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A functional Segregation along the Hippocampal Anterior-posterior Axis

Thesis for the degree of Philosophiae Doctor

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En funksjonell segregering langs hippokampus' lengdeakse i menneske

Bakgrunn: Hippokampus er en struktur i hjernen som er viktig for hukommelse og navigasjon. Det er blant annet funnet «Place cells», celler som fyrer for et bestemt sted i et miljø i hippokampus. Hippokampus har ofte blitt delt opp på ulike måter for å prøve å øke vår forståelse av hvilken rolle ulike deler av denne strukturen spiller for forskjellige funksjoner. For eksempel er det funnet at ulike områder langs hippokampus lengdeakse understøtter forskjellige fuksjoner. I rotter har man funnet at bak i hippokampus, hippokampushalen, er mer detaljert informajon om romlige forhold bearbeidet, mens i fremre hippokampus, hippokampushodet, undersøttes en oversikt over miljøet.

Formål: Formålet med avhandlingen er å kartlegge i hvilken grad en funksjonell segregering for romlig informasjon eksiterer langs lengdeaksen i hippokampus.

Metode: Fire studier har blitt gjennomført. I alle disse ble funksjonell magnetisk resonans bildedannelse, fMRI, benyttet. fMRI er en teknikk som måler aktiveringen i hjernen indirekte basert på endringer okygerings nivået i blod relatert til hjernecellefyring. Forsøkene ble utført av friske, frivillige menn som bevegde seg rundt i enten kjente eller ukjente virtuelle miljø mens det ble tatt opp fMRI bilder.

Hovedfunn: I studie 1 observerte vi at aktiveringen i den fremre delen av hippokampus økte for den initielle perioden under navigering, assosiert med en global representasjon av miljøet, mens aktiveringen i den bakre delen av hippocampus økte med jevne mellomrom gjennom hele navigasjonsperioden, assosiert med lokale representasjoner av miljøet. I studie 2 fant vi at aktiveringen i den bakre delen av hippokampus økte når finkornede lokale representasjoner av miljøet ble benyttet under navigering, mens aktiveringen i den fremre delen av hippocampus økte når en grovkornet global representasjon ble benyttet. De personene som i større grad benyttet en global representasjon av miljøet hadde i tillegg et større fremre, og et mindre bakre, hippokampusvolum. I studie 3 ble det funnet at aktiveringen i den bakre delen av hippokampus var høyest når en finkornet representasjon av posisjonene til miljøets objekter ble innkodet, i den midtre delen av hippokampus var aktiveringen høyest når en middels kornet representasjon av posisjonene ble innkodet, mens i den fremre delen av hippokampus var aktiveringen i større grad like høy for alle typer kornethet samtidig som den korrelerte med antallet miljø med posisjonene innkodet når man tillot en grovkornet representasjon av objektenes posisjon. I studie 4 fant vi at aktiveringen i den bakre delen av hippokampus økte når lokale representasjoner av miljøet ble benyttet under navigering, mens aktiveringen i den fremre delen av hippokampus økte når man integrerte separat innkodede nærliggende og fjerntliggende representasjoner til en ny sammenstilt representasjon.

Konklusjon: Den bakre delen av hippokampus er viktig for lokale finkornede representasjoner av miljøet, den midtre delen av hippokampus middels kornede representasjoner, mens den fremre delen av hippokampus er viktig for en grovkornet, global representasjon av miljøet som også støtter fin- og middels kornede representasjoner.

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LIST OF PAPERS

Paper 1	Xu J, Evensmoen HR, Lehn H, Pintzka CWS, Håberg AK (2010) Persistent posterior and transient anterior medial temporal lobe activity during navigation. *Neuroimage 52:1654-1666.*
Paper 2	Evensmoen HR, Lehn H, Xu J, Witter MP, Nadel L, Håberg AK. The anterior hippocampus supports coarse, Global environmental representations, and posterior hippocampus fine-grained, local environmental representations. *Accepted for publication in J Cogn Neurosci May 21 2013.*
Paper 3	Evensmoen HR, Ladstein J, Hansen TI, Møller JA, Witter MP, Nadel L, Håberg AK. Variations in the granularity of environmental representations along the hippocampal anterior-posterior axis. *Submitted.*
Paper 4	Evensmoen HR, Xu J, Iversen C Witter MP, Nadel L, Håberg AK. Proximal and distal landmarks are integrated in the hippocampal head. *Manuscript.*

OTHER PUBLISHED PAPERS

1. Kjelvik G, Evensmoen HR, Brezova V, Håberg AK (2012) The human brain representation of odor identification. Journal of Neurophysiology 108:645-657.
2. Poppenk J, Evensmoen HR, Moscovitch M, Nadel L (2013) Long-axis specialization of the human hippocampus. Trends in Cognitive Sciences 17:230-240.

ABBREVIATIONS

CA(1-3)	CornuAmmonis (fields 1-3)
V4	Visual area number 4 in the brain
fMRI	functional Magnetic Resonance Imaging
BOLD	Blood Oxygen Level Dependent
VR	Virtual Reality
PET	Positron Emission Topography
MRI	Magnetic Resonance Imaging
MP-Rage	Magnetization-Prepared Rapid Acquisition With Gradient Echo
T	Tesla, unit of magnetic field strength
TR	Repetition time, time required for acquisition of one fMRI volume
TE	Echo Time
FOV	Field Of View
MNI	Montreal Neurological Institute
GLM	General Linear Model

INTRODUCTION

In this thesis, the possibility of a specialization along the anterior-posterior axis of the hippocampus, but also entorhinal cortex, parahippocampal cortex and inferior parietal cortex, for the representation of environmental representations will be investigated, using blood oxygen level dependent (BOLD) functional magnetic resonance imaging fMRI and structural MRI.

HIPPOCAMPAL ANATOMY

The hippocampus is positioned on top of the anatomical hierarchy within the medial temporal lobe (Lavenex and Amaral, 2000). Cytoarchitectonical differences and connectivity data gave early rise to a subdivision of the hippocampus in the transverse plane into dentate gyrus, cornu ammonis (CA1-3), and subiculum (Andersen et al., 1971). There is also evidence for an anatomical segregation along the hippocampal anterior-posterior axis. Already in 1901 differences in connectivity along the longitudinal axis were observed, i.e. two afferent paths from the entorhinal cortex were observed to project either to posterior or anterior hippocampus (Cajal, 1901; Fanselow and Dong, 2010). Furthermore, in 1934 the hippocampus was divided into three subregions along the anterior-posterior axis based on afferent input differences (Lorento de Nó, 1934). There is now strong anatomical evidence for a subdivision of the hippocampus along the anterior-posterior axis (Ruth et al., 1982; Amaral and Witter, 1989; Witter, 1993; Duvernoy, 2005; Chrobak and Amaral, 2007; Dong et al., 2009; Aggleton, 2012) which will be presented below

THE HIPPOCAMPAL ANTERIOR-POSTERIOR AXIS

SUBFIELDS AND MACROANATOMY

Along the anterior-posterior axis, the hippocampus can be divided into tail (posterior part), body (intermediate part) and head (anterior part) (figure 1). In a recent human study the ratios of the different transverse subfields were quantified along the hippocampal anterior-posterior axis. For the dentate gyrus, the hippocampal tail had the highest proportion (~39%), the hippocampal body a slightly lower proportion (~38%), while the head had the lowest proportion (~25%). For CA1-3,the hippocampal tail (~51%) and head (~50%) had the highest proportions, while the hippocampal body had the lowest proportion (~35%) (Malykhin et al., 2010). The dentate gyrus is typically associated with pattern separation through sparse representations (Treves and Rolls, 1994; Yassa and Stark, 2011), suggesting that the hippocampal tail and body might be more inclined to pattern separation and the hippocampal head to pattern completion. CA 1-3 involves both CA1, associated with match-mismatch detection (Lisman and Otmakhova, 2001; Duncan et al., 2012), and CA3, associated with pattern completion (Treves and Rolls, 1994; Yassa and Stark, 2011), resulting in that it is difficult to make any functional interpretations based on the overall proportion of CA 1-3. Macro-anatomically, the hippocampal head and tail are oriented nearly perpendicular to the hippocampal body in the transverse plane (Figure 1). In the hippocampal tail, CA3 and CA1 are located to the surface of the intraventricular part, and the choroidal plexus, covering the intraventricular part of the hippocampus, is thicker. At the point where the hippocampal head starts, the choroidal plexus and fimbria ends. The fimbria is a thick white matter fiber bundle which runs along the intraventricular part of the hippocampus. The fibers in the fimbira connects the hippocampus with the septal nucleus, nucleus accumbens and via mammiliary bodies and thalamus with the cingulate and retrosplenial cortices(Duvernoy, 2005). The extraventricular part of the hippocampal head is more highly developed in humans and primates compared to other species (Tilney, 1939), suggesting that the most complex cognitive processing might take place in the hippocampal head. In this introduction, the hippocampus will mainly be divided into posterior hippocampus, including the hippocampal body and tail, and the anterior hippocampus, i.e. the hippocampal head. The intermediate hippocampus, corresponding to the hippocampal body, will only be mentioned briefly. This is because theories of the functional segregation along the anterior-posterior hippocampal axis only distinguish between anterior and posterior hippocampus for humans.

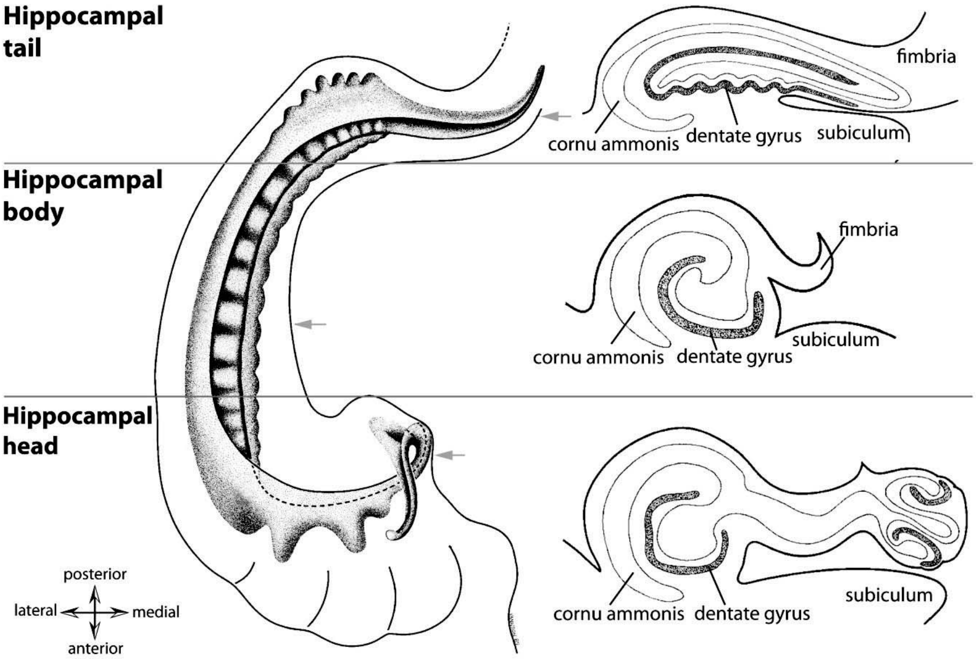

Figure 1. Hippocampal anterior-posterior axis anatomy. The grey horizontal lines mark the boundaries between the hippocampal tail, body and head. The small grey arrows in the figure to the left mark the origin of the coronal sections to the right. Adapted with kind permission of Springer Science+Business Media (Duvernoy, 2005).

AFFERENT AND EFFERENT EXTRINSIC CONNECTIVITY

EVIDENCE FROM MONKEYS

The density of afferent projections varies along the hippocampal anterior-posterior axis (Figure 2). The main afferent hippocampal projections are provided by the entorhinal cortex (Lavenex and Amaral, 2000). The entorhinal cortex as a whole has a connectivity that is organized along the lateral to medial axis starting at the rhinal/collateral sulcus laterally and extending medially to the parasubiculum/entorhinal-hippocampal transition. Lateral entorhinal cortex, the part of the entorhinal cortex closest to the rhinal/collateral sulcus, projects predominantly to posterior hippocampus, while medial entorhinal cortex, the part of the entorhinal cortex closest to the parasubiculum/entorhinal-hippocampal transition, projects predominantly to anterior hippocampus (Witter et al., 1989; Witter and Amaral, 1991; Chrobak and Amaral, 2007). The medial and lateral entorhinal cortex have few intrinsic connections, suggesting that the information which enters medial and lateral entorhinal cortex is, to a large extent, kept separate (Chrobak and Amaral, 2007). The connections from the perirhinal and parahippocampal cortex, via entorhinal cortex, to the hippocampus are organized in a graded manner, going from a high number of projections to posterior hippocampus to a low number of projections to anterior hippocampus (Figure 2) (Amaral et al., 1987; Witter et al., 1989; Suzuki and Amaral, 1994). It is believed that these fibers from the perirhinal and parahippocampal cortex via lateral entorhinal cortex convey the main environmental input (Lavenex and Amaral, 2000). One interpretation of this structural arrangement is that more fine-grained (environmental) information is transmitted to posterior hippocampus, while only coarse-grained (environmental) information reaches anterior hippocampus in a parallel but separate manner. There is also evidence for differences in sensory projections along the hippocampal long-axis. Unimodal visual and auditory cortices projects only to posterior hippocampus, via lateral entorhinal cortex. Polymodal association cortex, on the other hand, projects to both the posterior hippocampus via lateral entorhinal cortex, and to the anterior hippocampus via medial entorhinal cortex (Mohedano-Moriano et al., 2008). The olfactory bulb and insula project most densely to anterior hippocampus via medial entorhinal cortex (Mohedano-Moriano et al., 2007). Other afferent connections tend to segregate hippocampus along the anterior-posterior axis as well. For example amygdala projects directly only to anterior hippocampus (Aggleton, 1986). For retrosplenial cortex, the dorsal part projects to posterior hippocampus while the caudoventral part projects to anterior hippocampus (Kobayashi and Amaral, 2007). To sum up, the afferent hippocampal projections divide the hippocampus into a posterior and an anterior part, mainly receiving input from lateral and medial entorhinal cortex respectively, similar to findings in rats (Dolorfo and Amaral, 1998a, b).

Efferent hippocampal projections also divide the hippocampus along the anterior-posterior axis. It has been observed that the posterior hippocampus projects to dorsal retrosplenial cortex, and anterior hippocampus to caudoventral retrosplenial cortex, i.e. the afferent and the efferent retrosplenial–hippocampal fibers are reciprocal (Kobayashi and Amaral, 2003). For the mammillary bodies most projections originate from posterior hippocampus. In addition posterior hippocampus projects to central and dorsal parts of the mammillary bodies while anterior hippocampus projects to ventral and lateral parts (Aggleton et al., 2005).

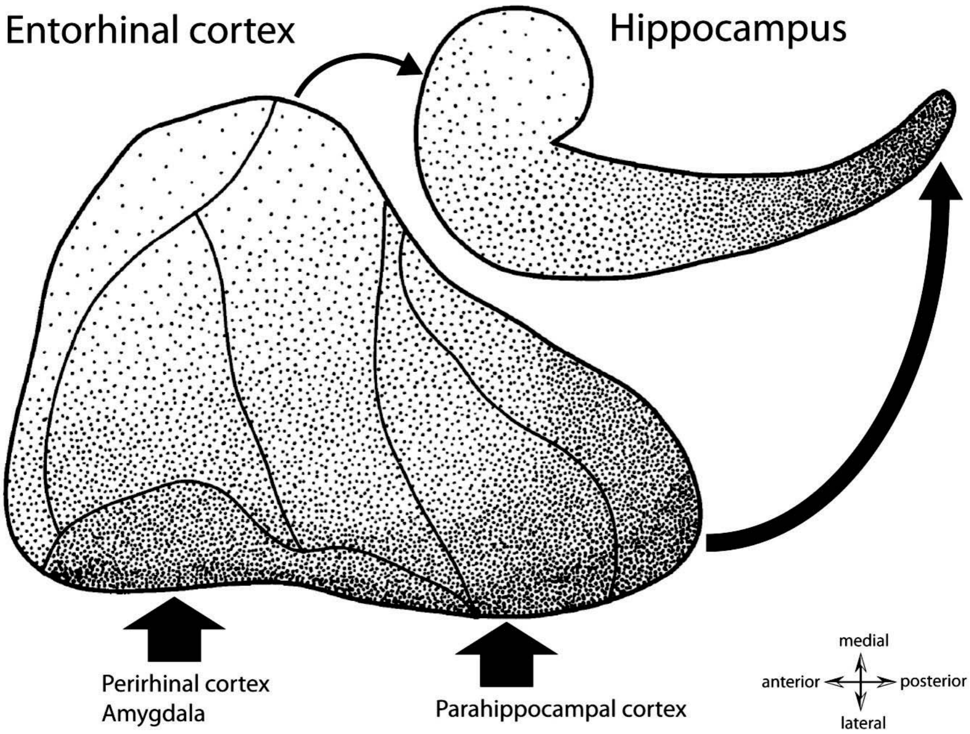

Figure 2. The entorhinal-hippocampal connectivity gradient. This figure shows that perirhinal and parahippocampal cortex, which contribute with the main environmental input to the hippocampus, projects most densely to posterior hippocampus via lateral entorhinal cortex, in monkeys. Each dot indicates one projection. Adapted with permission from (Witter et al., 1989).

