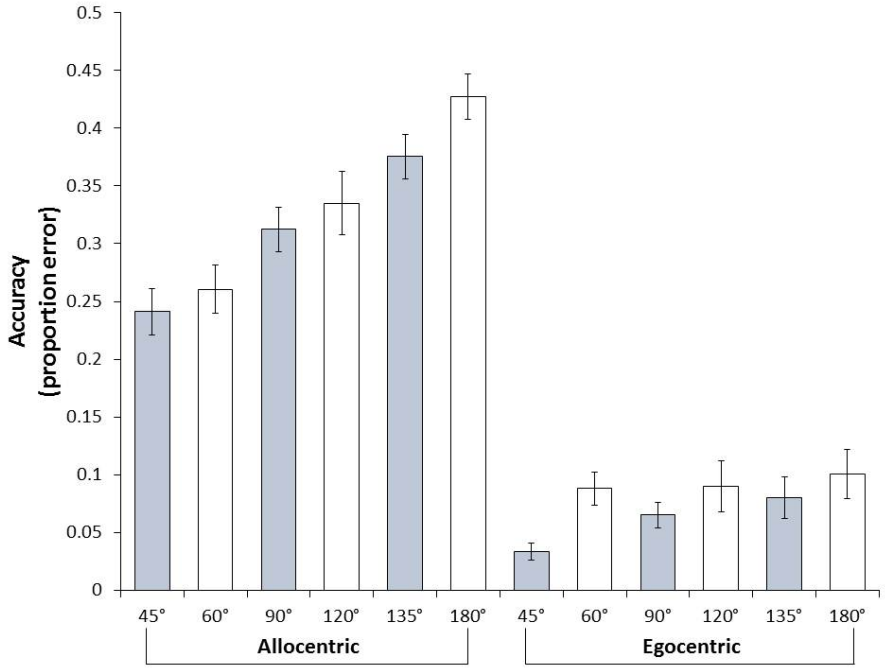


Figure 4-10: Qualitative comparison between accuracy performance resulting from different angles of rotation in the modified version (unfilled bars) and the original version of the task (filled bars). This figure was based on target-foil distances of 2 and 3 units.

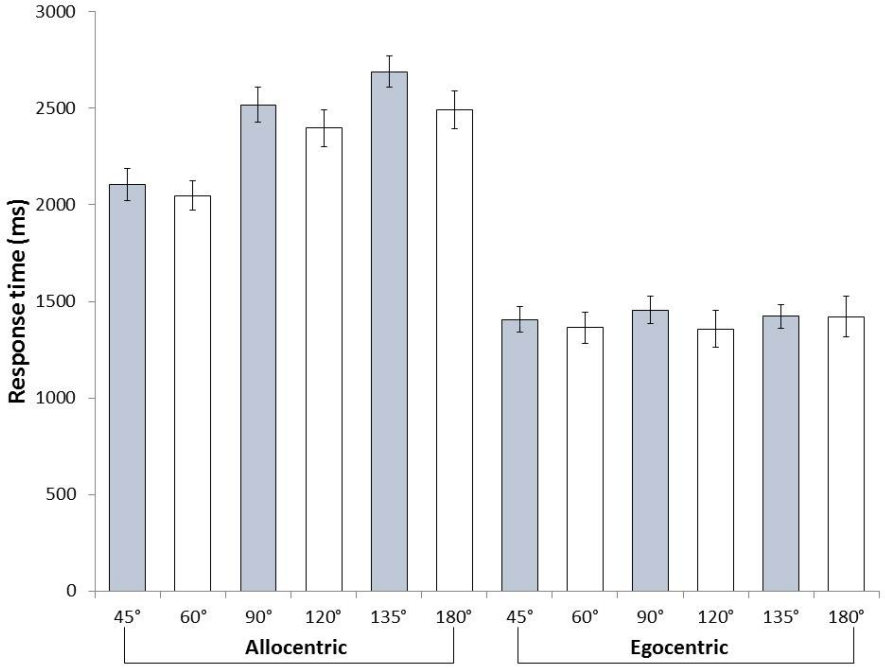


Figure 4-11: Qualitative comparison between response time performance resulting from different angles of rotation in the modified version (unfilled bars) and the original version of the task (filled bars). This figure was based on target-foil distances of 2 and 3 units.

4.3.4 Discussion

The results of Experiment 3 revealed that the combined effect of the changes to the task had a beneficial effect that was limited to the allocentric condition. However, in a follow-up analysis, which was based on the target-foil distances that the original and modified versions had in common, it became evident that a more salient reference direction did not improve performance in any of the conditions. In contrast, there was a strong trend towards generally higher error rates in the modified version compared to the original version. The poorer performance in the modified version is likely to be accounted for by the greater angles of rotations used in this version. Namely, the average rotation of 120° in the modified version is likely to have resulted in generally higher error rates compared to the average rotation of 90° in the original version. It therefore appears that any potential beneficial effect of the increased salience of the reference direction was not sufficient to outweigh the negative effect of increased rotation magnitudes.

It is possible that the presence of three environmental axes may not have accentuated the reference direction sufficiently. Specifically, following the viewpoint-shift in the allocentric condition, any of the three environmental axes could indicate the reference direction. The visual input from the inter-object vectors in the NGT environment may therefore not have provided sufficiently salient indications of the reference direction to improve performance. It therefore remains possible that performance could be improved if only the actual reference direction, as defined by the initial viewpoint, was highlighted following the viewpoint-shift (Mou *et al.*, 2009). Furthermore, previous research has indicated that interobject vectors are specified with respect to a small number of axes, typically one or two (Mou and McNamara, 2002), which may have resulted in a general reluctance to use such axes to represent the target location.

It can therefore be concluded that although larger target-foil distances had a beneficial effect in the allocentric condition, the introduction of subtle environmental axes to aid recovery of the reference direction did not improve allocentric performance.

4.4 Experiment 4: The effect of elevating the viewpoint

4.4.1 Introduction

Experiment 2 and Experiment 3 both failed to reduce error rates in the allocentric condition. Although the manipulations were relatively subtle, the complete lack of an effect indicated that the difficulty in the allocentric condition is not entirely due to lacking familiarity or a lack of environmental axes. As previously mentioned, the allocentric condition is thought to engage an allocentric subsystem, in which object-object vectors are represented relative to a fixed reference direction. If such vectors cannot be accessed reliably, the quality of the representations used in the allocentric condition is likely to be compromised.

There were two features of the NGT that could be highlighted as potentially reducing the reliability of the object-object vectors. First, the field of view in Experiment 2 and Experiment 3 had been set to approximately 100° to maximize the number of landmarks visible. At close inspection, this makes the NGT environment appear oval with an apparent stretching in a direction aligned with the current viewpoint (see Figure 3-2). This type of distortion is referred to as a perspective projection distortion and is defined as the mismatch between normal vision and the emulation of normal vision by graphics or photography (Kelso, 2008). Critically, in the allocentric condition where a viewpoint-shift changes the direction of the distortion, the spatial relationships between environmental landmarks become unreliable. The second feature, which may affect the use of spatial relationships in the NGT, is that the observer is positioned at the periphery of the arena. This perspective makes spatial relationships in the more distant part of the arena appear very small, which arguably increase the ambiguity of the spatial relationships further. In Experiment 4, the position of the viewpoint was changed to reduce such ambiguity and to avoid the effect of the perspective projection distortion. As a result, improved performance in the allocentric condition was predicted in Experiment 4, as compared to results derived from Experiment 1.

4.4.2 Methodology

4.4.2.1 Participants

33 students (31 females) with an average age of 20.7 (*SD*=4.72, range=18-42) completed Experiment 4 for participation credit. This sample was compared with the sample tested in Experiment 1 (section 3.2.1; *n*=36). The two samples differed significantly in terms of sex

proportion with significantly more females in the sample tested in Experiment 3 (M=0.061, SD=.24) than in the original version of the task (M=.28, SD=.45; $t(67)$=2.44, p=.017). The samples did not differ in terms of age ($t(67)$=-1.53, p=.13).

4.4.2.2 Apparatus and procedure

In Experiment 4, the viewpoint of the observer in the virtual arena was elevated to serve two purposes: first, to increase visibility of the spatial relationships in the arena and, second, to reduce the likelihood of a perspective projection distortion. In relation to the first purpose, the elevated position allowed participants an improved overview of the arena, which reduced the ambiguity of distances in the more distant part of the arena.

To avoid the perspective projection distortion, the emulation of normal vision by the graphics in the NGT has to match that of normal vision (Kelso, 2008). This can be considered achieved when,

$$((y/2)/s) = ((w/2)/d)) = \tan(\theta/2)$$

where w is the width of the monitor, y is the width of the projection, d is the distance from the observer to the monitor, s is the distance from the observer to the projection and θ is the field of view angle (Figure 4-12).

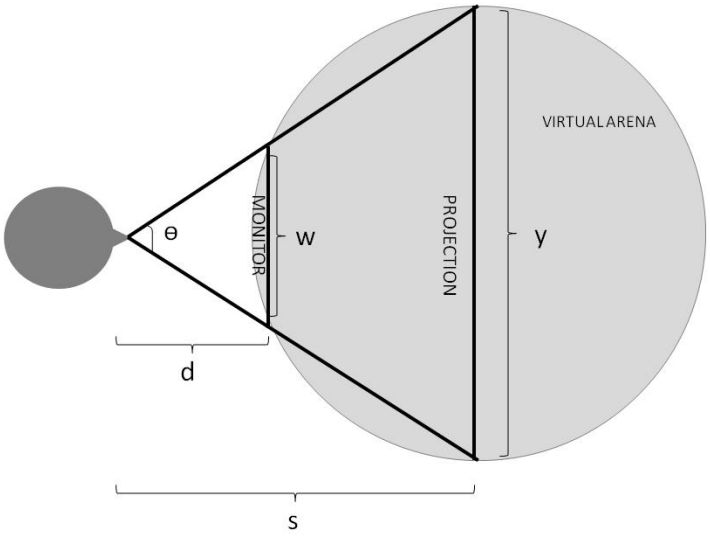


Figure 4-12: Schematic illustration of perspective projection.

In Experiment 1, a field of view of 100° was used to make four to five landmarks visible on a normally sized monitor (w=40cm). Based on the equation above, participants would need to sit very close to the monitor (d=17cm) to avoid being affected by a distortion under these conditions. To avoid the distortion at the normal viewing distance of 50cm, however, the field of view would have to be reduced to 44°. This would result in a reduction of the width of the projection from 1000cm in Experiment 1, which allows coverage of the full diameter of the virtual arena, to approximately 400cm. Consequently, the number of visible landmarks would be significantly reduced, which has obvious drawbacks for the visibility of object-object vectors in the NGT environment.

In Experiment 4, the distance between the observer and the projection (s) was increased by an elevation of the virtual viewpoint. This, in combination with a reduced field of view, allowed for a width of projection that was comparable to Experiment 1, whilst using a more realistic viewing distance. More specifically, the virtual viewpoint was elevated by d_1 and moved away from the edge of the wall by x (Figure 4-13). The new distance from the virtual viewpoint to the projection (d_2) was calculated by Pythagoras theorem,

$$d_1^2 + ((s-d)+x)^2 = d_2^2$$

When d_1=290cm, (s-d)=450cm and x=130cm, d_2 comes out to be approximately 650cm. Consequently, at the more realistic viewing distance (d) of 25cm, the new distance between the (actual) observer and the projection (s) is 675cm. Using this distance and a field of view

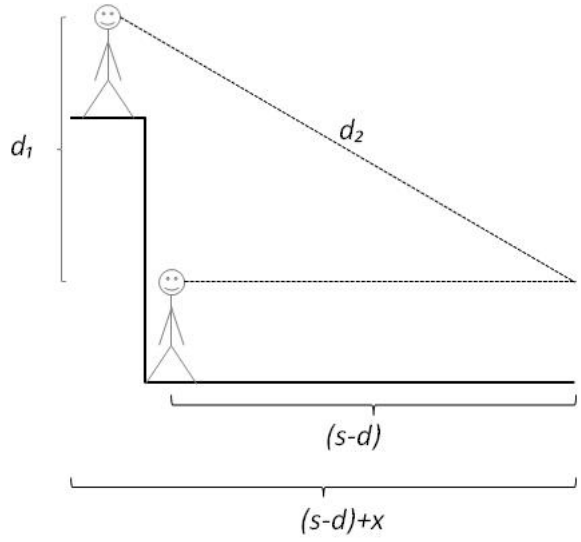


Figure 4-13: Schematic illustration of the viewpoint change implemented in Experiment 4.

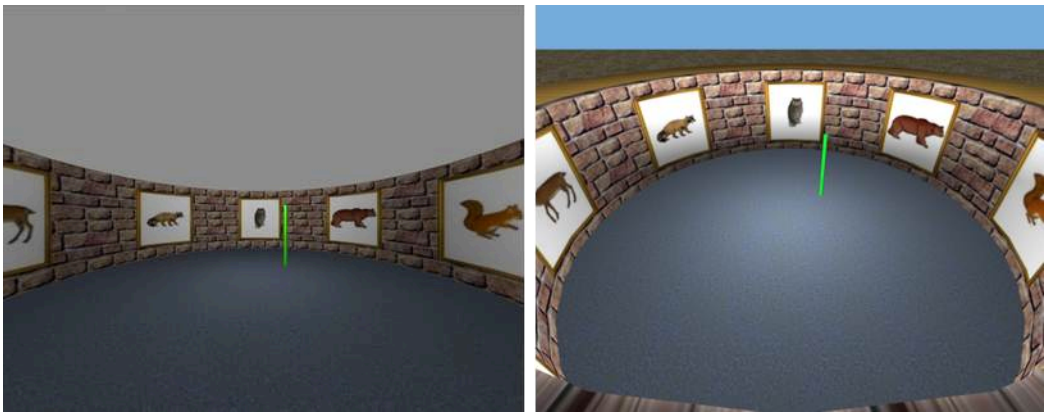


Figure 4-14: Qualitative comparison of the perceived circularity in the original version of the NGT task in Experiment 1 (left) and the elevated version in Experiment 4 (right).

of 75°, we could achieve a width of projection that is comparable to Experiment 1 (y=1037cm). Visual inspection of the NGT environment following these changes demonstrates the improved perceived circularity compared to the same environment in Experiment 1 (Figure 4-14).

The design of the NGT remained the same as in Experiment 1 with the exception of the elevated view and the use of larger target-foil distances (2, 3 and 4 units). The original training paradigm (section 3.2.2) and the instruction animation (section 4.3.2) were used for Experiment 4.

4.4.3 Results

4.4.3.1 Main analyses

A 2x3 mixed ANOVA with task version (original, elevated) as a between-subject factor and condition (egocentric, allocentric, control) as a within-subject factor revealed a significant main effect of task version for both accuracy and response times (Table 4-6, Table 4-7) with lower error rates and shorter response times in the elevated version of the task (Table 4-8). For accuracy, there was also a significant interaction between task version and condition with improved performance in the elevated version in the allocentric and control condition but not in the egocentric condition (Figure 4-15).

Table 4-6: Mixed ANOVA for the effect of condition and task version (original, elevated) on accuracy for all target-foil distances.

Source	MS	df	*F*	*p*
Condition	1.15	2	316.094	**<.001**
Condition X Task Version	0.117	2	32.091	**<.001**
error (condition)	0.004	134		
Task Version	0.181	1	639.636	**<.001**
error (task version)	0.006	67		

Table 4-7: Mixed ANOVA for the effect of condition and task version (original, elevated) on response times for all target-foil distances.

Source	MS	df	*F*	*p*
Condition	26850694.74	2	420.283	**<.001**
Condition X Task Version	21854.02	2	0.342	0.711
error (condition)	63887.103	134		
Task Version	1512885.788	1	5.618	**0.021**
error (task version)	269311.224	67		

Table 4-8: Main effect of task version on accuracy and response times for all target-foil distances.

Task Version	mean	s.e.
Original (accuracy, error rate)	0.162	0.007
Elevated (accuracy, error rate)	0.103	0.008
Original (response time, ms)	1740.569	49.936
Elevated (response time, ms)	1569.427	52.157

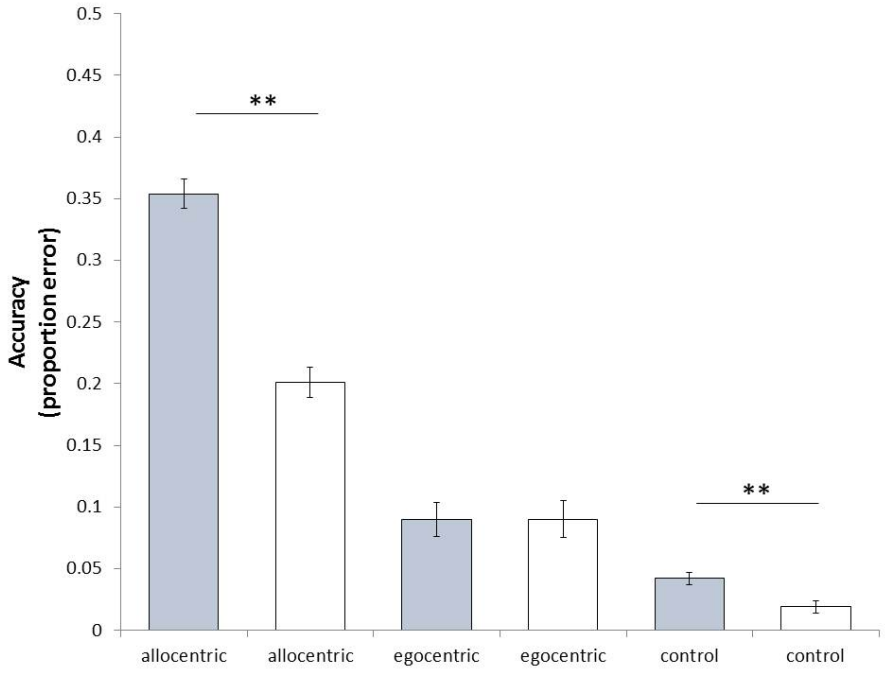


Figure 4-15: Interaction effect between condition and task version on accuracy and outcome of pairwise comparisons (* p<.05; ** p<.01) based on all target-foil distances. Filled bars reflect the original version of the task. Unfilled bars represent the elevated version of the task.

Improved performance in the allocentric and control conditions of the elevated version of the task could be due to the larger target-foil distances used in this version of the task. An additional 2x3 ANOVA based on trials using target-foil distances of 2 and 3 units was therefore conducted. For response times, there was no main effect of task version ($F(1,67)=1.812$, $p=.183$) or interaction between task version and condition ($F(2,134)=.722$, $p=.488$). For accuracy, however, there was a significant interaction between condition and task version with a significant improvement in performance in the allocentric condition (Table 4-9; Figure 4-16). Note that adding age as a covariate did not make a difference to the outcome in any of the analyses.

Table 4-9: Mixed ANOVA for the effect of condition and task version (elevated, original) on accuracy for target-foil distances of 2 and 3 units.

Source	MS	df	*F*	*p*
Condition	1.245	2	239.295	**<.001**
Condition X Task Version	0.048	2	9.218	**<.001**
error (condition)	0.005	134		
Task Version	0.002	1	0.296	0.588
error (task version)	0.007	67		

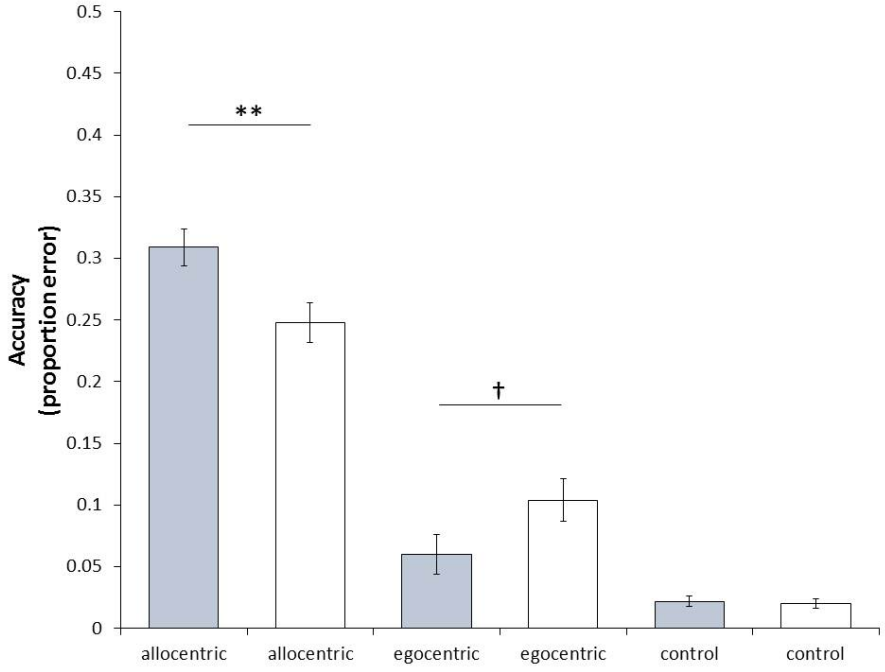


Figure 4-16: Interaction effect between condition and task version on accuracy and outcome of pairwise comparisons (* p<.05; ** p<.01; † .05<p>.1) based on target-foil distances of 2 and 3 units. Unfilled bars represent the elevated task version. Filled bars represent the original task version.

4.4.4 Additional analyses

The pattern of results for the elevated version was found to be very similar to that of the original version used in Experiment 1. For both accuracy and response times, the typical main effect of condition ($F(1,32)=28.708$, $p<.001$; $F(1,32)$-122.717, $p<.001$) and interaction between condition and angle of rotation were therefore observed ($F(2,64)=10.260$, $p<.001$; $F(2,64)=48.446$, $p<.001$; Figure 4-17, Figure 4-18).

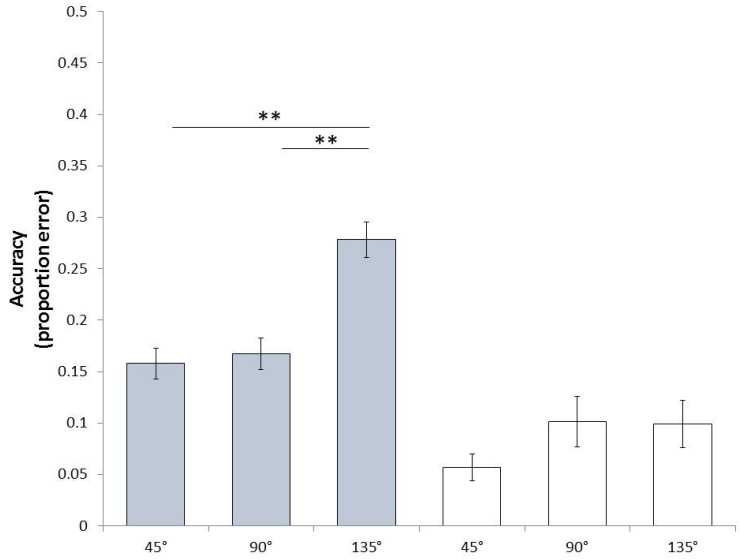


Figure 4-17: Interaction effect between condition and angle of rotation on accuracy and outcome of pairwise comparisons (* p<.05; ** p<.01). Filled bars represent the allocentric condition. Unfilled bars represent the egocentric condition.

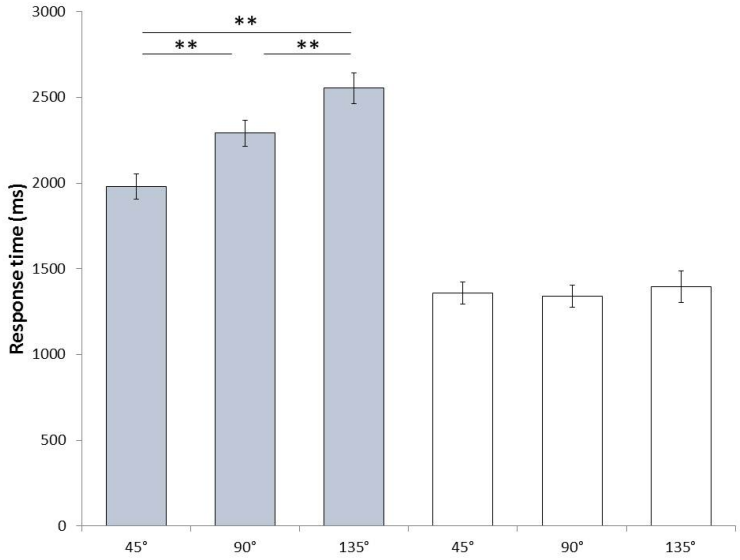


Figure 4-18: Interaction effect between condition and angle of rotation on response times and outcome of pairwise comparisons (* p<.05; ** p<.01). Filled bars represent the allocentric condition. Unfilled bars represent the egocentric condition.

4.4.5 Discussion

In Experiment 4, the virtual viewpoint in the NGT was elevated to increase the visibility of object-to-object relationships in the environment and to prevent the effect of the perspective projection distortion. When the analysis was limited to the target-foil distances that the elevated and the original task versions had in common (i.e. 2 and 3 units), a significant increase in accuracy was revealed in the allocentric condition (16.7% reduction in error

rates). This result provides support for the use of more precise object-object vectors in the allocentric condition, as a result of the combined effect of increased visibility of spatial relationships and reduced visual distortion in the elevated version of the task. The lack of an effect on error rates in the egocentric and control condition supports the assumption that participants do not rely heavily on such object-to-object relationships in these conditions.

The replication of the previously demonstrated pattern of performance in the allocentric and egocentric condition was equally important. The alignment effect in the allocentric condition was replicated and the absence of an effect of landmark-shifts was furthermore demonstrated. It is also worth mentioning that the typical incremental increase in error rates for increasing viewpoint-shifts in Experiment 1 was not observed in Experiment 4, with no difference between 45° and 90° viewpoint-shifts in Experiment 4. Although there could be several explanations for this, I propose that the general improvement in performance in Experiment 4 resulted in that error rates became less sensitive to viewpoint-shifts. Importantly, however, response times still show the typical incremental effect of increasing viewpoint-shifts, replicating the alignment effect previously observed.

Finally, the absolute improvement of performance in the NGT task was of interest. When trials for all target-foil distances were considered, the elevated version was found to produce shorter response times and lower error rates overall. In terms of reducing the discrepancy between accuracy levels in the egocentric and allocentric conditions, the elevated version of the task revealed an approximately 45% reduction, from a mean discrepancy of 0.26 in the original version in Experiment 1 to 0.14 in the elevated version in Experiment 4. Thus, although a significant difference between the two conditions remained, the discrepancy has been greatly reduced. Considering the additional requirement of a recovery of the reference direction in the allocentric condition, it is possible that performance levels cannot be entirely equalised without changing the cognitive processes involved. Given the time constraints of the present project, the performance levels in the elevated version of the NGT were therefore considered sufficient to proceed.

4.5 Experiment 5: The effect of age

4.5.1 Introduction

It important to consider the young age of the samples tested in the previous experiments, ranging from as low as 19.4 years in the Experiment 1 to 23.7 years in Experiment 2. Age is an important factor both in terms of cognitive decline and in terms of changes in brain structure (Gunning-Dixon and Raz, 2000). More specifically, previous research has demonstrated an age-related decline in experimental paradigms that requires the use of allocentric spatial memory (Moffat *et al.*, 2001; Moffat *et al.*, 2006; Antonova *et al.*, 2009). In addition, the hippocampus appears to show an accelerated volume loss starting in the middle age, after an initial volume increase in the early 20s (Walhovd *et al.*, 2011). It is therefore possible that a middle-aged sample will show worse performance in the NGT, particularly in the allocentric condition, which is of importance for Part II of the present project. Specifically, the average age of depressed samples frequently fall over the age of 30 (Porter *et al.*, 2003; Hinkelmann *et al.*, 2009) and over the age of 40 (Elliott *et al.*, 1996; Ravnkilde *et al.*, 2002), which necessitates that the NGT can be used successfully in middle-aged samples. Experiment 5 therefore aimed to evaluate the use of the NGT in a sample of healthy middle-aged adults.

4.5.2 Methodology

4.5.2.1 Participants

22 participants (16 females) with an age of 40 years or over were tested in Experiment 5. Participants were recruited mainly via a volunteer pool provided by the Institute of Neuroscience (http://www.ncl.ac.uk/ion/involved/volunteer/) but also via flyers and word of mouth. The middle-aged sample was compared to the younger sample tested in Experiment 4. One participant in the generally young sample of Experiment 4 was 42 years old and was therefore included in the middle-aged group for all analyses. The remaining participants in the young sample were 25 years or younger, except for one participant who was 30 and was excluded for this reason. This resulted in a middle-aged sample of 23 participants (17 females) with a mean age of 49.9 (*SD*=7.54, range=40-63) and a young sample of 31 participants (29 females) with a mean age of 19.7 (*SD*=2.00, range=18-25). Unsurprisingly, the two samples differed significantly in terms of age ($t(52)=-21.29$,

p<.001). The two groups also differed significantly in terms of sex proportion (t(52)= -2.05, p=.046).

4.5.2.2 Apparatus and procedure

The apparatus and procedure were identical to that described in Experiment 4 (see section 4.4.2.2).

4.5.3 Results

A 2x3 mixed ANOVA, one for accuracy and one for response times, with age group (middle-age, young) as between-subject factor and condition (allocentric, egocentric, control) as within-subject factor was conducted to investigate general group differences in the NGT. For accuracy, there was no main effect of age group (F(1,52)=1.538, p=.221) or interaction between age group and condition (F(2,104)=1.214, p=.301). For response times, however, there was a trend towards a significant main effect of age group with longer response times in the middle-aged group, although this trend disappeared when sex proportion was added as a covariate (Table 4-10; Table 4-11).

Table 4-10: Mixed ANOVA for the effect of condition and age group on response times. * when sex proportion was entered as a covariate the interaction between condition and task version became non-significant (F(1,51)=2.313, p=.135).

Source	MS	df	*F*	*p*
Condition	20726382.5	2	244.467	**<.001**
Condition X Age Group	11688.92	2	0.138	0.871
error (condition)	84782.001	104		
Age Group	1136485.3	1	3.672	*0.061**
error (age group)	309509.905	52		

Table 4-11: Descriptive statistics for accuracy and response times in the young and middle-age samples.

Age Group	mean	s.e.
Young (accuracy, error rate)	0.103	0.01
Middle-age (accuracy, error rate)	0.122	0.012
Young (response time, ms)	1568.644	57.689
Middle-age (response time, ms)	1738.028	66.975

An additional analysis was then conducted to explore whether the two groups differed in terms of the interaction effect between angle of rotation and condition. This 2x2x3 mixed ANOVA implemented age group (middle-age, young) as a between-subject factor and condition (allocentric, egocentric) and angle of rotation (45°, 90°, 135°) as within-subject factors. There was no significant three-way interaction for accuracy ($F(2,104)=2.143$, $p=323$) or response times ($F(2,104)=1.462$, $p=.236$), indicating that the task was solved similarly in both age groups (Figure 4-19, Figure 4-20). As was indicated in the previous analysis, there was also a trending main effect of age group on response times ($F(1,52)=3.018$, $p<.09$). Note, however, that this trend became non-significant after controlling for differences in age proportion ($F(1,51)=1.777$, $p=.188$). There were no other significant interactions with age group.

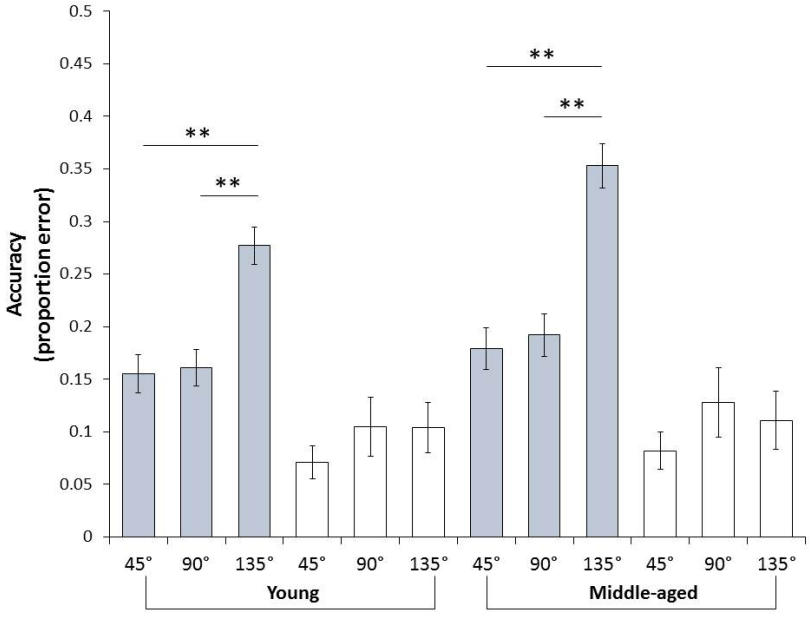


Figure 4-19: Descriptive statistics for accuracy in the allocentric condition (filled bars) and the egocentric condition (unfilled bars) in the young and middle-age samples. Note that pairwise comparisons (* p<.05; ** p<.01) correspond to the interaction between angle of rotation and condition *within* each sample.

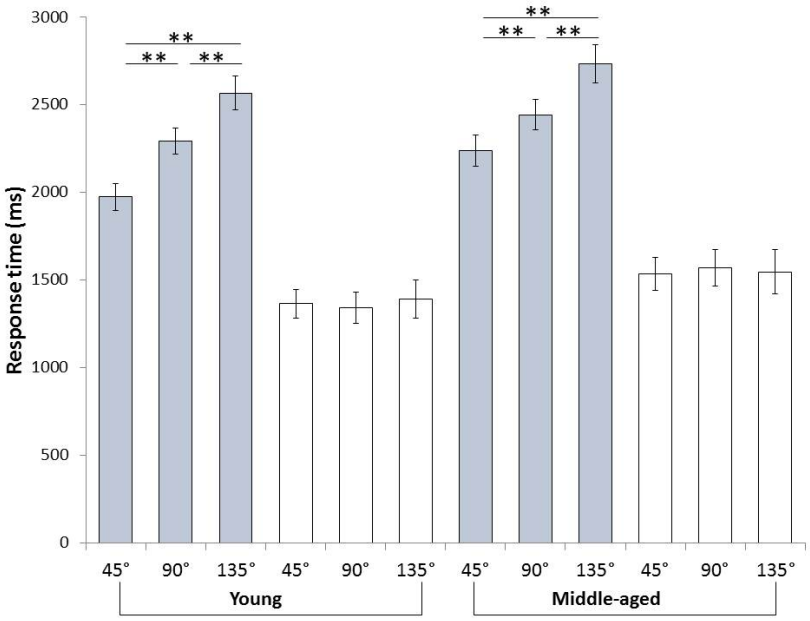


Figure 4-20: Descriptive statistics for response times in the allocentric condition (filled bars) and the egocentric condition (unfilled bars) in the young and middle-age samples. Note that pairwise comparisons (* p<.05; ** p<.01) correspond to the interaction between angle of rotation and condition *within* each sample.

4.5.4 Discussion

Middle-aged participants were found not to differ from their younger counterparts in terms of accuracy in the NGT. Although the absence of a general effect of age on performance in the allocentric condition may appear contradicting to previous research (Moffat *et al.*, 2001), it is important to highlight that the average age of the middle-aged sample in Experiment 5 can be considered young in the context of other studies. For example, Moffat *et al.* (2001) found that adults who were older than 65 were significantly impaired in a virtual navigation task whilst no such impairment was demonstrated in adults between the ages of 45 and 65. Similarly, the average age of the older adult samples tested in the navigation tasks of Moffat *et al.* (2006) and Antonova *et al.* (2009) were both well above 65. Further to this, the potentially corresponding loss of hippocampal volume has been suggested not to start until middle age, which arguably makes any substantial volume reduction unlikely before the age of 50 (Walhovd *et al.*, 2011). Thus, the lack of an allocentric memory impairment in a sample with an average age of 50 years can be considered consistent with previous research. Thus, it can be concluded that the NGT produces consistent results in middle-aged healthy participants.

4.6 Experiment 6: The effect of abbreviating the task

4.6.1 Introduction

In investigations of cognition in clinical populations, a task is rarely used in isolation but as part of a larger battery. Therefore, it is important that each individual task is convenient to administer. The NGT has 216 trials, which takes approximately 30 minutes to complete. Including a break, the training paradigm and the instructions, the task takes up to an hour to administer. For Experiment 6, an item analysis was conducted to inform the selection of trials for a shorter version of the NGT: the Northumberland Gallery Task Revised (NGT-R). The NGT-R was then piloted in a sample of healthy participants as part of a larger and independent protocol designed and conducted by Michael Craig (MRes student at Newcastle University, supervised by Dr. Tom Smulders).

The item analysis was based on the pooled sample sizes of Experiment 4 and Experiment 5, which constituted a total sample size of 55 participants. It was the aim of the item analysis to reduce the number of trials from 216 to 108. Since the target and foil locations are identical for the three conditions, the item analysis was based on the allocentric condition. From a total of eight available trials for each item type, as defined by manipulation magnitude and target-to-foil distance, four trials were selected for the NGT-R. This selection process was based on two criteria: discrimination and difficulty. Specifically, the correlation between the average performance produced by a specific item and the overall average performance produced by the relevant item type was used in an attempt to select the most informative trials for the NGT-R. Only when the average difficulty for a specific item was close to or at chance level was an item with a lower correlation selected over one with a higher correlation. The corresponding egocentric and control trials were then identified and included in the NGT-R. However, only half of the corresponding control trials, as determined by a random selection procedure, were included in the NGT-R. Thus, the NGT-R included 36 allocentric trials, 36 egocentric trials and 18 control trials.

4.6.2 Methodology

4.6.2.1 Participants

49 participants (28 females) with a mean age of 29.7 years (SD=12.45, range=19-62) were tested in the NGT-R by Michael Craig as part of a larger test battery. Participants were

recruited mainly via a volunteer pool provided by the Institute of Neuroscience (http://www.ncl.ac.uk/ion/involved/volunteer/) but also via a participation credit system. To ensure that the abbreviated version produced consistent results with the original long version, the results of Experiment 6 (abbreviated version) were compared to performance of the combined sample of Experiment 4 and 5 (long version). Importantly, the pooling of the samples in Experiment 4 and 5 was justified by comparable performance in the two samples (section 4.5.3). As a result of such pooling, the comparison sample constituted a sample of 55 participants (47 females) with a mean age of 32.5 (SD=15.72, range=18-62). The two samples did not differ in terms of age ($t(102)=.98$, $p=.33$). However, the samples differed significantly in terms of sex proportion ($t(102)=-3.35$, $p<.001$) with a larger proportion of males for the abbreviated version ($M=.43$, $SD=.50$) than for the long version ($M=.15$, $SD=.36$).

For the additional analyses, the two samples were combined. The total sample consisted of 104 participants (75 females) with a mean age of 31.2 ($SD=14.27$, range=18-63). This sample was used to assess the general outcome of the NGT and sex differences in a large sample. The female and male groups did not differ in terms of age ($t(102)=-.63$, $p=.53$). Given the distribution of age (Figure 4-21), with a minority of participants falling between the age of 26 and 39 (5 participants; 4.8%), the effect of age was tested by a division of participants into a young group of 18-25 year olds and a middle-aged group of 40-62 year-olds. The young group consisted of 63 participants (43 females) with a mean age of 20.8 ($SD=2.13$, range=18-25) and the middle-aged group consisted of 36 participants (28 females) with a mean age of 49.4 ($SD=7.20$, range=40-63). Unsurprisingly, the two groups differed significantly in terms of age ($t(97)=-29.52$, $p<.001$). The groups also differed in terms of sex proportion ($t(97)=1.01$, $p=.025$) with the young group having a greater proportion of males ($M=.32$, $SD=.47$) than the middle-aged group ($M=.22$, $SD=.42$).

4.6.2.2 Apparatus and procedure

The original training paradigm (section 3.2.2) and the instruction animation (section 4.3.2) were used for Experiment 6. The NGT was administered in its short version (NGT-R) with six practice trials preceding the task.

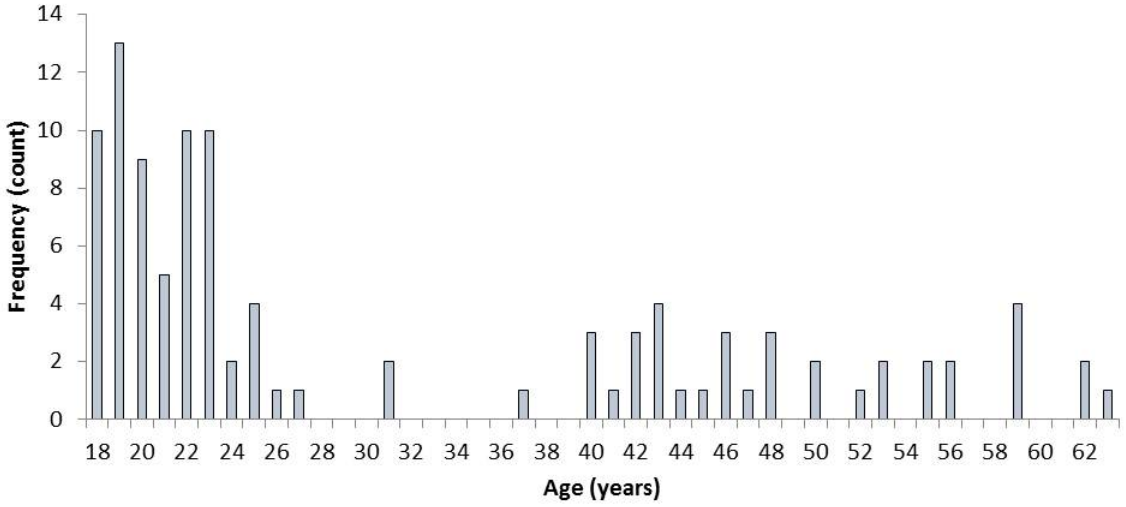


Figure 4-21: Age distribution for the combined samples of Experiment 3, 4 and 5 (*n*=104).

4.6.3 Results

4.6.3.1 Main analyses

A 2x3 mixed ANOVA with task length (abbreviated, long) as a between-subject factor and condition (allocentric, egocentric, control) as a within-subject factor for accuracy and response times was conducted to compare performance in the NGT and the NGT-R. There was no main effect of task length for accuracy ($F(1,102)=.831$, $p=.364$) or response times ($F(1,102)=1.284$, $p=.26$). There was also no interaction between task length and condition for accuracy ($F(2,204)=.484$, $p=.617$) or response times ($F(2,204)=.869$, $p=.421$). The descriptive statistics in Table 4-12 clearly demonstrated the similar performance in the NGT and the NGT-R. Note that adding sex proportion as a covariate did not change the outcome of any of the analyses

Table 4-12: Descriptive statistics for the long and the abbreviated version of the NGT in the allocentric, egocentric and control conditions.

Task Length	Condition	mean	s.d.
Long	Allocentric	0.2146	0.07858
(accuracy, error rate)	Egocentric	0.0982	0.11349
	Control	0.0195	0.02133
Abbreviated	Allocentric	0.1923	0.09493
(accuracy, error rate)	Egocentric	0.0946	0.11866
	Control	0.0147	0.03162
Long	Allocentric	2345.3454	428.7161
(response time, ms)	Egocentric	1442.0954	495.4216
	Control	1138.7304	234.0411
Abbreviated	Allocentric	2217.939	431.9325
(response time, ms)	Egocentric	1380.6995	417.0009
	Control	1108.6994	256.2736

4.6.3.2 Additional analyses

Considering the comparable results produced by the NGT and the NGT-R, the sample tested in Experiment 6 was combined with the comparison sample (n=104). The large sample produced similar results to that demonstrated previously with a significant main effect of condition (F(1,103)=75.602, p<.001; F(1,103)=387.443, p<.001) and a significant interaction between condition and angle of rotation (F(2,206)=36.660, p<.001; F(2,206)=72.885, p<.001) for accuracy and response times, respectively (Figure 4-22, Figure 4-23).

Sex differences were explored in a 2x3 mixed ANOVA with sex (female, male) as a between-subject factor and condition (allocentric, egocentric, control) as a within-subject factor. For accuracy and response times, there was no main effect of sex (F(1,102)=.013, p=910; F(1,102)=1.653, p=.201) and no interaction between sex and condition (F(2,204)=.320, p=.727; F(2,204)=.757, p=.470).

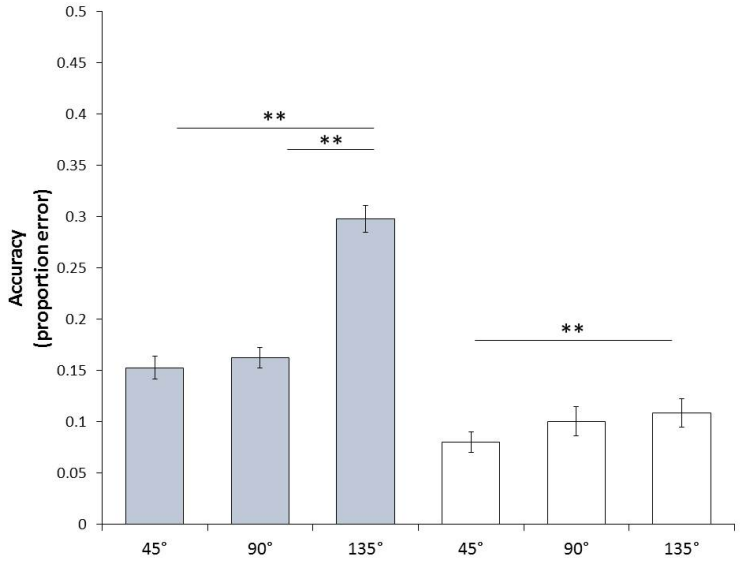


Figure 4-22: Interaction effect between condition and angle of rotation on accuracy and outcome of pairwise comparisons (* p<.05; ** p<.01) in the full sample (*n*=104). Filled bars represent the allocentric condition. Unfilled bars represent the egocentric condition.

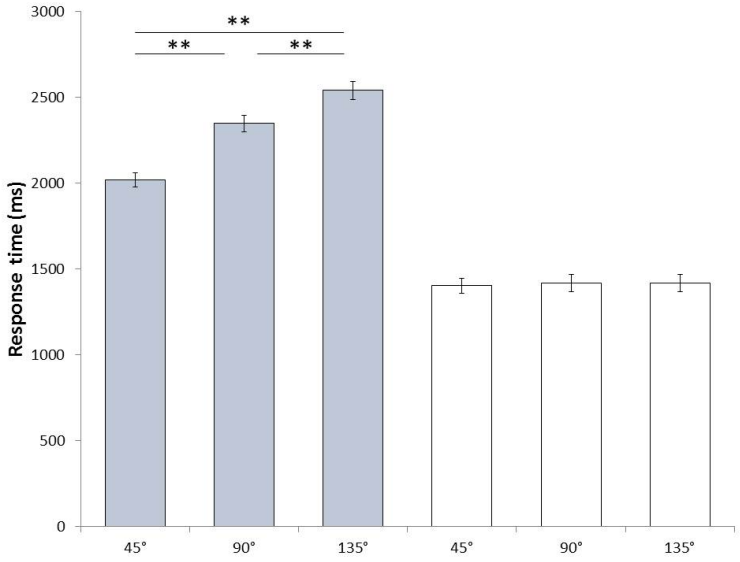


Figure 4-23: Interaction effect between condition and angle of rotation on response times and outcome of pairwise comparisons (* p<.05; ** p<.01) in the full sample (n=104). Filled bars represent the allocentric condition. Unfilled bars represent the egocentric condition.

A 2x3 mixed ANOVA with age group (young, middle-age) as a between-subject factor and condition (allocentric, egocentric, control) as a within-subject factor was used to assess the effect of age in the combined sample. For response times, there was a significant main effect of age group with significantly longer response times in the middle-aged sample compared to the young sample (Table 4-14, Table 4-15). For accuracy, there was only a

weak trend towards higher error rates in the middle-aged sample (Table 4-13, Table 4-15). Pearson's correlational coefficients confirmed the relationship between age and response times in the allocentric ($r(102)=.32$, $p=.001$), egocentric ($r(102)=.27$, $p=.006$) and control conditions ($r(102)=.28$, $p=.004$). In contrast, error rates correlated with age only in the allocentric condition ($r(102)=.24$, $p=.013$; Figure 4-24) but not in the egocentric ($r(102)=.10$, $p=.30$) and control conditions ($r(102)=.05$, $p=.61$). Note that adding sex proportion as a covariate did not make a difference to the outcome of any of the analyses.

Table 4-13: Mixed ANOVA for the effect of condition and age group on accuracy. * when sex proportion was entered as a covariate the main effect of age group remained non-significant ($F(1,96)=2.889$, $p=.092$).

Source	MS	df	*F*	*p*
Condition	0.88	2	145.128	**<.001**
Condition X Age Group	0.013	2	2.210	0.112
error (condition)	0.006	194		
Age Group	0.028	1	2.906	*0.091**
error (age group)	0.01	97		

Table 4-14: Mixed ANOVA for the effect of condition and age group on response times. * when sex proportion was entered as a covariate the main effect of age group remained significant ($F(1,96)=6.396$, $p=.013$).

Source	MS	df	*F*	*p*
Condition	34177090.28	2	448.294	**<.001**
Condition X Age Group	113269.497	2	1.486	0.229
error (condition)	76238.133	194		
Age Group	2220305.547	1	6.992	**0.01**
error (age group)	317537.161	97		

Table 4-15: Descriptive statistics of accuracy and response times in the young and the middle-aged age groups.

Age Group	mean	s.e.
Young (accuracy, error rate)	0.101	0.007
Middle-age (accuracy, error rate)	0.121	0.009
Young (response time, ms)	1539.545	40.989
Middle-age (response time, ms)	1719.284	54.223

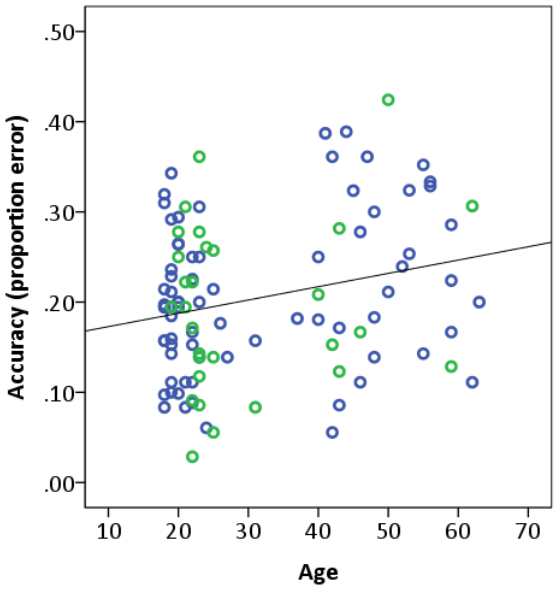


Figure 4-24: Scatterplot demonstrating the relationship between accuracy in the allocentric condition and age in years (R^2=.059). Green circles represent male participants. Blue circles represent female participants.

4.6.4 Discussion

The NGT-R was found to produce comparable results to the full-length version of the task. The two tasks produced remarkably similar results, which confirmed the usefulness of the item analysis in selecting the trials for the abbreviated version. It is also worth mentioning that the NGT-R was administered in a different lab by Michael Craig who, except for a brief training session in the administration of the task, was entirely independent from the present project. Thus, it appears as if the NGT produces consistent results under a different set of circumstances.

Following the absence of any differences between the abbreviated and the long version of the NGT, the two samples were pooled to produce a large sample of 104 healthy adults of mixed ages. The pattern of results were found to be remarkably similar to that found in the original study of the NGT in Experiment 1 (section 4.3) with evidence of an alignment effect in the allocentric condition, as indicated by longer response times and higher error rates for increasing viewpoint-shifts. Similarly, although response times were not affected by increasing landmark shifts in the egocentric condition, error rates were found to increase as a result of such shifts. It is worth noting that when the samples of Experiments 4 and 5 were considered separately there was no effect of increasing landmark shifts on accuracy (see sections 4.4.3 and 4.5.3). It therefore remains unclear what factors that contribute to

the potentially distracting effect of increasing landmark shifts in the egocentric condition. Importantly, the pooled sample of Experiment 6 showed a substantial improvement in accuracy in the allocentric condition compared to the original version of the task (43% reduction in error rates), confirming the beneficial effect of the elevated viewpoint and the larger target-foil already demonstrated in section 4.4.3.

In an age comparison based on the pooled sample, the middle-aged group was found to produce longer response times in all conditions of the NGT. Such an effect of age was also supported by the correlational analyses, in which age was found to correlate inversely with response times in all conditions. Such a general slowing of responses is consistent with previous research on normal ageing (Fozard *et al.*, 1994). In terms of accuracy, although there was no significant main effect of age and no interaction between age and condition, correlational analyses indicated that age was inversely correlated with error rates in the allocentric condition but not in the other conditions. This finding would be consistent with an age-related decline in hippocampal volume and a corresponding decline in allocentric memory performance (Moffat *et al.*, 2001; Walhovd *et al.*, 2011).

In terms of sex differences, results derived from the pooled showed no evidence of the slight male advantage in overall accuracy previously demonstrated in the original version of the NGT in Experiment 1 (section 4.3.2.4). Although the sample sizes for the two groups differed in Experiment 6, there appears to be no substantial sex differences in the elevated version of the NGT.

In summary, Experiment 6 demonstrated that the NGT-R produces comparable results to the full-length version and the combined results of Experiment 4, 5 and 6 confirmed the general pattern of results in the NGT in a large sample. Importantly, an effect of age on performance in the NGT was also identified, which will require careful consideration for Part II of the present project.

Chapter 5 Experiment 7: The neural basis of the NGT-R

5.1 Introduction

The NGT was developed to allow a valid investigation of role of the hippocampus in allocentric short-term memory when no navigation is required. Following the successful use of the NGT in a behavioural setting (see Chapter 3 and Chapter 4), it was integral to explore the neural underpinnings of the task and thereby directly test the hypothesis of a hippocampal contribution to the allocentric condition of the NGT. To achieve this, functional magnetic resonance imaging (fMRI) was used as a proxy measure of neural activity. This non-invasive technique has been used extensively in previous studies of hippocampal function (Hartley *et al.*, 2003; Viard *et al.*, 2011). In brief, the technique relies on the different magnetic properties of oxygenated and deoxygenated blood to detect local changes in relative blood oxygenation, which in most cases can be assumed to be associated with corresponding changes in neural activity (Matthews and Jezzard, 2004; Buxton, 2012). Relative to other neuroimaging methods, such as PET and electroencephalography (EEG), such blood-oxygenated-level-dependent (BOLD) fMRI provides a good compromise of spatial and temporal resolution whilst also allowing for reliable measurement of subcortical structures.

The primary hypothesis of Experiment 7 and Part I of the project concerned the recruitment of the hippocampus in the allocentric condition of the NGT and has been described and supported in detail in Chapter 2. Importantly, however, the NGT will undoubtedly recruit brain regions extending well beyond the hippocampus. To arrive at some general predictions of what additional regions that may underpin performance in the NGT, a brief overview of the navigation-relevant parieto-medial temporal pathway will be provided in the following section. In section 5.1.2, predictions for the neural underpinnings of the NGT, including the precise involvement of the hippocampus, will be presented.

5.1.1 The parieto-medial temporal pathway

The background in Chapter 2 demonstrated that the hippocampus is critical for anchoring spatial memory representations in the external environment. Undoubtedly, however, the hippocampus does not function in vacuum but is supported by a number of regions to allow successful navigation. A parieto-medial temporal pathway, in which the hippocampus

represents the ultimate target, is thought to underlie spatial navigation in man (Burgess, 2008; Kravitz *et al.*, 2011). This pathway, which represents a distinct part of the traditionally defined 'where' dorsal processing stream (Goodale and Milner, 1992), extends medially from the posterior parietal lobe to the medial temporal lobe via the retrosplenial cortex (RSC). Activation of the pathways has been associated with a range of cognitive processes relevant to navigation, including retrieval of topographical memories (Maguire *et al.*, 1997), recall of the spatial context of an event (Burgess *et al.*, 2001), way-finding (Hartley *et al.*, 2003), navigation-based spatial learning (Rodriguez, 2010) and landmark-based referencing (Committeri *et al.*, 2004). Thus, further to the predicted hippocampal involvement in the allocentric condition of the NGT, the parieto-medial temporal pathway can be expected to play an important role.

Regions incorporated in the parieto-medial temporal pathway are thought to make distinct contributions to the mental representations underlying navigation, with the parietal lobe providing egocentric representations, the medial temporal lobe providing allocentric representations and the RSC allowing interaction between the two (Burgess, 2008). In support of a role of the posterior parietal cortex in egocentric representations of space, damage to this region has been found to result in perceptual impairments relative to egocentrically defined principles. For example, lesions to the posterior-inferior parietal cortex results in unilateral neglect, which involves a failure to explore the contralesional side of space in the absence of primary sensory or motor deficits (Vallar, 1998). Damage to the more dorsal part of the posterior parietal cortex results in optic ataxia, which is a disorder of visuomotor coordination characterised by impaired reaching for targets in the contralesional side of space (Perenin and Vighetto, 1988). The deficits associated with unilateral neglect and optic ataxia therefore concern the egocentrically defined principle of the body midsagittal plane. Further to this, neuroimaging evidence has shown increased posterior parietal activation when healthy participants make judgments relative to the body midsagittal plane (Galati *et al.*, 2001). Importantly, the posterior parietal cortex is also thought to be involved in the transformation between different egocentric systems. In support of this, in patients with unilateral neglect, the detection rate of a visual target in the neglected hemifield can be improved by rotating the trunk towards that side, even when retinal stimulation is kept constant (Karnath *et al.*, 1993), which indicates a breakage of the link between the retinotopic and body-centred egocentric coordinate systems. Thus, it

appears as if the posterior parietal lobe is likely to contribute to navigation by translating the transient sensory-centred representation of location to a more stable body-centred representation.

Further down the pathway, the posterior parietal cortex links to the RSC, which is part of the posterior cingulate region just posterior to the splenium. The RSC has been suggested to be particularly important for spatial transformations between allocentric and egocentric reference frames in navigation (Maguire, 2001; Byrne *et al.*, 2007; Burgess, 2008), by which the critical translation and coordination of an egocentric representation of the current position (e.g. "you are here") to navigational goals in an allocentric representation (e.g. "your goal is south of X") can occur (Epstein, 2008). In support of such a translational role, spatial navigation tasks, which necessarily involve a translation between the egocentric viewpoint and the stored allocentric representation, consistently engage the RSC (Vann *et al.*, 2009). The RSC is also physiologically well positioned for such a function, just between the posterior parietal lobe and the medial temporal lobe. Furthermore, damage to this region results in a selective deficit in spatial orientation characterised by a loss of "heading" within the environment (Aguirre and D'Esposito, 1999). Patients with this type of topographical disorientation show impaired learning of new routes and appear to be unable to derive directional information from correctly recognised landmarks to support navigation in familiar environments (Maguire, 2001). Thus, RSC damage appears to impair the ability to coordinate the current egocentric perspective with a stored allocentric representation.

In contrast to the egocentrically anchored representations of the posterior parietal cortex, regions in the medial temporal lobe are thought to be more concerned with representing the external environment (Kravitz *et al.*, 2011). For example, the parahippocampal place area (PPA), which encompasses the posterior parahippocampal gyrus and adjacent regions of the fusiform gyrus, has been proposed to be responsible for the encoding and later recognition of the local scene (Epstein and Kanwisher, 1998; Epstein, 2008). Consistent with this, damage to the PPA results in an inability to recognise scenes as wholes whilst the ability to recognise individual landmarks within the same scene is preserved (Mendez and Cherrier, 2003). In addition to being preferentially active during passive viewing of scenes compared to objects and faces (Epstein and Kanwisher, 1998), the PPA also shows a preference for scenes when the stimulus is imagined, which is likely to be useful in navigation (O'Craven

and Kanwisher, 2000). Furthermore, the PPA has also been found to be sensitive to a change in viewpoint around a scene, indicating a role in the representation and updating of the relationship between the observer and the scene (Epstein *et al.*, 2003; Schmidt *et al.*, 2007). Another region that has been proposed to play an important role in representing the external world is the lingual gyrus, which is situated just posterior to the PPA. Damage to this region results in a selective inability to use salient environmental features for way-finding although the same landmarks can be correctly identified (Aguirre *et al.*, 1998). Consequently, the lingual gyrus appears to represent the orientational value of landmarks whilst the PPA represents scenes.

Representing the end-point of the parieto-medial temporal pathway, the hippocampus acts as a point of convergence for a range of navigation-relevant contributions from different regions. It is therefore evident that although the hippocampus is important in providing spatial representations in an absolute framework of landmarks (O'Keefe, 1978), the parieto-medial temporal pathway is vital in supporting the use of such representations. Specifically, the posterior parietal lobe appears to be concerned with representations relative to egocentric coordinate systems whilst regions in the medial temporal lobe and the lingual gyrus appear to represent space relative to environmental features. Critically, the RSC appears to provide the invaluable translation between such coordinate systems. Similarly to the argument made in relation to hippocampal function, regions in the parieto-medial temporal pathway may therefore be particularly important in the cognitive processes preceding navigation, predicting its involvement in the NGT.

5.1.2 Predictions

Based on the background provided in Chapter 2 and the brief overview of the parieto-medial temporal pathway in the previous section, specific predictions could be made in relation to the likely neural underpinnings of the NGT in the retrieval phase. Both the allocentric and egocentric conditions were assumed to require an appraisal of the scene through egocentrically defined sensory systems, such as the retina and the orientation of the head and trunk, predicting recruitment of the posterior parietal cortex in both conditions. Similarly, given the identical scenes used in the allocentric and egocentric conditions, scene perception was predicted to play an equal part in the two conditions, predicting equivalent PPA involvement.

In contrast, relative to the egocentric condition, the allocentric condition was hypothesised to require the recruitment of additional regions of the parieto-medial temporal pathway. Most importantly, the allocentric condition was hypothesised to uniquely engage the hippocampus. This primary hypothesis followed from the extensive review in section 2.2, constituting a role of the hippocampus in allocentric spatial memory, which is likely to support the initial self- and target-localisation that precedes actual navigation execution. The viewpoint-shift in the allocentric condition was hypothesised to result in reliance on an allocentric subsystem (Shelton and McNamara, 2001), which in turn was hypothesised to necessitate the recruitment of the hippocampus (O'Keefe, 1978; Maguire *et al.*, 1998a). In contrast, the landmark-shift in the egocentric condition prevented the use of landmarks to represent the target location, predicting a relative independence from the hippocampus in this condition. Based on the hypothesis that the hippocampus is involved in the allocentric but not in the egocentric condition of the NGT, increased hippocampal activity was predicted in the allocentric condition relative to the egocentric condition.

The allocentric condition of the NGT was also predicted to uniquely engage the RSC and the lingual gyrus. The RSC was hypothesised to be involved as a result of the necessary coordination of the landmark-based representation with the current egocentric perspective whilst the lingual gyrus was thought to provide the necessary distance and orientation information associated with the environmental landmarks. Importantly, the egocentric condition did not allow for any references to landmark positions, which predicted a lesser involvement of the RSC and the lingual gyrus in this condition. Consequently, for the contrast between the allocentric and egocentric condition, increased signal was predicted in the hippocampus, the RSC and the lingual gyrus. In contrast, no differential activation was expected in the posterior parietal cortex and the PPA in this contrast.

Further predictions were made in relation to the extent of the viewpoint-shift in the allocentric condition. Based on evidence suggesting that the hippocampus is not involved in the calculation of the viewpoint-shift *per se* (Schmidt *et al.*, 2007; Hannula and Ranganath, 2008), the extent of the viewpoint-shift was not predicted to influence hippocampal activation. In contrast, the lingual gyrus was predicted to play a role in this process. This prediction followed from the arguably greater sense of disorientation resulting from more substantial viewpoint-shifts, which in turn would increase the importance of the orientation value of landmarks to recover the reference direction (Aguirre *et al.*, 1998; Li *et al.*, 2012).

Such a role for the lingual gyrus has also been evidenced in previous research (Schmidt *et al.*, 2007). A similar sensitivity to the extent of viewpoint-shift was predicted in the PPA. This prediction followed from its proposed role in the updating of self-scene relationships, which is likely to be a more substantial process for greater viewpoint-shifts (Epstein *et al.*, 2003; Schmidt *et al.*, 2007). Thus, in addition to the primary hypothesis of a hippocampal involvement, an effect similar to that of the behavioural alignment effect was predicted in the lingual gyrus and the PPA in the allocentric condition of the NGT.

5.2 Methodology

5.2.1 Participants

Twenty young adults with no history of psychiatric or neurological illness were recruited. Participants were recruited mainly via a volunteer pool provided by the Institute of Neuroscience (http://www.ncl.ac.uk/ion/involved/volunteer/) but also via word of mouth. None of the participants were taking any medication with the exception of contraceptives. All participants were right-handed, as ascertained with the Edinburg Handedness Inventory (EHI; (Oldfield, 1971)). Two participants were excluded from the analysis; one due to excessive motion during scanning, and one due to difficulties seeing the stimulus display, which the participant only reported after the scan. The remaining sample included nine females and nine males with an average age of 26.6 years (SD=3.38, range=19-33). Females and males did not differ in terms of age ($t(16)$=.83, p=.42).

To explore whether the NGT-R produced a comparable level of performance inside the scanner as outside, performance of the sample tested in Experiment 7 was contrasted with that of the sample tested in Experiment 6 (section 4.2.2.1). Although the size of the sample tested in Experiment 6 (n=49) was considerably larger than that tested in Experiment 7 sample (n=18), the two sampled did not differ in terms of age ($t(65)$=-1.06, p=.29) or gender proportion ($t(65)$=.51, p=.61). It should also be emphasised that the control condition and the precise timing of events in the NGT-R differed between Experiment 6 and Experiment 7 (see section 5.2.2).

5.2.2 Apparatus and procedure

The training procedure preceding the NGT was identical to that described in Chapter 3. A new animation, which demonstrated the manipulations in the allocentric and egocentric

condition from a first-person perspective, was used to support verbal instructions of the task. The NGT-R was used to limit the total length of the task and therefore also time spent in the scanner (section 4.6). Consequently, the 36 allocentric trials and the 36 egocentric trials derived from the item analysis were used. However, the NGT-R task subsequently underwent minor changes to optimise it for the scanner.

None of the original control trials of the NGT-R were used. Instead, 36 trials of a new control condition were implemented. This control condition was designed to require the same visuomotor response as the experimental conditions but without a memory component. As such, no target location appeared during the presentation phase and following a delay phase depicting the instruction "None", which acted as a reminder that no location was to be remembered for that trial, participants were presented with the usual response options (Figure 5-1). However, a green pole was standing on top of one of the response options and participants were simply required to respond in accordance to the colour of that particular option. The locations for the response options were derived from the original control trials, which were equivalent to the allocentric and the egocentric trials. The new control condition, referred to as the no-memory control condition, was therefore identical in terms of the visual scene and the motor response required but involved no memory for location. To reduce visual differences between the delay phase and the presentation and response phases, the one-word instruction in the delay phase was overlaid on a scrambled image of the virtual screen in all conditions (Figure 5-1).

Minor changes were also implemented to the timing of the NGT. The delay phase lasted for 4.75 seconds, as opposed to 4.5 seconds, and the response options appeared 0.25 seconds after the onset of the response phase, as opposed to 0.5 seconds. Thus, the total duration of the delay phase remained 5.0 seconds. The time window for the response was reduced from 4.0 seconds to 3.5 seconds. This limit was supported by the average response time in the 90th percentile of the allocentric condition at the 135° rotation in the combined young and middle-aged samples (n=55, M=3425.2 seconds). To ensure identical task length for all participants, the scene of the response phase remained on the screen for the full 3.5 seconds independently of whether a response had been recorded within that time. With the new timing, each trial lasted for 11.75 seconds. There were a total of 108 trials with 36 trials in each condition, which resulted in 21.2 minutes of effective task time. Between each trial, a

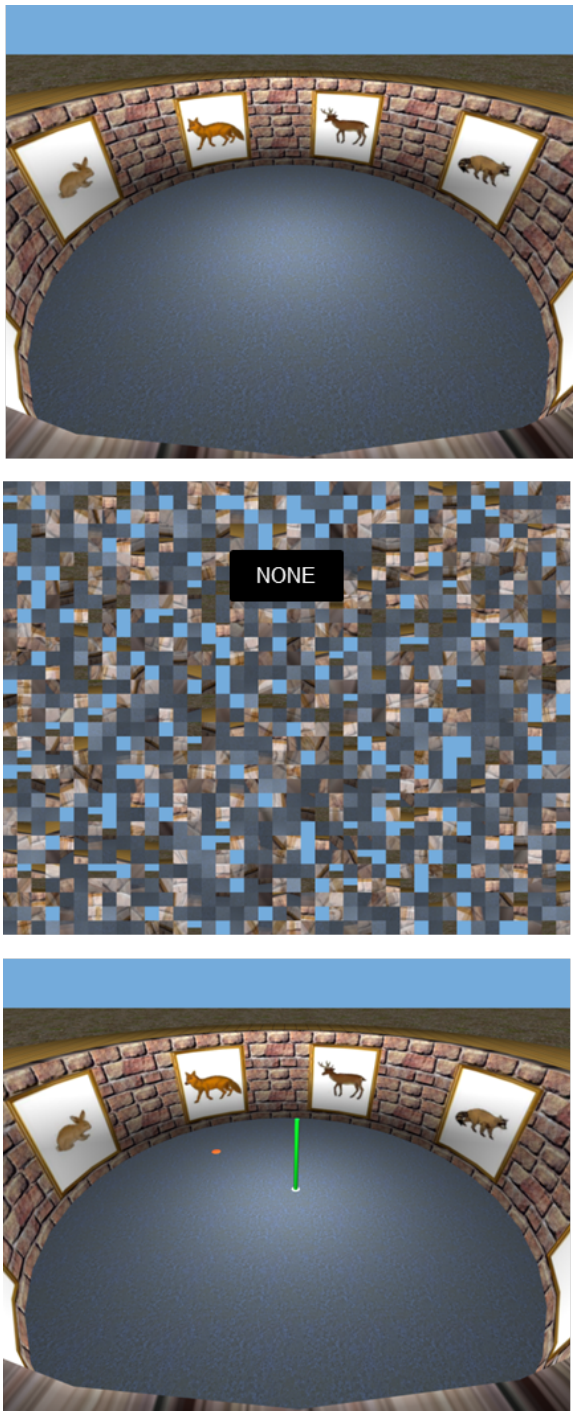


Figure 5-1: Sequence of events for the no-memory control condition. Note that the same scrambled image was used in the delay phase of the allocentric and egocentric conditions.

grey screen with a central white fixation cross was presented for 1.0 second. In addition to this, there were 36 longer fixation events, which lasted for 8.0 seconds each. Thus, the NGT took 28.4 minutes to complete in the scanner. The trial order was unique for each participant and was pseudorandom to ensure that two 8-seconds long fixation periods did not appear consecutively and that no more than two trials of the same condition appeared

consecutively. Participants were given a brief break midway through the task. After completing the task, participants were asked to complete the NGT Experience Questionnaire outside of the scanner.

The task was projected on a screen outside of the scanner and viewed via a mirror. To increase the proportion of the visual field covered by the task scene, a pair of specifically constructed binoculars was used. As a result, the size of the projection was made more comparable to that of a computer screen at a normal viewing distance. Responses were made using a MR-safe response box, which was strapped into place along the side of participants, in level with their right hand. Participants were required to make all responses using their right hand with index finger responses corresponding to the orange response option and the middle finger to the white response option.

5.2.3 Image acquisition

MR scans were collected on a Phillips Achieva 3T MR scanner using an 8-channel SENSE coil. A standard T1-weighted TFE scan sequence (voxel size 0.76x0.77x0.80mm^3, 225 slices, TE=4.6ms) was used to acquire a structural scan for each participant. Two separate runs of functional scans were collected for the NGT using a single-shot EPI sequence (TE=30ms, TR=2600ms, voxel size 2.5x2.5x3.5mm^3, 40 axial slices, tilted up approx. 20 degrees from the AC-PC line), with a total of 330 volumes per run. Three dummy volumes at the beginning of each run were immediately discarded. Stimulus presentation started after a further three volumes. Between both functional runs, a spoiled gradient echo (T1-FFE) field mapping sequence (voxel size 2x2x2mm3, TR=27ms, TE1=2.6ms, TE2=5.9ms,) was used to reconstruct magnetic field inhomogeneity.

5.2.4 fMRI pre-processing and analysis

5.2.4.1 Whole-brain analyses

The MR data analysis was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) in Matlab R2010b (The MathWorks, Inc.). Standard pre-processing of functional images consisted of slice-time correction to the first slice, realignment and unwarping using the constructed fieldmap, normalization to standard anatomical space using normalization parameters previously estimated from the structural scans (MNI), and spatial smoothing with an 8 mm FWHM Gaussian smoothing kernel. The first-level model consisted of three

separate events per trial and condition to model the three phases of a trial: presentation, delay and response. Since the presentation phases for the allocentric and egocentric trials were indistinguishable for the participants, the onsets of the presentation phase for these two conditions were combined. The onsets were convolved with the canonical hemodynamic response function (HRF) of SPM. Motion parameters for each session were added to the first-level model to serve as regressors of no interest. In addition, for each of the three retrieval phases, response times were added to the model as parametric modulators of BOLD amplitude for the primary analysis. Trials in which no response was recorded (1.6% of trials) were allocated a fixed response time of 3.5s for the parametric modulator.

Parameter estimates for the various predictors were then combined across both sessions and entered into second-level models. The primary second level analysis included the contrasts for the response phase of the three conditions (Allocentric, Egocentric, Control) along with a subject factor. A secondary analysis, which included the same subject factor, included the contrasts for the no-memory control condition and the combined signal of the allocentric and egocentric conditions for the presentation phase to contrast encoding of spatial material (Encoding) with the absence of such encoding (Control). Since there were no a priori predictions concerning brain regions involved at encoding, this analysis was conducted for completeness. Family-wise error correction (FWE) was used to correct p-values for multiple comparisons to a Type-I error probability of 0.05 with an additional cluster extent threshold of 10 voxels.

5.2.4.2 Time course analysis

To explore the time course of the BOLD signal in regions indicated as important in the primary whole-brain analysis, a finite-impulse response analysis was conducted. For this analysis, BOLD signal time-courses for the entire trial were based on additional first-level models using a finite-impulse basis set of order 12 for the three conditions. Here, the beginning of the encoding phase was used to define the onset of each trial. In contrast to the canonical HRF analysis described above, the allocentric and egocentric conditions were therefore modelled separately from encoding phase onwards (as part of the entire trial). Since finite-impulse response analyses make no assumptions about the haemodynamic response (Dale and Buckner, 1997), this analysis aimed to provide additional information about the BOLD response in task-relevant regions.

5.2.4.3 Exploratory whole-brain analysis

The expected differences in response times in the allocentric and egocentric conditions required some additional considerations. Specifically, if such differences are the result of the distinct cognitive processes involved, adding response time as a covariate at the second level could be expected to result in a general loss of the effects of interest (Gilbert *et al.*, 2012). To explore this scenario, an exploratory whole-brain analysis was conducted, in which response times were added as a covariate. Relative to the primary whole-brain analysis, which included response times as a covariate within each condition at the first level and therefore accounted for trial-by-trial variation in response times (see 5.2.4.1), the exploratory whole-brain analysis instead accounted for variation of average response times between conditions and participants at the second level.

5.2.4.4 Parametric analyses

The effect of response times on BOLD signal was explored in two different analyses. In the first analysis, the effect of response times in the exploratory whole-brain analysis (see section 5.2.4.3) was investigated in its own right. This analysis investigated the effect of average response times independent of condition at the second level. In the second analysis, the parametric modulation of response times at a trial-by-trial basis was investigated within the allocentric and egocentric conditions. As such, this analysis involved an exploration of the parametric modulator of trial-by-trial variation of BOLD amplitude as a function of response time (section 5.2.4.1).

For the parametric analysis, response times were considered a proxy of task difficulty. Response times were favoured over error rates as a proxy of task difficulty for several reasons. First, the continuous measure of response times was thought to provide a more sensitive measure of perceived difficulty compared to the dichotomous accuracy measure (i.e. correct versus incorrect). Second, when entered as a parametric modulator independent of condition, the greater number of error trials in the allocentric compared to the egocentric conditions would have biased the analysis towards the effect of error in the allocentric condition. Third, when entered as a parametric modulator separately for each condition, the generally small number of error trials in the egocentric condition would have made an analysis in this condition unreliable. Thus, the effect of accuracy on BOLD amplitude was

not included in any of the first level models. However, the effect of accuracy on hippocampal BOLD signal was explored in a between-subject analysis (see section 5.3.2.5).

In an additional parametric analysis, angle of rotation and target-foil distance were added as parametric modulators separately for the allocentric and egocentric conditions. This analysis was based on a first-level model identical to that of the primary second level analysis with the only exception of the parametric modulators (section 5.2.4.1).

5.2.4.5 Between-subject analyses

Average BOLD signal for the right and left hippocampus during the response phase was extracted for use in between-subject analyses. The precise boundaries for the hippocampal region were based on clusters of differential signal identified for the contrast between the allocentric and egocentric conditions in the primary whole-brain analysis (see * in Table 5-5). Relationships between performance in the egocentric and allocentric conditions and hippocampal BOLD signal were explored, as was the effect of sex on hippocampal BOLD signal.

5.3 Results

5.3.1 Behavioural results

5.3.1.1 The NGT-R inside and outside of the scanner

To allow a comparison of performance in the NGT-R inside and outside the scanner, the sample tested in Experiment 7 (young participants tested inside the scanned) was compared with the sample tested in Experiment 6 (young participants tested outside the scanner), a 2x2x3 mixed ANOVA with task context (fMRI, behavioural) as a between-subject factor and condition (allocentric, egocentric) and angle of rotation (45°, 90°, 135°) as within-subject factors was conducted. Although there was no main effect of task context on performance, there was a significant interaction between task context and condition for both accuracy and response times (Table 5-1, Table 5-2). However, post-hoc comparisons only revealed non-significant trends towards reduced error rates in the egocentric condition and increased error rates in the allocentric condition when the NGT-R was completed inside of the scanner as opposed to outside (Figure 5-2). Post-hoc comparisons also did not reveal any significant differences for response times (Figure 5-2).

Table 5-1: Mixed ANOVA on the effect of task context, condition and angle of rotation on accuracy.

Source	MS	df	*F*	*p*
Condition	1.7	1	71.151	**<.001**
Condition X Task Context	0.189	1	7.903	**0.007**
error (condition)	0.024	65		
Rotation	0.207	2	22.884	**<.001**
Rotation X Task Context	0.012	2	1.342	0.265
error (rotation)	0.009	130		
Condition X Rotation	0.195	2	24.391	**<.001**
Condition X Rotation X Task Context	0.018	2	2.310	0.103
error (condition X rotation)	0.008	130		
Task Context	0.002	1	0.066	0.799
error (task context)	0.032	65		

Table 5-2: Mixed ANOVA on the effect of task context, condition and angle of rotation on response times.

Source	MS	df	*F*	*p*
Condition	73584248.36	1	335.063	**<.001**
Condition X Task Context	1021617.816	1	4.652	**0.035**
error (condition)	219613.43	65		
Rotation	1648955.44	2	31.245	**<.001**
Rotation X Task Context	84204.867	2	1.596	0.207
error (rotation)	52774.336	2	28.101	
Condition X Rotation	1422832.315	2	0.444	**<.001**
Condition X Rotation X Task Context	22465.916	130		0.643
error (condition X rotation)	50631.92			
Task Context	142970.897	1	0.196	0.659
error (task context)	728071.923	65		

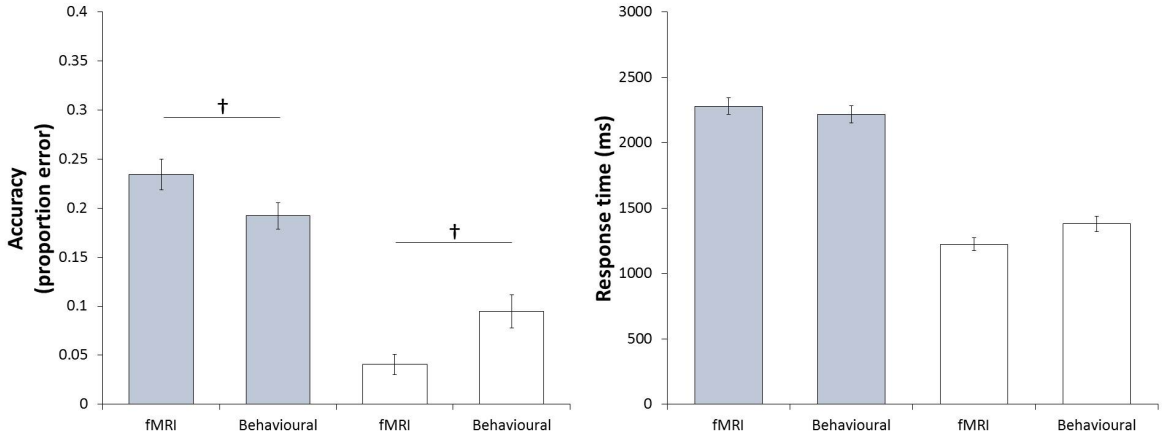


Figure 5-2: Interaction effect of task context on accuracy and response times, and outcome of pairwise comparisons (* p<.05; ** p<.01; † .05≤p<.10). Filled bars represent the allocentric condition. Unfilled bars represent the egocentric condition.