EVIDENCE FROM HUMANS

The connectivity evidence from humans for a hippocampal anterior-posterior axis segregation is scarce and primarily based on functional connectivity studies. Functional connectivity is not nearly as robust as tracer studies. However, they do open up the possibility to investigate connectivity more independent of anatomical connections which could be advantageous asynchronous activity rather than direct anatomical connections may define the functional networks in the brain (Singer, 1999; Fries, 2005; Canolty and Knight, 2010).

In humans, more direct investigations of anatomical connectivity suggest that a segregation of the hippocampus along the anterior-posterior axis does exist. Dissection has revealed direct connections from anterior hippocampus to amygdala (Duvernoy, 2005), and to insula and posterior orbitofrontal gyrus via the uncinate fasciculus (Kier et al., 2004). Using diffusion tensor imaging it was observed that lateral entorhinal cortex largely connects to posterior hippocampus, similar to what has been observed in monkeys, while medial entorhinal cortex was observed to connect to both anterior and posterior hippocampus (Zeineh et al., 2012).Functional resting state connectivity data also supports a dichotomization of the hippocampus along the anterior-posterior axis. In a recent study, connectivity was compared between anterior and posterior hippocampus. For activation in anterior hippocampus, increased correlation was observed with the temporal pole, amygdala and pons. For activation in posterior hippocampus increased correlation was observed with dorsolateral prefrontal cortex, anterior cingulate gyrus, thalamus, inferior parietal lobe, precuneus and lingual gyrus (Poppenk and Moscovitch, 2011). Investigating both correlation and anticorrelation, activation in posterior hippocampus was found to be most strongly correlated with thalamus and anticorrelated with prefrontal cortex, while activation in anterior hippocampus was correlated with prefrontal cortex and anticorrelated with thalamus (Zarei et al., 2013). When comparing the connectivity between perirhinal and parahippocampal cortex, increased correlation was observed for anterior and posterior hippocampus, respectively (Kahn et al., 2008; Libby et al., 2012). This seems to be rather the opposite of what that has been observed in monkeys.

All the evidence from the human resting state connectivity studies supports a functional segregation between posterior and anterior hippocampus through separate functional networks. Anterior hippocampus seems to be more strongly connected to the perirhinal cortex, amygdala, prefrontal cortex in general, and insula, while posterior hippocampus seems more strongly connected to the parahippocampal cortex, thalamus and inferior parietal lobe.

THEORIES OF FUNCTIONAL SEGREGATION ALONG THE HIPPOCAMPAL ANTERIOR-POSTERIOR AXIS

“NON-SPATIAL” VS SPATIAL

In rats it has been suggested that only posterior hippocampus represents spatial information (Moser and Moser, 1998; Fanselow and Dong, 2010). This is based on the place cells place field being coarse-grained and less discriminating in anterior hippocampus(Jung et al., 1994),that lesions to posterior hippocampus impair maze learning more significantly than anterior lesions (Moser and Moser, 1998), and that posterior hippocampus seems to get a more continuous flow of environmental information, through the high number of afferent fibers, from perirhinal and parahippocampal cortices via entorhinal cortex (Witter et al., 1989; Suzuki and Amaral, 1994). However, there is evidence in rats that also anterior hippocampus has a spatial role. In a relatively recent study it was observed that when the rat walks back and forth in a long linear environment, the environmental representations were more correlated in anterior hippocampus compared to posterior hippocampus(Kjelstrup et al., 2008). In a rat stimulus array study, lesions to posterior hippocampus impaired separation of close but not remote locations in a spatial discrimination task (McTighe et al., 2009). Taken together, in rats, it seems as if fine-grained local environmental representations are positioned in posterior hippocampus, but that the anterior hippocampus also represents the environment based on a coarse, global perspective.

In humans, it has also been suggested that posterior hippocampus is especially important for spatial processing and anterior hippocampus for non-spatial processing (Ryan et al., 2009; Hoscheidt et al., 2010; Woollett and Maguire, 2011; Hirshhorn et al., 2012). In one of these studies, posterior hippocampus was found to be most important for representation of landmark position and anterior hippocampus for episodic memory (Hirshhorn et al., 2012).There is, however, evidence in humans indicating that spatial information is represented in both posterior and anterior hippocampus. Place related firing has been observed in anterior hippocampus(Ekstrom et al., 2003), and smaller anterior hippocampal volume results in reduced performance only on spatial tests (Woollett and Maguire, 2012). In fMRI studies, increased activation in anterior hippocampus has been associated with the relative position between distant landmarks (Iaria et al., 2003; Morgan et al., 2011), while increased activation in posterior hippocampus has been associated with local environmental representations(Janzen and Weststeijn, 2007; Hassabis et al., 2009; Ekstrom et al., 2011) and fine-grained representations of individual landmarks (Doeller et al., 2008; Baumann et al., 2010; Rodriguez, 2010; Hirshhorn et al., 2012). Structural data from London Taxi drivers revealed that in the period while more local, and fine-grained, information were added to their spatial representation of London, their posterior hippocampal volume increased (Woollett and Maguire, 2011). Thus, the human navigational data indicates that it is a link between posterior hippocampus and fine-grained, local environmental representations, while anterior hippocampus seems linked to representations involving a larger part of the environment. A similar granularity gradient along the hippocampal-long axis has been reported for spatial information in episodic memory. In a recent fMRI study it was observed that anterior hippocampus is important for the coarse, global representation of an episodic memory, i.e. the location in which a specific event took place, while posterior hippocampus is more important for fine-grained local spatial relationships within the episode (Nadel et al., 2012). This indicates that a similar functional segregation of environmental representations might exist in humans as in rats, with fine-grained local representations in posterior hippocampus and a coarse, global representation in anterior hippocampus,

Human studies have to a large extent ignored the intermediate hippocampus. However, within the spatial domain there are some highly interesting findings which should be mentioned. In rats, place-cell firing in the intermediate hippocampus indicates that this region involves medium-grained representations of the environment, creating a granularity gradient for representation of positional information along the entire hippocampal anterior-posterior axis with fine-grained representations in the most posterior hippocampus, medium-grained representations in the intermediate and coarse-grained representations in the anterior hippocampus (Kjelstrup et al., 2008). In humans, the intermediate hippocampus has been associated with route segments (Brown et al., 2010), and more fine-grained, but not coarse-grained, environmental representations (Hirshhorn et al., 2012). The intermediate hippocampus seems to position itself somewhere between the most posterior hippocampus and the anterior hippocampus also functionally, e.g. involving medium-grained environmental representations, at least in rats.

EMOTIONAL VS NON-EMOTIONAL STIMULI

In accordance with the direct projections from amygdala to anterior hippocampus, the anterior hippocampus has traditionally been given an especially important role for emotional processing (Bannerman et al., 1999; Fanselow and Dong, 2010; Murty et al., 2010). Studies in rats support this. Lesions to anterior hippocampus, but not posterior, have been shown to result in reduced emotionally linked behavior (Richmond et al., 1999; Bannerman et al., 2002; Kjelstrup et al., 2002). For example, reduced levels of freezing has been observed both for the chamber in which the foot shock together with a tone was delivered and when the tone was presented in a separate context (Richmond et al., 1999). In another study, rats with anterior hippocampal lesions did not show latency to eat when introduced to a novel, potentially anxious, situation (Bannerman et al., 2002). Similarly, rats with anterior hippocampal lesions spend more time in open, potentially fearful arms in a plus maze, and in a brightly lit empty water maze they fail to show fearful behavior (Kjelstrup et al., 2002). In rats, anterior hippocampus seems to be especially important for emotions.

In humans, emotions seem to be linked to both the anterior and posterior hippocampus. In one of the first fMRI studies with emotional stimuli in which the role of hippocampal anterior-posterior axis was investigated, it was observed that anterior hippocampus predicted memory for emotional and posterior hippocampus memory for neutral pictures (Dolcos et al., 2004). Supporting these findings, a recent meta-analysis found that only the anterior hippocampus was important for emotional memory (Murty et al., 2010). However, the posterior hippocampus has been linked to retrieval of emotional pictures after one year (Dolcos et al., 2005), encoding of negative and positive words and objects (Kensinger and Schacter, 2005), and perceptual and long term memory effects of evaluating the orientation of negative pictures (Shafer and Dolcos, 2012).In humans, anterior hippocampus seems to be especially important for emotional memory, but posterior hippocampus is also of importance.

NOVELTY VS FAMILIARITY OF STIMULI

In a recent study, the activation in anterior hippocampus was higher when imaging action/intention in novel scenes compared to highly familiar scenes, while the opposite was true for posterior hippocampus (Poppenk et al., 2010). In another study, anterior hippocampus was associated with both novel semantic and visual characteristics, while posterior hippocampus was associated with increased semantic familiarity (Strange et al., 1999). This point to an especially important role for anterior hippocampus in novelty. Supporting this, increased activation in anterior hippocampus has been associated with new compared to old complex pictures (Tulving et al., 1996), degree of novelty when presented with category-exemplar words pairs (Dolan and Fletcher, 1997), new compared to old or recollected items (Johnson et al., 2008; Suzuki et al., 2011; Kafkas and Montaldi, 2012), and sentences representing a novel episode or a novel semantic syntax compared to old sentences (Poppenk et al., 2008). Taken together, anterior hippocampus seems to be especially important for processing of novel stimuli, while posterior hippocampus seems to be more important with increased familiarity of the stimuli.

ENCODING VS RETRIEVAL OF INFORMATION

It was suggested that anterior hippocampus is especially important for encoding and posterior hippocampus for retrieval based on a review of Positron Emission Topography (PET) studies (Lepage et al., 1998). In a follow up investigation, fMRI studies were included in addition to more PET studies. Anterior and posterior hippocampus were then found to be equally important for encoding, and there was only a slight tendency that more retrieval studies observed increased activation in posterior hippocampus (Schacter and Wagner, 1999). Individual studies investigating the contribution of anterior and posterior hippocampus to encoding and retrieval respectively, show little consistency. Increased activation in both anterior and posterior hippocampus has been observed for both retrieval and encoding of individual words (Greicius et al., 2003), for retrieval of information from a highly familiar environment (Hirshhorn et al., 2012), for retrieval of information from personal episodic memories (Svoboda and Levine, 2009; Holland et al., 2011; Nadel et al., 2012), for retrieval of both positive and negative words learned one year in advance (Dolcos et al., 2005), for retrieval of odors (Lehn et al., 2013), for encoding of source memories (Peters et al., 2007; Gottlieb et al., 2010; Gottlieb et al., 2012), and for encoding of both emotional and non-emotional words (Kensinger and Schacter, 2006). Still, some data are in line with the proposed anterior-posterior encoding-retrieval model. For instance, an intracranial Electroencephalography (EEG) study, showed that encoding of words was associated with largest effects in anterior hippocampus (Ludowig, 2008). Furthermore, an even more recent meta-analysis of fMRI data demonstrated that activation was significantly higher in a cluster in anterior hippocampus for encoding as compared to retrieval (Spaniol et al., 2009). This result is in line with the original proposal that anterior hippocampus is especially important for encoding. However, a cluster of activation (MNI coordinates: -32 -22 10) was also located to the border between anterior and posterior hippocampus for one type of retrieval investigated(Spaniol et al., 2009). Although the results are mixed, there seems to be some indications that at the anterior hippocampus is especially important for encoding. This might, at least partially, be related to a link between encoding and novelty (Tulving and Kroll, 1995).

GIST VS DETAILS

The hippocampal head seems to be important for gist based recognition. Gist based recognition reflects the ability to retrieve the meaning and general information of an item, as opposed to the item specific details (Reyna and Brainerd, 1995). In support of this idea, patients with posttraumatic stress disorder have been shown to have reduced posterior hippocampal volume (Bonne et al., 2008), and to rely more strongly on gist representations (Hayes et al., 2011). In a verbal sentence study, increased activation was observed in anterior hippocampus to semantic gist, but not to changes related to syntactic details (Poppenk et al., 2008). In an object recognition study, which involved 54 categories, the activation in anterior hippocampus was related to false recognition as the number of objects within each object category increased. This indicates that anterior hippocampus is especially important for gist representations (Gutchess and Schacter, 2012).

SENSORY PROCESSING/STIMULUS MODALITY EFFECTS

It has been suggested that the hippocampus can be segregated along the anterior-posterior axis largely based on differences in sensory input along the axis (Small, 2002). However, auditory projections for example, end up both in anterior and posterior parts of the hippocampus (Amaral et al., 1983; Munoz-Lopez et al., 2010), and years of piano practice result in increased white matter in posterior hippocampus and increased gray matter in anterior hippocampus (Teki et al., 2012). Still, in support of a functional segregation based on sensory differences, a recent review proposed that anterior hippocampus is more important for vestibular processing and posterior hippocampus for visual processing (Hüfner et al., 2011a). The evidence associating posterior hippocampus with visual processing agrees with known anatomical connections (see above) and other findings in rodents and humans. For example, blind individuals have smaller posterior and larger anterior hippocampus (Leporé et al., 2009). Furthermore, in healthy controls increased activation in the posterior hippocampus has been observed for retrieval of objects compared to odors (Lehn et al., 2013). The evidence for anterior hippocampus being more important for vestibular processing, on the other hand, appears questionable. It was argued that a volume decrease in anterior hippocampus for groups with increased vestibular processing, i.e. professional dancers and slackliners, was evidence for this functional segregation (Hüfner et al., 2011b). A particular role for olfactory processing in the anterior hippocampus has also been suggested based on the input from the olfactory cortices via entorhinal cortex to the anterior hippocampus, and direct projections from the anterior hippocampus to the olfactory bulb. Supporting this, it has been observed in rodents that lesions to anterior hippocampus and not posterior hippocampus result in reduced performance for retrieval of the temporal sequence of odors (Kesner et al., 2010) but not objects (Hunsaker and Kesner, 2008), and olfactory memory (Kesner et al., 2011). In human imaging studies, the main effect of odor identification has been observed in posterior hippocampus (Kjelvik et al., 2012), for old and new odors increased activation was observed in both posterior and anterior hippocampus (Lehn et al., 2013), and correct recognition of odors, after a 10 minutes delay, was associated with posterior hippocampus only (Royet et al., 2011). To sum up, in rodents anterior hippocampus seems to be especially important for representation of olfactory information, while in humans both anterior and posterior hippocampus seems to be of importance. To conclude, sensory processing alone is not able to explain the functional specializations along the hippocampal anterior-posterior axis, however, there seems to be some relations between particularly visual input and the functional segregation along the anterior-posterior hippocampal axis. For the other modalities the findings are inconsistent.

A FUNCTIONAL SEGREGATION ALONG THE ANTERIOR-POSTERIOR AXIS IN OTHER MEDIAL TEMPORAL LOBE STRUCTURES

There are some indications that a functional specialization exists along the anterior-posterior axis of other subregions within the medial temporal lobe. In the entorhinal cortex, both the distance between the grid cells multiple place fields and the size of each place field increase linearly along the posterior-anterior axis (Brun et al., 2008). Additionally, the grid-cell firing in a more anterior entorhinal subregion adapts to a global reconfiguration of the environment, i.e. a shrinkage of the outer wall, while the posterior grid cells rather preserves fine-grained local representations, i.e. they ignore the global reconfiguration of the environment (Stensola et al., 2012). In humans, there is some evidence that the posterior entorhinal cortex is more important for processing of spatial information (Owen et al., 1996; Ghaem et al., 1997; Mellet et al., 2000; Spiers and Maguire, 2007), and the anterior entorhinal cortex a more general role in memory (Fernández et al., 1999; Davachi and Wagner, 2002; Jackson and Schacter, 2004; Kirwan and Stark, 2004; Adcock et al., 2006; Kumaran and Maguire, 2006; Hannula and Ranganath, 2008). Still, in a recent fMRI study, using morphed scenes, activation in anterior entorhinal cortex and anterior hippocampus decreased as the environmental scenes became more similar, indicating a relative coarse environmental representation in the anterior entorhinal cortex (Pustina et al., 2012). Activation of the posterior entorhinal cortex, on the other hand, has been found to correlate with distance left to a specific target landmark in a relative fine-grained manner within a virtual environment (Spiers and Maguire, 2007). Summarized, this indicates that, at least in rats, posterior entorhinal regions supports more fine-grained environmental representations and anterior entorhinal cortex coarse, global environmental representations, possibly graded along the anterior-posterior axis.