Following the lack of a significant main effect of task context, the interactions between condition and angle of rotation were explored within each sample. Consistent with previous findings, the NGT-R revealed a significant effect of angle of rotation on both performance measures in the allocentric condition but not in the egocentric condition, independently of whether the task was completed inside or outside of the scanner (Figure 5-3, Figure 5-4).

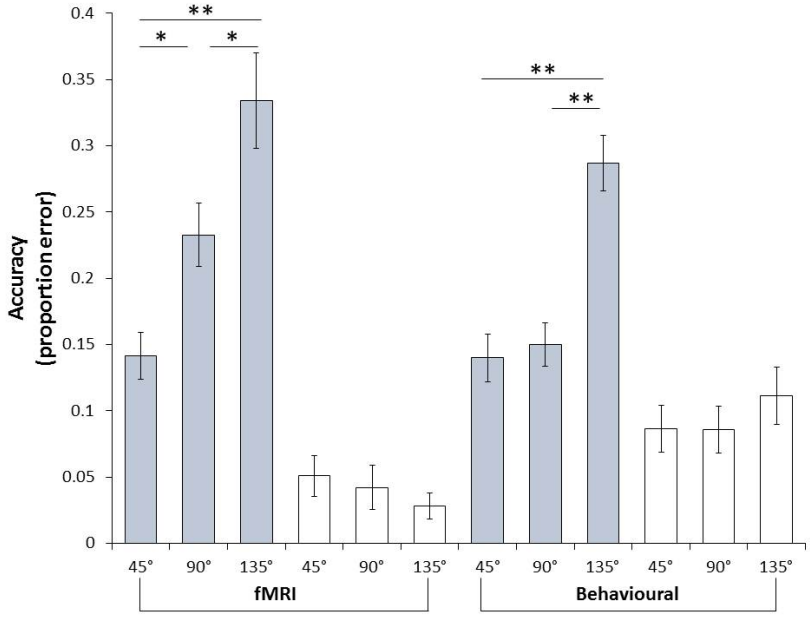


Figure 5-3: Descriptive statistics for accuracy in the allocentric condition (filled bars) and the egocentric condition (unfilled bars) as completed inside the fMRI scanner and behaviourally. Note that pairwise comparisons (* p<.05; ** p<.01) correspond to the interaction between angle of rotation and condition *within* each sample.

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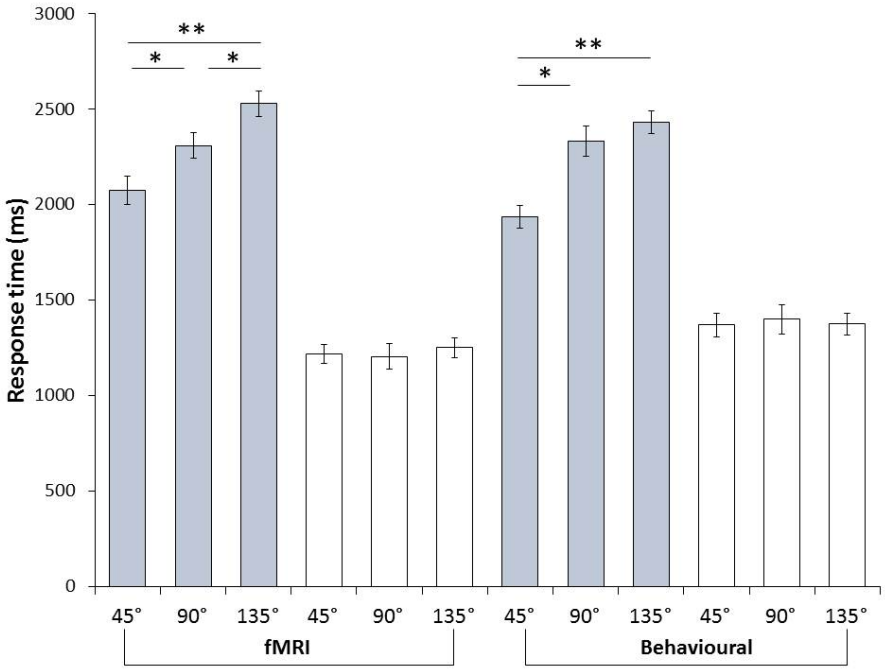

Figure 5-4: Descriptive statistics for response times in the allocentric condition (filled bars) and the egocentric condition (unfilled bars) as completed inside the fMRI scanner and behaviourally. Note that pairwise comparisons (* p<.05; ** p<.01) correspond to the interaction between angle of rotation and condition *within* each sample.

5.3.1.2 Performance in the no-memory control condition

Performance in the new no-memory control condition was explored in a one-way repeated measures ANOVA with condition (allocentric, egocentric, no-memory) as a within-subject factor. The analysis revealed significant effects of condition on accuracy ($F(2,34)=104.660$, $p<.001$) and response times ($F(2,34)=259.988$, $p<.001$) with lower error rates and shorter response times in the no-memory condition compared to the allocentric and egocentric conditions (Figure 5-5).

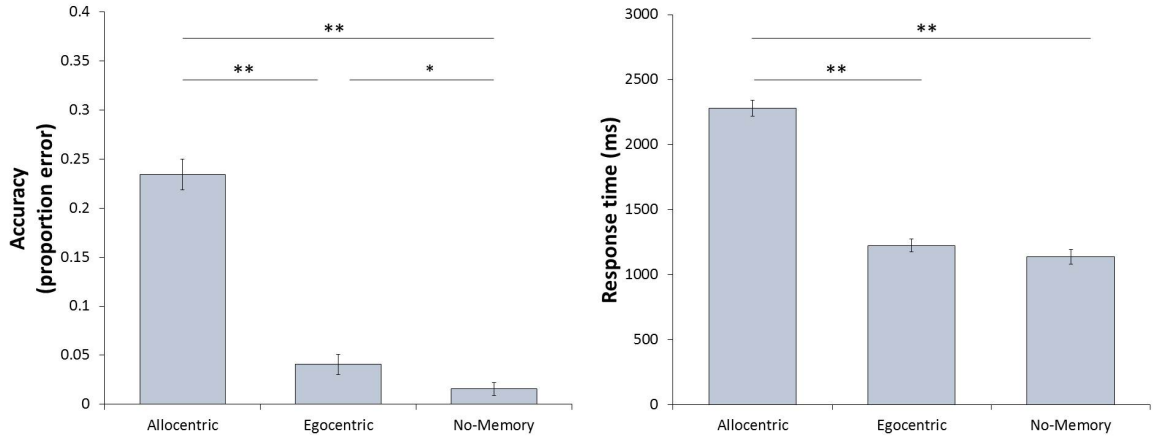

Figure 5-5: Main effect of condition on accuracy and response times, and outcome of pairwise comparisons (* p<.05; ** p<.01).

5.3.1.3 The effect of sex

Sex differences were explored in a 2x3 mixed ANOVA with sex (female, male) as a between-subject factor and condition (allocentric, egocentric, no-memory control) as a within-subject factor. For response times, there was no significant main effect of sex ($F(1,16)=.954$, $p=343$) and no interaction between sex and condition ($F(2,42)=.839$, $p=.441$). For accuracy, however, there was a significant main effect of sex (Table 5-3), which was constituted by a higher error rates in females ($M=.11$, $SE=.01$) than males ($M=.08$, $SE=.01$). There was also a significant interaction between sex and condition (Table 5-3), which reflected higher error rates in the female group only in the allocentric condition (Figure 5-6).

Table 5-3: Mixed ANOVA on the effect of condition and sex on accuracy.

Source	MS	df	*F*	*p*
Condition	0.258	2	125.541	**<.001**
Condition X Sex	0.009	3	4.392	**0.021**
error (condition)	0.002	32		
Sex	0.013	1	9.248	**0.008**
error (sex)	0.001	16		

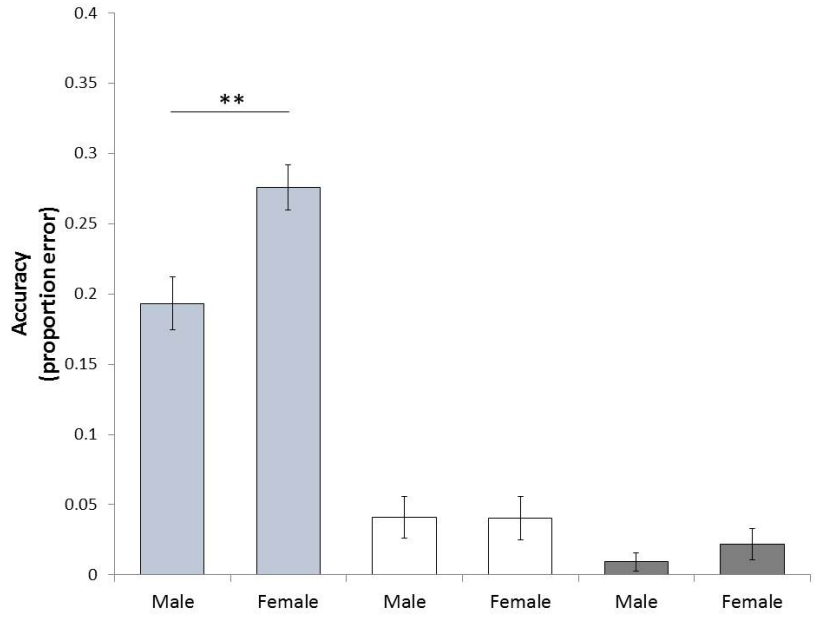

Figure 5-6: Interaction effect between sex and condition on accuracy and outcome of pairwise comparisons (* p<.05; ** p<.01). Light grey bars represent the allocentric condition, unfilled bars represent the egocentric condition and dark grey bars represent the no-memory control condition.

5.3.2 Imaging results

5.3.2.1 Whole brain analyses

To investigate the brain regions involved in landmark-based retrieval, the signal acquired during the response phase in the allocentric condition was contrasted with the egocentric condition (Allocentric>Egocentric). A large network of activation was observed, consisting of occipital, parietal, mediotemporal, as well as frontal regions (Figure 5-7, orange clusters). This large cluster extended dorsally and bilaterally from the inferior occipital lobe to cover large parts of the inferior and superior portions of the posterior parietal lobe. The cluster then continued medially and inferiorly from the precuneus, via the retrosplenial cortex, towards the fusiform gyrus bilaterally. Large parts of the fusiform gyrus were covered, extending anteriorly towards the parahippocampal gyrus and posteriorly to cover the lingual gyrus bilaterally. Local signal peaks were observed in regions of the parieto-medial temporal pathway, including the posterior parietal lobe, the RSC and the lingual gyrus (Table 5-4). In all clusters, the allocentric condition was associated with greater signal above baseline than the egocentric condition. For the reverse contrast (Egocentric>Allocentric), clusters of differential signal were observed in frontal, parietal and temporal regions (Figure 5-7, blue clusters) with local signal peaks in the posterior

cingulate cortex, the medial superior frontal gyrus and the hippocampus (Table 5-5; Figure 5-8). The contrast was generally characterized by the signal dropping below the baseline in the allocentric condition with a lesser drop or no change in the egocentric condition.

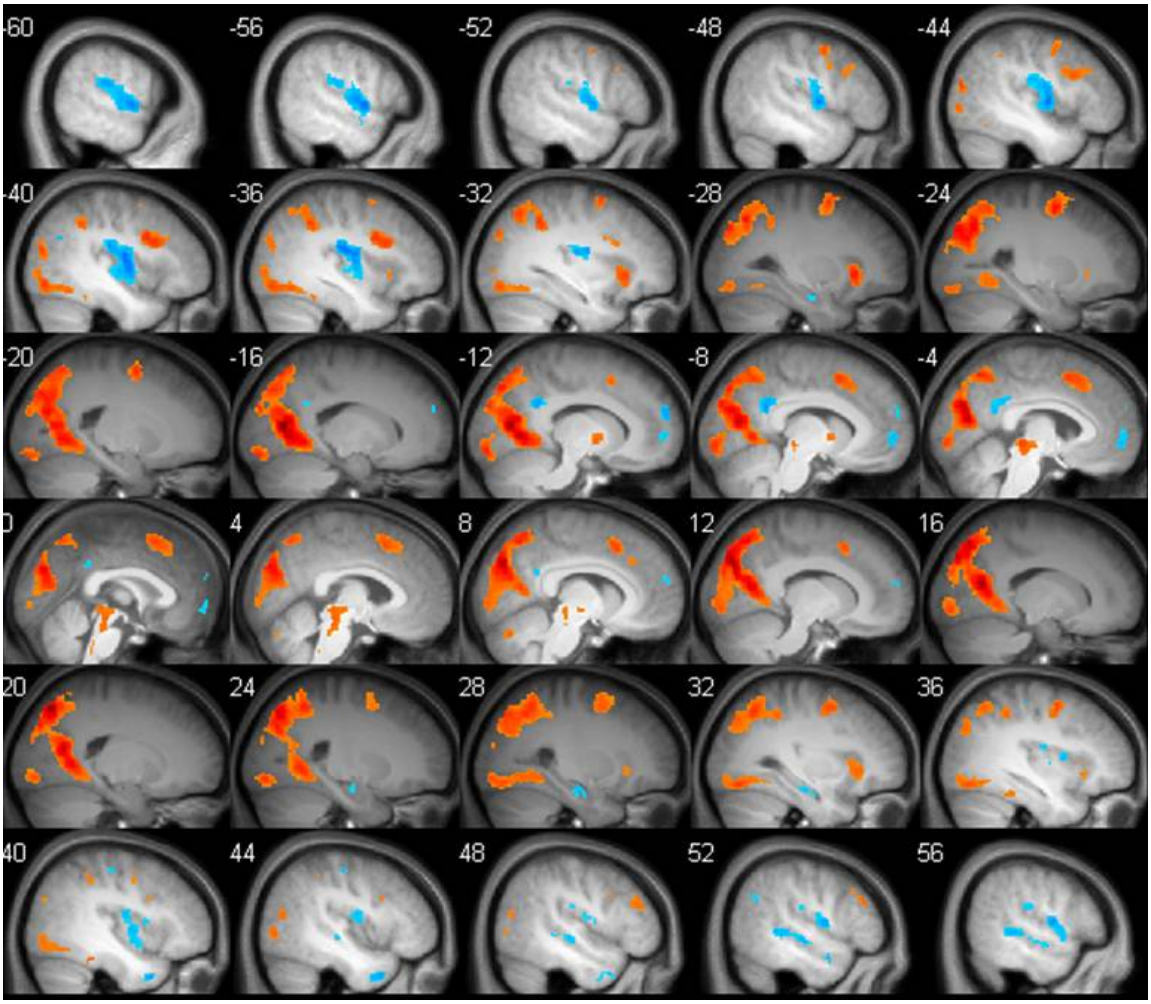

Figure 5-7: Activation maps at retrieval for the Allocentric vs. Egocentric contrast. Activations maps are shown in sagittal sections on the average normalised structural image computed from the sample data. Regions shown in orange exhibited greater signal in the allocentric condition whilst regions shown in blue exhibited greater signal in the egocentric condition ($p<.05$, FWE, $k\geq10$). Numbers represent XYZ coordinates in MNI space.

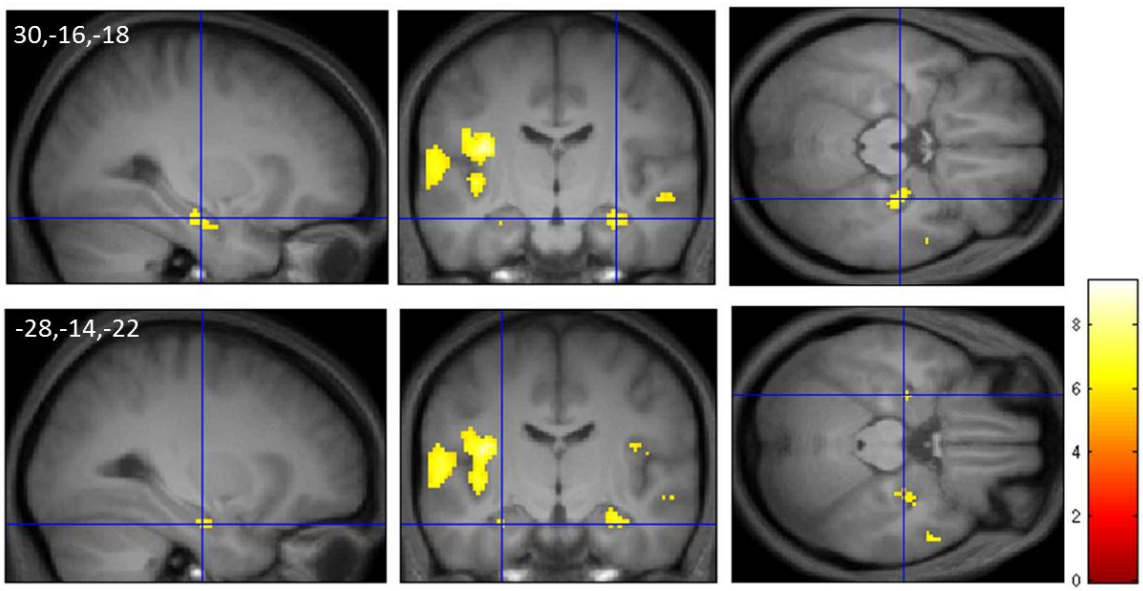

Figure 5-8: Activation maps demonstrating the hippocampal clusters of differential signal for the Egocentric>Allocentric contrast in the right (top) and left (bottom) hemisphere (p<.05, FWE, k≥10). Activations maps are shown in sagittal (left), coronal (middle) and axial (right) sections on the average normalised structural image computed from the sample data. Numbers represent XYZ coordinates in MNI space.

Table 5-4: Peak activations for the whole brain analysis for the Allocentric>Egocentric contrast (p<.05, FWE, k≥10). Differences from baseline for the two conditions are marked as + when positive, as - when negative and as 0 when not significant.

Region	Local peak	Left				Right			
		Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (allo/ego)	Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (allo/ego)
Parieto-occipital-temporal	Retrosplenial cortex	10830	13.48	-16,-70,10	+ / +	-	12.2	18,-62,16	+ / +
	Lingual gyrus	-	10.48	-12,-61,0	+ / +	-	8.15	26,-86,-10	+ / +
	Fusiform gyrus	-	6.55	-38,-44,-20	+ / +	-	6.74	38,-42,-22	+ / +
	Inf. occipital gyrus	-	7.9	-38,-76,-12	+ / +	-	7.16	38,-76,-12	+ / +
	Precuneus	-	8.88	-4,-64,52	+ / +	-	9.93	12,-66,52	+ / +
	Sup. parietal lobe	-	8.84	-16,-70,54	+ / +	-	13.24	20,-72,48	+ / +
	Mid. temporal gyrus	-	-	-	+ / +	41	6.49	46,-70,14	+ / +
Frontal	Insula	197	8.93	-28,24,-2	+ / +	119	6.69	32,26,-4	+ / +
	Medial frontal gyrus	671	8.33	-6,10,50	+ / +	-	7.83	2,14,50	+ / +
	Mid. frontal gyrus	442	9.39	-24,0,52	+ / +	319	7.74	34,0,50	+ / +
	Inf. frontal gyrus	64	6.85	50,32,24	+ / +	-	-	-	+ / +
	Precentral gyrus	402	8.74	-38,8,30	+ / +	18	6.02	46,12,30	+ / +
Other	Brain stem	302	7.91	-4,-28,-4	+ / +	-	-	-	
	Basal ganglia	48	7.28	-12,0,-2,	+ / +	-	-	-	
	Cerebellum	-	-	-		34	6.65	8,-72,-26	+ / +

Table 5-5: Peak activations for the whole brain analysis for the Egocentric>Allocentric contrast (p<.05, FWE, k≥10). Differences from baseline for the two conditions are marked as + when positive, as - when negative and as 0 when not significant. * clusters used for the extraction of BOLD signal for the between-subject analysis (see section 5.3.2.5).

Region	Local peak	Left				Right			
		Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (allo/ego)	Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (allo/ego)
Parietal	Posterior cingulate cortex	217	7.76	-10,-50,26	- / -	18	6.39	6,-50,24	- / -
Frontal	Insula	1624	9.34	-38,-10,14	0 / +	35	7.02	38,6,10	0 / +
	Angular gyrus	11	6.86	-42,-64,28	- / -	14	6.28	52,-58,28	- / -
	Sup. medial frontal gyrus	143	6.7	-8,54,0	- / -	24	6.34	8,58,18	- / -
	Sup. frontal gyrus	88	7.68	-14,54,24	- / -	-	-	-	
	Precentral gyrus	-	-	-		31	7.01	44,-20,52	- / 0
	Supramarginal gyrus	51	6.42	58,-24,22	0 / 0	-	-	-	
Temporal	Temporal pole	-	-	-		96	7.98	42,10,-34	- / -
	Mid. temporal gyrus	-	-	-		275	7.08	54,-38,0	- / 0
		-	-	-		21	6.55	52,2,-20	- / -
	Hippocampus	11*	6.31	-28,-14,-22	- / 0	86*	7.07	30,-16,-18	- / 0

Further to the contrast between the allocentric and the egocentric condition, such experimental conditions were contrasted with the no-memory control condition. For the Egocentric>Control contrast, clusters of differential activation were limited to the parietal lobe, with the exception of a small cluster in the middle frontal gyrus (Table 5-6). Considering the relatively limited number of brain regions identified for this contrast, it was not surprising to observe similar clusters for the Allocentric>Control contrast compared to those observed in the Allocentric>Egocentric contrast. Consequently, clusters of differential signal were observed mainly in the occipital, the parietal and the temporal lobe, but also in frontal regions (Table 5-7). Similarly, the Control>Allocentric contrast revealed similar clusters of differential signal to the Egocentric>Allocentric contrast. One difference worth noting is the absence of any differential signal in the hippocampus for this contrast (Table 5-8). Finally, the Control>Egocentric contrast revealed clusters in frontal, parietal and temporal regions (Table 5-9).

Table 5-6: Peak activations for the whole-brain analysis for the Egocentric>Control (p<.05, FWE, k≥10). Differences from baseline for the conditions (exp, ctrl) are marked as + when positive, as - when negative and as 0 when not significant.

Region	Local peak	Left				Right			
		Cluster (voxels)	t-value	x,y,z MNI)	Diff. baseline (ego/ctrl)	Cluster (voxels)	t-value	x,y,z MNI)	Diff. baseline (ego/ctrl)
Parietal	Sup. parietal lobe	146	8.49	-14, -68, 56	+/+	237	9.8	18, -72, 52	+/+
	Inf. parietal lobe	-	-	-		71	6.58	40, -40, 42	+/+
Frontal	Mid. frontal gyrus	-	-	-		10	6.35	46, 36, 20	+/0

Table 5-7: Peak activations for the whole-brain analysis for the Allocentric>Control (p<.05, FWE, k≥10). Differences from baseline for the conditions (allo, ctrl) are marked as + when positive, as - when negative and as 0 when not significant.

Region	Local peak	Left				Right			
		Cluster (voxels)	t-value	x,y,z MNI)	Diff. baseline (allo/ctrl)	Cluster (voxels)	t-value	x,y,z MNI)	Diff. baseline (allo/ctrl)
Parietal-occipital-temporal	Retrosplenial cortex	9468	10.33	-16,-68,12	+/+	-	11.8	20,-62,16	+/+
	Lingual gyus	-	6.98	-22,-50,-8	+/+	-	6.63	28,-46,-8	+/+
	Cuneus	-	8.05	-6,-74,-18	+/+	-	9.15	12,-78,36	+/+
	Sup. parietal lobe	-	13.04	-16,-70,54	+/+	-	17.23	18,-72,50	+/+
	Mid. occipital gyrus	-	-	-		-	8.49	36,-74,34	+/+
	Sup. occipital gyrus	-	10.67	-22,-72,34	+/+	-	-	-	
Frontal	Insula	237	9.16	-28,24,-2	+/+	267	7.85	34,24,-4	+/+
	Medial frontal gyrus	732	8.08	0,18,50	+/+	-	-	-	
	Mid. frontal gyrus	1641	10.27	-38,6,28	+/+	688	9.27	48,34,22	+/+
		-	-	-		717	10.11	26,6,54	+/0
	Orbitofrontal cortex	89	8.02	-44,50,-6	+/0	12	7.87	26,50,-14	+/0
Other	Cerebellum	39	8.36	-12,-54,-48	+/+	29	7.16	12,-54,50	+/+
		-	-	-		328	7.41	6,-76,-28	+/+
		-	-	-		66	7.75	30,-64,-32	+/+
		-	-	-		11	6.16	0,-60,-36	+/+
	Basal ganglia	27	6.89	-12,0,-2	+/+	15	6.34	14,0,-4	+/+
	Brain stem	-	-	-		176	6.73	4,-26,-18	+/+
		-	-	-		15	6.36	6,-18,4	+/+
		-	-	-		16	6.16	8,-40,-38	+/+

Table 5-8: Peak activations for the whole-brain analysis for the Control > Allocentric (p<.05, FWE, k≥10). Differences from baseline for the conditions (allo, ctrl) are marked as + when positive, as - when negative and as 0 when not significant.

Region	Local peak	Left				Right			
		Cluster (voxels)	t-value	x,y,z MNI)	Diff. baseline (allo/ctrl)	Cluster (voxels)	t-value	x,y,z MNI)	Diff. baseline (allo/ctrl)
Parietal	Posterior cingulate cortex	978	10.54	-6,-50,22	-/0	-	-	-	
	Angular gyrus	-	-	-		158	8.14	52,-60,30	-/0
Frontal	Sup. frontal gyrus	1678	9.59	-14,56,18	-/0	-	-	-	
	Insula	485	8.05	-34,-18,20	-/+	-	-	-	
Temporal	Mid. temporal gyrus	-	-	-		679	8.75	46,-26,-4	-/+
		-	-	-		305	8.64	44,10,-34	-/0
		465	10.56	-42,-64,28	-/-	-	-	-	

Table 5-9: Peak activations for the whole-brain analysis for the Control > Egocentric (p<.05, FWE, k≥10). Differences from baseline for the conditions (ego, ctrl) are marked as + when positive, as - when negative and as 0 when not significant.

Region	Local peak	Left				Right			
		Cluster (voxels)	t-value	x,y,z MNI)	Diff. baseline (ego/ctrl)	Cluster (voxels)	t-value	x,y,z MNI)	Diff. baseline (ego/ctrl)
Parietal	Posterior cingulate cortex	-	-	-		33	5.77	-6,-68,34	0/+
	Precuneus	-	-	-		57	5.86	-2,-68,34	0/0
Frontal	Medial frontal gyrus	-	-	-		47	6.6	6,56,22	-/0
Temporal	Angular gyrus	39	6.87	-42,-64,28	-/-	-	-	-	
Occipital	Mid. occipital gyrus	26	7.24	-28,-96,6	+/+	85	7.58	32,-92,4	+/+

For the analysis of the presentation phase, the signal associated with the allocentric and egocentric conditions at encoding were collapsed and contrasted with the no-memory condition (Encoding>Control). Clusters were observed in the occipital lobe, extending to cover large parts of the fusiform gyrus and a smaller part of the right parahippocampal gyrus, in inferior and superior parts of the parietal lobe and in frontal regions (Figure 5-9, orange clusters; Table 5-10). For the reverse contrast (Control>Encoding), only two small clusters of differential signal were observed (Figure 5-9, blue clusters; Table 5-11).

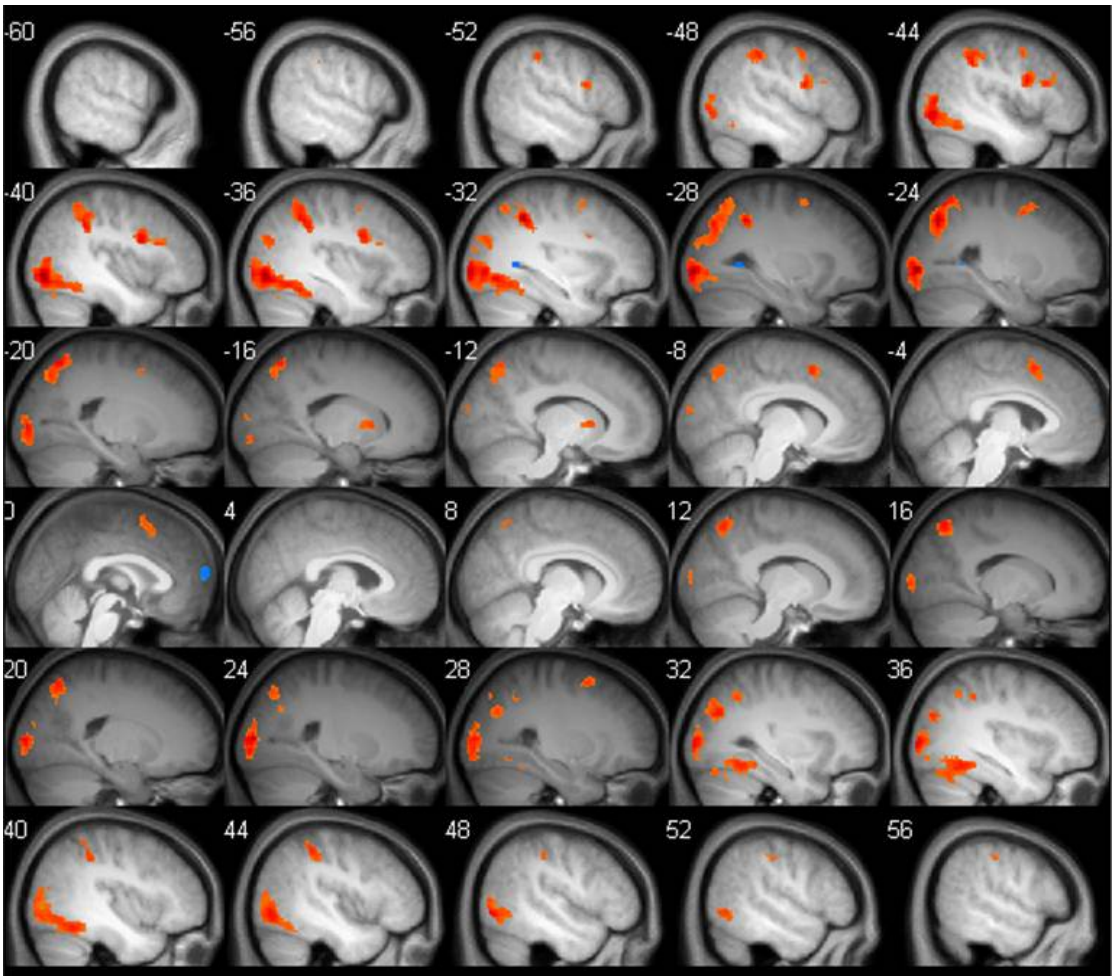

Figure 5-9: Activation maps at presentation for the Encoding vs. Control contrast. Activations maps are shown in sagittal sections on the average normalised structural image computed from the sample data. Regions shown in orange exhibited greater signal in the allocentric condition whilst regions shown in blue exhibited greater signal in the egocentric condition ($p<.05$, FWE, $k\geq10$). Numbers represent X coordinates in MNI space.

Table 5-10: Peak activations for the whole-brain analysis for the Encoding > Control contrast (p<.05, FWE, k≥10). Differences from baseline for the conditions (enc,ctrl) are marked as + when positive, as - when negative and as 0 when not significant.

Region	Local peak	Left				Right			
		Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (enc/ctrl)	Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (enc/ctrl)
Parietal	Sup. parietal lobe	1635	13.94	-30,-46,42	+ / 0	169	9.72	42,-40,48	+ / 0
		-	-	-		534	10.91	18,-66,54	+ / +
	Angular gyrus	-	-	-		65	8.64	32,-54,42	+ / +
Occipital-temporal	Mid. occipital gyrus	-	-	-		1727	12.94	24,-88,8	+ / +
	Inf. occipital gyrus	1904	14.71	-38,-78,-4	+ / +	-	-	-	
	Fusiform gyrus			-36,-50,-18	+/+			38,-52,-16	+/+
	Parahippocampal gyrus	-	-	-				34,-42,-14	+/+
	Cuneus	27	8.75	-10,-94,16	+ / +	-	-	-	
Frontal	Inf. frontal gyrus	385	11.42	-38,6,26	+/ 0	-	-	-	
	Mid. fontal gyrus	127	9.57	-22,4,48	+ / 0	-	-	-	
		55	9.22	-46,2,48	+ / +	-	-	-	
		-	-	-		48	9.61	28,8,56	+ / 0
	Medial frontal gyrus	199	9.88	-6,10,50	+ / 0	-	-	-	
Other	Putamen	75	9.06	-14,10,4	+ / 0	-	-	-	

Table 5-11: Peak activations for the whole-brain analysis for the Control > Encoding contrast (p<.05, FWE, k≥10). Differences from baseline for the conditions (enc,ctrl) are marked as + when positive, as - when negative and as 0 when not significant.

Region	Local peak	Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (enc/ctrl)
Frontal	L. Medial frontal gyrus	47	8.3	0, 62, 16	- / 0
Other	L. Sub-gyral temporal	32	8.95	-30, -54, 2	- / 0

5.3.2.2 Time-course analysis

Time course analyses were performed in voxels of local peak activation in the superior parietal lobe, retrosplenial cortex, hippocampus and posterior cingulate cortex (Figure 5-10). Given the typical time course of the canonical HRF implemented in SPM, signal related to the encoding phase should peak around 5 seconds after trial onset, signal related to the delay phase should peak between 8 and 13 seconds after trial onset, and signal related to the recall phase should peak around 13 to 15 seconds after trial onset. In the early part of the time series (0-10 seconds), BOLD signal changes in the allocentric and egocentric conditions appeared similar in all depicted regions, reflecting the necessarily identical encoding process for the two conditions. Later in the time series (13-16 seconds), however, the change in BOLD signal in the allocentric condition was observed to be more substantial compared to the egocentric condition, which was reflected in the greater increase above the fixation baseline in the superior parietal lobe and the RSC and a greater drop below the same baseline in the posterior cingulate cortex and the hippocampus. In this part of the time series, as opposed to mirroring the BOLD signal change of the allocentric condition, the signal change associated with the egocentric condition was observed to converge towards that of the no-memory control condition. Across the time series, the no-memory control condition consistently produced a BOLD signal closer to the baseline compared to the experimental conditions. It was also noted that whilst two peaks in signal change could be observed in the superior parietal lobe and the retrosplenial cortex, only one peak was observed in the hippocampus and posterior cingulate cortex.

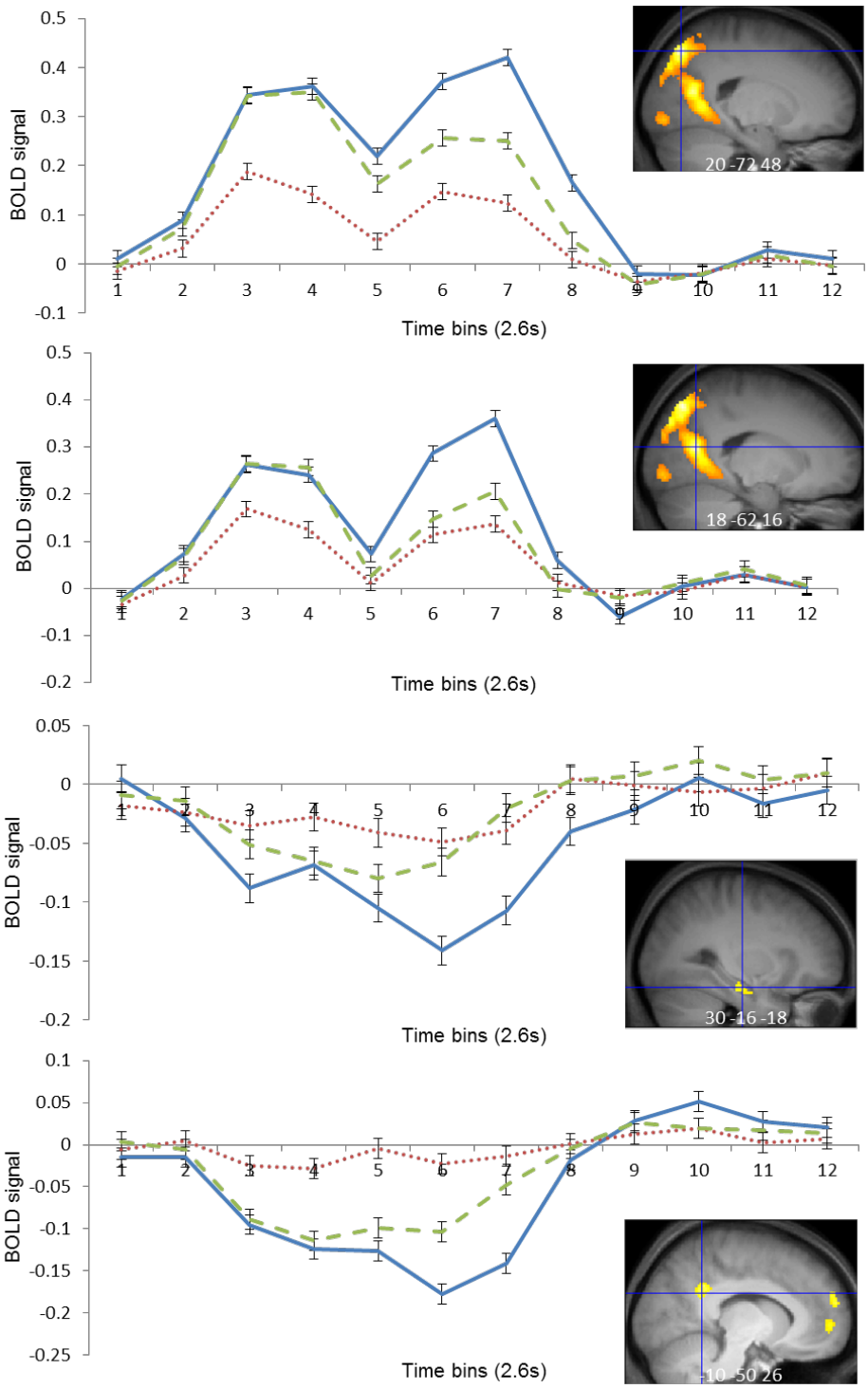

Figure 5-10: Plots of BOLD signal time course changes in the superior parietal lobe (20,-72,48), RSC (18,-62,16), hippocampus (30,-16,-18) and the posterior cingulate cortex (-10,-50,26). Time course are shown in sagittal sections on the average normalised structural image computed from the sample data (activation maps: $p<.05$, FWE, $k\geq10$). The baseline signal was the signal measured during the fixation trials. The voxels selected for analysis were the ones with peak differences in the contrast between the allocentric and egocentric conditions (see Table 5-4, Table 5-5). Signal changes in the allocentric condition (blue, solid), egocentric condition (green, dashed) and no-memory control condition (red, dotted) were modelled from the onset of the trial.

5.3.2.3 Exploratory whole brain analysis

To explore the effect of the longer response times produced in the allocentric condition relative to the egocentric condition, response time was added as a covariate of no interest at the second level. As would be expected if such differences in response times were closely related to cognitive processes, there was a general and substantial loss of effects compared to when response times were allowed to vary. No effects involving the allocentric condition survived the significance threshold in this analysis, although some of the effects previously seen for the Egocentric vs. Control contrast remained (Table 5-12). When the response time regressor was explored in its own right, no significant relationships with BOLD signal emerged in any regions.

Table 5-12: Peak activations for the exploratory whole-brain analysis (response time entered as a covariate) when contrasting all three conditions in the response phase (p<.05, FWE, k≥10). Differences from baseline for the conditions (ego, ctrl) are marked as + when positive, as - when negative and as 0 when not significant.