Another region in the medial temporal lobe, the parahippocampal cortex, is positioned at the bottom of the anatomical hierarchy within the medial temporal lobe. The parahippocampal cortex, receiving for example visuospatial information from area V4 and posterior parietal cortex, has cells which responds to complex environmental views (Lavenex and Amaral, 2000; Burwell and Hafeman, 2003; Ekstrom et al., 2003; Kravitz et al., 2011). In monkeys it has been observed that the parahippocampal cortex consists of a posterior region (TFO), which resembles area V4 (visual area 4), and two anterior regions (TF and TE) (Saleem et al., 2007). In humans, it has been suggested, similar to both hippocampus and entorhinal cortex, that posterior and anterior parahippocampal cortex is especially important for spatial and non-spatial associations, respectively (Bar and Aminoff, 2003; Aminoff et al., 2007). In fMRI studies a gradient has been observed within the parahippocampal cortex with posterior regions most important for representation of spatial scenes (Epstein, 2008; Litman et al., 2009; Liang et al., 2013). In a recent fMRI study it was observed that posterior parahippocampal cortex is important for source encoding of scenes only, while anterior parahippocampal cortex is important for source encoding of both scenes and objects (Staresina et al., 2011). It is appealing to suggest that this is related to posterior parahippocampal cortex representing specific details within the scenes, while anterior parahippocampal cortex is more concerned with the overall binding. Supporting this, the activation in the posterior parahippocampal cortex has been observed to increase with the complexity of the scene (Chai et al., 2010), and to be important for a local part of the scene, involving individual space-defining objects (Mullally and Maguire, 2011). Further, in studies involving virtual environments, activation in posterior parahippocampal cortex has been found to be important for correctly remembering local parts of the environment, but not for correctly binding these parts together across space or time (Janzen and van Turennout, 2004; Ekstrom et al., 2011). Anterior parahippocampal cortex, on the other hand, has been associated with initial search through a more global representation of a virtual maze (Marsh et al., 2010), and localization within a larger frame from a 2d overview perspective but not representation of individual objects (Sommer et al., 2005; Buffalo et al., 2006; Marsh et al., 2010). In a recent fMRI study, it was observed that activation in anterior parahippocampal cortex increased when the question, paired with a unique object, was repeated. It was suggested that the activation in the anterior parahippocampal cortex reflected visual gist (Diana et al., 2012). This suggests that posterior parahippocampal cortex is more important for local details within for example scenes, while anterior parahippocampal cortex supports coarse, global representations.

Taken together, the different subregions in the medial temporal lobe seemed to be organized in a somewhat similar fashion along the anterior-posterior axis, with fine-grained local representations posteriorly and coarse, global representations anteriorly.

EVIDENCE FOR A FUNCTIONAL SEGREGATION ALONG THE ANTERIOR-POSTERIOR AXIS IN OTHER BRAIN LOBES

A functional segregation along the anterior-posterior axis could exist throughout the brain. In the visual system, when going from posterior to anterior regions the receptive fields become larger and more complex, both within the occipital lobe and as a continuum across regions also in the other lobes (Serences and Yantis, 2006). For example the inferior parietal lobe, which is part of the visual stream (Silver and Kastner, 2009), can be divided into a posterior, intermediate and anterior region in humans based on tractography (Caspers et al., 2011; Ruschel et al., 2013) and receptor mapping (Caspers et al., 2013). The connectivity data show that only the posterior inferior parietal cortex is connected to the occipital lobe while the anterior inferior parietal cortex is connected to the inferior frontal gyrus (Ruschel et al., 2013). The distribution of neurotransmitter receptors demonstrates that the posterior inferior parietal cortex is more similar to the extrastriate visual cortex, and the intermediate inferior parietal cortex more similar to the superior parietal cortex (Caspers et al., 2013). In rats, the parietal cortex has been shown to be especially important for route oriented representations within the environment (Nitz, 2006; Nitz, 2009; Nitz, 2012; Whitlock et al., 2012), involving both action sequences (Whitlock et al., 2012) and connecting the different parts of the route into a global route representation (Nitz, 2012). It is tempting to suggest, based on the fact that the electrodes were slightly more posterior when recording the action sequences and the inferior parietal lobe being part of the visual stream, that posterior inferior parietal cortex is more important for local route representations like action sequences and anterior inferior parietal cortex for global route representations. Findings in other lobes also suggest that more complex and abstracted information is processes in the more anterior regions. For instance in the insula, independent interoceptive representations are processed posteriorly and subsequently integrated into a meta-representation anteriorly (Taylor et al., 2009; Kurth et al., 2010; Gu et al., 2013). Likewise, within the prefrontal cortex anterior regions seem to be more important for processing of abstract concepts, including complex relations and contexts, than are posterior regions (Badre, 2008; Barbey and Patterson, 2011). In conclusion, fine-grained local representations posteriorly and coarse, global representations anteriorly might be a general principle of functional organization throughout the brain.

AIMS OF THE THESIS

Both anatomical and functional data from rodents and humans supports a functional segregation along the anterior-posterior axis of the hippocampus and possibly also in other parts of the brain like the entorhinal cortex, parahippocampal cortex and inferior parietal lobe. Still, the nature of this functional specialization is highly debated, and several schemes for functional segregations exist. Within the hippocampus, both cell type, e.g. place cells, and the subfields in the transverse plane are continuously represented along the anterior-posterior axis. However, the electrophysiological characteristics of similar cell types vary along the hippocampal long axis, as do the proportion and hence possibly the relative importance of the different hippocampal subfields. Extrinsic and intrinsic hippocampal connectivity further supports the notion of a functional segregation along the hippocampal long axis. This may result in more segregated and fine-grained environmental representations in posterior hippocampus and coarse global environmental representations in anterior hippocampus.

Based on the animal and human data presented in the introduction, we hypothesized that posterior hippocampus involves separate, fine-grained (Paper 2, 3), local environmental representations (Paper 1, 2 and 4), intermediate hippocampus is especially important for medium-grained environmental representations (Paper 3), while the anterior hippocampus supports an integrated (Paper 4), coarse (Paper 2, 3) global environmental representation (Paper 1, 2, 4). We further hypothesize that a similar functional segregation for environmental representations might be observed along the anterior-posterior axis in the entorhinal cortex (Paper 3), the parahippocampal cortex (Paper 1), and the inferior parietal lobe (Paper 2).

MATERIALS AND METHODS

PARTICIPANTS

All participants were healthy male volunteers, n=18 (Paper 1), n=30 (Paper 2), n=31 (Paper 3), and n=18 (Paper 4).

MRI-SCANNING

All MRI data were acquired on a Siemens 3T Trio (Paper 1-4) and Skyra (Paper 3) MRI scanner with either a 12 channel (Paper 1, 2 and 4) or 32 channel (Paper 3) head coil (Siemens, Erlangen, Germany).

Blood-oxygen-level-dependent (BOLD) sensitive images fMRI images were acquired using an echo-planar imaging pulse sequence. For anatomical data, a T1 weighted 3D volume was acquired by using an MP-Rage (magnetization-prepared rapid acquisition with gradient echo) sequence.

STIMULUS AND DESIGN

In all papers (Paper 1-4), VR environments, of various sizes and complexity, were used. The VR-environments were developed in collaboration with Terra Vision AS (Terra Vision, Trondheim, Norway) using a Torque game engine (Garage Games, Eugene, Oregon, US). The participants experienced the virtual environments from a first person perspective, using a joystick.

For the fMRI, all stimuli were presented in a block design. For Paper 1 and 3 the block length was predetermined, while for Paper 2 and 4 the length of the block varied with performance.

DATA ANALYSIS

BOLD FMRI

fMRI data (Paper 1-4) were analyzed using FSL (Analysis Group, FMRIB, Oxford, UK). First, non-brain tissue was removed from the T1 anatomical images, and the resulting images were transformed to the MNI standard template (1x1x1mm; Montreal Neurological Institute, Montreal, QC, Canada) using nonlinear registration (FNIRT; reference). The fMRI data were motion corrected, smoothed with either a 3 mm (Paper 3) or 5 mm (Paper 1, 2, 4) full-width at half-maximum Gaussian filter, and temporally high-pass filtered. Each functional image series was co-registered to the corresponding anatomical T1 image and transformed into MNI space using the transformation matrix obtained with the T1 image. The statistical analysis of the fMRI data was carried out in FEAT (Smith et al., 2004). The experimental conditions were modeled according to a boxcar stimulus function convolved with a two-gamma hemodynamic response function (Boynton et al., 1996). The effect of each condition was estimated with a GLM and averaged across participants in a mixed effects analysis (Beckmann et al., 2003) (For details see papers).

SEGMENTATION

In Paper 2 the automatic segmentation tool within FSL (*FIRST*) was applied to the anatomical T1 images in order to estimate individual variations in shape and size of the right and left hippocampus. Each segmented hippocampus was transformed to a template based on the averages of all subjects' common mean native space, using six degrees of freedom, thus only differences in local shape or local volumes were assessed.

BEHAVIORAL DATA

Statistical analyses of the behavioral data were performed in SPSS (IBM 176 Corporation, NY).

SUMMARY OF THE PAPERS

PAPER 1

Persistent posterior and transient medial temporal lobe activity during navigation

Xu J, Evensmoen HR, Lehn H, Pintzka CWS, Håberg AK

BACKGROUND (PAPER 1)

Previous studies have indicated that the posterior and anterior medial temporal lobe might be important for local detailed environmental representations and a global environmental representation, respectively. The aim of this study was to investigate whether anterior medial temporal lobe was especially important for the initial navigational phase, associated with a global environmental representation, while the posterior medial temporal lobe was important also for the following execution phase, more closely associated with the local environment and its details.

METHODS (PAPER 1)

In order to investigate this, fMRI data (3T, Voxel size=3x3x3 mm, TR=2600ms, FOV=244mm) was acquired from eighteen males while finding the way to target landmarks, from random starting positions, in a learned complex virtual environment. The navigation period was divided into the initial phase, involving self-localization, target localization and planning how to get to the target landmark, and an execution phase, involving movement to the target. There were three navigation conditions presented in a pseudorandom order in 3 runs: Normal, the environment being unaltered; Without, all landmarks except the start and target being removed; Blocked, the most direct paths between start and target being blocked. The baseline condition was Line following (through the environment).

RESULTS (PAPER 1)

For the initial phase, compared to execution, increased activation was observed in anterior medial temporal lobe, including entorhinal cortex, hippocampal head and body and anterior parahippocampal cortex, across all wayfinding conditions. Throughout the navigation block increased activation was observed in posterior medial temporal lobe, including hippocampal tail and body and posterior parahippocampal cortex. The hippocampal activation throughout the navigation block was only observed for condition Normal. A time-course analysis revealed that activation in the hippocampal tail peaked regularly throughout the navigation period, while activation in the hippocampal head peaked transiently for the initial phase. Correlation with number of landmarks reached was observed for activation in the hippocampal head during the initial phase, and for activation in both hippocampal head and tail and posterior parahippocampal cortex throughout the navigation bloc.

CONCLUSIONS (PAPER 1)

More anterior medial temporal lobe, including hippocampal head and body, is especially important for the initial navigation phase, by global reinstatement of the environment and/or a coherent plan, while more posterior medial temporal lobe, including hippocampal tail and body, is important throughout the navigation period possibly providing local detailed representations of the environment.

PAPER 2

The anterior hippocampus supports a coarse, global environmental representation and the posterior hippocampus supports fine-grained, local environmental representations

Evensmoen HR, Lehn H, Xu J, Witter MP, Nadel L, Håberg AK

INTRODUCTION (PAPER 2)

There is some evidence, especially in rats but also for example from Paper 1, that posterior hippocampus might be important for fine-grained local representations and anterior hippocampus for a coarse possibly global representation of an environment. In this study we wanted to investigate, in humans, whether fine-grained local environmental representations are formed in the posterior hippocampus while a coarse-grained global environmental representation is established in the anterior hippocampus. We further explored the possibility for a similar functional organization in the parietal cortex.

METHODS (PAPER 2)

The participants (30 males) first learned a complex virtual environment, and then they had to find their way from a random start position to a target landmark during fMRI (3T, voxel size=3x3x3 mm, TR=2600 ms, FOV=244 mm). The type of spatial/environmental representations acquired was evaluated using tests of environmental knowledge, i.e. Multiple distance test, Global direction test, and Local direction test, after scanning. The multiple distance test only required a coarse, global environmental representation, while the Global and Local direction tests both required fine-grained, local representations. Type of representations used was evaluated using a questionnaire.

RESULTS (PAPER 2)

Activation in the hippocampal head correlated with the score on the Global direction and Multiple distance tests, and with the use of a coarse global representation, e.g. a Map, during wayfinding. The activation in the hippocampal tail, correlated with the score on both the Local and Global direction tests, and with the use of detailed local representations, e.g. Sequence and turns, during wayfinding. A segmentation analysis revealed that the volume of the right hippocampal head correlated positively and the volume of the right hippocampal tail negatively, with using a (coarse) global representation during wayfinding. Increased activation in the inferior parietal cortex was observed in posterior parts for local route representations, e.g. number of turns, and in anterior parts for global route representations.

CONCLUSIONS (PAPER 2)

In humans, the hippocampal tail supports fine-grained local environmental representations, while a coarse global representation of the environment is established in the hippocampal head. This is supported by both functional and structural MRI data. In the inferior parietal cortex, posterior parts support local and anterior parts global route representations.

PAPER 3

Variations in the granularity of environmental representations along the human hippocampal anterior-posterior axis

Hallvard R. Evensmoen, Jarle Ladstein, Tor Ivar Hansen, Jarle Alexander Møller, Menno P. Witter, Lynn Nadel, Asta K. Håberg

INTRODUCTION (PAPER 3)

In rats, a granularity gradient has been observed for representation of environmental positions along the hippocampal and entorhinal anterior-posterior axis, with fine-grained representations in the most posterior hippocampus and entorhinal cortex. The aim of this study was to investigate whether a similar gradient exists for the human hippocampal and entorhinal anterior-posterior axis as well.

METHODS (PAPER 3)

fMRI data (3T, voxel size=1.9x1.9x(1.9 or 2.0) mm, TR=2110 or 2253 ms, FOV= 220 mm) was acquired while participants (n=31) learned 35 small virtual environments, each including 5 object landmarks and an outer wall. The participants first moved freely within each environment for 30 sec (Stimulus presentation), and then encoded the environment with no stimulus present (Post-stimulus learning). After five environments had been presented, the subjects performed a Map-test requiring positioning of the object landmarks on a 2d overview of each room given in a random order. For each environment a score was calculated which indicated the participants ability to reproduce the positional pattern of the objects the in each environment.

RESULTS (PAPER 3)

For the hippocampal tail activation was highest for condition Fine-grained positional pattern. Moreover, the activation in the hippocampal tail correlated between subjects with how fine-grained their positional representations were. For the hippocampal body activation was highest for Medium-grained positional representations. For the hippocampal head no differences in activation was observed between Fine-grained, Medium-grained, or Coarse-grained representations. However, the activation in the hippocampal head correlated with being able to reproduce the positional pattern when allowing coarse representations. For the posterior and intermediate entorhinal cortex, increased activation was only observed for Medium-grained representations. For anterior entorhinal cortex, no differences in activation between granularity conditions were observed. The activation in the posterior entorhinal cortex correlated between subjects with the degree of positional fine-granularity.

CONCLUSIONS (PAPER 3)

A granularity gradient exists for positional representations along the human hippocampal long-axis, with fine-grained representations in the hippocampal tail, medium-grained in the hippocampal body, and a coarse overview in the hippocampal head. The activity in the hippocampal appears to be necessary also when fine-grained and medium-grained information is stored. The posterior and to some extent intermediate entorhinal cortex, seemed engaged in encoding of positional granularity. However, the results were less persuasive compared to the findings for the hippocampus. This suggests that although some sort of granularity gradient is established already at the level of the entorhinal cortex, a more complete granularity gradient depends on processing within the hippocampus.

PAPER 4

Proximal and distal landmarks are integrated in the hippocampal head

Hallvard R. Evensmoen, Jian Xu, Christian Iversen, Menno P. Witter, Lynn Nadel, Asta K. Håberg

INTRODUCTION (PAPER 4)

The neural correlates for environments which involve either proximal or distal landmarks, but not environments which involve both proximal and distal landmarks, have been investigated. The aim of this study was to investigate the neural correlates for the integration of proximal and distal landmarks.

METHODS (PAPER 4)

The participants (n=18) learned the virtual environment with both proximal and distal landmarks present at day one. At day two they had to find their way to target landmarks in the same environment with both proximal and distal landmarks present (Proximal&Distal), only proximal landmarks present (Proximal), or only distal landmarks present (Distal). After the scanning, a questionnaire was given related to distal and proximal representations acquired.

RESULTS (PAPER 4)

For the hippocampal head, increased activation was observed for contrast Proximal&Distal> Proximal and Distal. This activation correlated with integrating the proximal and distal landmarks and with number of landmarks reached. For the hippocampal tail the activation correlated with excess distance moved for condition Proximal&Distal.

CONCLUSIONS (PAPER 4)

The hippocampal head is important for the integration of initially separate proximal and distal representations, which in turn results in increased wayfinding performance. The hippocampal tail was observed to represent separate local environmental locations.

DISCUSSION

The aim of this thesis was to investigate the existence of a granularity gradient for spatial representations along the hippocampal anterior-posterior axis, as well as look for evidence for a similar functional organization in other brain regions, i.e. the entorhinal cortex, the parahippocampal cortex and the inferior parietal lobe. To investigate this in humans, we compared the contribution of activation primarily in the hippocampus, but also the parahippoocampal cortex, the entorhinal cortex, and the inferior parietal cortex, to different navigational phases and the use of local versus global representations (Paper 1, 2), and the contribution of the hippocampus and the entorhinal cortex, to the level of granularity in environmental representations stored (Paper 3). Finally, the hippocampal contribution to the integration between the proximal and distal environmental domains, compared to separate and local representations within one domain, was investigated (Paper 4). For the hippocampus we found that the hippocampal tail supports separate (Paper 4), fine-grained (Paper 2, 3), local environmental representations (Paper 1, 2, 4), the hippocampal body medium-grained environmental representations (Paper 3), and the hippocampal head an integrated (Paper 4), coarse (Paper 2, 3), global environmental representation (Paper 1, 2, 3). In the entorhinal cortex, a somewhat similar granularity gradient for environmental representations, as that noticed for the hippocampus, was observed (Paper 3). In the parahippocampal cortex, posterior and anterior parts seemed more important for local and global environmental representations, respectively (Paper 1), while in the inferior parietal lobe, posterior parts supported local and detailed route representations, e.g. number of turns, and anterior parts global route representations (Paper 2). Four main questions arose from these findings. First, is it possible that hippocampal processing supports one type of functional specialization that underlies and thus explain all functional specializations reported. Second, if so, is the same functional organization also present in other brain regions, i.e. the entorhinal cortex, the parahippocampal cortex and the inferior parietal lobe? Third, does the functional specialization of the hippocampus depend on intrinsic processing, or functional organization of input? Fourth, does the observed findings support the possibility that the hippocampal head engenders the initial encoding and/or retrieval based on a coarse, global representation, while the fine-grained and medium-grained local representations are likewise encoded and/or retrieved in the hippocampal tail and body, respectively. Further, the number of functional subregions along the hippocampal anterior-posterior axis and how segregated they are will also be discussed. In addition some methodological pitfalls will be considered.

IS THERE ONE FUNCTIONAL SPECIALIZATION SUPPORTING ALL TYPES OF PROCESSING ALONG THE HIPPOCAMPAL ANTERIOR-POSTERIOR AXIS?

The functional segregation along the hippocampal anterior-posterior axis, with fine-grained local environmental representations in the hippocampal tail, medium-grained representations in the hippocampal body, to a coarse, global environmental representation in the hippocampal head, was reproduced for both object encoding and wayfinding in our fMRI studies (Paper 1, 2, 3, 4). This suggests that the observed functional segregation might be applicable also outside the navigational domain. Indeed, results from studies using other types of tasks and stimuli support the notion that non-spatial stimuli and tasks are processed in a manner adhering to the anterior-posterior axis specialization described for spatial stimuli in this thesis. Emotional memory, which is most closely linked to activity in the hippocampal head, has been associated with gist-like representations (Adolphs et al., 2005). Gist involves coarse, global representations (Oliva and Torralba, 2006), thus pointing to an association between emotional memory and gist, which can be considered a non-spatial equivalent to a coarse, global spatial representation observed for the hippocampal head in Paper 1 and 2. Moreover, it has been shown that the hippocampal head is especially important for novelty (Tulving et al., 1996; Poppenk et al., 2010). Novelty has been argued to be related to either a rapid global match or match-mismatch detection mechanism (Kumaran and Maguire, 2007a). A rapid global match mechanism seems most likely for the novelty signal in the hippocampal head since match-mismatch activity was observed in the hippocampal body, and not the hippocampal head (Kumaran and Maguire, 2007b). Thus an alternative interpretation of the increased signal in the hippocampal head in Paper 1 and 2 is activity related to a rapid global match mechanism engendering a coarse overview of the environment used to self-localize and find targets. The hippocampal head has further been argued to be especially important for encoding. This is not supported by our model, i.e. we found increased activation in the hippocampal head during tasks associated with both encoding (Paper 3) and retrieval (Paper 1, 2 and 4). However, there is evidence that encoding is related to novelty (Tulving and Kroll, 1995). Other studies have shown that increased familiarity of a representation involves more contextual details and increased activation in the hippocampal tail (Poppenk et al., 2010; Poppenk and Norman, 2012). These observations agree with result in paper 2 and 3, which confirmed our prediction of a particular role of the hippocampal tail for fine-grained representations. Our observations are all based on visual-spatial stimuli, still the observed link between the hippocampal tail and visual processing might be related to the especially high degree of fine-grained details involved in visual memory (Brady et al., 2008), possibly processed primarily in the hippocampal tail through the high number of environmental projections. Summarized, the observed functional specialization for the hippocampal anterior-posterior axis, with fine-grained local representations posteriorly to a coarse, global representation anteriorly, is able to explain to some extent other functional specializations reported. What could the underlying mechanism be? Within the hippocampus, both cell type, e.g. place cells, and the subfields in the transverse plane repeats itself along the anterior-posterior axis. However, the place cells firing are more fine-grained posteriorly. Further, it has been observed that the hippocampal head has a lower proportion of dentate gyrus, possibly making the hippocampal head more prone to pattern completion and the hippocampal tail and body more prone to pattern separation. Finally, connectivity evidence has shown that the hippocampal tail receives more projections involving environmental information, suggesting that the hippocampal tail supports more detailed environmental representations. Still, the possibility that several functional specializations exists for the hippocampal anterior-posterior axis, through for example different functional networks for the same subregion, cannot be excluded (Poppenk et al., 2013).

The observed specialization along the anterior-posterior hippocampal axis seems to be of importance for memory in general. It has been reported that activation in the hippocampal head was associated with retrieving the global representation of an event (Holland et al., 2011), while the hippocampal tail and body showed increased activation in the phase when details were added (Addis and Schacter, 2008; Holland et al., 2011). In another fMRI study, the hippocampal head was observed to connect separate episodes together (Lehn et al., 2009). This indicates that the posterior hippocampus supports more fine-grained local representations and the anterior hippocampus coarse global representations also outside the spatial domain. In support of this notion a recent review provides experimental evidence for that the same neural circuits in the hippocampus (and entorhinal cortex) that is used for navigation is involved in memory and planning (Buzsaki and Moser, 2013). Supporting this idea, it has been argued that time is treated in a similar way as space in the hippocampus (Eichenbaum, 2013). Taken together these data suggests that observations from environmental learning and navigation studies can be generalized to memory in general and possibly also planning processes. A theory of episodic memory has claimed that our memories are organized in a hierarchy (Conway, 2009). It is tempting to speculate that the hippocampal head operates on a more overall level, in the hierarchical organization of our memories, from which for example individual environments are separated, while the hippocampal tail and body supports fine- and medium-grained local representations within (each environment). Supporting this, in rats it was observed that the environmental representations in the hippocampal tail were orthogonal both within and between environments, while environmental representations in the hippocampal head were orthogonal only between environments (Kjelstrup et al., 2008).

DOES THE SAME FUNCTIONAL SPECIALIZATION ALONG THE ANTERIOR-POSTERIOR AXIS EXIST THROUGHOUT THE BRAIN?

We have observed a similar functional specialization, with fine-grained local representations posteriorly and coarse, global representations anteriorly, for other brain regions (Paper 1-3).

In Paper 3 the posterior entorhinal cortex was found to be most important for fine-grained and medium-grained environmental representations, the intermediate entorhinal cortex for medium-grained environmental representations, while the anterior entorhinal cortex seemed less involved in this type of environmental representations. In humans, posterior entorhinal cortex has for example been associated with representation of distance to a specific target within a virtual environment (Spiers and Maguire, 2007), and anterior entorhinal cortex with a coarse representation of an environmental scene (Pustina et al., 2012). In rats, a gradient exists with fine-grained locally tuned grid cells posteriorly to coarse-grained globally tuned grid cells anteriorly (Brun et al., 2008; Stensola et al., 2012). In Paper 1 and 2, no such functional specialization could be observed along the anterior-posterior axis. In Paper 1 envrionmental representations used was not measured and in Paper 2 only average, and not trial specific, environmental representations used, was measured. Additionally, in these studies the entorhinal cortex was only divided into anterior and posterior entorhinal cortex. This indicates that the entorhinal cortex, as the hippocampus, consists of three rather than two subregions along the anterior-posterior axis. This is similar to findings in rats where firing of entorhinal grid cells suggests a gradient across three subregions along the anterior-posterior axis of the entorhinal cortex, with most fine-grained representations in the posterior entorhinal cortex (Brun et al., 2008).

In Paper 1 posterior parahippocampal cortex was associated with local environmental details throughout the navigation period and anterior parahippocampal cortex with an initial global reinstatement of the environment. In other fMRI studies, posterior parahippocampal cortex has been associated with local spatial representations (Janzen and van Turennout, 2004; Ekstrom et al., 2011; Mullally and Maguire, 2011), and anterior parahippocampal cortex with localization within a more global frame (Sommer et al., 2005; Buffalo et al., 2006; Marsh et al., 2010) and gist representations (Diana et al., 2012). This suggests that within the parahippocampal cortex, posterior parts involve local and detailed environmental representations and anterior parts more global environmental representations.

In Paper 2 it was shown that local route details and a global route representation were represented in posterior and anterior inferior parietal lobe, respectively. Supporting this, the posterior inferior parietal lobe has been linked to saccadic eye movements (Konen and Kastner, 2008). Saccadic eye movements are essential for fine-grained information in images (Loftus, 1972), but not coarse, global representations (Potter, 1976). Fine-grained, local route representations in the posterior inferior parietal lobe and coarse, global route representations in the anterior inferior parietal lobe align with this region being part of the dorsal visual stream (Serences and Yantis, 2006; Silver and Kastner, 2009).

Summarized, this suggests that the functional specialization observed for the hippocampus, with fine-grained local representations posteriorly to coarse, global representations anteriorly, is a general organizational principle also found in other subregions in the brain, including the parahippocampal cortex, the inferior parietal lobe, and the entorhinal cortex.

IS THE HIPPOCAMPAL ANTERIOR-POSTERIOR AXIS SPECIALIZATION A RESULT OF PROCESSING WITHIN THE HIPPOCAMPUS?

The regions to which the hippocampus is connected is of importance for the functional segregation along the hippocampal anterior-posterior axis. In Paper 3, we observed a somewhat similar functional specialization, as that observed for the hippocampal anterior-posterior axis in the entorhinal cortex, which provides the main input to the hippocampus. In Paper 1 the parahippocampal cortex and in Paper 2 the parietal cortex, both providing input to the hippocampus, showed a similar functional specialization along the anterior-posterior axis as that found for the hippocampus. Adding further evidence for the importance of extrinsic projections to the understanding of the functional segregation along hippocampus, most of the proposed schemes for specializations along the hippocampal anterior-posterior axis originate from connectivity evidence. For example, the hippocampal head, but not the hippocampal tail or body, receives direct projections from the amygdala a region tightly coupled to emotions (Phelps, 2006). These projections most likely contribute to the hippocampal head being most important for emotional processing. Taken together, this evidence suggests that extrinsic connectivity of the hippocampal tail, body, and head is of importance for the function of these regions. This interpretation is also supported by recent reviews (Ranganath and Ritchey, 2012; Poppenk et al., 2013). In the review by Ranganath and Ritchey, they argued for a posterior medial system in the brain, with the perirhinal cortex as the core-component, involving relationships between entities, recollection, representation of place and time, and an anterior temporal system, with the parahippocampal and retrosplenial cortex as the core-components, involving individual entities, familiarity, semantic concepts and single objects (Ranganath and Ritchey, 2012). The model presented in this review does not correspond that well with the findings in this thesis (Paper 1-4), or the proposed model in the review by Poppenk and colleagues which is similar to the model argued in this thesis (Poppenk et al., 2013). We observed that for example places and objects are represented in both the hippocampal head and tail (Paper 1 - 3). Further, the coarse, global representation of the environment in the hippocampal head, although it could be argued to be a single entity in itself, involves relationships between entities (Paper 2 and 4), while the representation of individual entities seems more strongly associated with the hippocampal tail and its fine-grained local representations (Paper 2) (Poppenk et al., 2013). The functional segregation between anterior and posterior hippocampus in the review by Ranganath and Ritchey is solely based on extrinsic connectivity differences (Ranganath and Ritchey, 2012). This indicates that, even though it for example has been argued that the hippocampus “indexes” information from other brain regions (Teyler and DiScenna, 1986; Nadel and Moscovitch, 1997), the functional segregation along the anterior-posterior hippocampal axis depends upon more than extrinsic connectivity. This assumption is strengthened by the finding that when using only visual stimuli as in Papers 1-4, increased activation was observed along the entire hippocampal axis. Thus providing direct evidence for an important role of intrinsic connectivity for the functional specialization of the hippocampus, rather than modality specific extrinsic connectivity. The review by Ranganath and Ritchey bases the conclusions for the hippocampus largely on human fMRI data, interpreted as anatomical connectivity, pointing to the perirhinal and parahippocampal cortex as more strongly connected to the hippocampal head and hippocampal tail, respectively (Libby et al., 2012). However, solid anatomical evidence from monkeys, using tracers, indicates that both perirhinal and parahippocampal cortex project most densely to the hippocampal tail (Witter et al., 1989; Chrobak and Amaral, 2007). It is of course possible that anatomical connectivity differs between monkey and human. Still, the observation with more dense environmental input to the hippocampal tail, as well as the general pattern of connectivity for the hippocampus, is reported to be consistent among all species investigated (Insausti, 1993; Dolorfo and Amaral, 1998a, b; Kerr et al., 2007). Overall, the state of the information which enters the hippocampus, through extrinsic projections, is important for the functional role of the hippocampal subregions along the anterior-posterior axis, still, processing within the hippocampal subregions also matters.

WHAT COMES FIRST; A FINE-GRAINED, LOCAL OR A COARSE, GLOBAL REPRESENTATION?

In Paper 3 we argued that the coarse global representation in the hippocampal head is established initially and that this global representation supports the encoding of fine- and medium-grained local representations in the hippocampal tail and body. Supporting this, it has been observed that the hippocampal head is more important for novelty (Strange et al., 1999; Poppenk et al., 2010), while the hippocampal tail is important in the following periods, when details are added to the representations (Strange et al., 1999; Poppenk et al., 2010). Further, the hippocampal head has been associated with an initial gist-representation. This coarse, global representation is used, for example to keep an overview of a scene, when fine-grained local information is added (Oliva and Torralba, 2006). In Paper 3, using small environments, which resembles scenes because it is easy to get a rapid intial overview, we observed that the coarse, global environmental representation in the hippocampal head to be of importance also when fine-grained representations in the hippocampal tail and medium-grained representations in the hippocampal body were acquired. What will happen for a larger environment where it is impossible to get an initial overview of the entire layout? We did not investigated activation related to encoding in a large environment. Still, in Paper 1 and 2 we observed that more or less all participants first walked once along the outer environmental border to try and get an initial overview of the environment during encoding of the environment (unpublished). Similar behavior is also observed in rats (Sutherland and Dyck, 1984). One could speculate that the coarse global representation and fine-grained local representations are encoded simultaneously, through the parallel extrinsic anatomical pathways, but that the global representation in hippocampal head, given the fact that it is a coarse and singular representation, is established faster and then used as support. The results in Paper 4 seem to give the impression of the opposite, i.e. the hippocampal head supports a global integration of initially stored proximal and distal landmarks. Hence, it is possible that when more segregated stimuli are used, a global overview is first acquired separately for parts of the stimuli, i.e. the proximal and distal landmarks, before a more overall integration takes place

There is evidence that a coarse global representation is also used first for environmental retrieval, i.e. initial reinstatement of a coarse-global representation in the hippocampal head and retrieval of fine-grained local information throughout in the hippocampal tail (study 1). This is in accordance with the hippocampal head being linked to initial retrieval of a coarse-global representation of an autobiographical memory and hippocampal body to the following phase when retrieving the details (Holland et al., 2011). A global reinstatement initially will for example help keep the overview when retrieving local information (Oliva and Torralba, 2006).