Contrast	Local peak	Left				Right			
		Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (ego/Ctrl)	Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (ego/Ctrl)
Ego>Ctrl	Sup. parietal lobe	87	8.04	-16,-70,54	+/+	178	9.25	18,-72,52	+/+
Ctrl>Ego	Mid. Occipital gyrus	104	7.38	-36,-90,2	+/+	135	8.48	30,-88,-6	+/+
	Precuneus	14	6.65	-2,-68,34	0/0				

5.3.2.4 Parametric analyses

When response times were added as a parametric modulator separately for the allocentric and egocentric conditions at the first level, signal in the right lingual gyrus and right cuneus showed a positive correlation with response times in the allocentric condition, whilst no regions showed a negative correlation (Table 5-13). It is also worth noting that response times were unrelated to BOLD signal in the hippocampus. In the egocentric condition, the left medial frontal gyrus was found to correlate positively with response times.

In a separate parametric analysis, signal in the left lingual gyrus and the left cuneus was found to show a positive correlation with angle of rotation in the allocentric condition (Table 5-14). No significant correlations were found for angle of rotation in the egocentric condition. Furthermore, no correlations were found between target-foil distance and BOLD signal in any region for the allocentric and egocentric condition.

Table 5-13: Results of the parametric analysis of response time (p<.05, FWE, k≥10).

Condition	Correlation	Region	Cluster (voxels)	t-value	x,y,z MNI)
Allocentric	Positive	R. lingual gyrus	50	5.45	18,-60,2
		R. cuneus	11	8.49	6,-80,34
Egocentric	Positive	L. med. frontal gyrus	26	8.95	-6,12,52

Table 5-14: Results of the parametric analysis of angle of rotation (p<.05, FWE, k≥10).

Condition	Correlation	Region	Cluster (voxels)	t-value	x,y,z MNI)
Allocentric	Positive	L. cuneus	44	9.79	-4,-74,16
		L. lingual gyrus	26	9.54	-20,-64,-4

5.3.2.5 Between-subject performance analysis

Hippocampal BOLD signal in the right and left hemisphere was extracted for each person based on the hippocampal clusters revealed in the Egocentric>Allocentric contrast in the whole-brain analysis (Table 5-15). Pearson's correlation coefficients revealed no significant correlations between hippocampal BOLD signal and performance in the allocentric and egocentric conditions in either of the hemispheres.

Table 5-15: Pearson's correlation coefficients for correlations between performance (accuracy, response time) and hippocampal BOLD signal (* p<.05; ** p<.01). Note that response time averages were based on both correct and incorrect trials.

			Accuracy (error rate)		Response time (ms)	
			Allocentric	Egocentric	Allocentric	Egocentric
BOLD signal	Allocentric	R. hippocampus	0.191	0.009	-0.188	-0.113
		L. hippocampus	-0.074	0.189	0.004	0.168
	Egocentric	R. hippocampus	0.064	-0.144	0.076	-.050
		L. hippocampus	0.233	-0.03	-0.069	-0.030

Following the demonstrated sex differences in NGT-R performance (section 5.3.1.3), it was interesting to explore sex differences in hippocampal BOLD signal. Given the different sizes of the hippocampal clusters in the right and left hemisphere, a 2x2 mixed ANOVA, with sex (female, male) as a between-subject factor and condition (allocentric, egocentric) as a within-subject factor, was conducted separately for the right and left hippocampi. As was already evident in the whole-brain analysis, there was a significant main effect of

condition on hippocampal BOLD signal in both hemispheres, with a greater negative BOLD signal in the allocentric condition compared to the egocentric condition (Table 5-16, Table 5-17). For the right hippocampus, but not the left, there was a significant main effect of sex, which constituted a greater negative BOLD signal in the male group compared to the female group (Table 5-16, Table 5-17, Figure 5-11).

Table 5-16: Mixed ANOVA on the effect on condition and sex on BOLD signal extracted from the right hippocampus.

Source	MS	df	*F*	*p*
Condition	91.575	1	53.157	**<.001**
Condition X Sex	2.618	1	1.520	0.235
error (condition)	1.723	16		
Sex	9.172	1	5.717	**0.029**
error (sex)	1.604	16		

Table 5-17: Mixed ANOVA on the effect on condition and sex on BOLD signal extracted from the left hippocampus.

Source	MS	df	*F*	*p*
Condition	81.473	1	54.384	**<.001**
Condition X Sex	0.323	1	0.215	0.649
error (condition)	0.1498	16		
Sex	4.558	1	2.626	0.125
error (sex)	1.736	16		

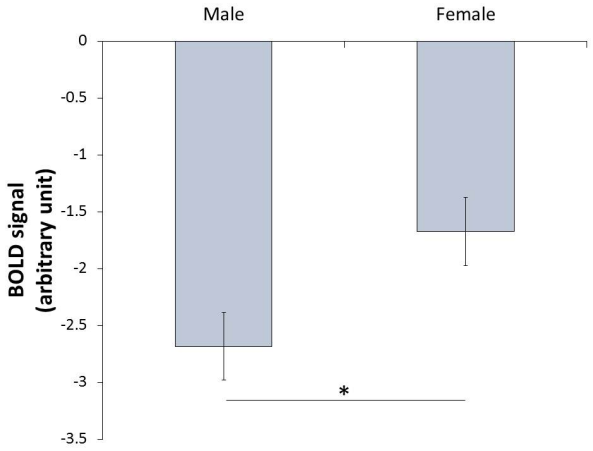

Figure 5-11: Main effect of sex on BOLD signal extracted from the right hippocampus.

5.4 Discussion

The aim of Experiment 7 was to investigate the neural underpinnings of the NGT. As such, the primary hypothesis concerned a hippocampal contribution in the allocentric condition, which was assumed to involve the use of an environment-centred representation to reorient and identify the target. Further to this, secondary hypotheses were proposed in relation to the involvement of additional regions in the parieto-medial temporal pathway, namely the RSC and the lingual gyrus, in the allocentric condition. Finally, the PPA and the lingual gyrus were proposed to be sensitive to increasing viewpoint-shifts, as a potential neural basis of the alignment effect in the allocentric condition. Results relevant to each prediction will be discussed in turn (sections 5.4.1, 5.4.2 and 5.4.3). Following this, performance-related effects will be discussed (section 5.4.4) and the behavioural results and the general administration of the NGT-R inside the scanner will be commented on (section 5.4.5).

5.4.1 The hippocampus and allocentric spatial memory

The prediction stemming from the primary hypothesis concerned increased hippocampal activation in the allocentric condition relative to the egocentric condition. In stark contrast to this prediction, the bilateral hippocampus showed a greater signal in the egocentric condition compared to the allocentric condition. Relative to the fixation baseline, however, this effect was characterised by a lack of signal change in the egocentric condition and a significant signal drop in the allocentric condition. Thus, the hippocampus appears to be uniquely engaged in the allocentric condition in the NGT even though this engagement was characterised by a negative BOLD signal.

Although contradictory to the prediction of an increased BOLD signal in the allocentric condition, it is important to emphasise that a negative BOLD response in the hippocampus is not an uncommon finding. Such a response has been associated with virtual versions of traditional spatial memory tasks, including the Morris Water Maze (Shipman and Astur, 2008) and the Radial Arm Maze (Astur *et al.*, 2005), as well as with increasing goal distance in a route-planning task (Viard *et al.*, 2011), autobiographical spatial judgments of long-term memories (Rekkas *et al.*, 2005) and detection of location changes following an imagined shift in viewpoint (Lambrey *et al.*, 2012). Such reports of negative hippocampal BOLD responses in spatially demanding and arguably hippocampus-relevant task

conditions not only indicate the reliability of the finding in Experiment 7 but also highlight the need for an interpretation.

Whilst the positive BOLD response has been consistently related to increased neural activity (Logothetis *et al.*, 2001), the mechanisms underlying the negative BOLD response are much less clear (Hayes and Huxtable, 2012). Three theoretical accounts are generally offered: a) the negative deflection could be the result of vascular steal by which oxygenated blood is diverted away from less active areas to more active areas, b) of an active neural suppression in the region, or c) of a contradictory *increase* in neural activity without a corresponding boost in blood flow (Wade, 2002). Whilst the vascular steal account is unlikely considering the small changes in cerebral blood flow accompanying cognition and the substantial hemodynamic reserve of the brain (Gusnard *et al.*, 2001), the two latter accounts are relevant in the present context. These two accounts of the negative BOLD signal will be discussed and evaluated in turn, after which I will propose an interpretation of the *differential* hippocampal BOLD signal in the allocentric condition.

5.4.1.1 Suppression of hippocampal activity

It is possible that the allocentric condition of the NGT, contrary to the prediction, is associated with a suppression of hippocampal activity. Previous research has demonstrated that task-specific factors such as memory load and spatial complexity can have an effect on whether hippocampal BOLD signal fall above or below a fixation baseline. In regards to memory load, Axmacher *et al.* (2007) showed that maintenance of a single item in memory resulted in a negative BOLD signal in the hippocampus whilst maintenance of four items resulted in a positive BOLD signal. Similarly, but in relation to spatial complexity, Lee and Rudebeck (2010) found evidence of a negative BOLD signal in a working memory task when the stimuli represented simple 2D displays but a positive BOLD signal when it represented complex 3D scenes. Thus, it could be suggested that the use of a single target location and the relatively simplistic environment in the NGT could account for the negative BOLD signal found in the allocentric condition. An obvious caveat of this account, however, is that the egocentric condition involves a similarly low memory load and an identical environment. In fact, relative to the egocentric condition, the allocentric condition is likely to have imposed a greater memory load and spatial complexity given the need to remember the single target location in relation to one or several landmark locations. Thus,

the decreased BOLD signal in the allocentric condition relative to the egocentric condition is unlikely to be accounted for by a lower memory load or lower spatial complexity.

A related task-specific account was proposed in the study conducted by (King *et al.*, 2002). In this study, a patient with hippocampal damage was shown to be disproportionately impaired when locations had to be remembered from a shifted viewpoint, but only for list lengths greater than one (for more detail, see section 2.2.4.2). It was argued that only for longer list lengths was it more efficient to store the target locations relative to a fixed reference direction compared to storing and manipulating self-object vectors individually. According to this account, the single target location in the allocentric condition of the NGT may have rendered a mental rotation strategy sufficient to solve the task, reducing the need for an allocentric representation and thereby the recruitment of the hippocampus. Although the parietal and frontal engagement in the allocentric condition could be indicative of a mental rotation strategy in the allocentric condition, it is unclear why such a hippocampus-independent strategy should result in a negative BOLD signal in this very region (Zacks, 2008). Conversely, a lack of a hippocampus-dependent strategy in the allocentric condition would be expected to make this condition more similar to the egocentric condition and thereby reduce the likelihood of differential hippocampal activation when the two conditions are contrasted. Consequently, the negative BOLD signal in the hippocampus is difficult to delineate as a simple lack of hippocampal involvement.

The above discussion indicates that the negative BOLD signal in the hippocampus is unlikely to be accounted for by factors such as the number of target locations and the complexity of the virtual environment. In contrast to such task-specific effects, the negative BOLD signal could also be explained by effects that are independent of the specific requirements of the NGT. Specifically, the suppression of the hippocampus in the allocentric condition could be due to the generally greater demand of the allocentric condition, as indicated by higher error rates and longer response times in this condition.

At rest, the hippocampus demonstrates functional correlations with the default network, which consistently shows deactivations during active compared to passive baseline conditions (Shulman *et al.*, 1997) and during difficult compared to easy task conditions (McKiernan *et al.*, 2003; Gimbel and Brewer, 2011). Thus, it is possible that the hippocampus is suppressed as part of a larger default mode network as a consequence of

the greater demand in the allocentric condition. In relation to such default suppression of hippocampal activity, it is noteworthy that several of the studies that have demonstrated hippocampal deactivations in arguably hippocampus-relevant conditions have also reported worse behavioural performance in that particular condition (Rekkas *et al.*, 2005; Shipman and Astur, 2008; Rodriguez, 2010; Lambrey *et al.*, 2012).

One specific example of a task-general effect was offered by Reas *et al.* (2011), who demonstrated a negative BOLD signal in the hippocampus during elaborate associative recall, which was greater for poorly remembered than for strongly remembered items. It was argued that the longer memory search accompanying poorly remembered items required a greater suppression of tonic encoding-related activity in the hippocampus, in favour of retrieval-related processes taking place elsewhere. In other words, a suppression of default hippocampal encoding activity was proposed to underlie the negative BOLD response. Compared to the egocentric condition, the allocentric condition indeed required a longer memory search, in addition to a potential retrieval of obscured relevant landmarks, which suggests that the negative BOLD signal in this condition could be the result of suppressed encoding-related activity. However, no evidence was found of an increased BOLD response in the hippocampus at encoding, which contradicts the idea that signal in this region is reflective of encoding processes in the NGT. Consequently, this particular default suppression is unlikely to explain the present findings.

Further to this, it is important to emphasise that the coupling of the hippocampus with other default regions during memory retrieval appears to vary according to task condition (Gimbel and Brewer, 2011; Huijbers *et al.*, 2011; Reas *et al.*, 2011), which indicates that the areas deactivated during memory retrieval may only partially overlap with those deactivated during non-memory tasks (Israel *et al.*, 2010). In relation to this, although the more difficult allocentric condition was associated with deactivations in classic default regions such as the medial prefrontal cortex and the posterior cingulate, it was associated with strong activations in another default region, the RSC (Buckner *et al.*, 2008). Furthermore, when the less demanding control condition was contrasted with the allocentric condition, no differential signal was demonstrated in the hippocampus whilst the typical default response was demonstrated in the posterior cingulate cortex. Thus, a suppression of classic default regions does not necessarily appear to be accompanied by a suppression of

the hippocampus, indicating that the negative BOLD signal may not be the simple result of differences in difficulty levels between conditions.

In relation to the effect of task difficulty, it is also important to mention the outcome of the exploratory whole-brain analysis, in which average response times were included as a covariate of no interest at the second level (section 5.3.2.3). In this analysis, no evidence was found of a negative BOLD signal in the hippocampus, suggesting that this result could be fully accounted for by the higher demand of the allocentric relative to the egocentric condition. However, responses times in the NGT are not only a proxy for difficulty but are also likely to be closely associated with the cognitive processes of interest. Consequently, by controlling for response times one is controlling not only for differences in difficulty levels but also for the cognitive processes of interest (Gilbert *et al.*, 2012). Furthermore, it could be argued that accounting for response times independently of conditions resulted in an inappropriate adjustment of the data. This follows from the elimination of all clusters previously associated with the contrast between the allocentric condition and the no-memory control condition. In contrast to the allocentric and egocentric conditions, which theoretically could involve similar cognitive processes and neural systems, the allocentric and the no-memory conditions can safely be assumed to involve distinct cognitive processes and neural systems. The lack of a modulating effect of response times on hippocampal BOLD amplitude at the second level further strengthens the argument that factors other than response time are likely to be more important.

In addition to the indications above, neurons in the hippocampus appear to show no or very low activity during baseline conditions whilst firing selectively in response to different categories of visual stimuli (Quiroga *et al.*, 2005; Kraskov *et al.*, 2007), which is contrary to the relatively high activity levels expected in default regions at baseline. Furthermore, when BOLD signal is not used as the measure of neural activity, results do not tend to support a suppression of hippocampal activity during spatial memory tasks. For example, when contrasted to a less demanding visuomotor control condition, goal-directed navigation has been found to be associated with increased cerebral blood flow to the hippocampus, as measured by PET (Maguire *et al.*, 1997), and with increased theta activity in the hippocampus, as measured by MEG (Cornwell *et al.*, 2008). Thus, although a task-independent effect of difficulty cannot be excluded in the present study, a general

suppression of the default network is unlikely to fully account for the negative BOLD response in the hippocampus in Experiment 7.

5.4.1.2 Increase of hippocampal activity

The negative BOLD response in the allocentric condition may not be a reflection of suppression of neural activity but of an increase of neural activity. This is possible because of the relative nature of the BOLD signal, which depends on a complex interplay between changes in cerebral blood flow (CBF), cerebral blood volume (CBV) and oxygen metabolism (cerebral metabolic rate of oxygen, $CMRO_2$) that results from neural activity (Buxton *et al.*, 2004; Logothetis and Pfeuffer, 2004; Buxton, 2012). In fact, measurable increases in BOLD signal rely on a relatively greater increase in CBF compared to $CMRO_2$ (Ogawa *et al.*, 1990). Consequently, if neural activity causes a greater increase in $CMRO_2$ relative to the increase in CBF, a decreased BOLD signal could theoretically result (Buxton, 2012).

Ekstrom (2010) proposed that the negative BOLD response in the hippocampus during memory encoding and retrieval tasks could be explained by such a neurovascular account. In support of this account, the coupling between CBF and $CMRO_2$ in the hippocampus appears more complex than that traditionally observed in the cortex (Leontiev *et al.*, 2007; Restom *et al.*, 2008), possibly as a result of a more limited blood supply in the hippocampus compared to cortex (Borowsky and Collins, 1989). For example, whilst BOLD changes in the parahippocampus were found to be positively correlated with local field potential (LFP) power changes in a sample of epilepsy patients during a spatial navigation task, BOLD changes in the hippocampus showed a weak or no correlation with LFP power changes (Ekstrom *et al.*, 2009). Furthermore, Schridde *et al.* (2008) found that induced seizures in the rat resulted in marked increases in LFP activity across the entire brain but that such increases were associated with negative BOLD responses in the hippocampus and with positive BOLD responses in the cortex. Importantly, the coupling between $CMRO_2$ and CBF was found to account for the negative BOLD response; the increase in $CRMO_2$ nearly matched the increase in CBF in the hippocampus whilst the normal CBF/$CMRO_2$ overshoot was observed in the cortex. Based on such results, Ekstrom (2010) proposed that demanding memory tasks may be associated with an increase in $CMRO_2$ that is just matched or even undershot by the increase in CBF, which, when

contrasted with a resting baseline condition, results in a negative BOLD signal. Considering the lack of signal change relative to the baseline in the egocentric condition, such a scenario could account for the present findings: the demand of the allocentric condition could have caused the oxygen consumption in the hippocampus to exceed its supply, which could have resulted in a negative BOLD signal in the face of increased neural activity. In agreement with Ekstrom (2010), I propose that relative to a suppression of default activity, such a neurovascular account is more likely to explain the negative hippocampal BOLD signal in the allocentric condition of the NGT and in previous spatial memory tasks.

5.4.1.3 Differential hippocampal activity

The discussion above has highlighted two valid but mutually exclusive accounts of the negative BOLD signal demonstrated in the hippocampus. Despite such interpretational difficulties, the present data allows me to conclude that the allocentric and egocentric conditions resulted in a differential engagement of the anterior hippocampus bilaterally. The lack of a significant signal change from the fixation baseline in the egocentric and control conditions further indicates that the anterior hippocampus was specifically implicated in the allocentric condition, albeit in the form of a negative BOLD signal. As such, the present results appear to add to the substantial evidence base that supports a role of the hippocampus in allocentric spatial memory (Muller *et al.*, 1987; Baumann *et al.*, 2010; Goodrich-Hunsaker *et al.*, 2010). The anterior hippocampus specifically has previously been implicated in the initial stages of navigation (Cornwell *et al.*, 2008; Shipman and Astur, 2008; Xu *et al.*, 2010), route planning (Spiers and Maguire, 2006) and mental navigation (Mellet *et al.*, 1995), which suggests a role for this particular subsection in providing the allocentric spatial representations that underlie goal-directed navigation. Importantly, the present results extend such findings by demonstrating a similar hippocampal involvement in a task that requires no navigation. Consequently, it can be proposed that the anterior hippocampus is particularly important for the allocentric process of self- and target-localisation based on available environmental landmarks and not for the execution of a navigational plan. As such, the results of Experiment 7 are in line with previous neuropsychological findings, which have demonstrated a disproportionate effect of hippocampal damage on allocentric short-term memory in similar viewpoint-shift tasks

(King *et al.*, 2002; Hartley *et al.*, 2007). Furthermore, the predominantly right-sided hippocampal engagement in the allocentric condition is consistent with the use of a landmark-based strategy (Iaria *et al.*, 2003; Bohbot *et al.*, 2004) and with a general right-sided lateralisation of spatial memory (Smith and Milner, 1981; Feigenbaum and Morris, 2004).It is important to emphasise the strength of the hippocampal effect in Experiment 7, which was revealed at a whole-brain level after correction for multiple comparisons. Such an obvious implication of the hippocampus when the two experimental conditions in the NGT were compared strongly supports that the inclusion of the egocentric condition provided a sensitive contrast. Indeed, when the much more general no-memory control condition was contrasted with the allocentric condition, no hippocampal involvement could be detected. This should be considered in the context of the study of Schmidt *et al.* (2007), who did not find evidence of hippocampal involvement when a comparable viewpoint-shift task was contrasted with a general no-memory control condition. Experiment 7 has therefore further emphasised the importance of the selection of an appropriate control condition when investigating hippocampal function (Stark and Squire, 2001) and highlights that the use of an over-general control conditions may prevent the detection of hippocampal involvement in a viewpoint-shift task (Schmidt *et al.*, 2007).

5.4.2 The parieto-medial temporal pathway and allocentric spatial memory

In addition to the hippocampal involvement, the allocentric condition of the NGT was hypothesised to uniquely engage the RSC and the lingual gyrus. In support of such predictions, the allocentric condition was associated with a substantial cluster of activation along the parieto-medial temporal pathway, which included both the RSC and the lingual gyrus bilaterally. However, this cluster also extended to another primary region of the parieto-medial temporal pathway, namely the posterior parietal lobe. Thus, the present study provides support for the recruitment of the full extent of the parieto-medial temporal pathway for allocentric short-term memory retrieval, even in scenarios in which no navigation execution is required. The proposed role of the regions in this pathway in the NGT will be explored in more detail below.

The implication of the RSC in the allocentric condition is consistent with its role in the translation between egocentric and allocentric spatial systems, which allows for the critical coordination of the egocentric perspective with the allocentrically represented target

location (Maguire, 2001; Epstein, 2008). It also supports a role for the RSC that extends beyond navigation to also include environment-centred referencing following a shift in viewpoint (Galati *et al.*, 2010). The recruitment of the RSC in the allocentric condition can also be considered in the context of a recent study, which demonstrated a specific sensitivity in this region to landmarks with a high degree of stability (Auger *et al.*, 2012). Given the stability of the landmarks in the allocentric condition and the instability of the same landmarks in the egocentric conditions, the implication of the RSC in the NGT can therefore be considered consistent with a role of this region in the identification of stable landmarks. The implication of the lingual gyrus is furthermore consistent with its proposed role in the representation of the orientation value of salient environmental landmarks, which only would have been important in the allocentric condition (Aguirre *et al.*, 1998; Aguirre and D'Esposito, 1999).

As expected, the PPA did not show differential activation in the allocentric and egocentric conditions, indicating that this structure makes equal demands in terms of scene perception and recognition in the two conditions (Epstein and Kanwisher, 1998). Alternatively, this null finding could be considered consistent with findings showing that the PPA is sensitive to both viewpoint-changes and scene changes (Epstein *et al.*, 2003), which arguably correspond to the manipulations in the allocentric and egocentric conditions, respectively. It is worth noting that when encoding of the target location was contrasted with the no-memory control condition in the presentation phase, increased activation was revealed in the right posterior parahippocampal gyrus. Assuming no incidental encoding occurred in the no-memory control condition, this finding is therefore consistent with a role of this region in the encoding of a local scene (Epstein, 2008).

Consistent with a role of the posterior parietal cortex in egocentric memory representations (Burgess, 2008), the egocentric condition of the NGT was associated with greater activity in this region relative to the no-memory control condition. In contrast, the posterior parietal involvement in the allocentric condition appears contradictory to its predominantly egocentric role. One potential account for this finding could be derived from recent proposals that the posterior parietal lobes are particularly important for one type of egocentric transformation, namely body referencing, which is defined as the coordination of body knowledge with sensory maps of space (Committeri *et al.*, 2004; Galati *et al.*, 2010). Although the egocentric condition is likely to require some basic mapping between

the retinotopic and the body-centred coordinates, the viewpoint-shift in the allocentric condition may have triggered a more explicit reference to the virtual position of the body in space. As a result, the allocentric condition may have necessitated a greater degree of remapping between the egocentric coordinate systems and thereby placed a higher demand on the posterior parietal lobe. Alternatively, the posterior parietal involvement in the allocentric condition can be considered consistent with proposals that the role of this region extends to egocentric-to-allocentric transformations (Byrne *et al.*, 2007; Calton and Taube, 2009; Save and Poucet, 2009). In the primate brain, neurons in area 7 in the posterior parietal cortex represent locations in eye-centred coordinated but show sensitivity to the orientation of the animal within the testing room (Snyder *et al.*, 1998) and neurons in more medial parietal areas respond to the position of stimuli in allocentric space (Dean and Platt, 2006). Posterior parietal activation has also been consistently associated with mental rotation, which is thought to require coordination of the frame of the rotated object relative to the environment-centred frame, both of which need to be computed from egocentric retinal coordinates (Zacks, 2008). Thus, it is possible that the coordination of the allocentrically represented target location and the egocentrically experienced perspective in the allocentric condition accounts for the posterior parietal involvement. In brief, the posterior parietal involvement in the allocentric condition of the NGT would be consistent with the greater reliance on translations between different coordinate systems.

Further to the lateral portions of the posterior parietal lobe, activation in the precuneus in the medial portion of the posterior parietal lobe was associated with the allocentric condition. This region has been associated with imagery of retrieved material (Fletcher *et al.*, 1996), with the retrieval of the spatial context of a life-like event (Burgess *et al.*, 2001) and with the construction of an updated spatial representation after movement through virtual space (Wolbers *et al.*, 2008). It is therefore conceivable that the precuneal involvement in the allocentric condition could be a reflection of imagination of the target location and of the parts of the scene that have become obstructed following the viewpoint-shift. In other words, the increased activation of the precuneus could be a reflection of the greater reliance on imagery of the retrieved material in the allocentric compared to the egocentric condition.

5.4.3 The neural basis of the alignment effect

Further to the involvement of the hippocampus and the parieto-medial temporal pathway in the NGT, predictions were made in relation the neural basis of the alignment effect, as reflected in the effect of increasing viewpoint-shifts in the allocentric condition. Consistent with the predictions and previous findings, BOLD signal amplitude in the hippocampus was found not to be sensitive to increasing viewpoint-shifts (Schmidt *et al.*, 2007). This suggests that although the hippocampus appears to be involved in the allocentric condition of the NGT, as evidenced by the negative BOLD signal in the whole-brain analysis, it does not appear to be implicated in the process of calculating the effect of increasing viewpoint-shifts *per se*. This is consistent with the general lack of hippocampal involvement during imagined viewpoint-shifts (Hannula and Ranganath, 2008; Lambrey *et al.*, 2012).

BOLD signal amplitude in the left lingual gyrus was instead found to be associated with increasing viewpoint-shifts, which is also consistent with the predictions and previous findings (Schmidt *et al.*, 2007). Considering the role of the lingual gyrus in representing the orientation value of landmarks (Aguirre *et al.*, 1998), an increased reliance on such landmark information for more substantial viewpoint-shifts could be proposed to underlie this finding. Specifically, it is conceivable that greater viewpoint-shifts resulted in greater disorientation, which in turn increased the reliance on landmarks to regain orientation. Importantly, the sensitivity to increasing viewpoint-shifts in this particular region also contradicts the use of a mental rotation strategy in this condition. This follows from findings that the superior parietal lobe, and not the lingual gyrus, exhibits sensitivity to the angular disparity in mental rotation tasks (Gauthier *et al.*, 2002). Thus, as opposed to an object-like rotation of the entire scene, the allocentric condition appears to involve a process of reorientation based on the orientation information of landmarks. In the context of the allocentric updating theory, the left lingual gyrus can therefore be proposed to play an important role in the process of recovering the reference direction from the interobject vectors present in the visual scene (Zhang *et al.*, 2011).

In addition to the lingual gyrus, the left cuneus was found to be sensitive to increasing viewpoint-shifts, which represents a novel finding compared to a similar study (Schmidt *et al.*, 2007). Being part of the occipital lobe, it could be suggested that the visual change resulting from the viewpoint-shift is underlying the cuneal response. However, since BOLD

signal in the cuneus did not appear to be modulated by the identical visual change resulting from the landmark-shift in the egocentric condition, the finding in the allocentric condition is unlikely to be explained by changes in the visual display. It is worth noting that the cuneus is situated next to the precuneus, which has been implicated in imagery of retrieved material (Fletcher *et al.*, 1996). It can therefore be speculated that the cuneus may play a role in relaying information about what parts of the scene that has become unavailable after the viewpoint-shift, which can then be used by the precuneus to determine what aspects that need to be imagined to retrieve the target location. Evidently, further research will be required to determine the exact role of the cuneus in the calculation of the effects of viewpoint-shifts.

In contrast to the predictions and previous findings (Schmidt *et al.*, 2007), BOLD signal in the PPA was not found to be sensitive to increasing viewpoint-shifts. One potential explanation for this null finding is the relatively small visual change in the scene following viewpoint-shifts in the NGT environment. In the study by Schmidt *et al.* (2007), the geometry and environmental detail of the roof top environment meant that a shift in viewpoint resulted in a relatively drastic visual change of the scene, more so for greater viewpoint-shifts. In contrast, the circular shape and the visually similar landmarks in the NGT environment meant that even larger viewpoint-shifts resulted in a limited change of the visual aspects of the scene. Considering the established sensitivity of the PPA to scene changes (Epstein *et al.*, 2003), it is possible that the small visual changes following viewpoint-shifts may not have provided sufficient sensitivity to detect variation in PPA BOLD signal in the NGT.

Finally, it is important to emphasise that no region was found to be sensitive to the extent of the landmark-shift in the egocentric condition. This confirms that such a change in the visual background was indeed appraised as irrelevant in remembering the target location in the egocentric condition. Thus, similarly to the pattern of behavioural results (section 5.3.1), angle of rotation only appears to have an effect on neural activity in the allocentric condition of the NGT.

5.4.4 Performance-related effects

Further to the parametric analyses of the magnitude of the manipulations of viewpoint and landmark positions in the NGT, the effect of response times on BOLD signal was

investigated. When considered as a covariate at the second level, response times did not show a significant effect on BOLD signal in any region of the brain (see section 5.4.1.1 for discussion). In contrast, when the effect of response times was considered as a parametric modulator at the first level, separately for the allocentric and egocentric conditions, significant modulating effects were revealed. Specifically, longer response times in the allocentric condition were associated with increased BOLD amplitude in the right lingual gyrus and cuneus. Considering the effect of increasing viewpoint-shifts on response times in the allocentric condition (section 5.3.1), this provides an interesting parallel to the sensitivity of the *left* lingual gyrus and cuneus in the previous section. Although the effects of response times and the size of the viewpoint-shifts are necessarily difficult to disentangle, this can be interpreted as further support for the possible role of the lingual gyrus and the cuneus in processing the orientation information of landmarks in order to recover the reference direction in the allocentric condition.

In the egocentric condition, longer response times were found to be associated with greater BOLD amplitude in an entirely separate region, the left medial frontal gyrus. This indicates that the processes underlying longer response times are different in the two experimental conditions, which in turn may explain the lack of an effect of response times when it is added as a covariate at the second level. Furthermore, the lack of a modulating effect of response times in the hippocampus in any of the analyses indicates that the negative BOLD signal in the allocentric condition is unlikely to be the sole result of variation in this particular proxy of difficulty.

The effect of response times was also investigated in a between-subject analysis. Hippocampal BOLD signal was not associated with any of the performance measures in the allocentric and egocentric conditions in this analysis, indicating that the negative BOLD signal in the allocentric condition occurs independently of the performance of individual participants. Although this provides important evidence for the consistency of the negative BOLD signal across participants, it is worth mentioning a coincidental link between sex differences in allocentric performance and hippocampal BOLD. Specifically, relative to females, males were found to make fewer errors in the allocentric condition and to exhibit a generally greater negative BOLD signal in the right hippocampus. This finding therefore indicates that a group of good allocentric performers coincidentally also showed greater negative BOLD signal in the right hippocampus. However, in the absence of any direct

relationship between hippocampal BOLD signal and performance in the NGT, it can only be concluded that the hippocampal involvement in the allocentric condition appears to be independent of individual performance.

5.4.5 The NGT-R in the scanner

In addition to the brain imaging results, it was important to consider how behavioural performance in the NGT-R inside the scanner compared to performance produced outside the scanner. The behavioural analysis revealed a significant interaction between condition and task context, which reflected non-significant trends of lower error rates in the egocentric condition and higher error rates in the allocentric condition when the NGT-R was performed inside of the scanner. One potential explanation for the trending effect in the egocentric condition could involve the fixed head position of participants in the scanner. Specifically, the stable head position may have reduced the need for remapping between the retinotopic representation and the head-centred representation of the target location. Considering that the absolute location of the target location remains the same after the delay in the egocentric condition, the gain resulting from a stable head position is likely to have been greater in this condition. The trend towards higher error rates in the allocentric condition could be the result of the way in which the NGT-R was presented in the scanner. Specifically, the task was projected onto a large screen outside of the bore of the scanner and was viewed through a pair of binoculars fitted inside of the coil. Relative to presentation of the task on a standard computer screen at close distance, the viewing conditions in the scanner may therefore have been affected. Since spatial relationships require more interpretation in the allocentric condition, such a limitation would be expected to have a greater effect in this condition.

With the exception of such non-significant trends in terms of error rates, the NGT-R was performed in an equivalent way in the scanner as outside the scanner. Thus, it can be concluded that the NGT-R produces comparable results inside as outside the scanner, which provides further support for the usability of the task.

Part II

Depression and Hippocampal Function

Chapter 6 Background (Part II)

Part I of the present project demonstrated that the NGT-R can be used reliably in young and middle-aged samples and that a contrast of the experimental conditions of the task reveals reliable differential hippocampal involvement in a neuroimaging context. In Part II of the project, the aim was to evaluate the potential use of the NGT-R as a measure of hippocampal function in clinical populations. Given the proposed role of the hippocampus in the pathophysiology of major depressive disorder (MDD; (Sapolsky *et al.*, 1986; Sahay and Hen, 2007; Palazidou, 2012)), depressed patients represented the clinical population of interest. In this chapter, after a general introduction of MDD, a thorough background of hippocampal volume, hippocampus-relevant cognition and hippocampal function in the disorder will be provided.

6.1 Major depressive disorder

The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (APA, 1994) characterizes MDD in terms of affective symptoms such as depressed mood, a loss of pleasure and interest, and feelings of worthlessness and guilt, but also in terms of observable symptoms, such as weight gain or loss, hypersomnia or insomnia, psychomotor agitation or retardation and fatigue. Further to this and in particular interest for the present project, depression is also characterised by cognitive symptoms, which are defined diagnostically as a reduced ability to concentrate and making decisions. Such cognitive symptoms represent a significant determinant of social and occupational functioning in depression and are likely to play an important role in functional recovery following remission of affective symptoms (Jaeger *et al.*, 2006; Hasselbalch *et al.*, 2011).

The importance of increasing the understanding of the symptoms of depression and their respective causes cannot be understated. Among the mental disorders, depression represents the most common with a lifetime prevalence of 5 to 25%, with women being affected more frequently than men to a ratio of 2:1 (Kessler, 2003). Among all diseases it is ranked as the fourth leading cause of burden and is expected to show a rising trend in coming years (WHO, 2001). The onset of depression can happen at any time in life (Fava and Kendler, 2000) and the severity of the symptoms can vary greatly. Depression also tends to be a recurrent disorder with more than half of patients experiencing a second episode following

recovery from a first episode (Kupfer, 1991). Following the second and third episode, the risk of further relapses increases to 70% and 90%, respectively (Kupfer, 1991) with around 12% of patients experiencing a chronic disorder without interleaving asymptomatic periods (Keller, 1992). The recurrent and debilitating nature of the symptoms of depression therefore warrants an effort to understand and ultimately prevent its causes.

One approach to increase our understanding of depression is to explore the neural underpinnings of the symptoms associated with the disorder. Given the complexity of the course and expression of MDD, the neural basis of the disorder can only be assumed to be equally complex (Palazidou, 2012). As such, Experiment 7 only focused on a small part of the proposed neural basis, namely the consistently reported structural abnormalities of the hippocampus and how this may translate into hippocampal dysfunction and spatial memory deficits (Campbell and MacQueen, 2004; Koolschijn *et al.*, 2009).

6.2 Hippocampal structure

6.2.1 Introduction

It is well established that depression is associated with structural brain abnormalities. In a meta-analysis of 64 MRI studies, including 2418 depressed patients and 1974 control participants, Koolschijn *et al.* (2009) concluded that patients consistently showed volume reductions in frontal regions, the hippocampus, putamen and caudate nucleus. A consistent bilateral reduction of the hippocampus was confirmed in a recent meta-analysis incorporating 4118 depressed patients (Arnone *et al.*, 2012). Earlier meta-analyses of hippocampal volume in MDD reached the same conclusion and estimated the reduction to 8% in the left hippocampus and 10% in the right hippocampus (Campbell and MacQueen, 2004; Videbech and Ravnkilde, 2004).

More detailed investigations have indicated that all subsections of the hippocampus may not be similarly affected in depression. Structural reductions and shape abnormalities have been shown to be more prominent in the posterior compared to the anterior hippocampus (Neumeister *et al.*, 2005; Maller *et al.*, 2007; Cole *et al.*, 2010) and in the CA1 subfield compared to the CA2 and CA3 subfields (Cho *et al.*, 2010; Cole *et al.*, 2010). In a post-mortem study of depressed patients, Stockmeier *et al.* (2004) found evidence of increased

density of pyramidal neurons and glial cells in all subfields and a reduction of neural size, which could provide an account for the volumetric changes demonstrated in the MR studies.

An interesting contrast to the volumetric reduction of the posterior hippocampus in depression (Neumeister *et al.*, 2005; Maller *et al.*, 2007; Cole *et al.*, 2010) is the volumetric *increase* of the same subsection of the hippocampus in London taxi drivers (Maguire *et al.*, 2000). London taxi drivers undergo extensive training to learn the complex route network and are required to navigate flexibly between goal locations on a daily basis, supporting the importance of hippocampal volume for spatial behaviour. A similar volumetric increase is not present bus drivers, however, which suggests that navigation along a constrained set of routes is not sufficient to alter hippocampal volume (Maguire *et al.*, 2006a; Maguire *et al.*, 2006b). Given that an increased posterior hippocampus appears to allow London taxi drivers to represent and make use of an extensive allocentric map, it can therefore be proposed that a volumetric reduction of the same region may alter the way that depressed patients represent space in memory.

In depression, a hyperactive hypothalamic-pituitary-adrenal (HPA) axis is often proposed as the pathophysiological mechanism underlying the changes in hippocampal volume (Pariante and Lightman, 2008). Specifically, a disruption of the negative feedback loop of the HPA axis is thought to lead to elevated cortisol levels (Nelson and Davis, 1997; Vreeburg *et al.*, 2009), which in turn has a particularly toxic effect on the hippocampus (Sapolsky *et al.*, 1986). In a recent review, Palazidou (2012) highlighted that several additional factors, such as reduced levels of brain-derived neurotrophic factor (BDNF), reduced noradrenergic and serotonergic neurotransmission and a hyperactive inflammatory response system, are likely to reflect important pathophysiological mechanisms that also influence hippocampal volume in depression. Consistent with a relatively greater influence of mechanisms other than an abnormal HPA axis, O'Brien (2004) found no relationship between hippocampal volume reductions and level of hypercortisolemia in older depressed patients. Furthermore, although hippocampal volume in depression is likely to have a genetic basis, it is also likely to be affected by environmental stressors, such as early trauma and major life events (Vythilingam *et al.*, 2002; Kronmuller *et al.*, 2009; Chen *et al.*, 2010). The causes of the changes in hippocampal volume in depression can therefore be assumed to be complex. For the purposes of the present study, however, the causes of the

hippocampal abnormality are of less relevance than the functional consequences of such changes.

In summary, a reduction of hippocampal volume represents one of the most consistently reported structural abnormalities in MDD. In order to understand the nature of the hippocampal reduction in the disorder, it is important to explore whether it appears to be the result of an accumulative scarring of illness processes or whether it represents a marker of risk preceding and predisposing to depression. To achieve this, the following review will focus on how hippocampal volume changes as the depressive illness progresses.