THE NUMBER OF SUBREGIONS ALONG THE HIPPOCAMPAL ANTERIOR-POSTERIOR AXIS

Our papers, especially Paper 2, 3 and 4, provide evidence for a functional segregation of the hippocampus into three segments along the hippocampal anterior-posterior axis. Macro-anatomical features supports this (Duvernoy, 2005), and connectivity evidence shows that the entorhinal cortex, providing the major hippocampal input and output, is divided into three bands each projecting to a separate segment along the hippocampal anterior-posterior axis (Dolorfo and Amaral, 1998a; Lavenex and Amaral, 2000; Chrobak and Amaral, 2007). A recent analysis of the expression of hippocampal genes, in mice, revealed that individual genes are expressed in only one of three segments along the hippocampal anterior-posterior axis (Thompson et al., 2008; Dong et al., 2009; Fanselow and Dong, 2010). In rats, lesions along the hippocampal anterior-posterior axis and the corresponding performance in a Morris water maze supports three, rather than two, functional segments for the hippocampal anterior-posterior axis (Moser et al., 1995; Kjelstrup et al., 2008; Bast et al., 2009). In rats, the place cells in hippocampal tail, body, and head represents the environment fine-grained, medium-grained, and coarse-grained, respectively (Kjelstrup et al., 2008), mapping onto the findings in Paper 2 and 3. In Paper 1, we divided the hippocampus into anterior and posterior hippocampus, and in Paper 3 we argued that the environmental representations in the hippocampal body are more similar to the environmental representations in the hippocampal tail than the environmental representations in the hippocampal head. A segregation of the hippocampus into an anterior and posterior part has been done in several fMRI studies (Ryan et al., 2009; Poppenk et al., 2010; Hirshhorn et al., 2012; Nadel et al., 2012), still, the activation patterns in these fMRI studies (by other groups) suggest a tripartition of function, i.e. the hippocampal tail, body and head, along the hippocampal anterior-posterior axis.

HOW SEGREGATED ARE THE HIPPOCAMPAL SUBREGIONS?

Information is transmitted along the hippocampal anterior-posterior axis (Amaral and Witter, 1989; Kondo et al., 2008, 2009; Patel et al., 2012). For CA3 and dentate gyrus projections between all three segments have been found along the hippocampal anterior-posterior axis (Kondo et al., 2008, 2009). The significance of these longitudinal projections is reflected in the impact of a transverse cut through the dorsal hippocampus which disrupts a rat’s ability to retrieve a learned location, but not store a new location, in a watermaze. No impairment was observed in animals with longitudinally oriented cuts (Steffenach et al., 2002). Additionally, theta waves have been observed to travel along the hippocampal anterior-posterior axis, argued to both combine and separate representations (Patel et al., 2012). Taken together, the hippocampal tail, body, and head are connected along the anterior-posterior axis, however, the exact role of these connections are not yet known.

fMRI does not have an inherent baseline (Stark and Squire, 2001).Especially for the hippocampus, typical baselines used often result in increased activation compared to the condition of interest(Stark and Squire, 2001; Ekstrom, 2010). One solution to this problem is to make comparisons within the same condition, e.g. successful encoding of granularity compared to non-successful (Paper3).

BOLD fMRI is only an indirect measure of neural activity (Logothetis, 2008). In one of our studies (Paper 3), the BOLD signal decreased in the hippocampus and entorhinal cortex for the stimulus presentation period. When using BOLD fMRI, increased BOLD signal related to excitatory activity, e.g. due to processing of environmental information, can be cancelled out by inhibitory gabaergic activity, especially since gabaergic activity only demands 15-20 percent of the oxidative metabolism measured by BOLD fMRI (Patel et al., 2005; Buzsáki et al., 2007; Logothetis, 2008), and reduces post-synaptic calcium influx and excitatory postsynaptic potentials (Chiu et al., 2013). When learning an environment, the amount of input, and therefore also less relevant information, is enormous. Less relevant information will typically be inhibited by gabaergic activity (Buzsáki et al., 2007), resulting in a decreased BOLD signal (Muthukumaraswamy et al., 2009; Donahue et al., 2010). To conclude, the decreased BOLD signal observed in the hippocampus and entorhinal cortex for the stimulus learning period could be related to the inhibition of less relevant environmental information and not reduced excitatory neural activity per se.

BOLD fMRI data from the medial temporal lobe suffers from susceptibility artifacts, especially data acquired from the entorhinal cortex (Olman et al., 2009). In order to reduce these problems the echoplanar imaging sequence used was optimized to reduce the effect of susceptibility artifacts (Stöcker et al., 2006; Giannelli et al., 2010). The optimization seemed to work, because the correction method we tested did not show any improvement for the data (Paper 3) (Holland et al., 2009), a method which have shown positive results for a different data set (unpublished data).

We only acquired data from men. Behaviorally, significant gender differences have consistently been found for example for wayfinding (Moffat et al., 1998; Coluccia and Louse, 2004; Lawton, 2010;

Chamizo et al., 2011; Andersen et al., 2012). However, when it comes to activation and volumetric data, gender differences have both been observed (Grön et al., 2000) and not (Blanch et al., 2004). The reason why we only included data from men was that we did not want to induce additional variability in the data. We were not interested in gender differences per se, and the fact that several studies do not find differences in neural correlates between the genders makes it highly plausible that what is observed for men in our papers will be true for women as well.

CONCLUSIONS

The hippocampal tail supports fine-grained local environmental representations, the hippocampal body medium-grained environmental representations, and the hippocampal head a coarse, global environmental representation, possibly retrieved and/or encoded initially, within the functional networks in which these subregions are embedded. A somewhat similar functional segregation along the anterior-posterior axis also seems to exist within other regions in the brain, i.e. the entorhinal cortex, the parahippocampal cortex, and the inferior parietal lobe. Still, the existence of other functional specializations cannot be excluded.

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PAPERS IN THE DOCTORAL THESIS

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PAPER 1

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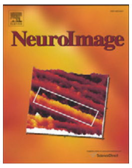

Persistent posterior and transient anterior medial temporal lobe activity during navigation

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ABSTRACT

A functional segregation along the posterior–anterior axis of the medial temporal lobe (MTL) has been suggested. In brief, it is thought that the posterior hippocampus represents environmental detail and/or encodes space, whereas the anterior part represents the environment more as a whole and/or subserves behavior. Different phases of navigation should thus recruit different structures within the MTL. Based on animal studies and neuroimaging data from humans, the initial phase of navigation, i.e., self-localization, target localization and path planning, should depend on the anterior MTL independent of upcoming navigational demands, whereas posterior MTL should be active throughout navigation. We tested this prediction using fMRI with navigation in a learned large-scale virtual office landscape with numerous complex landmarks under different navigational conditions.

The initial navigational phase specifically engaged the anterior MTL. Increased activity was found bilaterally in the rostral and caudal entorhinal cortex. This is, to our knowledge, the first report of entorhinal activity in virtual navigation detected in a direct comparison. Also bilateral anterior hippocampus and anterior parahippocampal cortex were significantly more active during the initial phase. Activity lasting throughout the navigational period was found in the right posterior hippocampus and parahippocampal cortex. Hippocampal activity for the entire navigation period was only detected when the virtual environment remained unaltered. Navigational success was positively correlated with activity in the anterior right hippocampus for the initial phase, and more posteriorly in the hippocampus for the whole navigation period. Plots of the BOLD signal time course demonstrated that activity in the anterior hippocampus was transient whereas activity in the posterior hippocampus peaked regularly throughout the entire navigation period.

These results support a functional segregation within the MTL with regard to navigational phases. The anterior MTL appears to complete associations related to the environment at large and provide a behavioral plan for navigation, whereas the posterior part keeps track of current location.

Introduction

The medial temporal lobe (MTL), which includes the hippocampus and the parahippocampal and entorhinal cortices, is pivotal for the ability to navigate (Bird and Burgess, 2008; Burgess et al., 2002; Moser et al., 2008; Spiers and Maguire, 2007b). Previous neuroimaging studies demonstrate that different regions within the MTL are recruited during navigation, depending on the specific nature of the task (Doeller et al., 2008; Jordan et al., 2004; Rauchs et al., 2008; Shipman and Astur, 2008; Spiers and Maguire, 2006; Wolbers et al., 2007). The aim of the present study was to examine neuronal activation during the initial phase of navigation, which involves self-localization, target localization and planning how to reach the target (Jeffery, 2007) compared to execution of the navigation plan.

Neuroimaging data have demonstrated increased activity in the anterior hippocampus during navigational planning and target localization (Shipman and Astur, 2008; Spiers and Maguire, 2006). Activity lasting throughout a navigation period has only been reported in the posterior hippocampus (Peigneux et al., 2004; Rauchs et al., 2008). These findings can be interpreted as reflecting differential sensitivity to spatial detail in the posterior and anterior hippocampus. Behavioral studies have shown that in the initial phase of navigation subjects first retrieve a global representation of the environment. Subsequently, subjects identify the target's location within this global representation, choose direction, and plan a route to reach the target (Hölscher et al., 2006; Spiers and Maguire, 2008). In the execution phase, subjects fill in the details in the environment as they proceed toward the target (Spiers and Maguire, 2008). Animal studies indicate that the environment is represented with increasing

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scale along the posterior–anterior axis of the hippocampus, i.e., local spatial detail is represented posteriorly whereas the environment at large is represented anteriorly (Jung et al., 1994; Kjelstrup et al., 2008). It should also be noted that spatial memory in rats depends in particular on the posterior two-thirds of the hippocampus (Moser and Moser, 1998) and that the anterior part is suggested to show greater involvement in non-spatial functions like behavioral control (Bast et al., 2009) and/or reward (Royer et al., 2010). Together these results suggest that the initial phase of navigation depends on a global representation of the space to be traversed, which should be processed in the anterior hippocampus, while the execution phase seems to be devoted to processing local environmental detail related to the current position engendered by the posterior hippocampus.

The entorhinal cortex, which is localized to the anterior part of the MTL, may also be particularly engaged in the initial phase of navigation. Mental navigation, which shares features with navigational planning, has been shown with PET to increase entorhinal cortex activity (Ghaem et al., 1997; Mellet et al., 2000). fMRI studies have shown that entorhinal activity increases during retrieval of landmark sequences from learned routes (Janzen and Weststeijn, 2007) and correlates positively with increasing distance to target (Spiers and Maguire, 2007a). In the initial phase, the subject is the farthest from the target and utilizes a global representation of the environment to plan the path to it (Hölscher et al., 2006; Spiers and Maguire, 2008, 2006). This implies that entorhinal activity could be recruited specifically in the initial phase of navigation. Animal studies suggest that the entorhinal cortex provides both temporal and spatial context signals, as “a crude sketch of locations traversed in a route” (Eichenbaum and Lipton, 2008; Lipton et al., 2007). Such a sketch may be the equivalent to the global environmental representation that subjects use to find the direction and route toward the target, described by human subjects (Hölscher et al., 2006; Spiers and Maguire, 2008).

There are also indications of a functional segregation along the anterior–posterior axis of the parahippocampal cortex. Visuospatial scenes particularly engage for the posterior part of the parahippocampal cortex (Epstein, 2008), with less in the anterior part (Litman et al., 2009). The more complex the scenes are, the greater the ensuing activation in this region (Chai et al., 2010). Furthermore, the posterior parahippocampal cortex has been shown to support encoding of both objects and their locations, while the anterior parahippocampal cortex engenders memory for location (Buffalo et al., 2006; Sommer et al., 2005). Thus, the posterior parahippocampal cortex can be regarded as having a more perceptual role, involving processing of scenes and details in them, while the anterior parahippocampal cortex subserves spatial memory.

The human and animal studies reviewed above suggest that the anterior parts of the MTL, i.e., anterior hippocampus, entorhinal cortex and anterior parahippocampal cortex, subserve the initial phase of navigation, while the posterior MTL, i.e., the posterior hippocampus and the posterior parahippocampal cortex, is the main contributor in the execution phase. To test this hypothesis, the current study set out to identify the subregions in the MTL that support the initial phase of navigation compared to the execution phase. We further predicted that activity in the initial phase of navigation is independent of upcoming navigational demands, so navigation was performed under three different conditions. The previous findings reviewed above are suggestive of this distinction between the initial phase of navigation and execution of a navigational plan, but to the best of our knowledge, it remains to be tested directly. To this end, we designed a large-scale, realistic virtual office landscape with 56 complex landmarks (Fig. 1). Subjects were first familiarized with the environment through free exploration and structured learning. Next, brain activity was investigated with fMRI during navigation in the learned environment. Navigation occurred under different navigational conditions; navigation in an unaltered version of the learned environment (condition Normal) in the same environment but with all landmarks removed except the start and target landmarks (condition Without) or in an environment where everything was unaltered expect that the most direct routes between the start position and target landmark were blocked (condition Blocked). The participants were placed at new locations within the environment and presented with a new target landmark (Fig. 1) at the beginning of each trial, thus forcing the subjects to self-localize, localize target landmark and formulate a navigation plan.

Methods

Participants

Twenty men (21–30 years, mean = 24.2 years) with no history of neurological disorders, head trauma or current DSM-IV axis I diagnosis of psychiatric illness, including substance abuse, were recruited from the university campus. They were all right-handed, ascertained with the Edinburgh Handedness Inventory with mean score of 89.7%. All participants provided written informed consent prior to participation and received 500 Norwegian kroner as reimbursement. The study was approved by the National Committee for Medical Research Ethics in Midt-Norge, Norway.

Virtual environment

The virtual environment was developed in collaboration with Terra Vision AS (Terra Vision, Trondheim, Norway) using Torque game engine (Garage Games, Eugene, Oregon, USA). The environment is 115.28 × 138.46 units of size, which corresponds to 62 × 74 m in “real life”. Player moving speed was fixed at 3.73 U/s. The environment mimics the inside of a modern office building with rooms, corridors and open areas of various sizes, but it lacks exterior windows. All doors inside the environment are “locked”, i.e., subjects are only allowed to navigate through the corridors and open areas. Fifty-six distinct landmarks made up of 195 objects and 60 pictures are placed at various locations (Fig. 1). Most of the landmarks comprised of several objects. All objects making up a complex landmark had a common theme. Wall structure, ceiling, carpeting and lighting of the interior were similar throughout the environment and modeled to make it as realistic as possible.

Pre-scanning

Using a standard desktop computer and a sidewinder pro joystick (Logitech, Romanel-sur-Morges, Switzerland), participants first explored the virtual environment freely in two 12-min sessions. After the second free exploration session, participants performed structured navigation tasks. This was done in order to ensure that all subjects had seen every landmark. In all these navigation tasks, all starting landmarks and target landmarks were positioned in the east-west direction of each other. Task order was randomized between subjects. Participants were given a maximum of 60 min to complete the structured learning session.

Subsequently, the participants performed three computer-based tests to ascertain their level of proficiency of the virtual environment: recognition of landmarks, judgments of distance and judgments of direction between landmarks.

Finally participants were given a brief demonstration of each task condition in the fMRI experiment and practiced one of each task type. Before MRI, participants were given a 30-min break.

Scanning procedure

Scanning was performed on a 3-T Siemens Trio scanner with a 12-channel Head Matrix Coil (Siemens AG, Erlangen, Germany). Foam

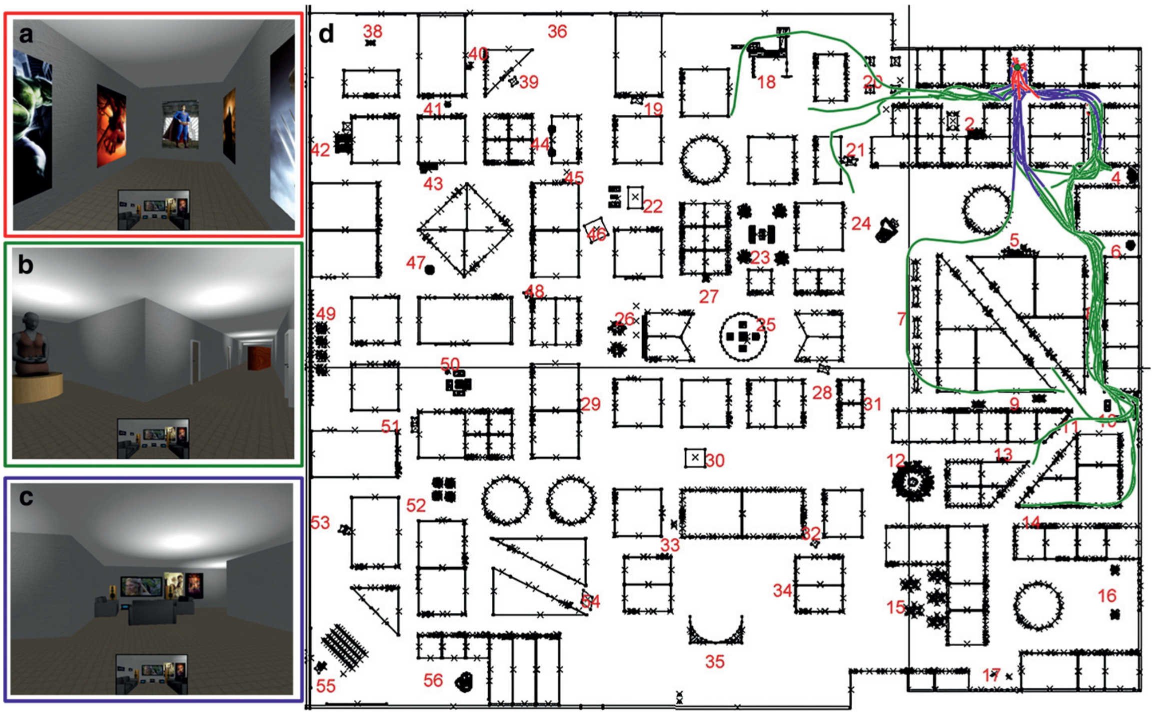

Fig. 1. Overview of the virtual environment. (a) The initial view presented to the participant when entering at a random location within the virtual environment at the start of each new navigation block. The target landmark was shown as a small image in the middle, bottom of the screen. The initial phase consisting of self-localization, target localization and path planning were determined from participants' post-scan self-reports to last 4.6 s. The movements for all 18 participants during the initial 4.6 s are marked as red lines on the map of the virtual environment to the right in the figure. (b) View of the environment as the participants moved toward the target in the phase directly following the initial phase. The movements of all participants during the subsequent 4.6 s following the initial phase are represented as blue lines in the map of the virtual environment. (c) View of the target landmark presented in the bottom left panel. The movements for all participants for the remainder of the execution phase are represented as green lines in the map of the virtual environment. (d) A map of the virtual office landscape, each number indicates the location of one landmark. Most landmarks consisted of several objects as can be seen in panels a and c. Participants could use different pathways but still reach the target successfully.

pads were used to minimize head motion. The fMRI stimuli were presented using MRI compatible LCD goggles with 640×480 resolution (Nordic Neuron Lab, Bergen, Norway). Subjects moved inside the environment using an MRI compatible joystick (Current Designs, Philadelphia, USA).

The participants were first allowed to familiarize themselves with the presentation equipment and joystick. Then the subjects completed four practice trials, one from each experimental condition (see below). Scanning was commenced when complete task compliance was assured.

fMRI paradigm

The fMRI paradigm was jittered, with variable block duration and alternating blocks of navigation (30 ± 2 s) and rest (i.e., fixation; 10 ± 2 s). There were three navigation conditions and one baseline condition. In all three navigation conditions, participants were placed at a different landmark at the start of each block, and an image of a target landmark was inserted at the bottom center of the screen (Fig. 1). The participants were instructed to navigate towards the target landmark as fast and accurately as possible. All combinations of starting positions and targets were unique to the fMRI experiment and had not been presented during the learning session. The three navigation conditions were condition Normal, Without and Blocked, and the baseline condition was Line following. In condition Normal, the environment was the same as during the learning session, consisting of both borders (i.e., walls) and landmarks. In order to explore the importance of landmarks for successful navigation, condition Without was introduced. In condition Without, all landmarks, except start and target landmarks, were removed. The effect of navigational re-planning when target location was known but blockades directly in front of the target obstructed direct access to it was investigated with condition Blocked. In condition Blocked, all landmarks were in place, but the corridors leading directly to the target landmark were temporally blocked. The blockage, a stop sign, was not visible before the subject came upon it. In all three navigation conditions, the participants were instructed to move as fast and accurately as possible to the target landmark. If the participant reached the landmark before the block ended, a new target landmark was presented. If participants did not find target, they kept on trying until the block was terminated. Block duration was set to 30 ± 2 s. Based on pilot studies, the tasks were designed so that arrival at the first landmark could be achieved well within the time limit of the block, while the second landmark was always beyond range. The baseline condition (Line following) was designed to control for motor and visual components of navigation. Here participants moved in the environment by following a yellow line on the floor. In this condition, all landmarks were removed from the environment, including the start and target landmarks. This was done to prevent subjects from using this condition to learn the environment better, which was found to take place in the pilot studies leading up to the present design. The four navigation and the Line following conditions were separated by 10 s (± 2 s) of fixation, which was a white central cross on a black screen. Each participant completed three experimental runs, with five of each of the four conditions plus 20 fixation blocks in each run. The order of runs was randomized between participants.

Performance data were logged throughout the experiment and extracted with in-house developed software written in Python (Python Software Foundation, Hampton, NH, USA). Success rate was computed as percentage of first target landmarks reached within each block since it was impossible to reach the second target landmark within the given time. Position data of the participants' movements inside the environment were logged with a time interval of 30 ms and can be displayed as a trace (see Fig. 1). Based on the behavioral data obtained from all participants, the speed of the movement and movement paths for all condition Normal trials were estimated and plotted (for example, see Fig. 1).

Imaging parameters

T2*-weighted, blood-oxygen-level-dependent (BOLD) sensitive images were acquired using an echo-planar imaging pulse sequence (TR = 2600 ms, TE = 30 ms, FOV = 244 mm, slice thickness = 3.0 mm, slice number = 47, matrix = 80 × 80 giving an in-plane resolution of 3 × 3 mm). Each functional run contained 327 volumes, with slices positioned as close to 90° on the anterior–posterior direction of the hippocampus as possible. For anatomical reference, one T1-weighted 3D volume was acquired with an MPRage sequence (TR = 2300 ms, TE = 30 ms, FOV = 256 mm, slice thickness = 1.0 mm, matrix 256 × 256, giving an in-plane resolution of 1.0 × 1.0 mm).

Post-scanning

After scanning, the volunteers were given a random sample of tasks performed in the scanner and asked to indicate when the initial phases (self-localization, target localization and path planning) were completed.

Data analysis

Behavioral data

Behavioral data were analyzed in SPSS 14.0 (SPSS Inc., Chicago, Illinois, USA). ANOVA analyses followed by paired *t*-tests for within-subjects comparisons were carried out in order to compare the number of correct answers on the tests of recognition, judgment of direction and judgment of distance and also for comparison of the success rates in condition Normal, Without and Blocked. The distances moved during the initial 4.6 s and the subsequent 4.6 s in condition Normal were compared using a paired *t*-test. Significance level was set to $p<0.05$ for all statistical comparisons. All values are given as Mean ± SD.

MRI data analysis

Imaging data were analyzed using FSL 4.0 (Analysis Group, FMRIB, Oxford, UK). First, non-brain tissue was removed from the T1-weighted anatomical images using BET (Brain Extraction Tool, FMRIB, Oxford, UK), and the resulting images were transformed to the MNI 152 1 × 1 × 1 mm template (Montreal Neurological Institute, Montreal, QC, Canada) with FLIRT (FMRIB, Oxford, UK). The fMRI data were motion corrected using FLIRT, with the median volume of each run as reference. Then each functional run was co-registered to the corresponding anatomical T1 image and transformed into MNI space by using the transformation matrix obtained with the T1 image. The functional data were filtered with a 5-mm full-width at half-maximum Gaussian spatial filter, and a temporal high-pass filter with a cutoff time of 250 s. The statistical analysis of the fMRI data was carried out in FEAT (FEAT, FMRIB, Oxford, UK). Conditions were modeled according to a boxcar stimulus function convolved with a two-gamma hemodynamic response function. The effect of each condition was estimated with GLM using FLAME 1 (FMRIB's local analysis of mixed effects).

A whole brain analysis was performed using first a statistical threshold of $Z\geq4$ ($p\leq0.000032$) for each voxel, and then a cluster threshold of $p=0.05$. The conditions Normal>Line following, Without>Line following and Blocked>Line following and the differences between conditions Normal, Without and Blocked were explored.

Since the region of interest for this study was the medial temporal lobe (MTL), a brain mask was created by combining the probabilistic maps of the Harvard Oxford Structural Atlases and the Juelich Histological Atlas (part of FSL; http://www.fmrib.ox.ac.uk/fsl/fslview/atlas-descriptions.html#ho) (Flitney et al., 2007), using max probability >50% as threshold. In total, the mask encompassed 16 180 1-mm voxels. The entorhinal cortex and the perirhinal cortex were segregated based on anatomical boundaries (Insausti et al., 1998). Contrasts between condition effects were tested for significance using voxel-based thresholding with corrected voxel threshold set to $p<0.05$ and a minimum cluster size of 45 contiguous voxels.

The time courses of the hemodynamic response in condition Normal were calculated for all individuals using PEARL (Pearl event-related time course extraction) 2.61 and each individual's data from FSL (www.jonaskaplan.com/fmritools.html). The percent change in the BOLD signal over time for condition Normal was extracted from a smoothed functional voxel in the anterior and the posterior hippocampus. The anterior voxel was chosen on the basis that it had increased activity in the contrast Initial>Execution phase. The MNI coordinates for this voxel were 25, −20, −18. The posterior voxel was associated with increased activity in the contrast Normal>Line following (whole block analyses), and had MNI coordinates of 29, −35, −14. In addition, the BOLD signal time course plots for unsuccessful versus successful trials in condition Normal were calculated separately for the anterior and posterior voxel.

In order to investigate differences in activation between the initial and the execution phase of the navigation period, each active navigation block was divided into two separate events. Based on the participants' reports, the initial phase (self-localization, target localization and path planning) lasted 4.6 ± 1.2 s (range 3–8 s). The execution phase was the time following the initial phase, lasting until either the first target landmark was reached, or until the block was terminated. In blocks where participants reached the first landmark, a second target landmark was presented, and thus some navigation blocks included two initial phases. A mixed effects FLAME 1 analysis of the contrast initial>execution phase for condition Normal, Without and Blocked was performed in the MTL ROI and on the whole brain level.

Combined fMRI and behavioral data analysis

The subject-specific scores for success rate in condition Normal were added as a separate regressor in the GLM in order to identify regions of activation that correlated with performance across subjects. This was done for activation in condition Normal, for the whole block (Normal>Line following) and for the initial phase (Initial>Execution) using a mixed effects analysis.

Results

Included participants

All 20 subjects were able to complete the structured learning session within the predefined 60-min time limit. However, only 18 individuals were able to complete the fMRI session, and hence only results obtained from these participants are included in the following. The two participants that had to withdraw during scanning experienced severe nausea. Several participants reported nausea but were able to complete scanning. Nausea is common in computer games that involves virtual environments, often referred to as simulation sickness (Slater et al., 1995), and is supposed to indicate that the participant is properly submerged into the virtual environment.

Tests of knowledge of the virtual environment

The number of correct answers on the recognition test was 9.9 ± 0.3, distance test 9.0 ± 1.0 and direction test 6.3 ± 1.7. The success rates were above chance level in all these tests, indicating that the participants were able to recognize the landmarks, and had a representation of their internal relationship.

fMRI performance and post-scanning assessment of duration of initial phase

In condition Normal, participants were able to reach a 9.0 ± 3.2 of the 15 target landmarks. However, in conditions Without and Blocked, only 5.0 ± 2.5 and 5.2 ± 1.8 landmarks were reached, respectively. The participants failed to reach the target landmark in some of the tasks not because they did not know where the target landmark was located but because they ran out of time. This was verified by the behavioral output. This was particularly noticeable in condition Blocked where all participants were close to the target landmarks but were unable to reach them as there was only one open entry point to the landmark. For the success rate, ANOVA showed a significant effect of condition ($F<0.001$). Post hoc paired comparisons revealed a significant difference both between conditions Normal and Without ($t = 5.5$, $p<0.001$) and conditions Normal and Blocked ($t = 4.9$, $p<0.001$). Conditions Without and Blocked were not significantly different.

Based on the participants' self-reports when represented with tasks performed during scanning, the initial phase (self-localization, target localization and path planning) lasted 4.6 ± 1.2 s (range 3–8 s). The initial phase was hence set to last 4.6 s for the analyses of the Initial>Execution phase.

Route plot results

The participants moved significantly shorter during the first 4.6 s (3.51 ± 2.91 units of size) compared to the subsequent 4.6 s (10.20 ± 5.39 units of size) ($p<0.001$) in condition Normal. As can be seen in Fig. 1, in the initial phase the subjects mainly remained standing or moved/turned in the vicinity of the start position. During the next 4.6 s, subjects moved towards the target at approximately double speed compared to the initial phase (Fig. 1). These behavioral data corroborate the participants' self-reports, i.e., that the initial phase lasted approximately 4.6 s.

fMRI results

MTL ROI analyses

Activity in the entire navigation blocks for conditions Normal, Without and Blocked. The contrast Normal>Line following gave activations in the posterior part of the right hippocampus, the mid-posterior part of the left hippocampus and bilaterally in parahippocampal cortex (Fig. 2; Table 1). The contrasts Blocked>Line following and Without>Line following gave activations in the parahippocampal cortex, bilaterally (Fig. 2; Table 1).

The contrasts Normal>Without showed significantly increased activity in the left posterior hippocampus, whereas Normal>Blocked had significantly increased activity in the right anterior and posterior hippocampus plus the left posterior hippocampus. Also the parahippocampal cortex had increased activity bilaterally in Normal>Blocked (Table 2). The left and right anterior hippocampi were significantly more active in condition Without>Blocked. The contrasts Blocked>Normal and Without>Normal showed no increase in activation.

Initial versus Execution phase for conditions Normal, Without and Blocked. For conditions Normal and Blocked, a comparison of the initial phase with the execution phase yielded activation in bilateral anterior and posterior hippocampus, rostral and caudal right entorhinal cortex and right anterior parahippocampal cortex (Fig. 3; Table 3). For condition Blocked, activation was also observed in the caudal part of the left entorhinal cortex and in the left perirhinal cortex. The same comparison for condition Without revealed activation in the posterior right hippocampus, the anterior and posterior left hippocampus, the caudal part of the right entorhinal cortex and the left parahippocampal cortex. No significant differences were found when comparing the initial phases between conditions indicating that the initial phases recruited similar regions independent of upcoming navigational demands.

Comparison of execution phases for conditions Normal, Without and Blocked. In the execution phase in the contrast Normal>Without, increased activations were observed bilaterally in the hippocampus and in the right parahippocampal cortex. In the contrast between the execution phases for condition Normal>Blocked increased activations in bilateral hippocampi and parahippocampal cortices were observed. There were no significant activations when contrasting the execution phases for Without>Normal and Blocked>Normal.

Activity correlated with performance for condition Normal. In condition Normal>Line following, there was a positive correlation with activity in the right anterior hippocampus and left parahippocampal cortex and success rate (Fig. 4; Table 4). For the initial phase of navigation (Initial>Execution), activation in the anterior right hippocampus showed a significant correlation with performance (Fig. 4; Table 4).

Whole brain analyses

Conditions Normal, Without and Blocked versus Line following. Contrasts Normal>Line following, Blocked>Line following and Without>Line following all revealed increased activation bilateral in the occipital cortex, anterior insula, precuneus, fusiform gyrus and parahippocampal cortex and in the right lateral prefrontal cortex and thalamus (Fig. 5; Table 5). In both hemispheres, the precuneus and fusiform gyrus activations were interconnected and spread anteriorly into posterior cingulate cortex and inferiorly into lingual gyrus in both hemispheres. Activation in the right hippocampus was only observed for contrast Normal>Line following at the whole brain level.

Differences between conditions Normal, Without and Blocked. In the contrast Normal>Without, increased activation was found in bilateral lateral occipital cortex, spreading inferomedially into the fusiform gyri (Table 6). The contrast Normal<Without showed no regions with increased activity. Normal>Blocked had increased activation bilaterally in lateral occipital cortices and hippocampi. In both hemispheres, the parieto-occipital activations spread into the entire hippocampus. In Normal<Blocked, increased activations were present in bilateral superior medial prefrontal cortex, left dorsolateral and right inferior prefrontal cortex (Table 6). There was also increased activity in bilateral angular gyrus and right middle temporal gyrus. In Without>Blocked, increased activation was found in the right hippocampus. Condition Without<Blocked had increased activation in the bilateral cingulate cortex spreading into the precuneus, right medial superior frontal gyrus and left dorsolateral prefrontal cortex. There was also increased bilateral supramarginal gyrus activity spreading inferiorly and increased activity in the right superior temporal gyrus (Table 6).