6.2.2 Recurrent, long-lasting and severe depression

If mechanisms associated with the illness have an accumulative toxic effect on hippocampal volume (Fossati *et al.*, 2004), longer illness duration should be associated with smaller hippocampi. In support of this prediction, MacQueen *et al.* (2003) demonstrated that patients with multiple episodes had smaller hippocampi than first-episode patients and that only the former group differed significantly from control participants. This pattern of results was confirmed in a subsequent meta-regression analysis, in which the total number of episodes was found to correlate inversely with right hippocampal volume (Videbech and Ravnkilde, 2004). However, it is also worth noting that multi-episode patients do not always exhibit smaller hippocampi than first-episode patients and control participants (Vythilingam *et al.*, 2004).

In terms of the total illness duration across depressive episodes, an inverse correlation has been found with hippocampal volume in samples of depressed patients in remission (Sheline *et al.*, 1996; Sheline *et al.*, 1999). More recently, Sheline *et al.* (2003) found that the duration during which the depressive episodes went untreated was associated with reductions in hippocampal volume in a sample of recurrently depressed patients currently in remission. Consistent with this, Caetano *et al.* (2004) found an inverse correlation between length of untreated illness and hippocampal volume. Similarly, Colla *et al.* (2007) demonstrated an association between illness duration and reduced hippocampal volume in a sample of symptomatic depressed inpatients. However, as in the case of the number of episodes, longer total illness duration has not always been associated with smaller hippocampal volumes (Vythilingam *et al.*, 2004; Neumeister *et al.*, 2005).

Further to the effect of the number of episodes and illness duration, smaller hippocampal volumes also appear to be associated with greater severity of symptoms. In a large recent meta-regression analysis, Arnone *et al.* (2012) found that depressive mood state at the time of testing was the only significant clinical predictor of hippocampal volume. In the study by Vakili *et al.* (2000), depressed patients were found to have equal hippocampal volume to control participants but that left hippocampal volume correlated inversely with depression severity. Similarly, Weniger *et al.* (2006) found that smaller left hippocampal volumes were associated with higher anxiety scores. Such evidence appears to suggest that severity as well as the duration of symptoms influence alterations of hippocampal volume in depression.

Consistent with the effect of illness duration on hippocampal volume in depression, McKinnon *et al.* (2009) found in a meta-analysis of 32 MRI studies that the reduction was limited to patient who had been depressed for longer than two years or who had experienced more than one depressive episode. Furthermore, when the analysis was limited to young adult patients, no difference in hippocampal volume was detected. Similarly, Eker and Gonul (2010) concluded in a qualitative review that patients with a mean age older than 40 years and samples consisting of patients who had severe or multiple episodes were more likely to demonstrate smaller hippocampal volumes. Thus, hippocampal reductions may be more prominent in older patient samples, as well as in patients with a longer and more severe illness history.

6.2.3 1st episode depression and premorbid risk

The above evidence appears to suggest a hippocampal reduction is only a feature in recurrent, more long-lasting and more severe cases of depression, indicating that they occur as a result of the accumulative effect of the state of the illness. In contrast to such a conclusion, hippocampal volume reductions have been demonstrated in an early stage of the illness. In a meta-analysis of seven studies of first-episode depression, Cole *et al.* (2011) concluded that patients exhibited an approximate 4% bilateral reduction of the hippocampus relative to control participants. Similarly, Zou *et al.* (2010) demonstrated reduced hippocampal volume in a sample of first-episode drug naïve patients. The occurrence of hippocampal reduction at such an early stage of illness indicates that it is not

simply a "scar" of depression but that it may reflect a marker of risk for depression (Cole *et al.*, 2011).

Evidence in support of a pre-dispositionary role of a small hippocampal volume has also been found in studies investigating healthy participants who are at high risk of developing depression from having a first-degree relative suffering from the disorder (e.g. Williamson, 2004). Chen *et al.* (2010) investigated 55 healthy girls, 23 of who were daughters of mothers with recurrent depression. Voxel-based morphometry revealed that daughters of depressed mothers exhibited reduced hippocampal grey matter bilaterally relative to low-risk control participants, indicating that hippocampal reductions may be present even before the onset of depressive illness. Similarly, Amico *et al.* (2011) found smaller hippocampal volume in healthy relatives of depressed patients when compared to control participants without a family history of psychiatric illness. Furthermore, Baare *et al.* (2010) found that twins who had a depressed co-twin (high-risk) had smaller hippocampal volumes than twins who had no first-degree family history of major psychiatric disorder (low-risk). Thus, it appears as if hippocampal reductions can occur before illness onset, as well as early in the illness course, indicating its potential as a trait marker of depression.

6.2.4 Treatment response and remission

Further to the evidence indicating that hippocampal volume may be important as a risk factor for developing depression, recent investigations have shown that it may also be important in determining the subsequent course of the illness. Frodl *et al.* (2008) followed patients with recurrent depression over three years and found that patients with small hippocampi at baseline demonstrated a worse clinical outcome, as indicated by yearly HAM-D scores, compared to patients with large hippocampi. Small hippocampal volume at baseline was furthermore associated with a greater number of relapses over the three years. There was also no evidence of volume decline during the depressive episodes, indicating a relative stability of hippocampal volume in depression over time. However, hippocampal volume at baseline did not appear to predict full remission. This last null finding was in contrast to an earlier study in which depressed patients who had smaller hippocampal volume at baseline were less likely to be remitted from an episode of depression one year after discharge (Frodl *et al.*, 2004). Similarly, MacQueen *et al.* (2008) demonstrated that patients who remitted after eight weeks of treatment had larger hippocampal volume at

baseline than patients who did not achieve remission. Furthermore, a subdivision of the hippocampus in this study revealed that the finding was accounted for by variation in the volume of the body and the tail of the hippocampus and not of the hippocampal head. Taken together, such evidence supports a role of the hippocampus not just as a risk factor but also as a predictor of clinical outcome in depression.

It is important to note that although hippocampal reductions in depression compared to control participants may occasionally persist in remission (Sheline *et al.*, 1996), this is not always the case. In an longitudinal study, Ahdidan *et al.* (2011) found that the reduction of the right hippocampus that was present when patients were depressed did not remain in patients who had achieved remission 11 years later. Similarly, Hviid *et al.* (2010) found no evidence of hippocampal abnormalities in a sample of remitted depressed patients in an 8-year follow-up study. In a cross-sectional study of medication naïve patients, Caetano *et al.* (2004) found that currently depressed patients had smaller hippocampal volumes than remitted patients. This apparent restoration of hippocampal volume in remission may be indicative of 'healing' following removal of the neurotoxic effect of the illness (Fossati *et al.*, 2004) or of neuroprotective effects of the factors leading to remission of symptoms. Treatment with antidepressant medication may represent one such neuroprotective factor.

The negative relationship between the duration of untreated depression and smaller hippocampal volume indicates the presence of a neurotoxic effect on the hippocampus in the absence of treatment (Sheline *et al.*, 2003; Caetano *et al.*, 2004). Interestingly, continuous treatment may not only protect patients from such neurotoxic effects (Hviid *et al.*, 2010; Ahdidan *et al.*, 2011) but may even have a positive effect on hippocampal volume. Frodl *et al.* (2008) found that a subgroup of depressed patients who had been taking antidepressants over the full three years of the study showed a significant *increase* in left hippocampal volume compared to baseline. In the study by Amico *et al.* (2011), healthy relatives of depressed patients were found to have *smaller* hippocampi than depressed patients, indicating that treatment in the latter group may have influenced hippocampal volume. However, not all evidence speaks to an increase in hippocampal volume following treatment. Vythilingam *et al.* (2004) found no changes in hippocampal volume after an average of seven months successful treatment with selective serotonin re-uptake inhibitors (SSRI). Therefore, although a large preclinical literature implicates the hippocampus as a key target of antidepressant medication (Santarelli *et al.*, 2003), it is unclear if and how this

translates into changes in hippocampal volume (Sahay and Hen, 2007). However, it can be speculated that an increase in hippocampal volume following successful treatment (Frodl *et al.*, 2008) could contribute to the restored hippocampal volume relative to control participants in remission (Ahdidan *et al.*, 2011). An alternative explanation is that patients who achieved remission exhibited larger hippocampi at baseline (MacQueen *et al.*, 2008).

6.3 Hippocampus-relevant cognitive function

6.3.1 Introduction

It is possible that the reduced hippocampal volume in depression can account for some of the cognitive deficits associated with the disorder. Depressed patients demonstrate impairment across a broad range of cognitive domains, including attention, executive function, psychomotor speed and memory (Elliott *et al.*, 1996; Landro *et al.*, 2001; Stordal *et al.*, 2004; Murrough *et al.*, 2011). Unfortunately, however, great heterogeneity between studies has prevented a detailed neuropsychological characterisation of depression to be made (Porter *et al.*, 2007; Beblo *et al.*, 2011). The heterogeneous picture of neuropsychological function in depression is likely to be due to methodological differences as well as complex interactions between patient characteristics, such as the severity and subtype of illness, demographic factors and comorbidities (Porter *et al.*, 2007; Beblo *et al.*, 2011; Hasselbalch *et al.*, 2011). A more focused investigation, in which a specific factor is defined as influencing cognitive performance, has been put forward as a more fruitful approach (Porter *et al.*, 2007; Beblo *et al.*, 2011). In the following review, this specific factor will constitute the volumetric reduction of the hippocampus. As such, focus will be directed towards mnemonic functions and when possible towards the spatial domain specifically. After a brief and general introduction of memory function in depression in this section, the course of the memory deficits as the illness progresses will be explored to provide a potential parallel to the changes in hippocampal volume.

It is generally accepted that depression is associated with memory deficits (Burt 1995; Austin, 2001). Such memory deficits tend to affect the declarative domain, particularly episodic memory, whilst leaving implicit memory intact (Ilsley *et al.*, 1995; Zakzanis *et al.*, 1998; MacQueen *et al.*, 2002). However, the relative effect on mnemonic abilities in the verbal and visuospatial domains remains elusive. Whilst some studies have shown impairments in both domains (Hickie *et al.*, 2005; Hinkelmann *et al.*, 2009), others have

found deficits that are limited to the visuospatial domain (Ravnkilde *et al.*, 2002; Porter *et al.*, 2003) or to the verbal domain (Vythilingam *et al.*, 2004; Thomas, 2009). Furthermore, it should be noted that there are studies that have failed to find memory deficits in either domain (Purcell *et al.*, 1997; Grant *et al.*, 2001). Therefore, as in the literature on neuropsychological function in depression at large, findings relevant to mnemonic abilities in depression appear difficult to reconcile. For the purposes of the present project, it was particularly important to explore whether memory deficits may parallel hippocampal volume reductions in depression. Therefore, as opposed to taking a general approach to memory function in depression, the following review will specifically focus on evaluating at what stages of the illness process memory deficits occur.

6.3.2 Recurrent, long-lasting and severe depression

Similarly to hippocampal reductions, memory impairments in depression tend to be more prominent in more severe and recurrent variations of depression. MacQueen *et al.* (2002) found that the number of depressive episodes correlated inversely with performance in an associative verbal memory task in a sample of currently depressed and remitted patients. In a large study comprising over 8000 depressed outpatients, Gorwood *et al.* (2008) used the delayed paragraph recall index from the Wechsler Memory Scale (Wechsler, 1981) to assess verbal declarative memory. The number of correct delayed recall responses was found to correlate with both depression severity and the number of past depressive episodes. However, in a structural equation modelling analysis, path coefficients were substantially higher for past depressive episodes than for mood at the time of testing, indicating that past illness burden was more important than current symptomatology. Furthermore, the decline in memory performance as the illness progressed could be estimated to occur at a rate of 2-3% for each previous episode. However, it is worth noting that first-episode patients do not always outperform patients who have had multiple episodes in memory tasks (Wang *et al.*, 2006).

In terms of depression severity, Elderkin-Thompson *et al.* (2003) compared cognitive performance of MDD patients with patients with minor depression (APA, 1994). Out of the range of cognitive measures, tasks loading on components of verbal recall and maintenance of set separated MDD patients from patients with minor depression. Interestingly, the non-verbal component, which required patients to recognize complex designs after a delay, did

not separate the groups from each other or from the control group. Elliott *et al.* (1996) found significant correlations between depression severity and performance in pattern recognition, delayed-match-to-sample and spatial span. Similarly, in the study by Porter *et al.* (2003), depression severity was found to be associated with impaired verbal and visuospatial learning and memory performance. Furthermore, Austin *et al.* (1999) found that melancholic patients were more impaired than non-melancholic patients relative to a control group in tests of spatial and verbal memory, although both groups differed significantly from the control group. Of direct relevance to the present project, Gould *et al.* (2007) tested a mixed sample of currently depressed patients with a diagnosis of MDD or bipolar disorder in a virtual navigation task, which had previously been shown to involve the hippocampus (Maguire *et al.*, 1998a). In addition to a general impairment in the navigation task in the patient group, depression severity was found to correlate inversely with the number of locations found in the task. Taken together, it appears that whilst memory impairments in general appear to get worse as the severity of the illness worsens, the relative effect on spatial and verbal memory is not yet clear (McClintock *et al.*, 2010).

In summary, it appears as if memory deficits in depression are more severe in patients who have experienced more depressive episodes (MacQueen *et al.*, 2002; Gorwood *et al.*, 2008), and in patients who are experiencing more severe depressive symptoms (Elliott *et al.*, 1996; Austin *et al.*, 1999; Porter *et al.*, 2003).

6.3.3 1st episode depression and premorbid risk

Although neuropsychological impairments appear to become more prominent as illness severity and duration increase, memory deficits also seem to occur at an early stage of the illness. In a recent meta-analysis of 15 independent samples of first-episode depression, Lee *et al.* (2012b) found evidence of impairment in several cognitive domains. Pooled effect sizes revealed that first-episode patients performed worse relative to control participants in visual but not verbal memory tasks. It is therefore evident that memory deficits can occur at an early stage of the illness, contradicting that such deficits are the sole consequence of accumulative effects of the disease process.

Extending the findings above, other studies have indicated that memory deficits may even pre-date the onset of the illness. In the study by Mannie *et al.* (2009), healthy young women with a familial risk of depression were found to have impaired verbal learning and memory

relative to control participants without such familial risk. Similarly, Christensen *et al.* (2006) found widespread cognitive impairment, including declarative memory deficits, in healthy twins with a co-twin with depression when compared to twins without such familial risk. Furthermore, memory performance in healthy individuals has been found to predict later development of depression. In a population-based sample of non-depressed individuals, poor performance in an immediate verbal recall task was found to be a reliable predictor for the development of depression three years later (Airaksinen *et al.*, 2007). Similarly, in a separate population-based study, poor performance in the Rey Auditory Verbal Learning Test (RAVLT; (Spreen, 1998)) was found to predict subclinical depressive symptoms over a two-year follow-up period (Simons *et al.*, 2009). Thus, although the memory deficit appears to be worsened by the state of depression, it appears that memory impairments in depression can precede illness onset and serve as a premorbid trait marker.

6.3.4 Treatment response and remission

As opposed to predicting response to treatment in depression, memory impairments have been shown to improve in parallel with depressive symptoms. Peselow *et al.* (1991) found that changes in performance in a set of difficult memory tasks following treatment with imipramine for four weeks correlated with improvement of depressive symptoms. Similarly, Biringer *et al.* (2007) found in a two-year follow-up study that remission of depressive symptoms was accompanied by an improvement in verbal memory function. In contrast, visual memory function remained the same at follow-up and did not change with improvement in depressive symptoms. In a six-month follow-up study, Gallagher *et al.* (2007) similarly found a greater improvement in verbal memory in remitted compared to non-remitted patients.

The persistence of memory impairments following remission of depressive symptoms has received mixed support. In a review, Hasselbalch *et al.* (2011) highlighted that there has been great variability in the criteria used to establish remission and concluded that although several studies have demonstrated neuropsychological impairments in remission, it is difficult to draw any conclusions in regards to specific cognitive domains. As a reflection of this, some studies have demonstrated a persistent memory deficit in remission (Sheline *et al.*, 1999; Preiss *et al.*, 2009) whilst others have found evidence of normalised memory performance when depressive symptoms have resolved (Clark *et al.*, 2005; Hviid *et al.*,

2010). Since the level of residual symptoms differed between the studies, it remains unclear whether memory deficits would reliably resolve if complete remission was to be ensured.

6.4 Hippocampal function

Despite the large number of anatomic MR studies and neuropsychological investigations using hippocampus-relevant tasks, few studies have investigated hippocampal function directly in depression using functional imaging. Milne *et al.* (2012) recently highlighted this as a "striking paucity of research using functional imaging methods to study hippocampal function in patients with MDD" ((Milne *et al.*, 2012), p 28). Below, I describe the small set of studies that have investigated hippocampal function in depression.

In an early PET study, Videbech *et al.* (2002) investigated resting blood flow in 42 inpatients with depression. Relative to matched control participants depressed patients were found to have increased blood flow to the hippocampus, in addition to the cerebellum, anterior cingulate gyrus and the basal ganglia. A comparable task-related increase in blood flow to the hippocampus was demonstrated in a PET study of 18 severely depressed patients (Bremner *et al.*, 2004). In a verbal encoding task, participants listened to a paragraph and were instructed to form a mental image of the scene and to remember it. In a control condition, participants recalled words that had been implicitly presented prior to scanning. Relative to control participants, depressed patients showed a greater increase in blood flow in the hippocampus bilaterally during encoding compared to the control task. However, no behavioural difference was found between the two groups in the task.

Werner *et al.* (2009) used fMRI to investigate hippocampal function during associative encoding and retrieval in eleven mildly to moderately depressed patients. At encoding, participants learned associations between faces and professions or simply watched face silhouettes in a control condition. At retrieval, participants retrieved the profession in response to the presented faces or decided which ear was the biggest in the silhouettes. No behavioural difference was found between the patients and the control participants in the associative memory task. Furthermore, no differential activation was found in the hippocampus for any of the contrasts, although depressed patients did show greater activation in the neighbouring left parahippocampal gyrus for the contrast between encoding and the control condition. The authors proposed that the lack of differential activation in the hippocampus could have been due to the mild depression severity or to the

high proportion of medicated patients included in the depressed sample. Furthermore, since no volumetric measures were included in the study, hippocampal volume reductions could not be assessed alongside the functional measures.

Fairhall *et al.* (2010) used fMRI to test eight young patients with mild to moderate depression and matched control participants in an associative encoding task. Participants encoded face-name pairings whilst being scanned, after which a recall test was completed. Consistent with a previous study (Sperling, 2003), encoding success was associated with bilateral anterior hippocampal activation in the control participants. In contrast, the depressed patients did not show such a relationship. However, there was no main effect of group in the hippocampus. Furthermore, the patients did not differ behaviourally from control participants in the associative memory task.

In a recent fMRI study, Milne *et al.* (2012) tested 22 euthymic patients with at least three previously treated depressive episodes and matched control participants. In a process dissociation task, participants were exposed to word pairs prior to scanning. Frequently presented word pairs engaged habit memory whilst rarely presented word pairs engaged recollection memory, of which only the latter was proposed to be dependent on the hippocampus. Once inside the scanner, participants were presented with a list of the word pairs and were instructed to read and remember them in preparation for a subsequent memory test (control task). At test, participants were shown one of the words in a word pair and a fragment of the second word (e.g. BARN _AR_) and were asked to complete the word fragment verbally. For the contrast between retrieval of recollection items and the encoding control condition, depressed patients were found to show reduced activation in the right hippocampus and the left parahippocampal gyrus relative to the control group. No group differences were found for the contrast between habit items and the control condition, however. Furthermore, consistent with the findings of Fairhall *et al.* (2010), performance for the recollection items was associated with greater activity in the right hippocampus in control participants but not in patients. At a behavioural level, depressed patient were found to be impaired for both recollection and habit word pairs.

In direct relation to the current project, Cornwell *et al.* (2010) used MEG to assess hippocampal function in a virtual version of the MWM in a sample of 19 patients with moderate depressive symptoms. In a hidden platform condition, participants navigated to a

fixed hidden platform from four different start locations. In a control condition, participants navigated to a visible platform that changed location on each trial. Two environments with different distal cues were used for the two conditions to prevent incidental encoding. Relative to control participants, patients were found to take longer paths to the platform in both conditions but to spend longer finding the platform only in the hidden platform condition. Patients were also found to exhibit less oscillatory activity in the right hippocampus and the parahippocampal cortices during goal-directed navigation whilst no such differences were found in the control task. Furthermore, left posterior hippocampal theta activity was positively correlated with navigation performance in both groups.

To summarise, PET investigations have provided evidence of increased regional blood flow to the hippocampus in depression (Videbech *et al.*, 2002; Bremner *et al.*, 2004) whilst fMRI studies have provided mixed findings (Werner *et al.*, 2009; Fairhall *et al.*, 2010; Milne *et al.*, 2012). Taken together with an MEG study, however, there appears to be some indications of a functional abnormality of the right hippocampus in depression (Cornwell *et al.*, 2010; Fairhall *et al.*, 2010; Milne *et al.*, 2012). However, whilst two studies revealed a significant group effect in this region during allocentric navigation and recollection retrieval (Cornwell *et al.*, 2010; Milne *et al.*, 2012), a third study failed to find such a group effect during associative encoding (Fairhall *et al.*, 2010). Furthermore, whilst two studies have revealed a behavioural deficit in the measure used to demonstrate hippocampal dysfunction (Cornwell *et al.*, 2010; Milne *et al.*, 2012) others have not (Bremner *et al.*, 2004; Fairhall *et al.*, 2010). It is also worth mentioning that none of the studies presented have included volumetric measurements of the hippocampus, which arguably complicates an interpretation of the presence or lack of hippocampal dysfunction. Therefore, although neuroimaging investigations have started to explore the possibility of hippocampal dysfunction in depression, the nature of this dysfunction and its relationship with structural abnormalities and cognitive impairments is far from clear.

6.4.1 Summary

In summary, it appears as if structural abnormalities of the hippocampus in depression are particularly prominent in older patient groups with recurrent or more severe depression (McKinnon *et al.*, 2009; Eker and Gonul, 2010). However, hippocampal reductions have also been demonstrated in first-episode depression and in healthy individuals at risk of

developing depression (Chen *et al.*, 2010; Cole *et al.*, 2011), which contradicts proposals that such abnormalities are the sole result of an accumulative toxic effect of the disease process (Fossati *et al.*, 2004). Furthermore, small hippocampal volume at baseline appears to be predictive of subsequent poor clinical outcome (Frodl *et al.*, 2008), although hippocampal volumes may return to normal in remission (Ahdidan *et al.*, 2011). Taken together, it appears as if small hippocampal volume represents a trait marker of depression, which is subsequently exacerbated by the state of a depressive episode. Further to this, antidepressant treatment may modulate the state-effects of depression, protecting it from the otherwise neurotoxic effects (Frodl *et al.*, 2008). Interestingly, it appears as if memory impairments in depression may parallel changes in hippocampal volume. As such, memory impairments appear to be particularly prominent in more severe cases of depression (Gorwood *et al.*, 2008) but also occur early (Lee *et al.*, 2012b) and even before the onset of the illness (Airaksinen *et al.*, 2007). Furthermore, memory impairments appear to improve alongside depressive symptoms following successful treatment and may resolve in remission (Gallagher *et al.*, 2007; Hviid *et al.*, 2010). Although the heterogeneity in the neuropsychological profile of depression should not be underestimated (Beblo *et al.*, 2011), it appears as if memory impairments could potentially be associated with the hippocampal volume reductions of the disorder. Consistent with this, a very limited number of studies have provided indications that hippocampal dysfunction may underlie some of the memory deficits in depression (Cornwell *et al.*, 2010; Milne *et al.*, 2012).

Chapter 7 Experiment 8: The NGT-R in depression

7.1 Predictions

From the background provided in Chapter 6 it is evident that depression has been consistently associated with a volumetric reduction of the hippocampus and cognitive impairments in the memory domain. Importantly, hippocampal abnormalities and mnemonic deficits appear to occur in parallel as the disorder progresses, which support the existence of a link between cognitive symptomology and brain pathology in depression. It can therefore be proposed that the structural abnormalities in the hippocampus translate into a functional deficit in this region, which in turn may account for the reported memory deficits in the disorder.

In Experiment 8, the NGT-R was used to assess hippocampal function in a small sample of depressed patients and sex- and age-matched controls. Following the working hypothesis of Part II of the project, depressed patients were predicted to show evidence of hippocampal dysfunction. At a behavioural level, this was expected to result in a disproportionate deficit in the allocentric condition relative to the egocentric condition in the patient group. At a neural level, hippocampal dysfunction was predicted to be reflected in an abnormal hippocampal engagement for the contrast between the allocentric and egocentric conditions. Specifically, for this contrast, depressed patients were expected to exhibit an attenuated differential signal in the hippocampus relative to matched control participants. Importantly, a replication of the previously demonstrated volumetric reduction of the hippocampus was also predicted for the patient group in Experiment 8.

Both depressed patients and control participants were expected to be more reliant on spatial transformations and landmark information in the allocentric condition relative to the egocentric condition. Consequently, when the two groups were considered together, a greater involvement of the parieto-medial temporal pathway in the allocentric condition relative to the egocentric condition was predicted, consistent with the results of Experiment 7. Similarly, although the differential BOLD signal in the hippocampus was predicted to be attenuated in the patient group, an on average negative hippocampal BOLD signal was expected to emerge in the pooled sample.

Experiment 8 was conducted in collaboration with Lucy Stevens (MPhil student at Newcastle University, supervised by Hamish McAllister-Williams).

7.2 Pilot

To test the general feasibility of using the NGT-R in a depressed population, a small-scale pilot study was conducted as part of a separate protocol. Eight depressed patients, three of who were currently symptomatic and five of who were recovered, were recruited via their consultant psychiatrist and tested in the NGT-R as described in Chapter 4 (section 4.6). Currently depressed patients had a Hamilton Depression Rating Scale (HAM-D; (Williams *et al.*, 2008)) score of 15 or greater and remitted depressed patients had a score of seven or less. As a comparison, ten healthy participants without a personal or family history of psychiatric illness were also tested in the same task. Further inclusion and exclusion criteria for the depressed and the control groups were similar to that of the subsequent study (see section 7.3.1) and can be found in Appendix C. Demographic information and clinical characteristics for the two samples can be found in Table 7-1.

The pilot confirmed that the NGT-R could be administered in a sample of currently symptomatic and remitted depressed patients. Although the small sample sizes prevented any statistical analyses, average error rates and response times indicated that the task was performed appropriately in both groups (Figure 7-1, Figure 7-2). It is worth noting that depressed patients appeared to produce higher error rates than the younger control group

Table 7-1: Demographics and clinical characteristics of the depressed, remitted and control groups of the pilot. HAM-D= Hamilton Depression Rating Scale. NART=National Adult Reading Test. BDI=Beck Depression Inventory.

	Depressed (n=3)	Remitted (n=5)	Control (n=10)
Sex (female/male)	1/2	3/2	7/3
Age (years)	54.0±3.0	45.6±13.9	35.3±6.2
NART	118.7±4.0	117.0±7.2	112.7±7.1
HAM-D 17 (score)	20.7±4.1	3.8±2.4	.50±.53
BDI (score)	29.7±14.7	5.3±3.6	
Number of episodes	2±1.7	3.4±1.3	
Illness duration (years)	17.7±16.1	22.6±16.1	
Age at onset (years)	36.3±16.8	23±8.2	
Number of hospitalisations	2.0±2.0	.60±.90	
Antidepressant (yes/no)	3/0	5/0	

and the similarly aged remitted group in the allocentric condition of the NGT-R (Figure 7-1). The results of the pilot study therefore indicated that the NGT-R presented a viable methodology for testing in the clinical population of interest.

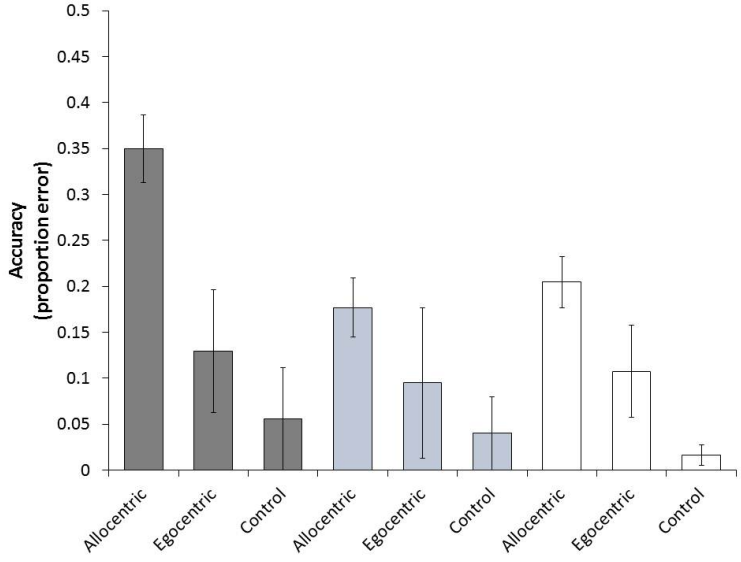

Figure 7-1: Average error rates in the three conditions of the NGT-R in the depressed group (dark grey bars), remitted group (light grey bars) and the control group (unfilled bars).

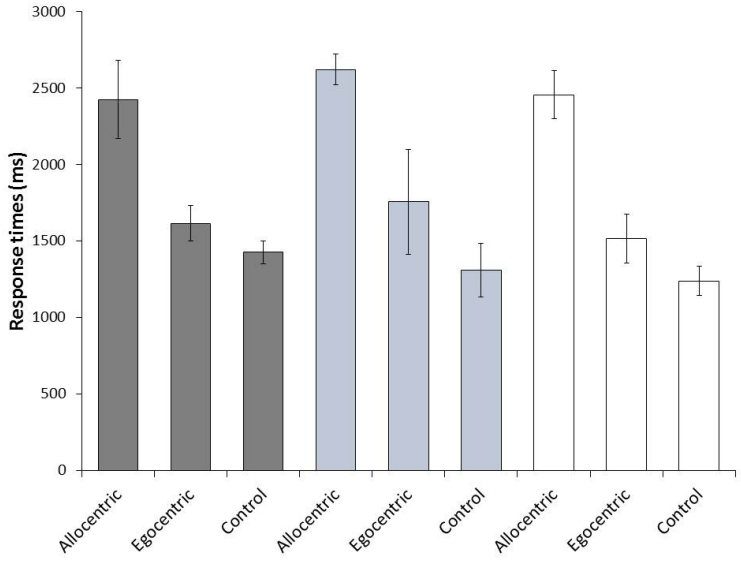

Figure 7-2: Average response times in the three conditions of the NGT-R in the depressed group (dark grey bars), remitted group (light grey bars) and the control group (unfilled bars).

7.3 Methodology

7.3.1 Participants

Patients with a DSM-IV confirmed diagnosis of current major depressive disorder, as assessed by the Mini International Neuropsychiatric Interview (MINI; (Sheehan *et al.*, 1998)), were recruited via their consultant psychiatrists. A total of 41 patients were contacted about the study, of which 24 attended the initial screening session (see Table 7-3). Ten patients were subsequently found to be eligible and completed the study. All patients had a HAM-D score of 16 or greater, as assessed by the GRID HAM-D (Williams *et al.*, 2008). Patient exclusion criteria included the presence of any other DSM-IV Axis 1 disorder other than anxiety disorder considered secondary to a primary diagnosis of depression, present or past electroconvulsive therapy (ECT), a change in psychiatric medication in the last four weeks, dependence or harmful use of alcohol or any other drug in the past 12 months and recent participation in another research study that could affect the results of the current one.

Thirteen healthy volunteers were recruited to act as a comparison to the patient group. Healthy volunteers were recruited mainly via a volunteer pool provided by the Institute of Neuroscience (http://www.ncl.ac.uk/ion/involved/volunteer/) but also via flyers and word of mouth. Exclusion criteria for the healthy volunteers comprised any history of psychiatric illness, as assessed by the MINI, any major physical health problem, one or more first degree relatives with a history of psychiatric illness, dependence or harmful use of alcohol or any other drug in the past 12 months and recent participation in another research study that could affect the results of the current one. Both healthy volunteers and patients had to be right handed, as assessed by the Edinburgh Handedness Inventory (Williams, 1986), and could not have any fMRI contraindications, such as a pacemaker or other metal implants.

Three of the healthy volunteers had to be excluded from analyses due to epilepsy, which was not disclosed until after completion of the study, an incidentally discovered cyst in the right mesial temporal lobe and substantial head motion in the scanner, respectively. Demographic information and clinical characteristics of the control group and the patient groups can be found in Table 7-2. The groups were well matched in terms of sex, age, handedness and pre-morbid intelligence, as assessed by the NART (Nelson, 1982). With one exception, all patients were taking antidepressant medication, of whom seven patients

Table 7-2: Demographics and clinical characteristics of the depressed and control groups of Experiment 8. EHI=Edinburgh Handedness Inventory. NART=National Adult Reading Test. HAM-D=Hamilton Depression Rating Scale. STAI= Spielberg State and Trait Anxiety Inventory * note that data was missing for one patient for the STAI measure and for one patient for the illness duration measure.

	Depressed (n=10)	Control (n=10)	*t*	*p*
Sex (female/male)	3/7	3/7	0	1.00
Age (years)	43.9±14.6 (range=21-59)	43.2±13.4 (range=22-55)	.11	.99
EHI (% right handed)	95±10.5	95±0.83	0	1.00
NART	106.3±11.6	111.3±5.3	-1.24	.23
HAM-D 17 (score)	21.4±5.3	0.30±0.95	12.50	<.001
BDI	35.2±11.9	0.80±0.92	9.10	<.001
STAI state*	52.1±17.1	26.6±6.7	4.37	<.001
STAI trait*	67.4±10.5	26.7±6.3	10.39	<.001
Number of episodes	4.2±3.8			
Illness duration (years)*	7.7±6.7			
Age at onset (years)	29.1±15.0			
Number of hospitalisations	1.8±.4			
Antidepressant (yes/no)	9/1			

were taking one antidepressant and two patients were taking two antidepressants. One patient was taking an anticonvulsant and a benzodiazepine, in addition to antidepressant treatment.

To ensure that the control group of Experiment 8 produced comparable performance in the scanner to what had previously been observed outside of the scanner, the pooled middle-aged sample of Experiment 6 (n=36; see section 4.6.2.1) was used as a comparison group. This comparison allowed an exploration of NGT performance in a middle-aged sample inside and outside of the scanner. The control group of Experiment 8 was marginally younger (M=43.2, SD=13.4) than the pooled middle-aged sample from Experiment 6 (M=49.4, SD=.7.20; $t(44)$=-1.98, p=.054), although the groups did not differ in terms of gender proportions ($t(44)$=.50, p=.62). It should be emphasised, however, that the pooled sample of Experiment 6 completed the NGT *or* the NGT-R, which both differed subtly from the task used in Experiment 8 in terms of the precise timings of events (see section 7.3.3.1). Thus, the pooled sample of Experiment 6 should only be considered a general benchmark against which behavioural performance in Experiment 8 can be compared.

7.3.2 Ethics

The study was approved by the National Research Ethics Service committee (North East, Newcastle and North Tyneside 1; 11/NE/0329, 04/01/2012).

7.3.3 Neurocognitive assessment

The NGT-R was part of a larger and more comprehensive neurocognitive test battery, which included additional measures of spatial memory and perception, verbal memory, executive functioning and psychomotor speed. Although the primary aim of Experiment 8 was to investigate hippocampal function in depression, the inclusion of the additional measures was important for an evaluation of any potential deficits detected in the NGT-R. In particular, a measure of mental rotation was included to evaluate whether an inability to mentally rotate objects could account for a potential deficit in the allocentric condition of the NGT-R. Further to this, the inclusion of measures of short-term memory for visual patterns and for object locations was important to explore whether a potential deficit was general to spatial short-term memory or specific to the demands of the NGT-R. Similarly, the assessment of verbal memory was important in determining whether any potential deficits were specific to the spatial domain. Finally, since impairments in executive functioning and psychomotor speed are likely to influence performance in the majority of cognitive tasks, the inclusion of such measures was justified. The tasks included in the test battery of Experiment 8 are described in more detail below.

7.3.3.1 Spatial memory and cognition

NGT-R

The NGT-R represented the primary neuropsychological test in the test protocol for Experiment 8. This was also the only task in the test protocol that was performed in the MR scanner. The task was administered as described in Experiment 7 with the exception of some minor changes that were implemented to optimise it for use in a clinical sample. Based on the findings in Experiment 6 (section 4.6.3.2), middle-aged control participants can be expected to take longer to respond in all conditions of the NGT-R compared to the young sample scanned in Experiment 7. Furthermore, previous research has provided evidence of reduced psychomotor speed in depressed samples (Ilsley *et al.*, 1995). Although no indications of such psychomotor speed impairments were indicated in the pilot

study (section 7.2), the likelihood of longer response times in the depressed sample emphasised the potential limitation of the 3.5 seconds response window used in Experiment 7. Consequently, to minimise the number of non-response trials, the response window was increased from 3.5 seconds to 5.0 seconds. To keep the timing of the task and the total length of each trial consistent with Experiment 7, the length of the delay was reduced from 4.75 seconds to 3.75 seconds and the two screens of the empty arena, which were previously shown before the pole appeared (0.25s) and before the response options appeared (0.25s), were excluded.

Following a trend towards significantly higher error rates when the NGT-R was performed inside compared to outside of the scanner (section 5.3.1.1), a further change relative to Experiment 7 involved the viewing conditions in the scanner. Instead of projecting the task on a screen outside of the scanner, the task was projected on a screen placed inside of the scanner at the head-end of the bore. Consequently, the size of the projection and the distance at which it was viewed was comparable to administration on a standard computer monitor. Furthermore, since the size of the projection no longer required magnification, the use of binoculars could be abandoned for Experiment 8.

With the exception of the slight modifications to the timings of the NGT-R and the way in which it was projected in the scanner, the procedure and administration of the task was identical to that of Experiment 7, including the preceding training.

Mental rotation

In the classic mental rotation task (Shepard and Metzler, 1971), participants are shown two 3D shapes and are required to determine whether the shapes are the same or mirror images. When the two shapes are presented in different orientations, one shape has to be 'mentally rotated' to arrive at a response. A specifically designed version of the mental rotation task was developed for Experiment 8 by Andreas Finkelmeyer (Institute of Neuroscience, Newcastle University). In this task, referred to as the disc rotation task, participants had to determine whether the symbols on two circular discs were the same or different as quickly and as accurately as possible (Figure 7-3). The symbols were based on the shapes used by Hochberg and Gellman (1977). In half of the 108 trials one of the discs was rotated and in the other half the two discs had the same orientation. Only in the former type of trial was a mental rotation process required, which was assumed to occur in the same plane as any

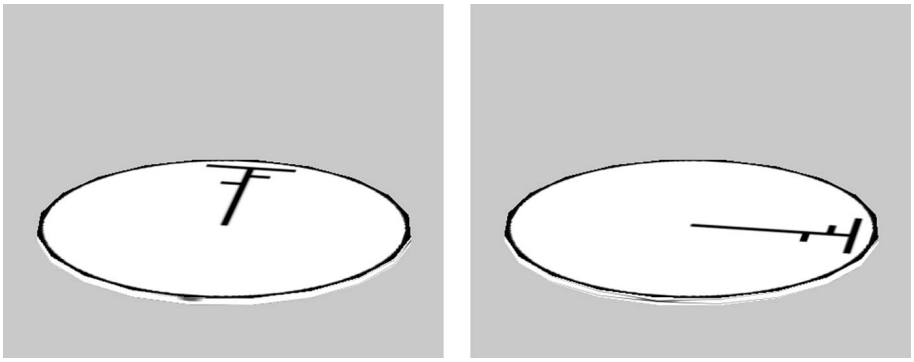

Figure 7-3: Example trial of the disc rotation task developed for Experiment 8. Note that this example trial required a 90° mental rotation of one of the discs to arrive at the correct answer (i.e. 'different').

equivalent process in the NGT. Similarly to the NGT, the disc rotation task involved different angles of rotation for the rotated trials (45°, 90°, 135°). The disc rotation task was piloted in a small sample of healthy volunteer prior to Experiment 8. Accuracy and response times were measured.

Visual Patterns Test

The Visual Patterns Test (VPT; (Della Sala, 1997)) was used to assess participants' short-term memory for visual patterns. In this task, participants were shown visual matrix patterns for two seconds and were then required to reproduce each pattern on an empty matrix after a short delay. The matrix patterns progressively increased in size with three trials for each size and difficulty level. The final score on the task constituted the last level at which all three trials were correct.