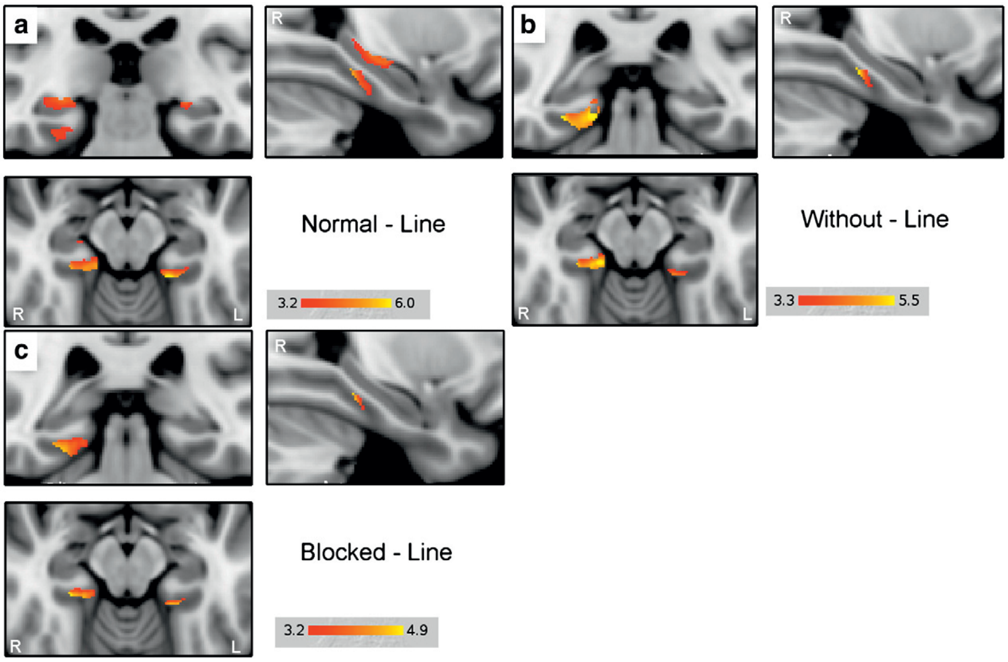

Fig. 2. Medial temporal lobe (MTL) regions with increased activity for the entire navigation block compared with the baseline condition Line following. (a) Condition Normal>Line following; (b) condition Without>Line following; (c) condition Blocked>Line following. The analysis was carried out using a hippocampal–parahippocampal gyrus mask and voxel-based thresholding, $p<0.05$ corrected. Minimum cluster size was 45 voxels. Activations are superimposed on the MNI, Montreal Neurological Institute 152 brain template. Left is right in the figure.

Initial versus execution phase for condition Normal. When comparing the initial phase and the rest of the way-finding block in condition Normal, increased activations were observed in both hippocampi, anterior and posterior cingulate gyrus, precuneus, middle temporal gyrus, fusiform gyri, caudate nuclei, occipital cortices and thalamus (Fig. 6; Table 7).

Time course analyses. In the smoothed functional voxel in the right anterior hippocampus (upper panel, Fig. 7), the BOLD signal increased initially and then decreased before it increased again at the end of condition Normal (Fig. 7). The second increase in the BOLD signal coincides with the participants reaching the first target and getting the second navigation task in condition Normal. The BOLD signal in the anterior hippocampus voxel was higher for the initial phases when navigation was successful than when navigation was unsuccessful (middle panel, Fig. 7). In the smoothed functional voxel in the posterior hippocampus, the BOLD signal fluctuated throughout condition Normal, independent of navigational phases and there was no apparent difference in BOLD signal and successful versus unsuccessful navigation (lower panel Fig. 7).

Table 1

Regions within the medial temporal lobe (MTL) with increased activity in the conditions Normal, Without and Blocked versus the baseline condition (Line following).

MTL region	Coordinates of peak activation (MNI)			Cluster size (no. of voxels)	*Z*-score
	X	*Y*	*Z*		
Normal>Line following					
R. Hippocampus	29	−35	−14	567	5.19
L. Hippocampus	−23	−29	−8	58	4.73
R. Parahippocampal cortex	29	−35	−14	632	5.19
L. Parahippocampal cortex	−21	−41	−13	209	6.00
Without>Line following					
R. Parahippocampal cortex	17	−34	−15	557	5.57
L. Parahippocampal cortex	−21	−41	−13	69	4.66
Blocked>Line following					
R. Parahippocampal cortex	28	−36	−14	305	4.83
L. Parahippocampal cortex	−21	−41	−13	53	4.94

The analysis was carried out using a hippocampal–parahippocampal gyrus mask and voxel-based thresholding, $p=0.05$ corrected for multiple comparisons. MNI, Montreal Neurological Institute 152 brain template, has voxel resolution of 1 mm^3. Only clusters with a cluster size >45 voxels were reported. R; right; L, left.

Table 2

Peak activations in the medial temporal lobe (MTL) ROI when comparing the conditions Normal, Without and Blocked.

MTL region	Coordinates of peak activation (MNI)			Cluster size (no. of voxels)	*Z*-score
	X	Y	Z		
Normal>Without					
L. Hippocampus	−21	−31	−7	102	4.25
Without>Normal (no significant increase in activation observed)					
Normal>Blocked					
R. Hippocampus	30	−39	0	102	5.33
	35	−18	−21	68	4.25
L. Hippocampus	−31	−38	−5	312	5.12
L. Parahippocampal cortex	−27	−32	−21	83	4.45
Blocked>Normal (no significant increase in activation observed)					
Without>Blocked (no significant increase in activation observed)					
Blocked>Without (no significant increase in activation observed)					

The analysis was carried out using a hippocampal–parahippocampal gyrus mask, i.e., an MTL ROI, and voxel-based thresholding, $p=0.05$, corrected for multiple comparisons. MNI, Montreal Neurological Institute 152 brain template, has voxel resolution of 1 mm^3. Only clusters with a cluster size >45 voxels were reported. R, right; L, left.

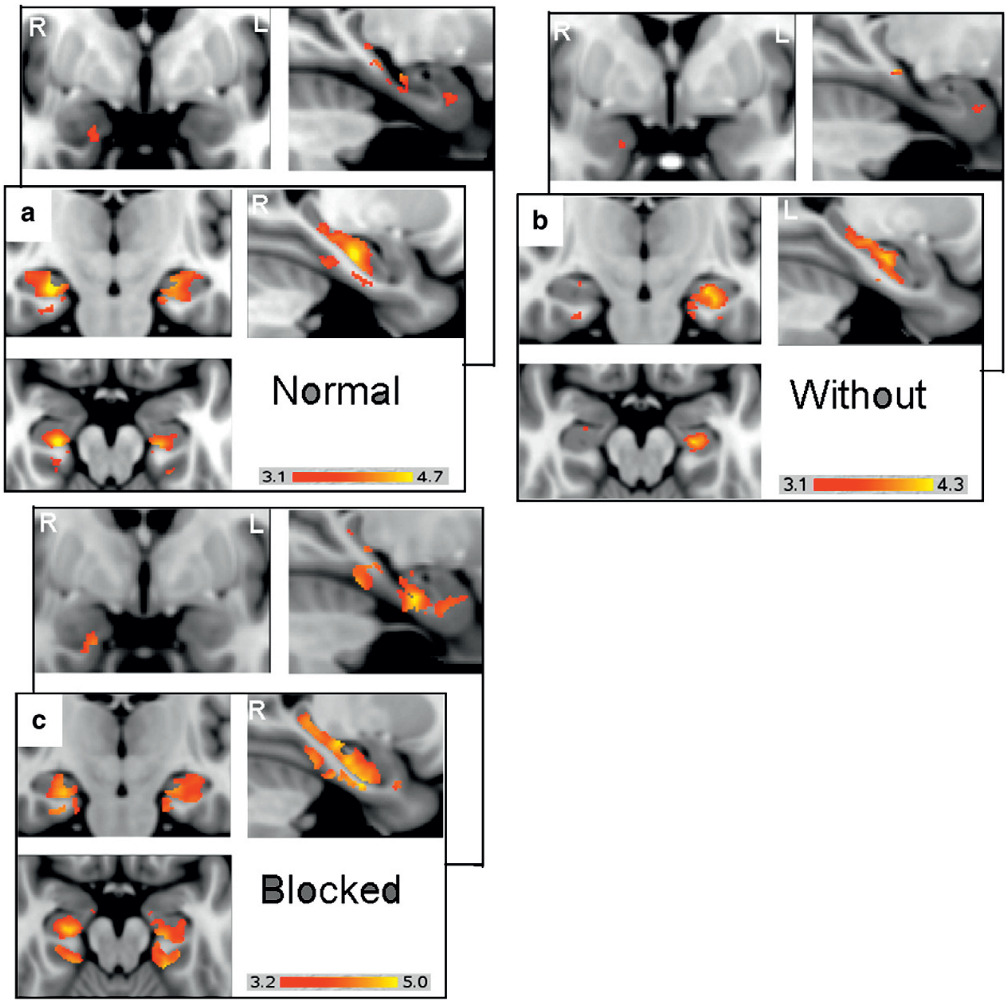

Fig. 3. Medial temporal lobe (MTL) regions with increased activity in the initial phase compared to the execution phase of the navigation block. (a) Condition Normal; (b) condition Without; and (c) condition Blocked. The analysis was carried out using a hippocampal–parahippocampal gyrus mask and voxel-based thresholding, $p<0.05$ corrected for multiple comparisons. Minimum cluster size was 45 voxels. Activations are superimposed on the MNI, Montreal Neurological Institute 152 brain template. Left is right in the figure.

Discussion

The aim of the present study was to compare activation of MTL subregions in the initial phase and execution phase of navigation, measured during different navigational demands. The main finding is a functional segregation within the MTL with regard to navigational phase. In the initial phase of navigation, there was increased activation of the anterior MTL, i.e., the anterior hippocampus, entorhinal cortex and anterior parahippocampal cortex, whereas activity in the posterior MTL, i.e., posterior hippocampus and posterior parahippocampal cortex, was present throughout navigation. An additional finding was that the posterior hippocampal activity depended on both environmental features and navigational demands, i.e., presence or absence of landmarks and blockades.

The finding of increased anterior MTL activity in the initial phase suggests that this region is specifically engaged in self-localization, target localization and/or path planning. The posterior MTL, on the other hand, appears to be involved in processing input from the current location, i.e., representing information necessary for recognition and/or recall. To our knowledge, this study is also the first human imaging study to detect entorhinal activation in a direct comparison between specific navigational conditions, substantiating that the human entorhinal cortex, like the rodent entorhinal cortex, is active during spatial navigation.

The duration of the initial phase of navigation was determined based on the participants' self-reports following scanning and gave a crude estimate of the amount of time required for self-localization, target localization and planning. The self-reported duration of the initial phase concurred with the behavioral changes observed in the participants' movement plots and the significant increase in their speed of movement after the initial 4.6 s. The BOLD signal time course plots in the anterior hippocampus associated with the initial phase similarly showed a transient initial increase lasting approximately five seconds. This finding corroborates the self-reports and the movement data. Unfortunately, an option for more direct measures of self-localization, target localization and path planning was unavailable.

Table 3
Peak activations within the medial temporal lobe (MTL) ROI when comparing Initial phase>Execution phase in conditions Normal, Without and Blocked.

MTL region	Coordinates of peak activation (MNI)			Cluster no.	Cluster size (no. of voxels)	*Z*-score
	X	*Y*	*Z*			
Normal						
R. Hippocampus	25	−20	−18	1	1223	4.80
	23	−25	−11	*(1)*		4.37
	24	−32	−8	*(1)*		3.89
	31	−17	−14	*(1)*		3.77
L. Hippocampus	−22	−23	−15	2	1311	4.49
	−20	−16	−15	*(2)*		3.90
	−20	−30	−10	*(2)*		3.82
R. Entorhinal cortex	20	−2	−23	3	45	3.65
	25	−19	−25	*(1)*		3.66
R. Parahippocampal cortex	28	−29	−23	4	116	3.73
L. Parahippocampal cortex	−15	−32	−10	5	49	4.16
	−29	−35	−15	6	198	4.00
Without						
R. Hippocampus	20	−31	−6	1	69	3.91
L. Hippocampus	−20	−34	−5	2	1042	4.37
	−27	−17	−20	(2)		4.12
	−24	−25	−11	(2)		3.94
R. Entorhinal cortex	27	−17	−28	3	56	3.46
Blocked						
R. Hippocampus	26	−22	−12	*(1)*		5.00
	26	−12	−27	*(1)*		4.83
	23	−35	−3	*(1)*		4.53
L. Hippocampus	−19	−34	−7	4	2395	4.64
	−22	−24	−16	*(4)*		4.36
	−20	−17	−18	*(4)*		4.12
R. Entorhinal cortex	26	−13	−29	1	2930	5.00
	19	−3	−27	*(1)*		4.13
L. Entorhinal cortex	−17	−17	−27	*(4)*		4.10
L. Perirhinal cortex	−30	−7	−32	2	62	3.92
R. Parahippocampal cortex	21	−35	−18	3	759	4.51
	26	−24	−25	*(3)*		4.47
L. Parahippocampal cortex	−15	−32	−10	4	3535	5.01
	−24	−40	−14	*(4)*		4.73
	−24	−23	−25	*(4)*		4.24

The analysis was carried out using a hippocampal–parahippocampal gyrus mask and voxel-based thresholding, $p = 0.05$ corrected for multiple comparisons. MNI, Montreal Neurological Institute 152 brain template, has voxel resolution of 1 mm^3. The cluster number is given in parenthesis for secondary peaks within the respective clusters. Numbers in the cluster size column represent the actual number of voxels within the anatomical region in the respective row. R, right; L, left.

Such an approach would have been ideal to explore each component separately and also to take into account differences between subjects and between the different tasks.

In the initial phase of navigation, increased activity was detected in both the rostral and caudal entorhinal cortex. This was similar across all navigational conditions. In previous neuroimaging studies of spatial navigation, only a few have reported activation in the entorhinal cortex (Doeller et al., 2010; Spiers and Maguire, 2007a).

Table 4
Peak activations within the medial temporal lobe (MTL) ROI correlating with success rate in condition Normal for the whole block and for the Initial>Execution phase.

MTL region	Coordinates of peak activation (MNI)			Cluster No.	Cluster size (no. of voxels)	*Z*-score
	X	*Y*	*Z*			
Whole block						
R. Hippocampus	23	−38	4	1	70	2.43
	26	−20	−16	2	89	2.25
L. Parahippocampal cortex	−24	−34	−19	3	60	2.00
Initial>Execution phase						
R. Hippocampus	27	−10	−28	1	47	2.24

The analysis was carried out using a hippocampal–parahippocampal gyrus mask and voxel-based thresholding, $p = 0.05$ uncorrected. MNI, Montreal Neurological Institute 152 brain template, has voxel resolution of 1 mm^3. Only clusters with a cluster size >45 voxels were reported. R, right; L, left.

The initial increase in the caudal entorhinal activity can reflect processing of landmarks and perhaps more specifically their spatial arrangement. Several neuroimaging studies of spatial memory have reported activation in the caudal entorhinal cortex during recognition and retrieval of object locations as well as during spatial ordering of objects (Adcock et al., 2006; Johnsrude et al., 1999; Owen et al., 1996). Moreover, visually responsive cells in the caudal entorhinal cortex in monkeys respond to particular objects or places (Owen et al., 1996; Suzuki et al., 1997). In addition to engendering object–place associations, grid cells in the caudal entorhinal cortex may provide a representation of self-localization within an environment together with the hippocampal place cells (Doeller et al., 2010; Fyhn et al., 2004; Moser et al., 2008). It is possible that the increased activity in the initial phase of the navigation block reflects a transient re-setting of the entorhinal grid cell activity when the subjects enters at a new location at the beginning of each trial. In rats, it has recently been shown that grid cell representations are discontinuous within an environment divided by geometric boundaries (Derdikman et al., 2009). The rostral entorhinal activity detected in the initial phase is equivalent to activity observed during retrieval of stored associations (Kirwan and Stark, 2004; Tyler et al., 2004) and in response to objects presented in the same order as previously experienced in a virtual environment (Janzen and Weststeijn, 2007). It can be speculated that the complex landmarks used in this virtual environment may have particularly engaged the rostral entorhinal cortex since they were made up of combinations of objects rich in non-spatial content as compared to the more simplistic and/or solitary landmarks used in most other virtual navigation studies (Antonova et al., 2009; Doeller et al., 2008; Ekstrom and Bookheimer, 2007; Iaria et al., 2007; Parslow et al., 2005; Peigneux et al., 2004; Rauchs et al., 2008; Shipman and Astur, 2008).