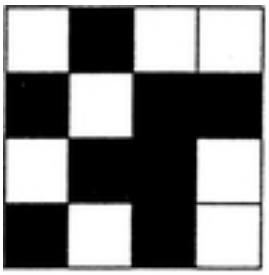

Figure 7-4: Example matrix pattern for the Visual Patterns Test.

Object location memory task

The object-location memory (OLM; Figure 7-5) task was developed to separate between three distinct processing mechanisms relevant to spatial memory: object processing, spatial-location processing and object-to-location binding (Kessels *et al.*, 1999). In this task, participants were presented with a square frame containing 10 objects for 30 seconds on a

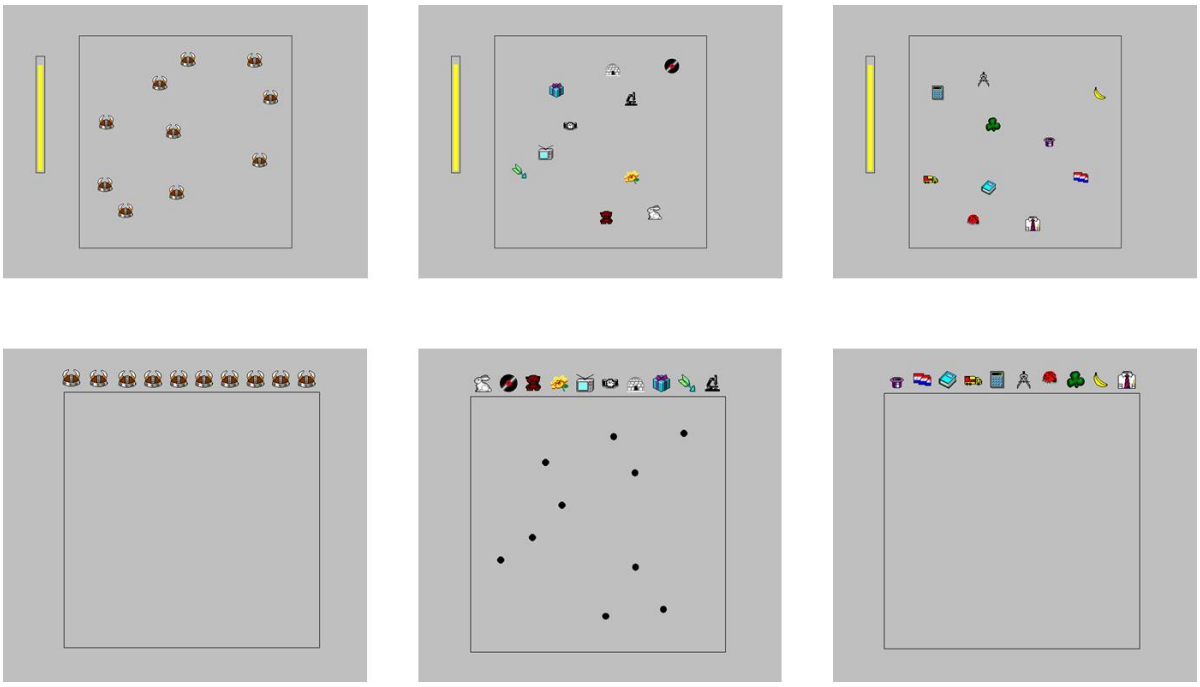

Figure 7-5: The presentation phase (top) and the test phase (bottom) of the object-location memory task. Left: position only condition. Middle: object-to-location binding condition. Right: combined condition.

computer monitor. Subsequently, the objects disappeared and reappeared in a random order on a row above the square frame. In the position only condition, all objects were the same and at recall participants were required to relocate the objects to their exact positions. In the object-to-location binding condition, all objects were different and at recall participants were required to relocate the objects to their previous positions, which were indicated by black markers in this condition. In a final experimental condition, the two processes were combined and participants were asked to relocate ten different objects without marked positions. Performance in the position only and combined conditions was measured in terms of displacement error. Performance in the object-location binding condition was measured in the number of objects that were correctly placed on their respective marker.

The object-location memory task also included two control conditions. In the first control condition, the object memory condition, memory for object identity was tested without any demands on memory for location. Performance was measured in terms of the number of objects correctly identified as having been seen previously. In the second control condition, the visuospatial reconstruction condition, perceptual precision was tested by asking participants to reconstruct the configuration of objects whilst it was still visible on the other

side of the screen. Each condition of the OLM task included two trials, which was preceded by a less demanding practice trial.

Newcastle Spatial Working Memory task

The Newcastle Spatial Working Memory (NSWM) task was designed by Dr Peter Gallagher (Institute of Neuroscience, Newcastle University) and constructed by Daniel Jackson (Newcastle Informatics Centre, Newcastle University) to function as an adapted version of the CANTAB (Cambridge Automated Neuropsychological Test Battery) Spatial Working Memory task. Subjects were required to search marked spatial locations for hidden tokens. The essential rule of the task was that once a token had been found in a particular location, a token would not be placed there again. There was always the same number of tokens to be found as there were marked spatial locations, starting with 4 marked locations and progressing to 12 locations. Two types of errors where measured: between-search errors, which constituted returning to a location in which a token had already been found, and within-search errors, which constituted returning to a location which had already been found to be empty in the same search. There was a 2D and a 3D version of the task. The 2D version displayed uniformly coloured circles to mark the spatial locations whilst the 3D version displayed upturned cups on a surface. The NSWM represented the primary task of interest for the MPhil project of Lucy Stevens.

Verbal memory

The Rey Auditory Verbal Learning Test (RAVLT; (Rey, 1964)) was used to assess verbal learning and immediate and delayed verbal memory. In this task participants were required to repeat a list of 15 aurally presented words immediately after presentation (A1). This procedure was repeated for the same list another four times (A2-A5). Subsequently, participants were presented with a second list, which also had to be repeated immediately after presentation (B), after which they were required to recall the first list again (A6, immediate recall). After an approximate delay of 20 minutes, participants were asked to recall the first list once more. In the subsequent recognition test, participants were presented with a list that contained words from the first and second lists and words that had not been presented before. For each word that was read out from the list, participants were required to determine whether it had been presented previously and if so whether it had been presented as part of the first list. Following inconsistencies in the administration of

this task, only the measures acquired before the 20-minute delay were included in the analysis.

Executive function

Three tasks were selected to capture three subcomponents of executive functioning (Miyake *et al.*, 2000). The backward digit span from the WAIS-R (Wechsler, 1981), in which participants were required to repeat a random series of aurally presented digits in reverse order, was used to assess the updating component of executive function. The number of digits in each string increased as the task progressed with two trials for each string length. Memory span was defined as the longest string length at which participants answered correctly on both trials.

The Stroop Neuropsychological Screening Test (Trenerry, 1989) was used to assess the inhibition component of executive function. In the incongruent condition of this task, interference was created between word reading and colour reading by presenting participants with names of colours that were printed in a different colour than the word itself denoted (e.g. green). By asking participants to name the colour of the ink, the habit of reading the word itself had to be inhibited. The task also included two control conditions, one in which participants were required to read colour words printed in black ink (e.g. green) and one in which they had to name the colour of crosses (e.g. XXXX). Response time was recorded for all conditions. The difference in response time between the incongruent condition and the colour naming condition constituted the measure of interference for this task.

Finally, Trail Making Part B (Reiten, 1958) was used to assess the set shifting component of executive functioning. In this task participants were required to connect a series of numbers and letters in ascending numerical and alphabetical order respectively, alternating between numbers and letters, as quickly as possible. Time taken to complete the task was measured.

Psychomotor function

In the Trail Making Part A task (Reiten, 1958) participants were required to connect a series of numbers in ascending order as quickly as possible. Time taken to complete the task was measured.

Table 7-3: Order of administration of the measures of Experiment 8. * completed in the scanner.

Screening	National Adult Reading Test
	Edinburgh Handedness Inventory
	Mini International Neuropsychiatric Interview (patients only)
	Illness history (patients only)
	Hamilton Depression Rating Scale
Questionnaires	Santa Barbara Sense of Direction Scale
	Beck Depression Inventory
	Spielberg State and Trait Anxiety Inventory
Neuropsych. Session 1	Rey Auditory Verbal Learning Test - Immediate
	Object Location Memory task
	Rey Auditory Verbal Learning Test - Delayed
	Newcastle Spatial Working Memory Task
	Disc Rotation Task
	Trail Making Test (A, B)
	Digit Span (forward, reverse)
	Stroop Test
	Visual Patterns Test
Neuropsych. Session 2	NGT Training
	NGT-R*
	NGT Experience Questionnaire

7.3.4 Questionnaires

The Santa Barbara Sense of Direction Scale (SBSOD; (Hegarty *et al.*, 2002)) was used to assess self-reported spatial awareness. The inclusion of this questionnaire was important to explore whether any potential spatial memory deficit was perceivable by patients in their every-day lives. The Spielberg State and Trait Anxiety Inventory Form Y (STAI; (Spielberger *et al.*, 1970) was be used to measure the nature of any anxiety present and the Beck Depression Inventory II (BDI; (Beck *et al.*, 1996)) provided a self-reported measure of depression severity. In addition, generic questions about illness duration and number of previous episodes were posed to the patient group.

7.3.5 Procedure

Total participation in Experiment 8 lasted approximately 4.5 hours (excluding breaks). The study was divided into three parts: screening and questionnaires (1 hour 30 minutes), a first session of neurocognitive testing (1 hour 40 minutes) and a second session of neurocognitive testing (1 hour 30 minutes, Table 7-3). The three sessions could be

completed in one or two visits, depending on participant preferences. In the case of two visits, the second visit was always completed within a week of the first. The administration order in Table 7-3 was generally adhered to, although deviation from this order was occasionally required. Specifically, the availability of the MR scanner occasionally meant that parts of the first session of cognitive testing had to be completed after the second session. To avoid any potential training effects carrying over from the disc rotation task to the primary task, the disc rotation task was always completed after the NGT-R in such cases.

7.3.6 Image acquisition

Image acquisition for Experiment 8 was identical to that of Experiment 7 (section 5.2.3).

7.3.7 fMRI pre-processing and analysis

7.3.7.1 Whole-brain analyses

Pre-processing stages and the first level model were identical to that of Experiment 7 (section 5.2.4). The initial whole-brain analysis focused on replicating the engagement of the parieto-medial temporal pathway in the allocentric condition in the response phase in the combined sample. As in Experiment 7, the analysis included the contrasts for the response phase of the three conditions (Allocentric, Egocentric, Control), along with a subject variable. To explore any potential effects of group in the response phase at the whole-brain level, an additional and otherwise identical whole-brain analysis was conducted for the response phase, in which the depressed group was distinguished from the control group. The presentation phase was not considered in the analysis of Experiment 8.

7.3.7.2 Region of interest analysis

In direct relevance to the predictions of Experiment 8, a region of interest (ROI) analysis of the hippocampus was conducted. The ROI analysis was based on manual tracings of the hippocampus, which separated the head, body and tail of the region (for tracing protocol, see section 7.3.7.3). This separation was important considering proposals that the anterior and posterior sections of the hippocampus play different roles in spatial cognition and behaviour (Cornwell *et al.*, 2008; Xu *et al.*, 2010; Viard *et al.*, 2011) and are differently affected in depression (Maller *et al.*, 2007; Cole *et al.*, 2010). In addition, the separation

was important to prevent a dilution of the specifically anterior effects demonstrated in Experiment 7. The SPM tool Marsbar (version 0.43; (Brett, 2002)) was used to extract the average BOLD signal from each subsection of the hippocampus in the right and left hemisphere for each participant. Considering the different number of voxels in the three subsections, there was a risk that the estimated averages of BOLD signal would vary in reliability between the subsections. Therefore, each subsection was considered separately for the ROI analyses.

7.3.7.3 Volumetric analysis of the hippocampus

Volumetric analyses were based on the same manual tracings as the ones used for the ROI analyses. The tracings were performed on the coronal T1-weighted images using the Analyze software (version 11.0; Brain Imaging Resource, Mayo Clinic, Rochester, MN). The tracings included the dentate gyrus, the hippocampus proper and the subicular complex (see Figure 2-2; (Duvernoy, 1999)). Tracing proceeded from anterior to posterior on the coronal slices according to the protocol proposed by Watson (1997) with the exception of the posterior portion of the hippocampal tail, which was included in the present tracings. The tail was defined as beginning on the slice where the crux of the fornix separates (Figure 7-6, a-b). The body was defined as beginning on the slice after which the superior-lateral aspect of the hippocampus proper was no longer present, as identified from a sagittal orientation (Figure 7-6c). Raw hippocampal volumes were expressed in mm^3.

Intracranial volume (ICV) was obtained using the segmentation function in SPM. Specifically, voxels were classified as grey matter, white matter or cerebrospinal fluid based on a combined estimated probability of 0.8 or greater for presence of any of the three tissue/fluid types. Raw hippocampal volumes were normalised by ICV, as expressed in litres, and used for all statistical analyses.

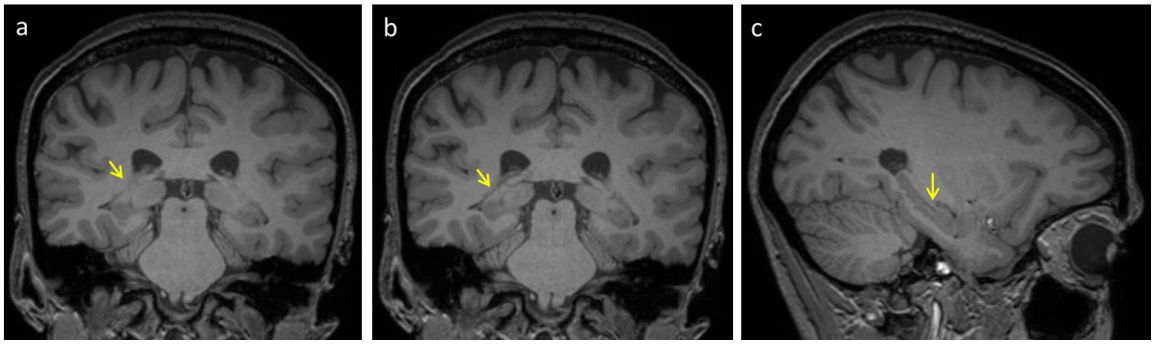

Figure 7-6: Examples of MR slices illustrating the boundaries between the head, body and the tail of the hippocampus. (a) Most posterior slice traced for the body of the left hippocampus; the fornix is indicated (b) One slice posterior to (a), the separation of the fornix is indicated. (c) The most posterior slice traced for the head of the hippocampus is indicated from a sagittal orientation.

7.3.7.4 Exploratory correlational analyses

To explore the relationship between performance in the allocentric condition and hippocampal structure and function, two sets of Pearson's correlation coefficients were calculated. In the first set, normalised volumes of the head, tail and body of the hippocampus in both hemispheres were correlated with error rates in the allocentric condition, separately for the depressed group and for the control group. The second set of analyses concerned hippocampal BOLD signal, as defined as the differential signal between the allocentric and egocentric conditions. Differential BOLD signal in all three subsections of the hippocampus in both hemispheres were correlated with error rates in the allocentric condition. To explore the effect of clinical characteristics in the depressed sample, illness duration (years) and depression severity (HAM-D 17 score) were similarly correlated with volume and differential BOLD signal in the three subsections in both hemispheres.

The wide age rage within each group represented an important consideration for the correlational analyses. This followed from previous demonstrations of changes in hippocampal volume (Walhovd *et al.*, 2011) and allocentric memory (Moffat *et al.*, 2006; Antonova *et al.*, 2009) in normal ageing. More specifically, age has been demonstrated to affect performance in the allocentric condition in the NGT-R (section 4.5). Consequently, correlational analyses were conducted between age and hippocampal volume and BOLD signal, which supported entering age as a covariate in the above analyses.

7.4 Results

7.4.1 Behavioural results

7.4.1.1 Replication of performance in the NGT-R in the scanner

Before proceeding with the comparison between the depressed group and the control group, it was important to investigate whether the NGT-R performance in healthy middle-aged participants was equivalent when performed inside and outside the scanner. To this end, performance of the control participants of Experiment 8 was compared to that of the middle-aged participants in the pooled sample of Experiment 6. For accuracy and response times, a 2x2 mixed ANOVA was therefore conducted with task context (fMRI, behavioural) as a between-subject factor and condition (allocentric, egocentric) as a within-subject factor. For accuracy and response times, respectively, there was no main effect of task context ($F(1,44)=.433$, $p=.514$; $F(1,44)=.020$, $p=.888$) and no interaction between task context and condition ($F(1,44)=.227$, $p=.636$; $F(1,44)=.057$, $p=.812$), evidencing that NGT performance in healthy middle-aged participants is comparable when performed inside and outside of the scanner.

7.4.1.2 NGT-R

Potential differences in NGT-R performance between depressed patients and control participants were investigated in a 2x2x3 mixed ANOVA with group (depressed, control) as a between-subject factor and condition (allocentric, egocentric) and rotation (45° 90°, 135°) as within-subject factors. There was no significant main effect of group for accuracy or response times (Table 7-4, Table 7-5). For accuracy, there was a significant three-way interaction between group, condition and angle of rotation (Table 7-4; Figure 7-7). However, pairwise-comparisons revealed no significant group differences for any of the sub conditions. Relevant to this, one-sample t-tests revealed above-chance performance in all sub conditions in both groups ($p<.001$) with the exception of the 135° rotation in the allocentric condition in the depressed group ($t(9)=-1.60$, $p=.15$; § in Figure 7-7). For response times, there was a non-significant trend of an interaction between group and angle of rotation (Table 7-5, Table 7-8).

To explore performance in the no-memory control condition, a 2x3 mixed ANOVA with group (depressed, control) as a between-subject factor and condition (allocentric, egocentric,

no-memory control condition) as a within-subject factor was conducted. For accuracy and response times, there was no main effect of group ($F(1,18)=.218$, $p=.646$; $F(1,18)=1.209$, $p=.286$) and no interaction between group and condition ($F(2,36)=.524$, $p=.600$; $F(2,36)=.274$, $p=.762$).

Table 7-4: Mixed ANOVA of the effect of group (depressed, control), condition and angle of rotation on accuracy.

Source	MS	df	*F*	*p*
Condition	0.904	1	38.525	**<.001**
Condition X Group	0.012	1	0.502	0.488
error (condition)	0.023	18		
Rotation	0.104	2	8.561	**0.001**
Rotation X Group	<.001	2	0.028	0.973
error (rotation)	0.012	36		
Condition X Rotation	0.049	2	6.498	**0.004**
Condition X Rotation X Group	0.045	2	6.015	**0.006**
error (condition X rotation)	0.008	36		
Group	0.002	1	0.022	0.884
error (group)	0.076	18		

Table 7-5: Mixed ANOVA of the effect of group (depressed, control), condition and angle of rotation on response times.

Source	MS	df	*F*	*p*
Condition	27068258.31	1	49.408	**>.001**
Condition X Group	123409.602	1	0.225	0.641
error (condition)	547584.242	18		
Rotation	973986.472	2	15.908	**>.001**
Rotation X Group	156773.046	2	2.561	*0.091*
error (rotation)	61226.015	36		
Condition X Rotation	345450.367	2	4.812	**0.014**
Condition X Rotation X Group	41726.107	2	0.581	0.564
error (condition X rotation)	71783.76	36		
Group	787201.045	1	0.932	0.347
error (group)	845079.342	18		

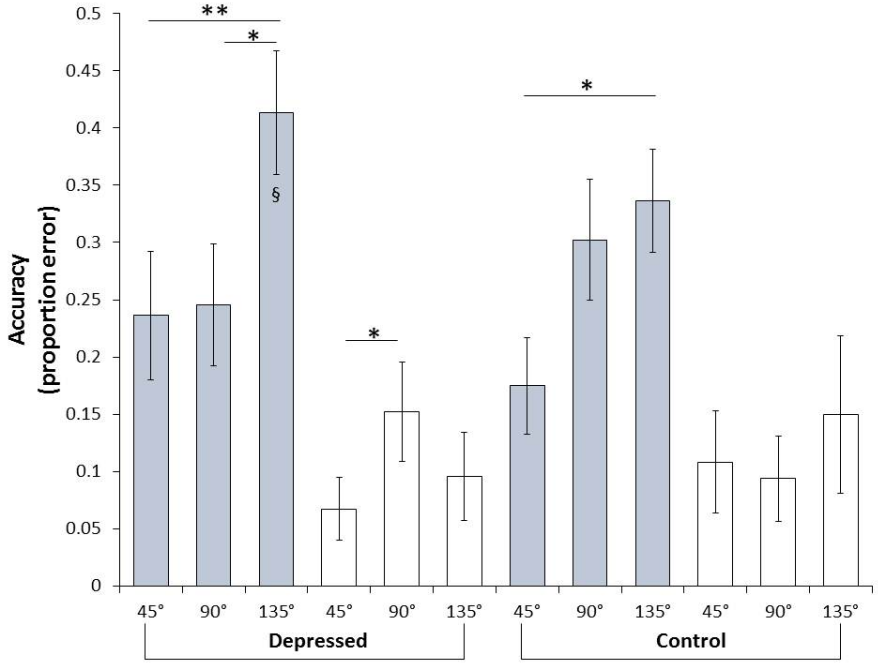

Figure 7-7: Interaction effect between group, condition and angle of rotation on accuracy. None of the pair-wise comparisons between groups were significant. Presented comparisons were performed for the interaction between condition and angle of rotation within each sample (* p<.05; ** p<.01). Filled bars represent the allocentric condition. Unfilled bars represent the egocentric condition.

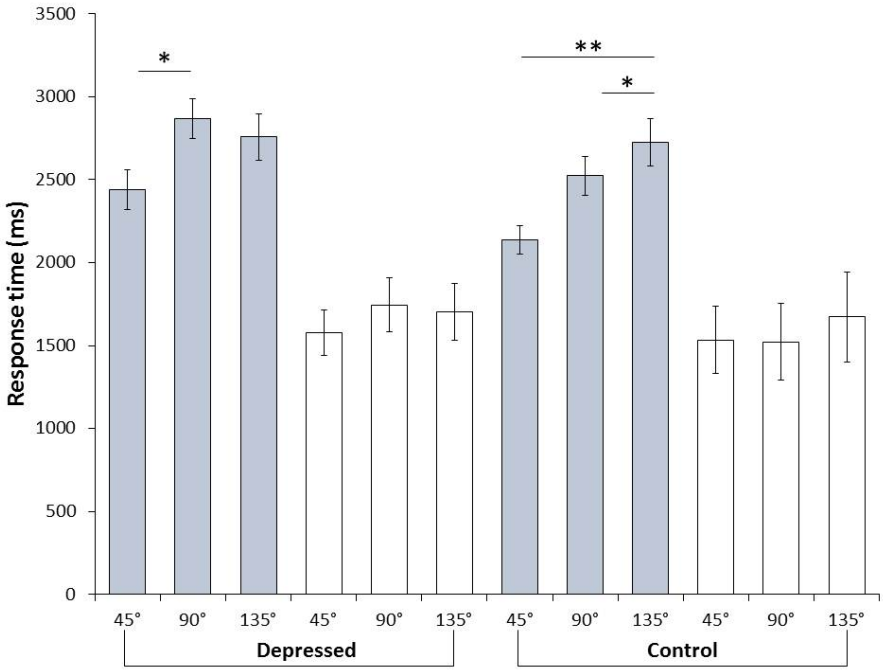

Figure 7-8: Effect of group, condition and angle of rotation on response times. None of the pair-wise comparisons between groups were significant. Presented pairwise comparisons were performed for the interaction between condition and angle of rotation within each sample (* p<.05; ** p<.01). Filled bars represent the allocentric condition. Unfilled bars represent the egocentric condition.

7.4.1.3 NGT-R training error and sense of direction

Independent t-tests revealed that depressed patients made significantly more errors (*M*=5.60, *SD*=5.76) than control participants (*M*=1.30, *SD*=1.95) in the training paradigm preceding the NGT-R ($t(18)=2.24$, $p=.038$). Number of training errors were positively correlated with errors in the allocentric condition ($r(19)=.56$, $p=.011$) but not in the egocentric condition ($r=.22$, $p=.35$). When the two groups were considered separately, the correlation between training errors and allocentric errors remained in the depressed group ($r(9)=.72$, $p=.018$) but not in the control group ($r(9)=.20$, $p=.60$). Depressed patients also reported having a worse sense of direction (*M*=60.80, *SD*=17.49) than control participants (*M*=79.30, *SD*=10.65; $t(18)=-2.86$, $p=.010$).

7.4.1.4 Mental rotation

For the disc rotation task, non-responses were excluded from the analysis (0.3%). The analysis made no distinction between trials in which the two symbols were the same and trial in which they were not and average response times were based on correct trials only. As such, the analysis of the disc rotation task was similar to the analysis of the NGT-R.

A 2x2 mixed ANOVA with group (depressed, control) as a between-subject factor and condition (rotation, no rotation) was conducted for accuracy and response times. For accuracy and response times, there was no main effect of group ($F(1,18)=.368$, $p=.542$; $F(1,18)=.084$, $p=.775$) and no interaction between group and condition ($F(1,18)=1.359$, $p=.259$; $F(1,18)=.013$, $p=.910$). For the rotation trials only, a 2x3 mixed ANOVA was subsequently performed with group (depressed, control) as a between-subject factor and angle of rotation (45°, 90°, 135°) as a within-subject factor. Although there was a significant main effect of rotation on both accuracy ($F(2,36)=4.710$, $p=.015$) and response times ($F(2,36)=41.588$, $p<.001$), there was no main effect of group ($F(1,18)=.663$, $p=.426$; $F(1,18)=.046$, $p=.833$) or interaction between group and rotation ($F(2,36)=.513$, $p=.513$; $F(2,36)=1.552$, $p=.226$) for accuracy or response times, respectively (Figure 7-9, Figure 7-10). One-sample t-tests furthermore revealed that accuracy was above chance in all sub conditions in both groups ($p<.001$).

Finally, Pearson's correlation coefficients were used to assess the relationship between performance in the rotation condition of the disc rotation task and in the allocentric condition of the NGT-R. There was a significant correlation between error rates in the

rotation trials of the disc rotation task and error rates in the allocentric condition ($r(18)=.65$, $p=.002$; Figure 7-11) but not in the egocentric condition of the NGT-R ($r(18)=.18$, $p=.46$). When the two groups were considered separately, the relationship with allocentric performance remained significant in the depressed group ($r(8)=.68$, $p=.031$) but not in the control group ($r(8)=.60$, $p=.069$).

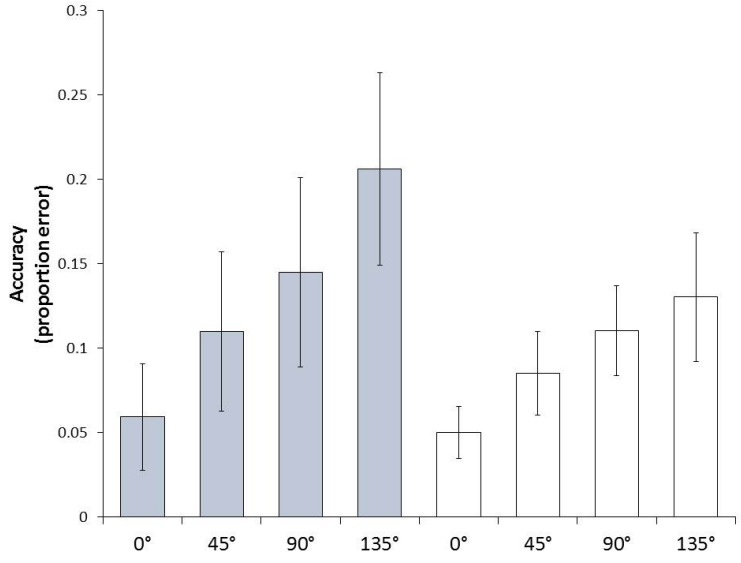

Figure 7-9: Error rates for the no-rotation condition (0°) and the rotation conditions (45°, 90°, 135°) in the disc rotation task in the depressed group (filled bars) and the control group (unfilled bars).

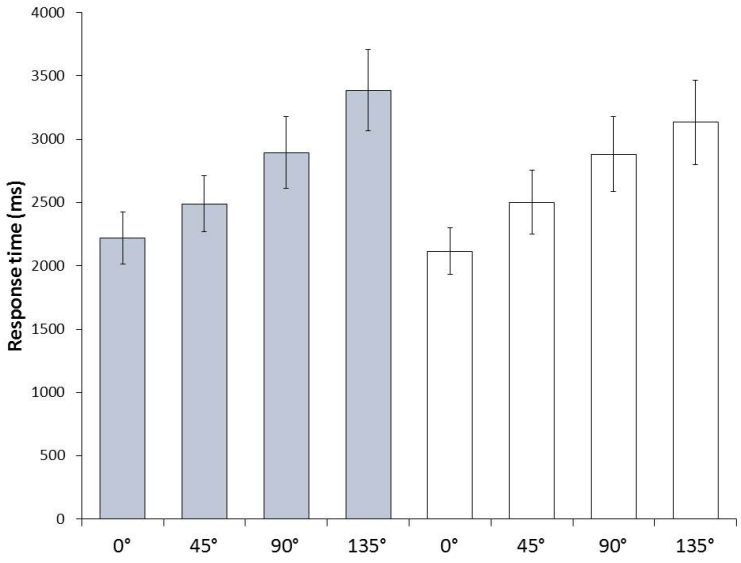

Figure 7-10: Response times for the no-rotation condition (0°) and the rotation conditions (45°, 90°, 135°) in the disc rotation task in the depressed group (filled bars) and the control group (unfilled bars).

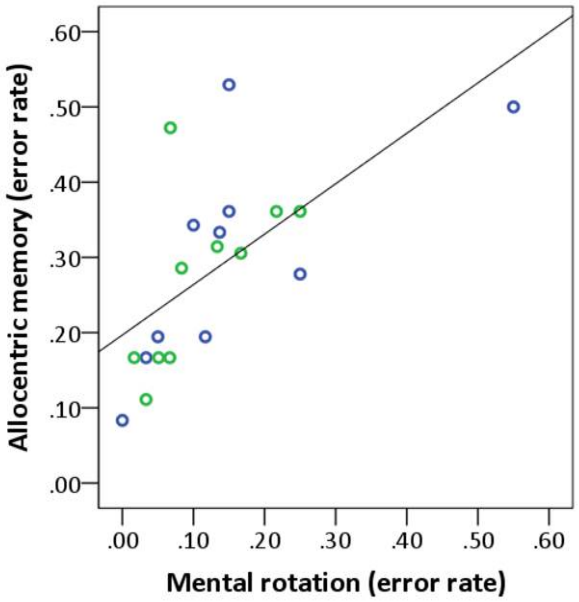

Figure 7-11: Scatterplot demonstrating the relationship between accuracy in the allocentric condition and accuracy in the rotation condition of the disc rotation task for the combined sample of depressed patients (blue circles) and control participants (green circles; R^2=.418). Note that the relationship in the depressed group did not reach significance when the outlier was excluded (*r*(8)=.61, p=.083).

7.4.1.5 Remaining neurocognitive measures

Independent sample t-tests were used to compare performance in the two groups for the remaining tasks in the protocol. No explicit correction was applied to account for multiple comparisons. The only task that was not fully analysed was the RAVLT for which the recognition test was incorrectly administered after the 20-minute long delay for five patients and two control participants. Consequently, only the learning and immediate memory sections before the delay could be reliably included in the analysis (i.e. sections A1-A5, B, A6).

For the spatial memory measures, depressed patients were significantly impaired in the position-only condition of OLM task (Table 7-6). Trending impairments were also identified in the object-location binding and the combined conditions of the OLM task and in the VPT. No impairments were found in the NSWM task. For the verbal memory measure, depressed patients performed normally on all sub-measures of the RAVLT, although there was a trend towards a significant impairment for the immediate recall of the first list (A6, Table 7-6). For the executive measures, there was a trend towards impairment in the incongruent condition and the interference measure of the Stroop task (Table 7-7). Similarly, patients showed a trend towards impairment in psychomotor speed (Table 7-7).

Table 7-6: Performance in the depressed group and the control group on measures of spatial and verbal memory (*df*=18). VPT=Visual Patterns Test. OLM=Object-Location Memory task. NSWM=Newcastle Spatial Working Memory task. RAVLT=Rey Adult Verbal Learning Test.

			Control		Depressed				
			mean	s.d.	mean	s.d.	*t*	*p*	CI 95%
Spatial Memory									
VPT			10.300	2.359	8.100	2.558	-1.999	*0.061*	[-4.512, .112]
OLM		Position Only	149.871	31.290	205.420	40.672	3.423	**0.003**	[21.456, 89.641]
		Object-Location Binding	19.500	15.890	39.000	24.810	2.093	*0.051*	[-0.074, 39.074]
		Combined	265.510	124.933	374.785	144.802	1.807	*0.088*	[-17.784,236.335]
		Object Memory	3.500	5.297	10.500	11.891	1.701	0.106	[-1.648, 15.648]
		Visuospatial Reconstruction	81.456	24.500	101.465	44.416	1.247	0.228	[-13.691, 53.708]
NSWM	2D	Between-search	122.500	70.900	178.800	82.820	1.610	0.125	[-16.932, 127.932]
		Within-search	12.900	10.826	24.800	23.701	1.444	0.166	[-5.411, 29.211]
	3D	Between-search	110.300	57.756	166.400	90.895	1.647	0.117	[-15.447, 127.647]
		Within-search	10.100	8.373	15.100	17.375	0.820	0.423	[-7.814, 17.814]
Verbal memory									
RAVLT		A1	5.800	1.549	5.900	1.449	0.149	0.883	[-1.309, 1.509]
		A1-A5	48.700	8.056	42.900	12.688	-1.220	0.238	[-15.785, 4.185]
		B	5.900	1.370	5.900	2.601	<.001	~1.000	[-1.953, 1.953]
		A6 (immediate recall)	10.700	2.058	8.400	3.565	-0.767	*0.094*	[-5.035, 0.435]

Table 7-7: Performance in the depressed group and the control group on cognitive measures of executive functioning and psychomotor speed (*df*=18).

		Control		Depressed				
		mean	s.d.	mean	s.d.	*t*	*p*	CI 95%
Executive Function								
Reverse Digit Span		5.300	1.418	5.100	1.663	-0.289	0.776	[-1.652, 1.252]
Stroop	Incongruent $_1$	109.728	23.670	144.719	51.244	1.960	*0.066*	[-5.972, 25.302]
	Colour naming $_2$	68.710	9.454	73.862	21.424	0.682	0.504	[-10.506, 20.610]
	Word reading	46.221	3.527	55.886	23.271	1.299	0.211	[-5.972, 25.302]
	Interference $_{1-2}$	40.918	17.732	70.857	44.340	1.983	*0.063*	[-1.787, 61.665]
Trail Making Part B		54.098	17.665	65.836	27.673	1.131	0.273	[-10.074, 33.550]
Psychomotor Speed								
Trail Making Part A		29.205	6.189	34.704	6.654	1.913	*0.072*	[-0.539, 11.537]

7.4.2 Imaging results

7.4.2.1 Whole-brain analyses

When no distinction was made between the patient group and the control group, the contrast between the allocentric and egocentric condition revealed clusters of differential activation in the occipital, lateral-temporal and frontal regions (Table 7-8). Relative to the equivalent analysis in Experiment 7, clusters in the superior and inferior parietal lobe and the mediotemporal regions were notably absent (Figure 7-12, red clusters). For the reverse contrast, clusters were limited to the temporal and frontal regions with an absence of any hippocampal clusters (Figure 7-12, blue clusters).

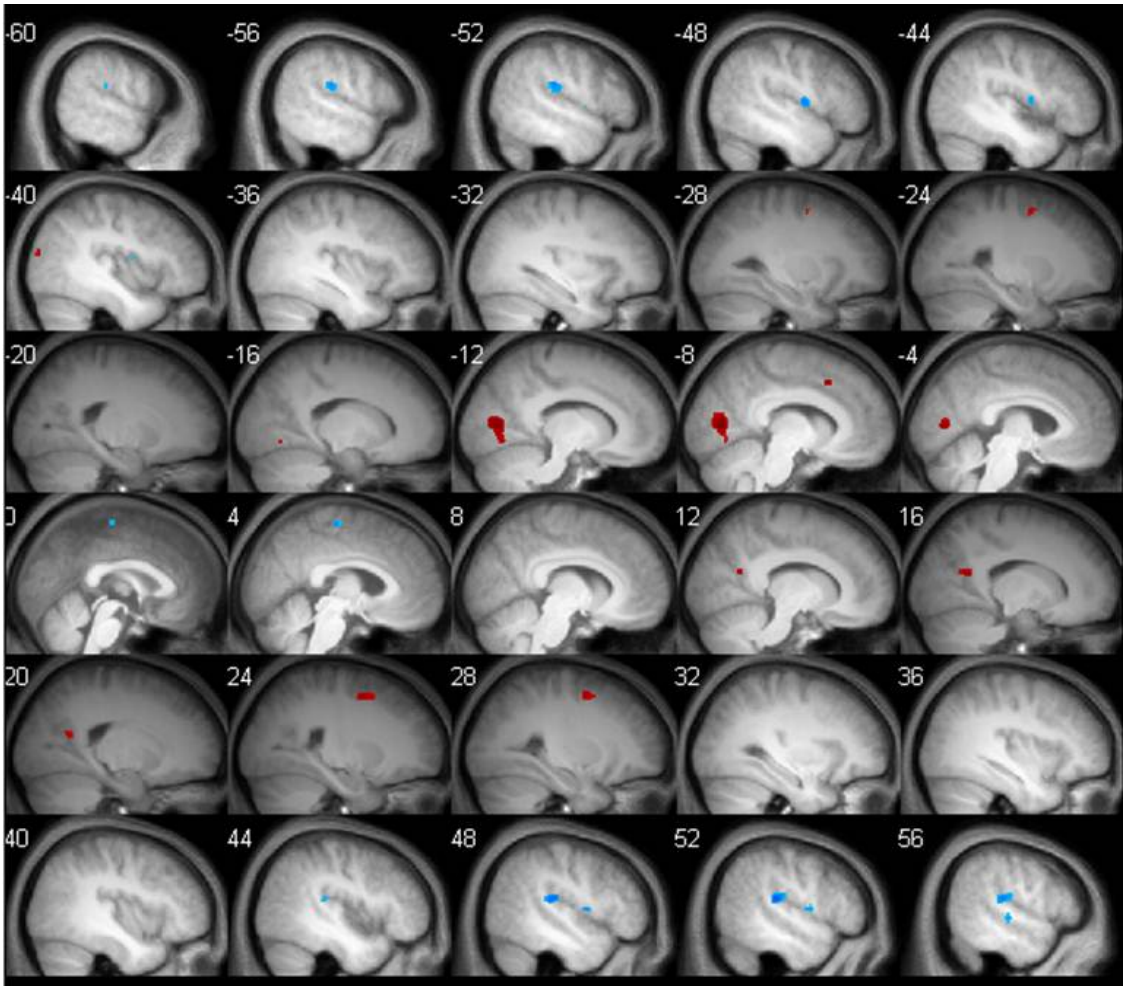

Figure 7-12: Activation maps at retrieval for the Allocentric vs. Egocentric contrast. Activations maps are shown in sagittal sections on the average normalised structural image computed from the full sample of Experiment 8. Regions shown in red exhibited greater signal in the allocentric condition whilst regions shown in blue exhibited greater signal in the egocentric condition ($p<.05$, FWE, $k\geq10$). Numbers represent X coordinates in MNI space.

Table 7-8: Peak activations for the whole brain analysis for the Allocentric vs. Egocentric contrast for the combined sample of depressed patients and control participants (p<.05, FWE, k≥10). Differences from baseline for the two conditions are marked as + when positive, as - when negative and as 0 when not significant.

Contrast	Region	Local peak	Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (allo/ego)
Allo>Ego	Occipito-temporal	L. cuneus	279	7.02	-10, -76, 8	+/+
		R. retrosplenial cortex	50	6.30	16, -58, 18	+/0
		L. mid temporal gyrus	11	5.76	-42, -84, 16	+/+
	Frontal	R. mid. frontal gyrus	81	6.37	26, 0, 50	+/+
		L. mid.frontal gyrus	23	3.06	-26, -2, 52	+/+
		L. media lfrontal gyrus	15	6.32	-8, 16, 44	+/+
Ego>Allo	Temporal	R. sup. temporal gyrus	161	7.34	50, -28, 16	-/0
		R. sup. temporal gyrus	26	6.09	58, -22, 0	-/-
		R. sup. temporal gyrus	23	5.98	66, -38, 2	-/-
		L. sup. temporal gyrus	81	6.78	-52, -26, 22	0/+
	Frontal	R. medial frontal gyrus	24	6.40	4, -22, 60	-/0
		R. precentral gyrus	65	6.37	50, 0, 6	-/0

For the contrast between Egocentric>Control contrast, the involvement of the superior parietal cortex revealed in Experiment 7 could be confirmed (Table 7-9). For Allocentric>Control contrast several regions of the parieto-medial temporal pathway were identified, including the RSC, the lingual gyrus and the parahippocampus (Figure 7-13, Table 7-10).

In an exploratory whole-brain analysis, the depressed group was distinguished from the control group in the analyses presented above. No regions were found to exhibit significant interactions between group and the Allocentric vs. Egocentric contrast. Similarly, no regions showed evidence of significant interactions between group and the Allocentric>Control or the Egocentric>Control contrasts.

Table 7-9: Peak activations for the Egocentric vs. Control contrast in the combined sample of depressed and control participants (Ctrl; p<.05, FWE, k≥10). Differences from baseline for the conditions (exp, ctrl) are marked as + when positive, as - when negative and as 0 when not significant.

Contrast	Region	Local peak	Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (exp/ctrl)
Ego>Ctrl	Parietal	R. angular gyrus	251	6.82	48, -44, 52	+/0
		R. sup. parietal cortex	65	6.30	4, -68, 68	+/0
		R. sup. parietal cortex	21	5.92	16, -72, 56	+/0
	Frontal	R. mid. frontal gyrus	19	5.97	30, 14, 56	+/0
Ctrl>Ego		R. inf. temporal gyrus	177	6.70	52, -4, -34	-/0
		L. sup. temporal gyrus	208	6.56	-66, -40, 18	0/0
		L. mid. occipital gyrus	26	6.32	-40, -58, 20	-/0
		R. medial frontal gyrus	10	5.85	4, 60, 10	-/0

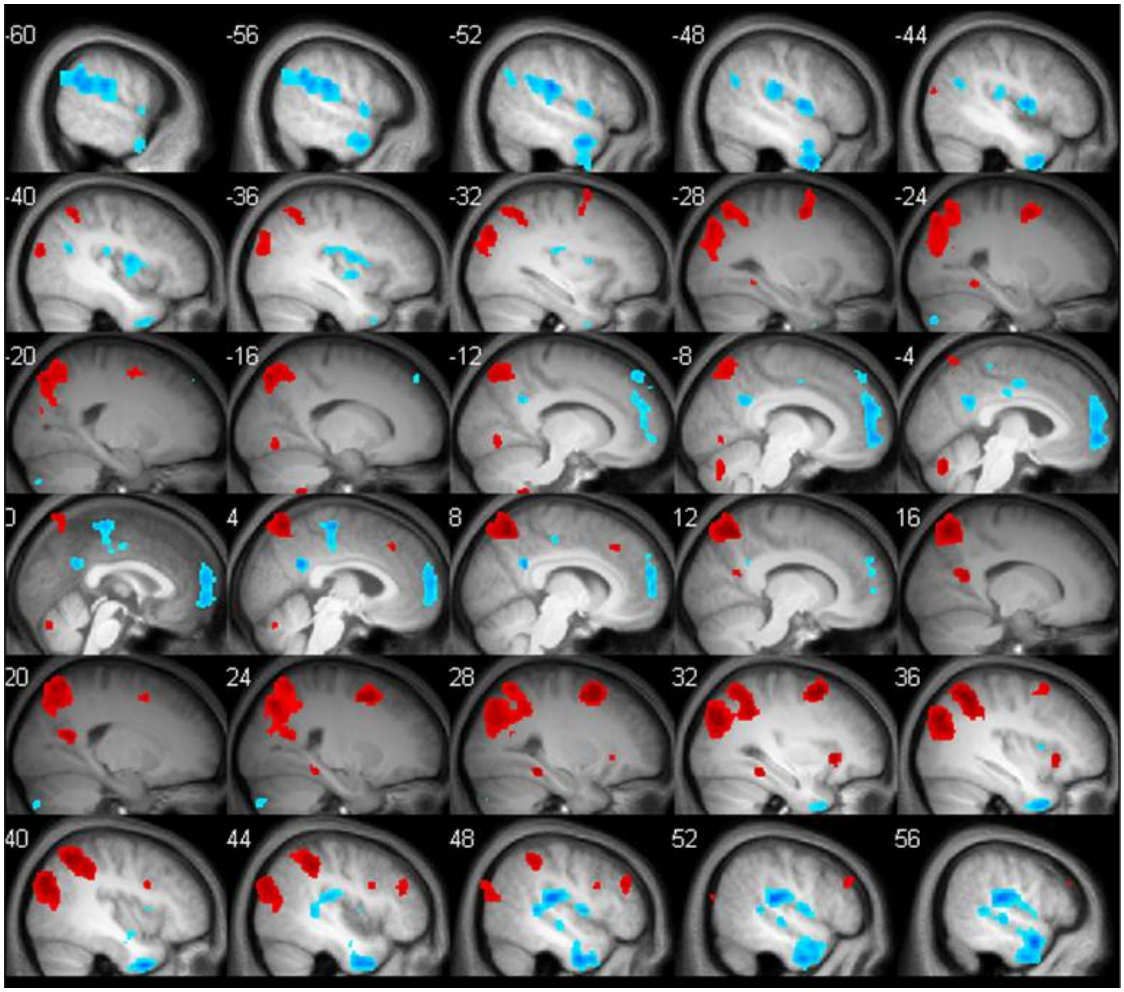

Figure 7-13: Activation maps at retrieval for the Allocentric vs. Control contrast. Activations maps are shown in sagittal sections on the average normalised structural computed from the full sample data in Experiment 8. Regions shown in red exhibited greater signal in the allocentric condition whilst regions shown in blue exhibited greater signal in the no-memory control condition ($p<.05$, FWE, $k\geq10$). Numbers represent X coordinates in MNI space.

Table 7-10: Peak activations for the Allocentric vs. Control contrast in the combined sample of depressed and control participants (Ctrl; p<.05, FWE, k≥10). Differences from baseline for the conditions (exp, ctrl) are marked as + when positive, as - when negative and as 0 when not significant.

Contrast	Region	Local peak	Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (exp/ctrl)
Allo>Ctrl	Parieto-occipital-temporal	R. angular gyrus	6842	8.55	38, -54, 48	+/+
		R. retrosplenial cortex		7.51	18, -58, 16	+/0
		L. lingual gyrus	77	6.35	-12, -72, -6	+/+
		R. parahippocampal gyrus	89	7.32	30, -40, -12	+/+
		L. parahippocampal gyrus	30	6.23	-24, -46, -8	+/+
	Frontal	R. insula	99	7.26	32, 24, 0	+/+
		R. mid. frontal gyrus	591	8.61	30, 12, 54	+/0
			156	6.60	48, 36, 28	+/0
			36	6.59	6, 28, 42	+/0
		L. mid. frontal gyrus	314	7.63	-26, 0, 53	+/+
		R. inf. frontal gyrus	61	6.33	46, 10, 26	+/+
	Other	L. cerebellum	64	7.37	-14, -52, -50	+/0
			137	6.96	-4, -74, -28	+/0
Ctrl>Allo	Parieto-temporal	R. angular gyrus	1919	8.91	50, -26, 16	-/0
		L. angular gyrus	2646	8.54	-52, -26, 22	0/+
		R. mid. temporal gyrus	1330	8.87	56, 2, -20	-/0
		L. mid. temporal gyrus	689	7.81	-52, 2, -24	-/0
		L. inf. temporal gyrus	11	5.85	-30, 6, -44	-/0
		Post. cingulate gyrus	315	7.85	6, -50, 26	-/-
	Frontal	R. insula	24	6.44	38, 8, 8	-/0
		R. precentral gyrus	369	8.12	4, -24, 58	-/+
		L. medial frontal gyrus	1218	7.85	-4, 58, -4	-/0
		L. sup. frontal gyrus	106	7.05	-10, 48, 48	-/0
	Other	R. cerebellum	52	6.48	22, -86, -40	-/0
		L. cerebellum	40	6.50	-24, -82, -40	-/0

7.4.2.2 Region of interest analysis

A 2x3x2 mixed ANOVA was conducted for each subsection of the hippocampus with group (depressed, control) as a between-subject factor and condition (allocentric, egocentric, no-memory control) and hemisphere (right, left) as within-subject factors. There was a significant main effect of condition in all three hippocampal subsections (Table 7-11, Table 7-12, Table 7-13). This main effect constituted a lower BOLD signal in the allocentric condition in all subsections of the hippocampus although this only reached significance relative to the egocentric condition in the body of the hippocampus (Figure 7-14). In the body of the hippocampus there was also a strong trend towards a significant interaction between hemisphere and group, which appeared to be a reflection of a greater drop in BOLD signal below the baseline in the control group in the right hemisphere but not in the left hemisphere (Figure 7-15). However, subsequent pairwise comparisons did not reveal any differences.

Table 7-11: Mixed ANOVA for the effect of condition, group (depressed, control) and hemisphere on BOLD signal in the head of the hippocampus.

Source	MS	df	*F*	*p*
Condition	50.846	2	9.111	**0.001**
Condition X Group	1.577	2	0.283	0.756
error (condition)	5.581	36		
Hemisphere	0.139	1	0.055	0.718
Hemisphere X Group	0.189	1	0.075	0.787
error (hemisphere)	2.522	18		
Condition X Hemisphere	0.097	2	0.119	0.888
Condition X Hemisphere X Group	0.061	2	0.075	0.928
error (condition X hemisphere)	0.816	36		
Group	2.599	1	0.130	0.723
error (group)	19.989	18		

Table 7-12: Mixed ANOVA for the effect of condition, group (depressed, control) and hemisphere on BOLD signal in the body of the hippocampus.

Source	MS	df	*F*	*p*
Condition	15.777	2	3.636	**0.036**
Condition X Group	0.989	2	0.228	0.797
error (condition)	4.340	36		
Hemisphere	0.386	1	0.223	0.643
Hemisphere X Group	7.277	1	4.194	*0.055*
error (hemisphere)	1.735	18		
Condition X Hemisphere	0.712	2	0.934	0.402
Condition X Hemisphere X Group	0.013	2	0.017	0.984
error (condition X hemisphere)	0.762	26		
Group	8.786	1	0.348	0.563
error (group)	25.240	18		

Table 7-13: Mixed ANOVA for the effect of condition, group (depressed, control) and hemisphere on BOLD signal in the tail of the hippocampus.

Source	MS	df	*F*	*p*
Condition	14.498	2	4.027	**0.026**
Condition X Group	0.032	2	0.009	0.991
error (condition)	3.600	36		
Hemisphere	3.114	1	0.851	0.369
Hemisphere X Group	3.602	1	0.984	0.334
error (hemisphere)	3.661	18		
Condition X Hemisphere	2.753	2	1.568	0.222
Condition X Hemisphere X Group	0.348	2	0.198	0.821
error (condition X hemisphere)	1.756	36		
Group	0.028	1	0.002	0.969
error (group)	18.182	18		

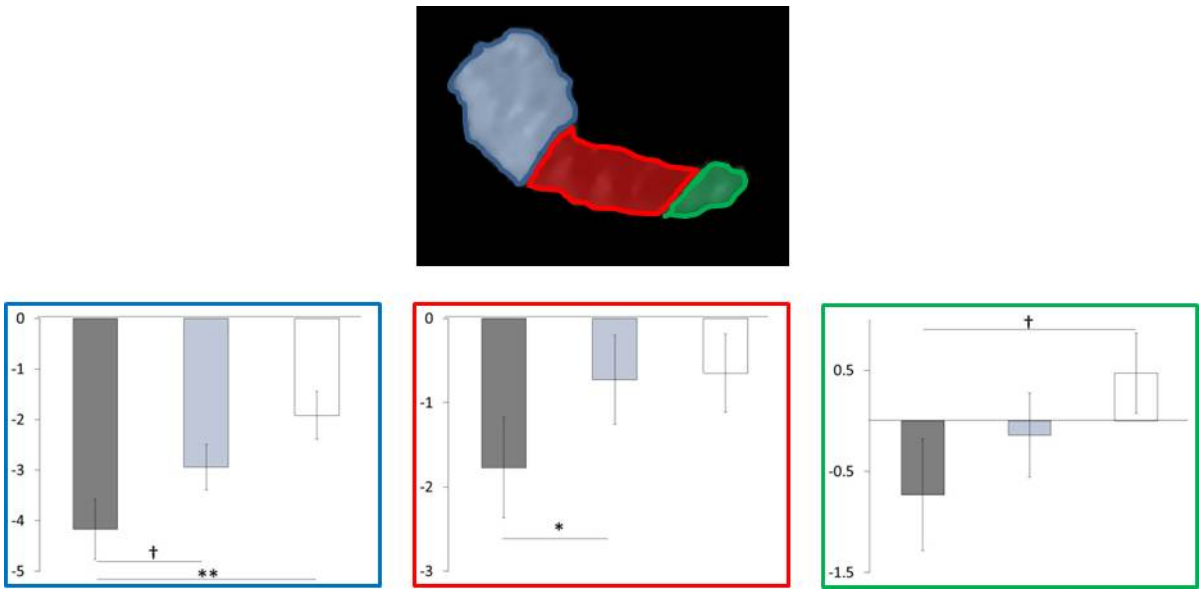

Figure 7-14: Main effect of condition in the head (blue), body (red) and tail (green) of the hippocampus and outcome of pairwise comparisons (* p<.05; ** p<.01; † .05<p>.1) for the response phase. Dark grey bars represent the allocentric condition, light grey bars represent the egocentric condition and unfilled bars represent the no-memory control condition. The subsections of the hippocampus are illustrated on a rendering of the left hippocampus from a single participant viewed from an axial orientation.

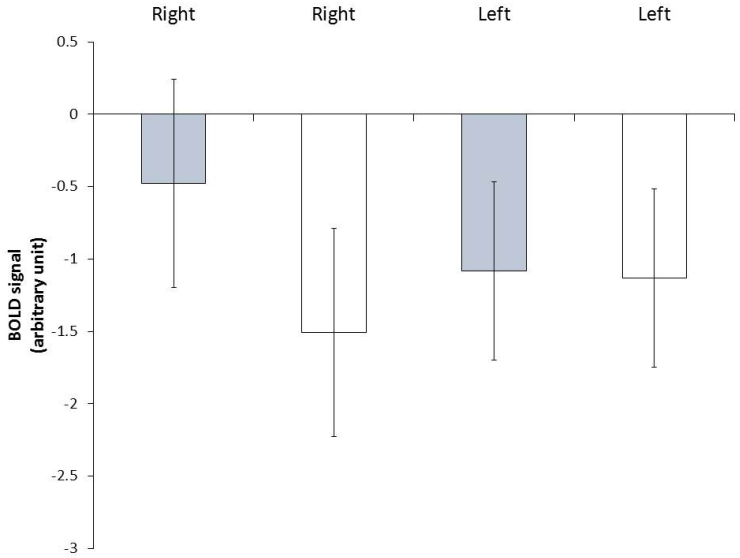

Figure 7-15: Interaction effect between group (depressed, control) and hemisphere on differential BOLD signal extracted from the body of the hippocampus. Filled bars represent the depressed sample. Unfilled bars represent the control sample.

7.4.2.3 Volumetric analysis of the hippocampus

A 2x3x2 mixed ANOVA was conducted for normalised hippocampal volumes with group (depressed, control) as a between-subject factor and hippocampal subsection (head, body, tail) and hemisphere (left, right) as within-subject factors. There was no significant main effect of group and no interaction effects between group and hippocampal subsection or hemisphere (Table 7-14, Figure 7-16). As could be expected, there was a significant main effect of hippocampal subsection on volume, with post-hoc tests revealing a larger volume for the head compared to the body ($p<.001$) and the tail ($p<.001$) and for the body compared to the tail ($p<.001$). There was also a significant interaction between hippocampal subsection and hemisphere, which was reflected by significant differences in volume between the hemispheres for the head and the body but not the tail of the hippocampus (Figure 7-17).

For comparisons with other studies, the average raw hippocampal volume was 4114.47mm^3 (*SD*=513.67) in the right hemisphere and 4155.08mm^3 (*SD*=543.88) in the left hemisphere when the two groups were combined.

Table 7-14: Mixed ANOVA for the effect of group (depressed, control), hippocampal subsection and hemisphere on normalised hippocampal volume.

Source	MS	df	*F*	*p*
HC Section	12024843.82	2	223.657	**<.001**
HC Section X Group	8832.90	2	0.164	0.849
error (HC section)	53764.73	36		
Hemipshere	3287.53	1	1.593	0.223
Hemipshere X Group	1817.28	1	0.881	0.360
error (hemipshere)	2063.63	18		
HC Section X Hemisphere	162606.50	2	15.053	**<.001**
HC Section X Hemisphere X Group	1935.45	2	0.179	0.837
error (HC section X hemisphere)	10802.00	36		
Group	2742.38	1	0.055	0.818
error (group)	50180.31	18		

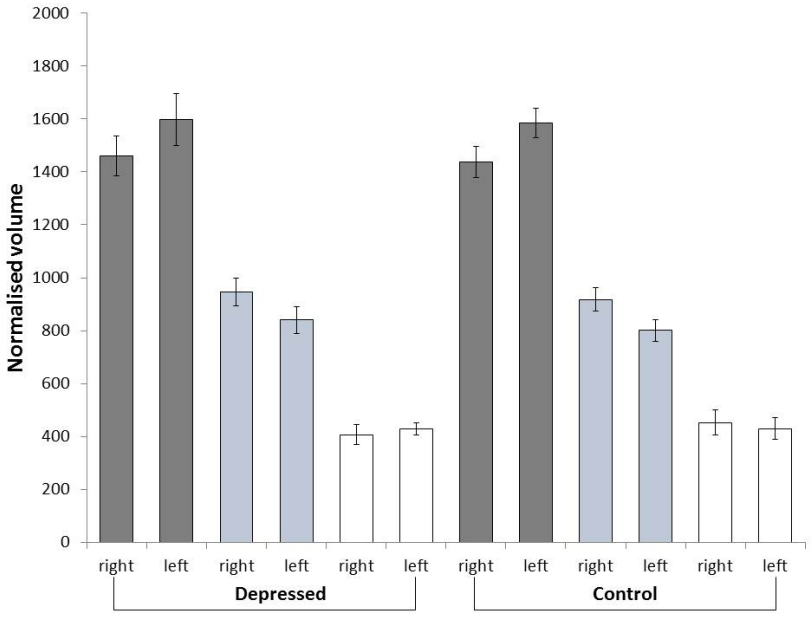

Figure 7-16: Volumes normalised for ICV for the head (dark grey bars), the body (light grey bars) and the tail (unfilled bars) of the right and left hippocampi in the depressed group and the control group.

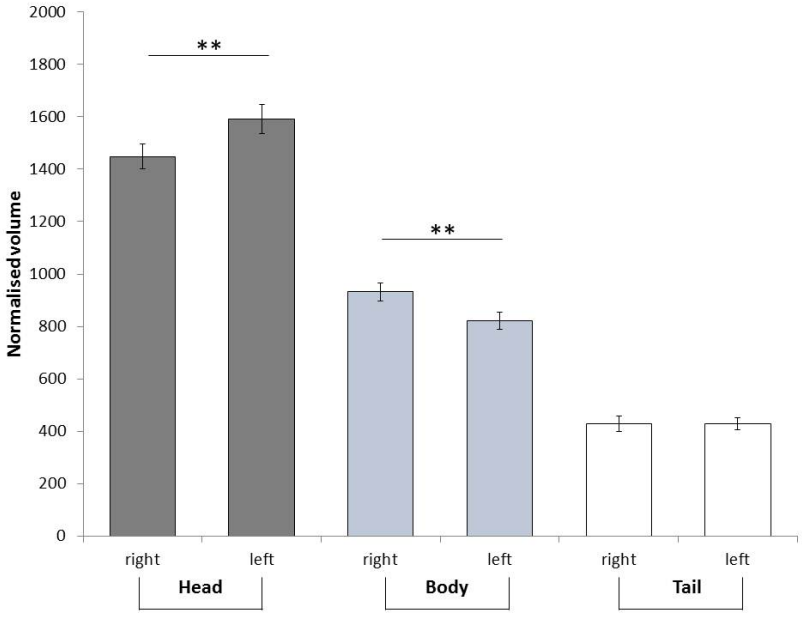

Figure 7-17: Interaction effect between hemisphere and hippocampal subsection and outcome of pairwise comparisons (* p<.05; ** p<.01).

7.4.2.4 Exploratory correlational analyses

Correlational analyses of the relationship between age and normalised hippocampal volumes and differential BOLD signal in the allocentric and egocentric conditions indicated that age had a significant effect in selected subsections in the two groups (Appendix D). Consequently, age was entered as a covariate in the subsequent correlational analyses.

In terms of normalised hippocampal volumes, the body of the left hippocampus showed a strong trend towards a negative relationship with error rates in the allocentric condition in the depressed sample and a weaker trend towards a positive relationship in the control sample (Table 7-15, Figure 7-18). In terms of the differential BOLD signal in the allocentric and egocentric conditions, there were no significant relationships with error rates in the allocentric condition (Table 7-16).

Table 7-15: Pearson's correlation coefficients for the relationships between normalised volumes of the hippocampal subsections and error rates in the allocentric condition, after controlling for age.

		Depressed		Control	
		r	*p*	*r*	*p*
Head	Right	0.029	0.942	-0.52	0.151
	Left	0.282	0.462	0.015	0.969
Body	Right	-0.321	0.399	*0.584*	*0.099*
	Left	*-0.648*	*0.059*	0.274	0.475
Tail	Right	0.116	0.767	-0.072	0.855
	Left	0.126	0.746	-0.201	0.604

Table 7-16: Pearson's correlation coefficients for the relationships between the difference in BOLD signal between the allocentric and egocentric condition in the hippocampal subsections and error rates in the allocentric condition, after controlling for age.

		Depressed		Control	
		r	*p*	*r*	*p*
Head	Right	-0.035	0.929	0.077	0.843
	Left	-0.071	0.556	0.406	0.278
Body	Right	-0.379	0.315	0.021	0.957
	Left	-0.493	0.178	0.448	0.226
Tail	Right	-0.203	0.601	-0.387	0.303
	Left	-0.237	0.540	-0.117	0.764

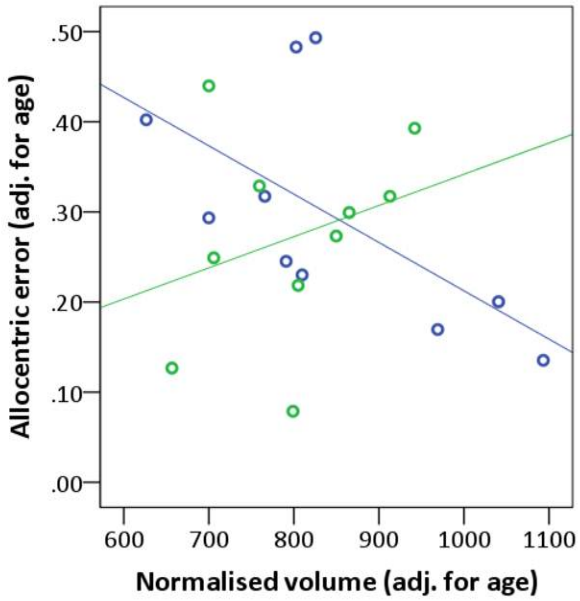

Figure 7-18: Scatterplot demonstrating the relationship between the proportion of error in the allocentric condition and normalised volume of the left body of the hippocampus. Blue circles represent depressed patients (R^2=.394). Green circles represent control participants (R^2=.087). Note that both variables have been adjusted for age.

In terms of illness characteristics, there were no significant relationships between illness duration and hippocampal volume or differential BOLD signal (Table 7-17). However, depression severity correlated negatively with differential BOLD signal in the left body of the hippocampus (Table 7-18). This indicates that more severe depressive symptoms were associated with a greater differential signal between the allocentric and egocentric condition in the left body of the hippocampus (Figure 7-19). It should also be noted that allocentric error rates did not correlate with illness duration ($r(7)$=.517, p=.154) or depression severity ($r(8)$=.337, p=.340). Note that data for illness duration was not available for one patient, resulting in a sample size of 9 patients for analyses involving this variable.

Table 7-17: Pearson's correlation coefficients for the relationships between illness duration and normalised volume and difference in BOLD signal between the allocentric and egocentric conditions in the three subsections of the hippocampus, after controlling for age.

		Normalised volume (mm^3)		BOLD signal (arbitrary signal)	
		r	*p*	*r*	*p*
Head	Right	-0.009	0.983	-0.045	0.915
	Left	-0.034	0.937	-0.193	0.647
Body	Right	-0.049	0.908	0.117	0.782
	Left	0.007	0.988	-0.451	0.262
Tail	Right	0.285	0.494	-0.358	0.384
	Left	0.323	0.435	0.397	0.330

Table 7-18: Pearson's correlation coefficients for the relationships between depression severity (HAM-D 17 score) and normalised volume and difference in BOLD signal between the allocentric and egocentric conditions in the three subsections of the hippocampus, after controlling for age.

		Normalised volume (mm^3)		BOLD signal (arbitrary signal)	
		r	*p*	*r*	*p*
Head	Right	-0.186	0.632	-0.016	0.967
	Left	0.256	0.506	0.073	0.852
Body	Right	0.493	0.178	-0.323	0.397
	Left	0.004	0.991	**-0.809**	**0.008**
Tail	Right	-0.499	0.171	*-0.627*	*0.071*
	Left	-0.255	0.507	0.175	0.652

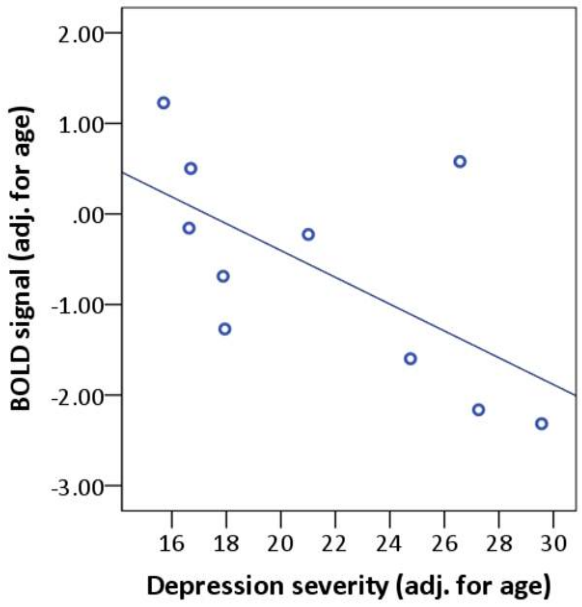

Figure 7-19: Scatterplot demonstrating the relationship between the difference in BOLD signal between the allocentric and egocentric conditions in the left body of the hippocampus and depression severity (HAM-D score) in the depressed sample (R^2=.402). Note that both variables have been adjusted for age.

7.5 Discussion

The primary hypothesis of Experiment 8 concerned the presence of hippocampal dysfunction in the depressed sample, as reflected in an attenuated differential signal in the anterior hippocampus for the contrast between the allocentric and egocentric condition and a behavioural impairment in the allocentric condition of the NGT-R. In addition, the volume of the hippocampus was predicted to be smaller in the depressed group. Finally, it was

hypothesised that the combined sample would show a similar pattern of results for the parieto-medial temporal pathway as was demonstrated in Experiment 7.

The following discussion will be initiated by an interpretation of the behavioural performance in the NGT-R in the context of a selection of other neurocognitive tasks included in the protocol. Subsequently, the results derived from the ROI analysis of the hippocampus and the associated volumetric analysis will be summarised and evaluated relative to the hypotheses. In the same section, the explorative analyses of potential relationships between performance, clinical variables and hippocampal structure and function will be referred to and commented on. In a final section, a qualitative comparison will be made to evaluate how the results of the combined sample of Experiment 8 compared to the findings of Experiment 7.

7.5.1 Spatial memory in depression

In contrast to the predictions, the depressed patients in Experiment 8 performed normally in all conditions of the NGT-R, evidencing an absence of a disproportionate impairment in the allocentric condition. Thus, at least at a behavioural level, depressed patients did not appear to show evidence of hippocampal dysfunction in the NGT-R.

Although the prediction of a disproportionate allocentric memory deficit in the depressed sample could not be supported, there were indications that the effect of increasing viewpoint-shifts on accuracy was different in the depressed sample relative to the control sample. Specifically, relative to control participants, who exhibited the typical incremental increase in error rates for increasing viewpoint-shifts, depressed patients exhibited an abrupt increase in error rates for the 135° compared to the 45° and 90° viewpoint-shifts, resulting in at-chance performance. Although a similarly abrupt increase in error rates for the 135° viewpoint-shift has been demonstrated in healthy participants previously (e.g. Experiment 5), performance has always been above chance. Thus, the abrupt drop to at-chance performance for the 135° viewpoint-shift has the potential of providing clues for future investigations in larger samples.

The differential effect of increasing viewpoint-shifts on error rates in the depressed sample should first be considered in the context of the outcome of the disc rotation task, which relevance to the NGT-R was indicated by a strong positive relationship between error rates in this task and error rates in the allocentric condition. In contrast to the effect of viewpoint-shifts in the allocentric condition, depressed patients showed the typical incremental decrease

in performance for larger rotations and above-chance performance for all rotation angles in the disc rotation task. Consequently, an impaired mental rotation ability is unlikely to underlie the poor performance for the 135° viewpoint-shift in the allocentric condition in the depressed sample.

One factor that may have played a role in the differential effect of viewpoint-shifts is the fact that depressed patients produced a greater number of errors in the preceding training paradigm compared to control participants. Although eight out of the ten patients managed to reach the criterion of no errors after three training sessions, a generally higher error rate indicated that learning the landmark locations in the NGT-R posed a greater challenge in this group. Importantly, there was a strong positive relationship between training error and error in the subsequent allocentric condition in the patient group, which supports that the efficacy of learning the landmark locations mattered for performance in the allocentric condition. As has been emphasised previously, larger viewpoint-shifts are more likely to result in that relevant landmarks disappear out of view. Thus, if patients were relying on a less accurate long-term representation of the landmark locations, greater viewpoint-shifts would be expected to be more detrimental to performance. However, if this was the case, it is unclear why a viewpoint-shift of 135° should result in an abrupt drop in performance when the increase from 45° and 90° resulted in no change. In contrast, the probability of the disappearance of a relevant landmark should increase incrementally for each increase in viewpoint-shift.

An alternative account rests on the outcome of the additional memory assessments in the protocol of Experiment 8 and postulates the use of a verbal strategy to compensate for a visuospatial memory deficit. The results of the additional memory assessments revealed that depressed patients were significantly impaired when required to remember the precise locations of ten identical objects over a brief delay (position-only condition, OLM task) whilst they exhibited no equivalent impairment in the verbal domain (RAVLT, immediate). Consequently, patients may have been more likely to opt for a predominantly verbal strategy to remember the target location in the allocentric condition, which may have acted to disguise a spatial memory deficit in the NGT-R. In other words, as opposed to remembering the vectors between the target location and the landmarks visually, depressed patients may have relied on verbalising its location (e.g. “to the right of the fox”). Such a verbal strategy to remember spatial locations can be considered particularly likely in the NGT-R environment,

which involves landmarks that are easily nameable (Rossion and Pourtois, 2004). In contrast, a verbal strategy would arguably be difficult to implement in the position-only condition of the OLM task considering the identical objects. A similar case can be made for the VPT, for which there was a strong trend towards a significant deficit in the depressed sample. Namely, the visual pattern matrices are not amenable to a verbal strategy, which means that depressed patients would have had to rely on an impaired visuospatial memory strategy.

Critically, a predominant use of a verbal strategy in the depressed sample may account for the abrupt drop to at-chance performance for the 135° viewpoint-shift in this group. Specifically, common verbal labels that are centred on the position of the observer, such as 'left' and 'right', become irrelevant or misleading after viewpoint-shifts that are greater than 90°. As such, the abrupt drop to at-chance performance for the 135° viewpoint-shift would be expected in the case of a predominantly verbal strategy in the depressed sample. A similar case of verbal scaffolding to compensate for visuospatial memory impairments has recently been proposed to explain a comparable pattern of cognitive deficits in bipolar disorder (Gallagher, 2011). In regards to the similar abrupt drop in performance for the 135° viewpoint-shift in healthy volunteers in previous experiments, it is conceivable that an intact visuospatial memory strategy would have allowed performance to remain above chance.

In relation to a compensatory verbal strategy in depression, it is worth mentioning that patients were significantly impaired in the training paradigm preceding the NGT-R, which required them to learn the locations of seven easily nameable landmarks. In contrast to the VPT and the position-only condition of the OLM task, a predominantly verbal strategy would arguably be sufficient to remember the landmark locations in this training paradigm. Thus, at least at training, depressed patients appeared to have problems with associating an easily nameable landmark with its respective location. This finding can be considered in the context of the object-location binding condition of the OLM task, for which there was a strong trend towards a significant deficit in the depressed sample. Similarly to the NGT-R training paradigm, this condition required participants to remember the association of a number of easily nameable objects with marked locations. Although the locations in this task were not organised in the same way as the landmarks in the NGT-R environment, such results indicate that depressed patients may also be impaired in associating nameable objects with their respective spatial locations. In this context, the lack of a deficit in the allocentric condition is more difficult to interpret. Specifically, if depressed patients were unable to efficiently

associate nameable objects with spatial locations, an impairment would reasonably be expected when a target location needs to be represented by its spatial relationship with one or several landmarks in the allocentric condition of the NGT-R.

One important difference distinguishing the allocentric condition from the NGT-R training paradigm and the object-location binding condition of the OLM task is the number of locations to be remembered. Namely, whilst only one location needs to be remembered in the allocentric condition, seven and ten locations have to be remembered in the NGT-R training paradigm and the OLM task, respectively. Thus, it appears as if depressed patients showed a deficit when a greater number of object-location associations needed to be represented. It is conceivable that a verbal strategy to remember target locations would become increasingly inefficient as the number of targets increases. Consequently, it can be speculated that the impairment in the NGT training paradigm and in the object-location binding condition of the OLM task is a reflection of a failing verbal memory strategy. Alternatively, it could be proposed that the use of a single target location in the NGT-R reduced the sensitivity of the task in detecting the impairment in object-location binding in the allocentric condition. Although a general lack of task sensitivity is a valid account, it should be mentioned that by increasing the number of locations to be remembered there is also a risk of increasing the actual and perceived demand of the task, which can be considered problematic in a clinical population with well documented motivational problems, executive deficits and frontal lobe abnormalities (Elliott *et al.*, 1996; Fossati *et al.*, 2004; Koolschijn *et al.*, 2009).

Independently of the results in the allocentric condition of the NGT-R, it is evident that the depressed patients were impaired in spatial memory tasks, in which both egocentric and allocentric strategies were possible. Specifically, both the OLM and the VPT involved a stable observer position, which allows for both an egocentric and an allocentric strategy to be used. This is consistent with previous studies showing a short-term spatial memory deficit in currently depressed individuals (Ravnkilde *et al.*, 2002; Porter *et al.*, 2003). The absence of a similar impairment in the verbal domain further indicates that spatial memory may be particularly sensitive to the effects of depression (Porter *et al.*, 2003; Lee *et al.*, 2012b). Based on the results of Experiment 8, however, the spatial memory deficit in depression does not appear to get worse when the location needs to be represented allocentrically, which would have been expected in the case of hippocampal dysfunction (O'Keefe, 1978; Goodrich-Hunsaker *et al.*, 2010). Since it remains unclear whether the use of a compensatory

verbal strategy could have disguised a behavioural allocentric deficit in the depressed sample of Experiment 8, an absolute conclusion can only be considered premature.

In summary, depressed patients did not show a disproportionate impairment in the allocentric condition, which contradicts the presence of hippocampal dysfunction in depression. However, a seemingly differential effect of the increasing viewpoint-shifts in the allocentric condition in the depressed sample relative to the control participants indicated that the two groups might rely on different memory strategies to solve the task. It was proposed that the NGT-R might be particularly amenable to a verbal strategy to support spatial memory, which may have prevented a behavioural deficit from emerging in the allocentric condition of this task. However, an alternative account is that the NGT-R lacks the necessary sensitivity to detect a short-term allocentric memory deficit. Importantly, the two accounts are not mutually exclusive and both should therefore be considered for future investigations in larger samples. It is also worth reiterating that a verbal scaffolding account represents only one of potentially several possible accounts for the present findings.

7.5.2 Hippocampal structure and function in depression

In contrast to the predictions, depressed patients did not show an attenuated differential BOLD signal for the contrast between the allocentric and egocentric condition in any of the subsections of the hippocampus. Further to this, they also did not show a volumetric reduction of the hippocampus. The first aspect to emphasise in terms of the absence of a hippocampal volume reduction concerns the interpretation of the spatial memory deficits discussed above. Namely, in the absence a structural abnormality, depressed patients would not necessarily be expected to show poor performance in the allocentric condition of the NGT-R. Further to this, the spatial memory deficits detected in the OLM and the VPT tasks are unlikely to be accounted for by volumetric differences of the hippocampus.

Although depressed patients did not differ from the control group in terms of overall hippocampal volume or condition-specific activity, the results of Experiment 8 provided some indication that hippocampal function may not have been identical in the two groups. Specifically, the ROI analysis provided evidence of a strong trend towards a significant interaction between group and hemisphere in the body of the hippocampus, independent of task condition. Although the post-hoc pairwise comparisons did not reveal any significant differences, this interaction appeared to be a reflection of a differential BOLD response in the

two groups in the right but not the left body of the hippocampus. More specifically, whilst patients did not appear to differ from control participants in the left body, they appeared to exhibit a smaller signal change from baseline in the right body of the hippocampus. Consequently, it can be speculated that the right hippocampus may not have been appropriately engaged in the depressed sample of Experiment 8. Importantly, however, this differential hippocampal response did not result in poorer performance in any of the condition of the NGT-R, which may indicate a reliance on a compensatory mechanism.

In relation to such a compensatory mechanism, a large body of evidence has indicated that there is a lateralisation of function in the medial temporal lobe, which is constituted by a right-sided specialisation for spatial memory (Smith and Milner, 1981; Spiers *et al.*, 2001a; Feigenbaum and Morris, 2004) and a left-sided specialisation for verbal and episodic memory (Nyberg *et al.*, 1996; Spiers *et al.*, 2001a; Banks *et al.*, 2012). It could therefore be proposed that depressed patients compensate for the functional abnormalities in the right hippocampus by shifting reliance to the left hippocampus, which behaviourally would be reflected in a shift from a predominantly visuospatial strategy to a predominantly verbal strategy to solve spatial memory tasks. As was discussed in the previous section, such a shift to a predominantly verbal strategy in the depressed sample could explain the behavioural results in the allocentric condition of the NGT-R.

The above discussion will undoubtedly remain speculative until the indications of a differential BOLD response in the body of the right hippocampus can be confirmed in a larger sample. Nevertheless, it is worth mentioning that the exploratory correlational analyses appeared to provide preliminary support for a greater reliance on the left body of the hippocampus in the depressed sample. Specifically, after controlling for age, there was a strong trend towards a significant relationship between higher error rates in the allocentric condition and smaller volumes of the left body of the hippocampus in the depressed sample. Thus, it appears as if performance in the allocentric performance was particularly dependent on the volume of the left body of the hippocampus in the patient group, which in turn can be considered consistent with a greater reliance on a left-lateralised verbal memory strategy (Banks *et al.*, 2012). In the control group, there was a weak trend towards a significant relationship between error rates in the allocentric condition and volumes of the right body of the hippocampus in the control group. If reliable, such a finding would support a reliance on the right hippocampus for allocentric performance in the control group, which in turn would

indicate the use of a visuospatial memory strategy in this group (Spiers *et al.*, 2001a). However, the direction of the relationship was the opposite of that found in the depressed group, with higher error rates being associated with larger volumes. Although this appears paradoxical, it should be emphasised that previous research has provided little evidence for the bigger-is-better hypothesis in the context of memory performance and hippocampal size in participants without neurological or psychiatric disorders (Van Petten, 2004). Needless to say, the relationship between hippocampal volume and performance in the NGT-R will require further study in larger samples.

Further to the relationship above, greater differential BOLD signal between the allocentric and egocentric condition in the left body of the hippocampus was strongly associated with greater severity of the depressive symptoms in the patient group. If such a differential signal is interpreted as a measure of the relative hippocampal engagement in the allocentric and egocentric conditions, it appears as if more severe depressive symptoms are associated with an increased engagement of the left body of the hippocampus in the NGT-R. In terms of hippocampal volume, the left hippocampus has previously been found to be particularly sensitive to the severity of symptoms in MDD (Vakili *et al.*, 2000; Weniger *et al.*, 2006). More importantly, it can be speculated that as patients become more depressed they become increasingly more reliant on the engagement of the left body of the hippocampus to implement the compensatory verbal memory strategy.

The preliminary nature of Experiment 8 makes an evaluation in the context of previous investigations of hippocampal function in depression difficult. However, it can be mentioned that Experiment 8 is not the first study that has failed to find unambiguous evidence of hippocampal dysfunction in a similarly small sample of depressed patients (Werner *et al.*, 2009). Furthermore, in larger samples, Milne *et al.* (2012) and Cornwell *et al.* (2010) found evidence of an abnormal recruitment of the right hippocampus during a recollection memory task and during allocentric navigation, which can be considered consistent with the indications of an inappropriate engagement of the right hippocampus in the depressed sample of Experiment 8. Further to this, the implication of the body of the hippocampus specifically is consistent with previous proposals that the posterior portion of the hippocampus may be particularly affected in depression (Neumeister *et al.*, 2005; Maller *et al.*, 2007; Cole *et al.*, 2010).

In regards to the use of BOLD fMRI in depression, it is important to emphasise that the underlying relationship between CBF, CBV and $CMRO_2$ may differ from that of healthy control participants. Specifically, early PET studies indicated that depressed patients exhibit *increased* blood flow to the hippocampus at rest (Videbech *et al.*, 2002). More recently, Colloby *et al.* (2012) used arterial spin labelling (ASL; for more detail see section 8.3) to investigate CBF in late-life depression and found evidence of increases in white matter CBF. Considering the potential presence of such alterations of vascular function in depression, it follows that the coupling between blood flow and oxygen metabolism may also be different in this population. Such differences in the underlying physiology on the BOLD response necessarily complicates the detection and interpretation of any group differences in BOLD signal (Buxton, 2012). Thus, although the present and a previous fMRI study (Milne *et al.*, 2012) have indicated that depressed patients may exhibit an abnormal BOLD signal in the right hippocampus, the underlying neural cause and thereby meaningful interpretation of this finding remains elusive.

Another important consideration in terms of the use of the NGT to assess hippocampal function in a depressed sample is whether it targets the appropriate subsection of the hippocampus. Specifically, when the egocentric condition was contrasted with the allocentric condition in Experiment 7, a strong effect was demonstrated in the head of the hippocampus, which is distinct from evidence showing that the body and the tail of the hippocampus are particularly affected in depression (Maller *et al.*, 2007). Consequently, it could be argued that the failure to detect a task-specific dysfunction in Experiment 8 could be explained by the fact that the NGT only provides a measure of neural function in the head of the hippocampus. However, when the combined sample was considered in Experiment 8, the strongest hippocampal effect for the contrast between the allocentric and egocentric conditions was found in the body and not the head of the hippocampus. Importantly, the body was also the only hippocampal subsection in which indications were found in support of an altered hippocampal system in the depressed sample. Consequently, it appears as if the NGT provided a measure of hippocampal function that was relevant to the potential effects present in the depressed sample. Nevertheless, it remains possible that a task with a more posterior focus would have been more sensitive in detecting alterations in hippocampal function depression.

To summarise, although the predictions of a volumetric reduction and a condition-specific attenuation of BOLD signal in the depressed group could not be supported, Experiment 8 provided indications that the right body of the hippocampus may not be normally engaged in the depressed group throughout the NGT-R. Exploratory correlational analyses subsequently provided preliminary evidence that such a task-independent reduction of the involvement of right hippocampus may have resulted in a greater reliance on the left body of the hippocampus in the depressed group. Although the small sample size prevents an absolute conclusion to be made in regards to hippocampal function in depression, Experiment 8 has therefore provided some interesting indications for future investigations in larger samples.

7.5.3 On the absence of hippocampal volume changes

Considering the consistency in the literature on hippocampal volume in depression (Koolschijn *et al.*, 2009; Arnone *et al.*, 2012), the lack of a significant reduction in the depressed sample of Experiment 8 was unexpected. On the other hand, such a null finding is also not unprecedented (Vakili *et al.*, 2000; Vythilingam *et al.*, 2004). Normal hippocampal volume in depresses patients is commonly proposed to be accounted for by the specific characteristics of the sample (Vythilingam *et al.*, 2004), including variations in illness duration, symptomatology and age (Sheline *et al.*, 2003; Colla *et al.*, 2007; McKinnon *et al.*, 2009; Eker and Gonul, 2010; Arnone *et al.*, 2012). In regards to the small sample tested in Experiment 8, it is also important to mention that the effect sizes derived from meta-analyses of hippocampal volume in depression have been relatively modest (~0.3-0.4; (Koolschijn *et al.*, 2009; Arnone *et al.*, 2012)).

Although changes in hippocampal volume in depression are often more substantial in patients who have experienced multiple episodes or a long duration of illness (MacQueen *et al.*, 2003; Sheline *et al.*, 2003), volume reductions have also been consistently demonstrated in first-episode depression (Cole *et al.*, 2011). Consequently, the depressed sample of Experiment 8, who had experienced an average of 4.2 (*SD*=3.8) depressive episodes and a total illness duration of 7.7 years (*SD*=6.7), could reasonably be expected to exhibit such volumetric changes. However, it is also important to mention that the extent of the reduction appears to be more subtle in patients with fewer past episodes (MacQueen *et al.*, 2003), with estimates of a 4-4.5% reductions in first-episode depression (Cole *et al.*, 2011) compared to estimates of 8-10% reductions when no restrictions of number of past episodes are imposed (Videbech

and Ravnkilde, 2004). Considering the inclusion of three first-episode patients in Experiment 8, it is therefore possible that the overall volume reduction was too subtle to be reliably detected in such a small sample. A similar case can be made for age at the time of testing. In a meta-analysis, McKinnon *et al.* (2009) estimated the hippocampal volume reduction in depressed patients between the age of 18 and 33 to 1.5%. Consequently, the inclusion of three patients under the age of 30 may have further diluted any existing effects in the small sample.

In the context of illness characteristics, the results of Experiment 8 revealed no correlations between hippocampal volume in any of the subsections and illness duration. Although the small sample size is likely to have been the predominant limitation in such analyses, an additional factor to consider is the duration of untreated illness. It has been proposed that antidepressant treatment may protect against hippocampal volume loss with cumulative episodes of depression (Sheline *et al.*, 2003), which suggest that the duration of untreated depression may be more important as a predictor of hippocampal volume than total illness duration. Thus, the use of total illness duration for the correlational analyses in Experiment 8 may have prevented a significant relationship from emerging. In addition, it should be emphasised that the self-reported retrospective estimates of illness duration may not have provided a sufficient level of accuracy. Although information about the duration of untreated illness was not available in Experiment 8, nine out of ten patients were taking antidepressant medication at the time of testing. This raises the possibility antidepressant medication may have protected the depressed sample from the hippocampal atrophy that otherwise would have occurred as a result of the long illness duration (Sheline *et al.*, 2003; Frodl *et al.*, 2008).

From the above discussion, it is clear that variation in factors such as illness duration, age and medication status could have contributed to the failure to detect any hippocampal volume reductions in Experiment 8. Although the null finding can also be interpreted as an indication that hippocampal volume reductions may not play a role in the pathophysiology in all cases of MDD, the consistency of previous findings and the limited sample size of Experiment 8 favour the former interpretation (Koolschijn *et al.*, 2009; Arnone *et al.*, 2012).

7.5.4 Replication of the results in Experiment 7

An important aspect of Experiment 8 was to investigate whether the results of Experiment 7 could be replicated. It was hypothesised that the greater reliance on spatial transformations

and landmark information in the allocentric condition would result in a greater involvement of the parieto-medial temporal pathway in the combined sample of patients and control participants. The findings of Experiment 8 only partially supported this hypothesis. Specifically, whilst the recruitment of the RSC in the allocentric condition was confirmed, the involvement of the posterior parietal lobe and the lingual gyrus could not be supported. The RSC represented the global peak for the contrast in Experiment 7, which indicates that only the strongest effects could be detected in Experiment 8. A likely cause for such an apparent lack of statistical power is the considerable variability of the sample tested in Experiment 8. Although the effects of age, depression and antidepressant medication on overall brain function is beyond the scope of the present project, such factors are likely to have acted to increase variability at a neural level and thereby reduced the statistical power to replicate previous effects (Spreng *et al.*, 2010; Diener *et al.*, 2012; Hoflich *et al.*, 2012).

Relative to the contrast between the allocentric and egocentric conditions of the NGT-R, the contrasts between such experimental conditions and the no-memory control condition revealed a set of clusters that was more comparable to the results of Experiment 7. Consequently, the association between the allocentric condition and regions along the parieto-medial temporal pathway, including the posterior parietal lobe, the RSC and the lingual gyrus, could be replicated. In addition, clusters of differential activation were found in the parahippocampus bilaterally, which can be considered consistent with its proposed role in memory for scenes and in the updating of the relationship between the observer and the scene viewpoint-shifts (Epstein and Kanwisher, 1998; Epstein *et al.*, 2003; Schmidt *et al.*, 2007). For the contrast between the egocentric condition and the control condition, the implication of the posterior parietal lobe could also be replicated. In regards to the variability in age, mental health and medication status highlighted above, such factors may have had a lesser effect in the low-level no-memory control condition, explaining the more comparable results derived from this contrast.

Further to the recruitment of the parieto-medial temporal pathway, the negative hippocampal BOLD signal in the allocentric condition relative to the egocentric condition was expected to be present in both groups of Experiment 8. Although no evidence was found to support this prediction at the whole-brain level, the ROI analysis supported the previously demonstrated negative BOLD response in the allocentric condition. Although the differential BOLD signal between the allocentric and the egocentric condition was only reliable in the body of the

hippocampus, the nature of the effect was comparable to that found in the head of the hippocampus in Experiment 7. Furthermore, the effect did approach significance in the head of the hippocampus, providing additional support that the hippocampus responds to the allocentric condition of the NGT-R by a drop in BOLD signal. It should not be understated, however, that such effects were considerably weaker in Experiment 8. Similarly to the parieto-medial temporal pathway, the weaker effects in the hippocampus are likely to be the results of the greater variability of the sample tested in Experiment 8. A potential effect of depression was indicated in the ROI analysis, in which the depressed group and the control group appeared to differ in the relative reliance on the left and right body of the hippocampus. Furthermore, previous research has indicated that hippocampal recruitment in allocentric spatial memory tasks may not be as reliable in older adults as in younger adults (Moffat *et al.*, 2006; Antonova *et al.*, 2009).

7.5.5 Summary

In contrast to the working hypothesis of hippocampal dysfunction in depression, Experiment 8 did not support an attenuation of the hippocampal engagement during allocentric short-term memory retrieval. The results did also not reveal any evidence of structural abnormalities of the hippocampus or of a disproportionate behavioural deficit of allocentric memory in the depressed sample. Although such null findings contradict the idea that the hippocampus plays a pivotal role in the pathophysiology of all cases of major depressive disorder, it is critical to emphasise that the variability and size of the depressed sample may have prevented any existing effects from emerging. In the absence of any volumetric changes to the hippocampus, Experiment 8 nevertheless provided subtle indications that the hippocampal system may not function normally in depression. Specifically, the ROI analysis indicated that the depressed group may not have engaged the right body of the hippocampus appropriately, which may have underpinned the demonstrated memory deficit for precise locations (Smith and Milner, 1981). To compensate for such a deficit, it was speculated that the depressed patients may have opted for a verbal memory strategy to solve the allocentric condition of the NGT-R. Such a switch to a left-lateralised verbal memory strategy received some preliminary support in the exploratory correlational analyses and was proposed to provide a valid account for the behavioural findings in the NGT-R. Although this interpretation provides some interesting avenues for future investigations, it will be undoubtedly be paramount to confirm the reliability of the results in Experiment 8 in larger samples.

Chapter 8 General discussion

8.1 Summary of contributions

8.1.1 The Northumberland Gallery Task

The primary aim of Part I of the present project was to investigate the role of the hippocampus in allocentric memory when no navigation is required. To this end, the NGT was developed and represents an important contribution of the thesis. The design of the NGT is grounded in current models of spatial reference frames, which advocate the parallel workings of egocentric and allocentric subsystems (Shelton and McNamara, 2001; Burgess, 2006; Zhang *et al.*, 2011), and incorporates features from a range of tasks previously used to assess the contribution of the hippocampus in spatial memory (Morris, 1981; King *et al.*, 2002; King *et al.*, 2004; Parslow *et al.*, 2004; Schmidt *et al.*, 2007). As such, it utilises an instantaneous viewpoint-shift to encourage the use of environmental landmarks and thereby engage the hippocampus-dependent allocentric subsystem (O'Keefe, 1978; Muller and Kubie, 1987; Goodrich-Hunsaker *et al.*, 2010). At a theoretical level, such a disruption is thought to require participants to recover the reference direction of the allocentric representation of the target location from the inter-landmark vectors in the scene (Shelton and McNamara, 2001; Zhang *et al.*, 2011). In contrast to the vast majority of previous tasks (Maguire *et al.*, 1998a; Parslow *et al.*, 2004; Xu *et al.*, 2010), the NGT does not require participants to navigate, which makes it ideal for a focused investigation of allocentric spatial memory, independently of the cognitive processes associated with the act of navigation execution (King *et al.*, 2002; Schmidt *et al.*, 2007). A critical feature of the NGT is the inclusion of a contrasting egocentric condition, in which an instantaneous shift of environmental landmarks encourage the use of the observer position to support location memory and engages the hippocampus-independent egocentric subsystem (Burgess, 2008). Although similar strategies have been used to assess egocentric spatial memory in navigation-based tasks (Parslow *et al.*, 2004; Weniger *et al.*, 2012), the inclusion of a visually identical egocentric condition represents an improvement on previous viewpoint-shift tasks (King *et al.*, 2004; Schmidt *et al.*, 2007).

Based on the eight studies implementing the NGT in the present project, it is evident that the viewpoint-shifts and landmark-shifts have distinguishable effects on spatial memory performance, which support that participants are indeed relying on different reference

systems to solve the allocentric and egocentric conditions. The alignment effect, as reflected by increased response times for greater viewpoint-shifts, can be interpreted as constituting the greater cognitive cost associated with the recovery of the reference direction following more substantial viewpoint-shifts (Shelton and McNamara, 2001; Zhang *et al.*, 2011). Similarly, since the transient self-object vectors are directly accessible in the egocentric condition, the improved performance in this condition can be proposed to be a reflection of a corresponding cut in cognitive cost. Nevertheless, an effort was made to reduce the discrepancy in difficulty between the two conditions to optimise the task for a neuroimaging and a clinical context. Whilst a more extensive training paradigm and an introduction of subtle environmental axes did not improve performance in the allocentric condition, an elevation of the viewpoint significantly lowered error rates, arguably as a result of the improved visibility of object-to-object relationships and the prevention of the perspective projection distortion. The discrepancy in difficulty between the two conditions could not be completely eliminated, however. Although a further reduction of the discrepancy may have been achievable, it is important to emphasise that whilst the egocentric condition only requires the egocentric subsystem, the allocentric condition requires a coordination of both subsystems and a recovery of the reference direction, which necessarily increases the demand in the latter condition.

The NGT, as performed from the elevated viewpoint, produces consistent results in both young and middle-aged healthy volunteers. An abbreviated version of the task, the NGT-R, has been piloted in a different lab with results consistent with the full-length version. The behavioural version of the NGT-R takes approximately 30 minutes to administer, including the training paradigm, instruction and practice trials, allowing it to form part of a larger test battery. The NGT-R has also been optimised for administration in an MR scanner with fixed trial lengths and incorporated fixation events. With an administration time of approximately 30 minutes, excluding training and instruction, the neuroimaging version of the task produces consistent results with the behavioural version. The NGT and the NGT-R, as performed from the elevated viewpoint, has been administered to over 120 volunteers of a range of different ages with consistent results. Further to this, the NGT-R has been used successfully in a small sample of depressed patients. An important contribution of the present project is therefore a non-navigational task of short-term allocentric memory, which can be used in a range of different samples and contexts.

8.1.2 The hippocampus and allocentric memory

As would be predicted from an engagement of the allocentric subsystem (O'Keefe, 1978; Burgess, 2008), the hippocampus showed a differential involvement in the allocentric condition relative to the egocentric condition in a neuroimaging context. This involvement was characterised by a substantial drop in BOLD signal relative to the fixation baseline in the allocentric condition, which theoretically could be due to either a suppression of neural activity as part of a larger default network (Buckner *et al.*, 2008; Huijbers *et al.*, 2011) or to an increase in neural activity accompanied by a greater increase in $CMRO_2$ relative to the increase in CBF (Ekstrom, 2010; Buxton, 2012). Although arguments tended to favour an increase in neural activity, the two accounts could not be distinguished based on BOLD signal alone. Thus, the precise neural basis of the hippocampal involvement in the allocentric condition of the NGT-R remains elusive.

Hippocampal BOLD signal was only different relative to the fixation baseline in the allocentric condition, which indicated a specific involvement of the hippocampus in allocentric spatial memory. This is consistent with models assigning a role for the hippocampus in environmentally grounded representations of space (O'Keefe, 1978; Byrne *et al.*, 2007; Burgess, 2008) and with a vast evidence base linking the hippocampus to the allocentric subsystem of spatial memory (Muller and Kubie, 1987; Cornwell *et al.*, 2008; Goodrich-Hunsaker *et al.*, 2010). Importantly, the implication of the hippocampus in the allocentric condition of the NGT extends its role in providing landmark-centred representations to situations in which such representations do not form the basis for navigation (Burgess *et al.*, 2001; Schmidt *et al.*, 2007). It is also consistent with a role for the anterior hippocampus in the processes of self-localisation, target localisation and path planning in the initial stages of navigation (Spiers and Maguire, 2006; Cornwell *et al.*, 2008; Shipman and Astur, 2008; Xu *et al.*, 2010). In regards to the hippocampal involvement in the NGT, an interesting parallel can be drawn to the mental scene construction account proposed by Hassabis and Maguire (2007a, 2009). Specifically, it was proposed that the role of the hippocampus concerns the retrieval and integration of information into a coherent spatial context, both in processes of memory and imagination. In the context of the NGT, it is conceivable that the allocentric condition required a process of scene construction in order to retrieve and integrate the target location and the obscured landmarks into the context of the current scene. Considering the unlikely recruitment of a similar process in the egocentric

condition, it could therefore be argued that the apparent hippocampal involvement in the allocentric condition may be due to a memory-based scene construction element. Interestingly, memory-based scene construction has been associated with activation in the RSC and the posterior parietal lobe, as well as in the hippocampus (Hassabis et al., 2007b), which is consistent with the implication of these very regions in the allocentric condition of the NGT (see section 8.1.3).

The implication of the hippocampus in a viewpoint-shift task, such as the NGT, has important implications for the design of allocentric spatial memory tasks. For investigations that are not concerned with navigation execution *per se* but with spatial memory, the inclusion of a navigational element will be redundant and risks diluting the effects of interest. Although classic rodent memory tasks, such as the MWM and the RAM (Olton and Samuelson, 1976; Morris, 1981), have provided invaluable inspiration for the assessment of allocentric spatial memory in humans (Shipman and Astur, 2008; Goodrich-Hunsaker and Hopkins, 2010), it should be remembered that humans are able to demonstrate memory in ways other than actual navigation behaviour. Consequently, when navigation execution is not of interest, the NGT and other viewpoint-shift tasks appear to represent useful measures of allocentric spatial memory in humans (King *et al.*, 2002; Hartley *et al.*, 2007). The hippocampal involvement also supports the value of viewpoint-shift tasks in a neuroimaging context. Whilst viewpoint-shift tasks have been used to assess the effects of medial temporal lobe damage on allocentric memory in several investigations (Holdstock *et al.*, 2000; King *et al.*, 2002; King *et al.*, 2004; Hartley *et al.*, 2007), the use of this type of task in neuroimaging studies has been much more limited (Schmidt *et al.*, 2007). To my knowledge, the present project represents the first neuroimaging study to demonstrate hippocampal involvement in a viewpoint-shift task. Whilst Schmidt and colleagues found that hippocampal activity varied as a function of performance in a viewpoint-shift task, the hippocampus was not implicated when this task was contrasted with a no-memory control condition. In the NGT, the egocentric condition therefore appears to have provided a more precise comparison for the contrast analysis, which is likely to have contributed to the detection of hippocampal recruitment. The present project has therefore further emphasised the importance of selecting an appropriate control condition when investigating hippocampal function (Stark and Squire, 2001).

8.1.3 The parieto-medial temporal pathway and allocentric memory

The implication of the full extent of the parieto-medial temporal pathway in the allocentric condition of the NGT-R supports its role in landmark-centred cognition even when no navigation is required (Burgess *et al.*, 2001; Schmidt *et al.*, 2007; Galati *et al.*, 2010). It indicates that the posterior parietal lobe and the retrosplenial cortex both contribute to transformations between spatial coordinate systems, which allows for the critical determination of one's location in space relative to allocentrically represented stable landmarks (Maguire, 2001; Byrne *et al.*, 2007; Burgess, 2008; Calton and Taube, 2009). The engagement of the left lingual gyrus was found to be sensitive to the degree of viewpoint-shift, which is consistent with previous findings and indicate a greater reliance on environmental landmarks for re-orientation following more substantial viewpoint-shifts (Epstein and Kanwisher, 1998; Schmidt *et al.*, 2007). A similar sensitivity to viewpoint-shifts was demonstrated in a novel region, the left cuneus, which given its spatial proximity to the precuneus may reflect a contribution to the imagery of retrieved material (Fletcher *et al.*, 1996). As such, the left lingual gyrus and cuneus can be proposed to support the recovery of the reference direction from the inter-landmark vectors required following a shift in viewpoint (Shelton and McNamara, 2001; Zhang *et al.*, 2011).

8.1.4 Hippocampal function in depression

The NGT-R was successfully administered to a small sample of depressed patients inside of an MR scanner. Inconsistent with previous findings (Koolschijn *et al.*, 2009; Arnone *et al.*, 2012), depressed patients did not exhibit a reduction of hippocampal volume. The NGT-R did also not detect any abnormalities in the allocentric condition, neither at a behavioural nor at a neural level. Although there were indications of a deficient visuospatial strategy and of altered function of the right body of the hippocampus in the depressed sample, such findings must await confirmation in larger samples. Considering the limitations of the small sample, any firm conclusions in regards to hippocampal dysfunction in depression are considered premature. Nevertheless, the present project has demonstrated that the NGT can be used in a population with documented cognitive deficits, which indicates its potential use in a range of clinical populations.

8.2 Limitations

Limitations of the present project have been emphasised and discussed in detail in the previous chapters. Therefore, only the most significant drawbacks of the NGT, BOLD fMRI and the size and characteristics of the samples will be reiterated in the present section.

The NGT was developed to separate between location memory based on allocentric and egocentric reference frames. Although the manipulations of viewpoint and landmark positions act to engage one spatial subsystem over the other, it is critical to emphasise that the task does not achieve an absolute separation. Whilst it is the case that the landmarks can only be used to retrieve the target location in the allocentric condition, the appraisal of such landmarks necessarily depends on egocentric sensory systems. Conversely, allocentric cues, such as the arena wall or the edges of the screen, remain available after the landmark-shift in the egocentric condition. Whilst the influence of egocentric sensory systems in the allocentric condition is largely unavoidable, a cleaner distinction could have been achieved by preventing the use of non-landmark environmental cues in the egocentric condition. However, it is equally important to emphasise that a complete elimination of allocentric cues is unlikely to be possible (see section 3.1.1). Thus, whilst some overlap between the conditions should be expected as a result of the parallel workings of the allocentric and egocentric subsystems (Burgess, 2006), a more controlled egocentric condition could potentially have added further the sensitivity to the contrast analysis.

Another important limitation of the NGT is the different levels of difficulty in the allocentric and egocentric conditions. This limitation was particularly apparent in the neuroimaging component of the present project, in which any differential BOLD signal in the two conditions could be ascribed to such differences in difficulty. In the NGT, statistical control of such differences in performance is furthermore problematic since the cognitive processes of interest are thought to be closely related to such measures (Gilbert *et al.*, 2012). Although the nature of the allocentric condition may inherently make it more demanding, the discrepancy in performance between conditions was undoubtedly limiting for the interpretation of the negative BOLD signal in the hippocampus. Since the effects of difficulty could not be reliably estimated or statistically controlled for, the differential difficulty levels in the experimental conditions of the NGT must be considered an important confounding variable.

Further to the limitations above, the exploratory study in a depressed patient sample highlighted additional drawbacks of the NGT. First, the easily nameable landmarks in the NGT environment allow for a verbalised representation of the target location. Considering that both verbal and visuospatial memory strategies are likely to implicate the hippocampus, albeit in different hemispheres (Smith and Milner, 1981; Frisk and Milner, 1990; Spiers *et al.*, 2001a), this limitation is more concerned with the purity of the task rather than the contribution of the hippocampus in the task. Such task impurity is undesirable, however, and becomes particularly problematic for disentangling the cognitive processes associated with group differences. The second limitation to be highlighted was a potential lack of sensitivity of the NGT. As has been mentioned, the use of a single target location may have prevented the detection of subtler deficits in the patient group. Adding to this, the use of a single foil location at test means that a response can only be categorised as correct or incorrect. Considering that spatial memory representations are likely to vary continuously along dimensions of quality and precision, such a dichotomous response represents a relatively rough measure of performance. Thus, a potential lack of sensitivity of the NGT is an important limitation, particularly in relation to the detection of subtle group differences.

A more general point can also be made in regards to the lack of formal tests of reliability and validity. Although the NGT has been used extensively throughout the project with robust and repeatable results, slight differences between experiments in terms of task design, testing situation or population prevented formal testing of reliability. Furthermore, in terms of validity, an exploration of the relationship between performance in the NGT and other tasks designed to assess allocentric spatial memory, such as the MWM, could have provided additional information of the cognitive processes involved.

In addition to the limitations associated with the NGT, there are important limitations associated with measure of neural activity. In general terms, the use of BOLD fMRI is limited by a relatively poor understanding of the underlying physiological mechanisms of the signal (Buxton, 2012). Relative to the neocortex, the hippocampus is likely to show an even more complex relationship between CFB and $CMRO_2$, which makes an interpretation of the resulting BOLD signal in this region particularly difficult (Ekstrom, 2010; Buxton, 2012). Consequently, the negative hippocampal BOLD signal in the present and in previous studies (Rekkas *et al.*, 2005; Shipman and Astur, 2008) could be both a reflection of high-metabolic activity without a corresponding overshoot in cerebral blood flow and of an actual decrease

in metabolic activity. The inability to distinguish between such opposing accounts undoubtedly represents one of the most important limitations of the present project.

A final limitation to be emphasised here concerns the size and characteristics of the samples tested. Although the NGT has been used behaviourally in a large sample of healthy volunteers covering a range of different ages, the initial neuroimaging study was limited to a smaller sample of young volunteers. Thus, the results of this study cannot be generalised to volunteers of an older age. In the subsequent neuroimaging study, the tested sample covered a greater age range but also included patients with depression. Consequently, it is difficult to disentangle the effects of age and mental health in a direct comparison of the outcome derived from the two studies. More importantly, the sample of depressed patients was small and varied considerably in both demographic and clinical characteristics, which presents a major limitation in terms of the statistical power for the group comparison in this study.

8.3 Future directions

A central finding of the present project was the demonstration of a negative BOLD signal in the hippocampus during allocentric short-term memory retrieval. To arrive at a meaningful interpretation of such a hippocampal response in this and previous investigations (Rekkas *et al.*, 2005; Shipman and Astur, 2008) it will be critical to determine its physiological basis. An increased understanding of the complex relationship between CBF and $CMRO_2$ and possible dissociations between BOLD signal and underlying neural activity represent a challenging but important goal for future investigations of hippocampal function (Restom *et al.*, 2008; Schridde *et al.*, 2008). To achieve this it will be necessary to go beyond the BOLD signal and focus on the multiple physiological processes that underlie it. One fMRI technique that allows for an independent measure of cerebral blood flow is arterial spin labelling (ASL), which uses radiofrequency pulses from the MR system to transiently label flowing blood. The spin-labelled MR scan is subsequently compared to a control acquisition to isolate the purely flow-dependent ASL difference signal (Detre *et al.*, 2012). In calibrated fMRI, measurements of CBF from ASL and of regular BOLD during periods of activation and mild hypercapnia can be used to calculate $CMRO_2$ (Davis *et al.*, 1998). Information about hippocampal $CMRO_2$ in response to relevant cognitive tasks is likely to be particularly important as this variable shows a tight relationship with neural activity (Hyder *et al.*, 2001; Restom *et al.*, 2008). Although computationally complex, multi-modal measurements of

changes in $CMRO_2$, CBF and BOLD fMRI signal provide a way to validate and calibrate BOLD image-contrasts (Hyder *et al.*, 2001). As such, it would allow an investigation of whether negative BOLD responses in demanding memory tasks, such as the allocentric condition of the NGT, can be explained by a tighter coupling between $CMRO_2$ and CBF (Restom *et al.*, 2008; Ekstrom, 2010). Such an investigation would also have the potential of shedding light on why certain baseline conditions are more likely than others to reveal a positive BOLD signal in the hippocampus (Stark and Squire, 2001). Calibrated fMRI could also provide important information about a potentially different coupling between $CMRO_2$ and CBF in clinical populations, which would allow a more meaningful interpretation of differences in BOLD signal relative to healthy control groups. Until the physiological basis of the negative BOLD response is better understood, it will be critical for researchers not to assume a simple correspondence between BOLD signal and neural activity in subcortical regions, such as the hippocampus (Buxton, 2012). Furthermore, it will be important to continue to report findings of negative BOLD signal in the hippocampus, as defined relative to an independent baseline condition (Hayes and Huxtable, 2012), to increase understanding of the circumstances under which it occurs.

In contrast to the findings in the hippocampus, a number of regions exhibited a more unambiguous positive BOLD signal in response to the allocentric condition of the NGT. Considering its additional sensitivity to increasing viewpoint-shifts, the left lingual gyrus represents an interesting avenue for future research. The findings of the present project support a general role for the lingual gyrus in the decoding and representation of the orientation value of landmarks in memory and perception (Aguirre *et al.*, 1998; Committeri *et al.*, 2004; Schmidt *et al.*, 2007). An interesting proposal for future investigations is that the lingual gyrus plays an instrumental role in recovering the reference direction from the available environmental cues in the scene (Shelton and McNamara, 2001; Zhang *et al.*, 2011). Such a role could be tested empirically by contrasting the current allocentric condition of the NGT with a similar condition in which the need for recovery of the reference direction is removed by making it explicit in the scene. If the lingual gyrus underlies the recovery of the reference direction, its contribution can be considered critical for access to the stored spatial representations provided by the hippocampus.

For future investigations, changes to the NGT itself should also be considered. In particular, a continuous response, such as indicating the location of the target by the use of a computer

mouse or a joystick, is likely to provide a more precise measure of the accuracy of the spatial memory representation. In the context of patient groups with executive and motivational problems (Elliott *et al.*, 1996; Fossati *et al.*, 2002), such a shift to a continuous response in an effort to increase task sensitivity would appear preferable to an increase in the number of target locations. Efforts are also recommended to further reduce the discrepancy in difficulty between the allocentric and egocentric conditions of the NGT. This could be achieved by an increase of the difficulty in the egocentric condition, for example by a reduction of target-foil distances in this condition. Alternatively, an additional control condition with a difficulty level that corresponds to the allocentric condition could be included to evaluate effects of general task difficulty.

In addition to the modifications suggested above, the experimental control of the strategies available in the NGT could be improved further. In the egocentric condition, the wall of the NGT environment could be removed or altered in shape to prevent it from being used as a cue to location. Although such a manipulation would make the egocentric condition visually distinct from the allocentric condition and would not prevent the use of alternative environmental cues, such as the edges of the screen or the scanner bore, it would increase the probability of an egocentric strategy. Further to this, the NGT environment could be modified to be less amenable to a verbal memory strategy, for example by the use of abstract patterns as landmarks (Parslow *et al.*, 2004). To allow for a closer evaluation of a potential shift between spatial subsystems or memory strategies for viewpoint-shifts greater than 90°, a larger set of viewpoint-shifts could also be included in the NGT. Finally, formal tests of reliability and validity of the NGT should be considered for future investigations.

The NGT has the potential of being used to assess hippocampal function in a range of clinical populations. In the present project, the NGT was successfully administered to a sample of depressed patients. In the context of normal hippocampal volume in the depressed sample, no behavioural deficits or task-specific abnormalities of hippocampal dysfunction could be detected by the NGT. Although functional abnormalities are theoretically possible in the absence of structural abnormalities, it will be important to evaluate the NGT in a larger sample of depressed patients who also exhibit the typical hippocampal volume reduction (Arnone *et al.*, 2012). To increase the probability of recruiting such a sample, it would be advisable to target patients with a longer history of depression (MacQueen *et al.*, 2003). To explore the effect of past illness history on hippocampal volume and function, the duration of

untreated illness, in addition to total illness duration, should also be recorded (Sheline *et al.*, 2003).

A more ambitious suggestion for future investigations would be a longitudinal investigation of hippocampal function in depression. If hippocampal volume and function could be reliably measured at the point of diagnosis, before any antidepressant treatment is administered, and subsequently at regular intervals as the illness progresses or resolves, it would likely increase our understanding of the specific role of the hippocampus in the pathophysiology of depression. Considering the likely complex relationship between hippocampal volume, cerebral blood flow and BOLD signal in depression (Buxton, 2012), calibrated fMRI may be considered for such investigations. Furthermore, it is important to emphasise that depressed patients are not the only patient group with hippocampal abnormalities. For example, patients with bipolar disorder (Hajek *et al.*, 2012), schizophrenia (Shepherd *et al.*, 2012) and mild cognitive impairment (Yassa *et al.*, 2010) have all been shown to exhibit structural abnormalities of the hippocampus. Thus, the NGT may prove to be a useful measure of hippocampal function in such populations in the future. Importantly, since the NGT assesses the cognitive processes thought to underlie the initial stages of navigation, it provides a measure that is relevant for real-life functioning whilst also exhibiting a high degree of experimental control.

8.4 Conclusions

In Part I of the present thesis it was hypothesised that the hippocampus provides allocentric memory representations, independently of whether such representations form the basis for navigation. Results derived from an fMRI investigation supported a role for the hippocampus during allocentric short-term memory retrieval in a task that required no navigation, although this role was characterised by a substantial reduction of the BOLD signal below baseline. In Part II of the thesis, the working hypothesis implicated functional abnormalities of the hippocampus in depression. In the absence of structural abnormalities of the hippocampus, an fMRI investigation in a small sample of depressed patients and matched control participants revealed no evidence of task-specific functional abnormalities. Recommendations for future research include a detailed investigation of the physiological basis of the negative BOLD response in subcortical regions and further study of hippocampal function in depression and its relationship with illness characteristics in larger samples.

Appendix A

GALLERY TASK – EXPERIENCE QUESTIONNAIRE

Participant ID: …….

Did you find any of the conditions more difficult than the others?

Yes ☐ No ☐

If yes, which condition did you find more difficult?

You ☐ Walls ☐ None ☐

Why did you find this condition more difficult?

What strategies, if any, did you use to remember the pole location in the…

1) 'You' condition

……
……
……
…….

2) 'Walls' condition

……
……
……
…….

3) 'None' condition

……
……
……
…….

Appendix B

SANTA BARBARA SENSE-OF-DIRECTION SCALE

Sex: F M Today's Date:_____

Age:_____ V. 2

This questionnaire consists of several statements about your spatial and navigational abilities, preferences, and experiences. After each statement, you should circle a number to indicate your level of agreement with the statement. Circle "1" if you strongly agree that the statement applies to you, "7" if you strongly disagree, or some number in between if your agreement is intermediate. Circle "4" if you neither agree nor disagree.

1. I am very good at giving directions.

strongly agree 1 2 3 4 5 6 7 strongly disagree

2. I have a poor memory for where I left things.

strongly agree 1 2 3 4 5 6 7 strongly disagree

3. I am very good at judging distances.

strongly agree 1 2 3 4 5 6 7 strongly disagree

4. My "sense of direction" is very good.

strongly agree 1 2 3 4 5 6 7 strongly disagree

5. I tend to think of my environment in terms of cardinal directions (N, S, E, W).

strongly agree 1 2 3 4 5 6 7 strongly disagree

6. I very easily get lost in a new city.

strongly agree 1 2 3 4 5 6 7 strongly disagree

7. I enjoy reading maps.

strongly agree 1 2 3 4 5 6 7 strongly disagree

8. I have trouble understanding directions.

strongly agree 1 2 3 4 5 6 7 strongly disagree

9. I am very good at reading maps.

strongly agree 1 2 3 4 5 6 7 strongly disagree

10. I don't remember routes very well while riding as a passenger in a car.

strongly agree 1 2 3 4 5 6 7 strongly disagree

11. I don't enjoy giving directions.

strongly agree 1 2 3 4 5 6 7 strongly disagree

12. It's not important to me to know where I am.

strongly agree 1 2 3 4 5 6 7 strongly disagree

13. I usually let someone else do the navigational planning for long trips.

strongly agree 1 2 3 4 5 6 7 strongly disagree

14. I can usually remember a new route after I have traveled it only once.

strongly agree 1 2 3 4 5 6 7 strongly disagree

15. I don't have a very good "mental map" of my environment.

strongly agree 1 2 3 4 5 6 7 strongly disagree

Appendix C

INCLUSION AND EXCLUSION CRITERIA FOR THE PILOT

Inclusion criteria for all depressed patients:

1) Aged between 18-65

2) Primary diagnosis of major depressive disorder

3) No other axis-I diagnosis

Additional inclusion criterion for remitted depressed patients:

1) Free of depressive symptoms for at least 4 weeks and scored ≤ 7 on the 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton 1960) on the day of testing

Additional inclusion criterion for currently depressed patients:

1) Symptomatic for at least two weeks and scored ≥ 15 on the HAM-D on the day of testing.

Exclusion criteria for all depressed patients:

1) A change of medication within four weeks of testing

2) Use of steroidal medication

3) Any other current axis-I diagnosis

4) A history of mania or hypomania

5) Current alcohol or drug dependence

6) Electro-convulsive therapy in the last six months

7) History of head injury with loss of consciousness exceeding 5 minutes

8) Any other significant, uncorrected physical or neurological illness

Inclusion criterion for the control group:

1) Aged between 18-65

Exclusion criteria for the control group:

1) Not currently using any medication (other than the oral contraceptive pill)

2) No personal history of psychiatric illness

3) No history of affective disorder in a first degree relative

4) Score of < 7 on the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock & Erbaugh 1961)

Appendix D

Supplementary Table 1: Pearson's correlation coefficients for the relationships between age and normalised hippocampal volume and difference in hippocampal BOLD signal between the allocentric and egocentric conditions in the depressed sample.

		Normalised volume (mm^3)		BOLD signal (arbitrary signal)	
		r	*p*	*r*	*p*
Head	Right	-0.009	0.981	-0.167	0.644
	Left	0.065	0.858	0.022	0.952
Body	Right	-0.382	0.276	-0.084	0.817
	Left	-0.376	0.284	-0.427	0.219
Tail	Right	**0.635**	**0.049**	-0.111	0.761
	Left	0.109	0.763	**-0.788**	**0.007**

Supplementary Table 2: Pearson's correlation coefficients for the relationships between age and normalised hippocampal volume and difference in hippocampal BOLD signal between the allocentric and egocentric conditions in the control sample.

		Normalised volume (mm^3)		BOLD signal (arbitrary signal)	
		r	*p*	*r*	*p*
Head	Right	0.035	0.924	*0.609*	*0.062*
	Left	0.055	0.881	0.592	*0.071*
Body	Right	-0.457	0.184	0.494	0.146
	Left	**-0.682**	**0.03**	0.505	0.136
Tail	Right	**-0.714**	**0.02**	**0.437**	**0.048**
	Left	**-0.646**	**0.043**	-0.116	0.75

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