The virtual environment used in the present experiment was large compared to those used in most neuroimaging studies of navigation (Antonova et al., 2009; Doeller et al., 2008; Ekstrom and Bookheimer, 2007; Grön et al., 2000; Iaria et al., 2007, 2008; Jordan et al., 2004;

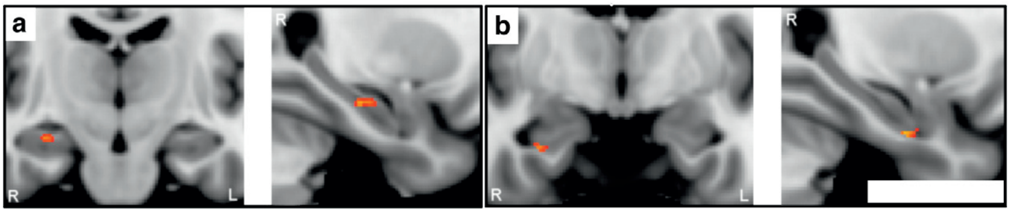

Fig. 4. Correlation between activation and the navigation success in condition Normal. (a) Whole block activity for condition Normal>Line following and (b) Initial>Execution phase in condition Normal. The analysis was carried out using a hippocampal–parahippocampal gyrus mask and voxel-based thresholding, $p<0.05$ uncorrected. Minimum clusters cluster size was 45 voxels. Activations are superimposed on the MNI, Montreal Neurological Institute 152 brain template. Left is right in the figure.

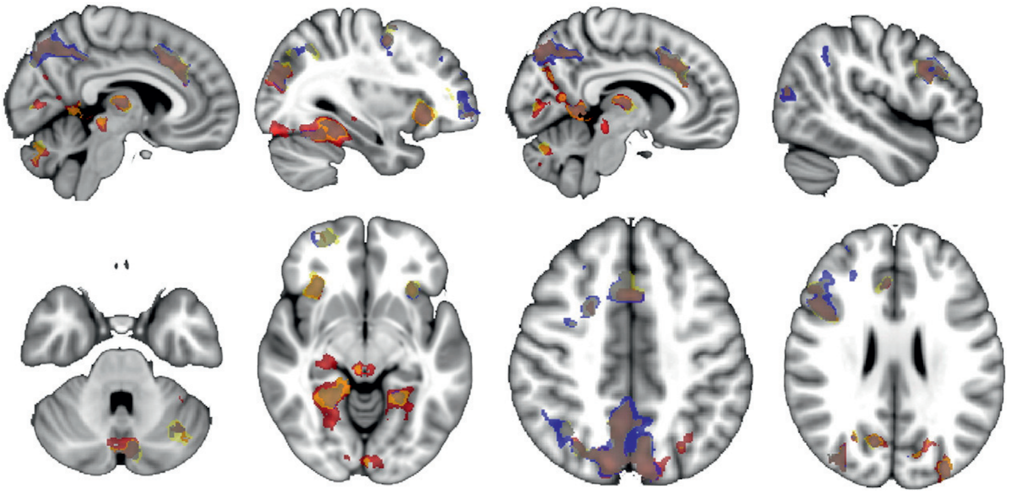

Fig. 5. Statistical parametric maps of increased brain activity for the different navigational conditions superimposed on top of each other on the MNI, Montreal Neurological Institute, 152 template brain. Condition Normal > Line following in red, condition Without > Line following in blue and condition Blocked > Line following in yellow. Voxel-based thresholding, $p < 0.05$ corrected for multiple comparisons, was applied. Right hemisphere is on the left in the figure.

Ohnishi et al., 2006; Parslow et al., 2005; Peigneux et al., 2004; Rauchs et al., 2008; Shipman and Astur, 2008). The size of the virtual environment to be mentally represented may be an important determinant for increasing the entorhinal activity. Supporting this notion is the positive correlation between entorhinal activity and increasing distance to target (Spiers and Maguire, 2007a). Based on previous behavioral studies (Spiers and Maguire, 2008), subjects appear to engender a more global representation of the entire virtual environment in order to determine target location and choose the appropriate path. When executing the navigational plan, a limited representation of the virtual environment may suffice, possibly leading to a decline in entorhinal activity. Indeed, spatial reference memory has been shown not to be updated during locomotion in humans (Mou et al., 2004), and one human lesion study demonstrates that entorhinal cortex is not necessary for path integration (Shrager et al., 2008).

Lack of entorhinal activation in many fMRI studies of navigation studies could be due to susceptibility artifacts in T2*-weighted BOLD fMRI. These artifacts are most pronounced in the entorhinal cortex (Ojemann et al., 1997). The slice orientation in the present study reduces this problem (Chen et al., 2003). The presence of such susceptibility artifacts in BOLD fMRI may explain why PET studies have detected entorhinal activity in mental navigation (Ghaem et al., 1997; Mellet et al., 2000), which has not been reproduced in comparable fMRI studies (Avila et al., 2006; Kumaran and Maguire, 2005). It should be noted that brain activity detected using fMRI only depicts differences in activity in one condition relative to another. Persistent entorhinal cortex activity across all conditions can therefore not be visualized. Still, our results clearly demonstrate a dynamic role for the entorhinal cortex, with increased engagement in the initial phase of navigation.

The initial phase of navigation was also associated with increased activation in the anterior hippocampus. This activation may reflect a type of mental navigation and also as a type of self-projection or prospection, i.e., looking into the future. This is supported by behavioral data demonstrating that individuals use mental imagery as strategy for navigational planning (Spiers and Maguire, 2008). Also consistent with this interpretation, bilateral anterior hippocampal activity has been found in self-projection (Addis et al., 2009; Szpunar et al., 2007), and the location of this activity is similar to the bilateral anterior hippocampal activity detected in the initial phase in the present navigation study. Equivalent anterior hippocampal activity has also been reported in studies of mental navigation (Ghaem et al., 1997; Mellet et al., 2000), bird's eye view navigation (Jordan et al., 2004) and during navigational planning (Spiers and Maguire, 2006). Mental and bird's eye view navigation entail entering an imaginary, non-actual view of one's position and actions in space. Changing one's point of view from first to third person's perspective also correlates with bilateral anterior hippocampal activity (Schmidt et al., 2007). The bilateral anterior hippocampal activity in the initial phase of navigation thus seems to draw on similar regions in the MTL as mental imagery, prospection and third person's point of view (Addis et al., 2009; Szpunar et al., 2007). This suggests that self-localization, target localization and path planning involve construction of a mental representation of the environment based on a meta-perspective of the layout. Furthermore, in rats the hippocampus is also involved in planning of future actions, i.e., vicarious trial and error (Hu and Amsel, 1995), which is considered the rodent equivalent of self-projection.

Right anterior hippocampal activity similar to that in the initial phase of navigation has also been associated with target localization (Doeller et al., 2008; Schmidt et al., 2007; Shipman and Astur, 2008), especially when there is increasing demands on memory-based navigation (Shipman and Astur, 2008), as well as with navigational planning and re-planning (Spiers and Maguire, 2006). The finding that navigational success in condition Normal correlated with activation in the right anterior hippocampus for the initial phase demonstrates an important role for the anterior hippocampus in accurate navigation. Indeed, time course plots of the BOLD signal in the functional voxel in the anterior hippocampus clearly showed that unsuccessful trials had no increase in the BOLD signal while successful did. Activity in this voxel hence predicted the subject's success 15 to 20 s later. Previously, path integration (Wolbers et al., 2007) and spatial coding (Schmidt et al., 2007) have been shown to correlate with activity in similar locations in the right anterior hippocampus as in the current study. The anterior hippocampus is considered to support relational processing (Kirwan and Stark, 2004; Schacter and Wagner, 1999), including flexible (re)combination of elements extracted from previous learned associations (Preston et al., 2004), and may therefore be ideally suited to build a mental model based on previous experiences in the virtual environment. This is corroborated

Table 5
Peak activations for the whole brain analyses when comparing the conditions Normal, Without and Blocked, with the baseline condition (Line following).

Brain region	Coordinates of peak activation (MNI)			*Z*-score
	X	*Y*	*Z*	
Normal>Line following				
R. Frontal pole	29	55	−5	4.78
R. Superior frontal gyrus	25	8	54	5.02
R. Inferior frontal gyrus	47	13	30	5.11
L. Medial frontal gyrus	0	13	46	6.47
R. Insular cortex	33	22	−6	5.53
L. Insular cortex	−30	23	−2	5.17
R. Precuneus	14	−59	15	6.43
L. Lingual gyrus	−21	−43	−14	6.53
R. Occipital cortex	25	−49	−10	6.92
	33	−80	17	5.30
L. Occipital cortex	−32	−86	23	6.61
L. Fusiform gyrus	−24	−45	−15	6.56
R. Hippocampus	26	−22	−11	4.86
R. Thalamus	7	−17	9	5.75
L. Thalamus	−7	−17	9	5.57
Without>Line following				
R. Frontal pole	26	57	−8	5.30
	28	38	31	4.93
	28	55	21	4.72
R. Superior frontal gyrus	26	7	53	5.75
R. Middle frontal gyrus	28	38	31	4.93
R. Inferior frontal gyrus	48	12	29	5.61
R. Medial frontal gyrus	5	32	31	6.45
R. Insular cortex	32	22	−3	6.09
	41	−79	18	5.13
L. Insular cortex	−31	24	−2	5.36
R. Precuneus	12	−77	43	6.11
L. Precuneus	−3	−67	54	5.99
R. Lingual gyrus	8	−49	−1	5.89
L. Lingual gyrus	−21	−45	−14	5.90
R. Occipital cortex	26	−49	−10	6.37
L. Occipital cortex	−32	−86	24	6.65
L. Fusiform gyrus	−35	−76	−22	
R. Thalamus	7	−19	9	5.32
Blocked>Line following				
R. Frontal pole	30	57	−5	5.47
R. Middle frontal gyrus	49	21	34	5.31
R. Orbitofrontal cortex	32	24	−6	5.38
L. Orbitofrontal cortex	−30	24	−7	5.29
R.&L. Precuneus	0	12	47	6.30
R. Precuneus	12	−77	43	6.47
L. Precuneus	−3	−67	54	6.14
L. Lingual gyrus	−9	−52	−1	5.02
R. Occipital cortex	34	−84	30	5.43
L. Occipital cortex	−31	−83	22	5.33
	−32	−62	39	4.77
	−24	−45	−15	5.79
L. Fusiform gyrus	−36	−74	−21	5.90
R. Thalamus	8	−13	7	4.85

Whole brain analysis was carried out using first a voxel threshold ($Z \geq 4$), and then a cluster threshold ($p = 0.05$, corrected for multiple comparisons). MNI, Montreal Neurological Institute 152 brain template, has voxel resolution of 1 mm^3. Only clusters with a cluster size >45 voxels were reported. R, right; L, left.

by animal studies where the anterior hippocampus has been shown to support a unitary representation of the environment at large (Kjelstrup et al., 2008). All together, these findings suggest that successful initial retrieval and/or re-encoding of the environment at large in the anterior hippocampus is required in order to find the target. Another possibility is that the anterior part of the hippocampus supports more non-spatial aspects (Jung et al., 1994; Royer et al., 2010), for example, associating information into a coherent plan.

In condition Normal, hippocampal activity was observed throughout the entire navigational period. The center of gravity for this enduring activity was in the right posterior hippocampus, similar to

Table 6
Peak activations in the whole brain analyses comparing the conditions Normal, Without and Blocked.

Brain region	Coordinates of peak activation (MNI)			*Z*-score
	X	*Y*	*Z*	
Normal>Without				
R. Lateral occipital cortex	30	−94	−12	6.05
L. Lateral occipital cortex	−30	−94	−11	5.91
Without>Normal (no significant increase in activation observed)				
Normal>Blocked				
R. Lateral occipital cortex	25	−97	−12	5.38
L. Lateral occipital cortex	−21	−94	−10	5.45
R. Parieto-occipital sulcus[a]	34	−41	−2	5.45
L. Parieto-occipital sulcus[a]	−28	−41	1	5.13
Blocked>Normal				
R. Superior frontal gyrus	13	51	30	5.70
L. Superior frontal gyrus	−19	57	26	4.95
R. Middle temporal gyrus	59	−57	−5	5.08
L. Middle frontal gyrus	−39	18	40	5.06
R. Inferior frontal gyrus	48	46	−14	5.19
R. Angular gyrus	54	−41	39	5.69
L. Angular gyrus	−55	−52	36	5.26
Without>Block				
R. Hippocampus	31	−40	1	4.65
Blocked>Without				
R. Middle frontal gyrus	34	27	43	4.84
R. Supramarginal gyrus	58	−42	19	5.08
L. Medial superior frontal gyrus	5	48	25	4.81
L. Supramarginal gyrus	−58	−44	34	4.46
R. Cingulate sulcus	0	−17	46	4.64
R. Precuneus	3	−54	63	5.24

Whole brain analysis was carried out using first a voxel threshold ($Z \geq 4$) and then a cluster threshold ($p = 0.05$, corrected for multiple comparisons). MNI, Montreal Neurological Institute 152 brain template, has voxel resolution of 1 mm^3. Only clusters with a cluster size >45 voxels were reported. R, right; L, left.

[a] Cluster includes activation in the hippocampus.

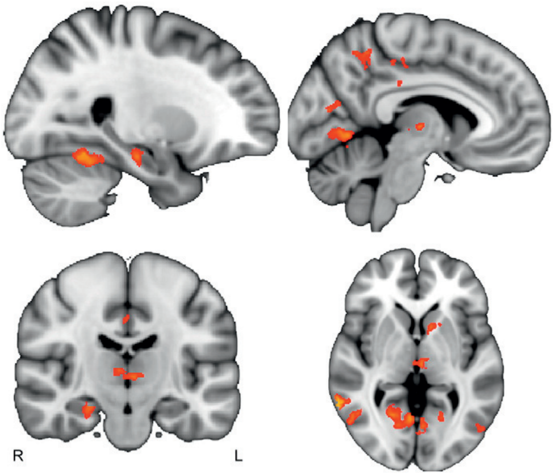

Fig. 6. Comparison between the initial phase and the execution phase for condition Normal on the whole brain level presented on the MNI, Montreal Neurological Institute 152 template, brain. The thresholding was voxel based, $p < 0.05$, corrected for multiple comparisons. Right hemisphere is on the left in the figure.

Table 7
Peak activations for whole brain analyses comparing the contrast Initial>Execution phase in condition Normal.

Brain region	Coordinates of peak activation (MNI)			*Z*-score
	X	*Y*	*Z*	
R. Cingulate gyrus, anterior part	2	−11	41	4.71
R. Cingulate gyrus, posterior part	1	−38	29	4.42
L. Cingulate gyrus, posterior part	−12	−38	38	4.94
L. Postcentral gyrus	−37	−36	57	5.19
R. Middle temporal gyrus	62	−52	3	5.30
	52	−61	0	5.09
L. Precuneus	−6	−50	52	4.49
L. Lateral occipital cortex	−51	−63	7	5.18
R. Cuneal cortex	2	−83	22	5.09
L. Primary visual cortex	−7	−76	14	4.52
L. Lingual gyrus	−17	−64	−4	5.27
R. Hippocampus	25	−20	−18	4.80
L. Caudate nucleus	−11	10	0	4.64
L. Thalamus	−4	−17	2	4.71
L. Cerebellum	−36	−50	−26	5.37

Whole brain analysis was carried out using first a voxel threshold ($Z \geq 4$), and then a cluster threshold, $p = 0.05$, corrected for multiple comparisons. MNI, Montreal Neurological Institute 152 brain template, has voxel resolution of 1 mm^3. Only clusters with a cluster size >45 voxels were reported. R, right; L, left.

that observed in numerous fMRI studies of way finding in familiar virtual towns or indoor environments (Antonova et al., 2009; Iaria et al., 2007; Peigneux et al., 2004; Rauchs et al., 2008). A time course analysis of the BOLD signal revealed that this posterior hippocampal activation peaked regularly throughout the navigation epoch. Using multivariate pattern analysis, a recent study demonstrated that accurate allocentric differentiation of position within a familiar environment is located to the right hippocampus (Hassabis et al., 2009), with coordinates similar to those observed in condition Normal for the entire navigation block in this study. This may be taken to suggest that the posterior hippocampal activity represents environmental detail, supporting theories based on rodent models (Moser and Moser, 1998). The fact that posterior hippocampal activity was observed only in condition Normal indicates that a familiar, stable environment is important to produce positional activity within the hippocampus. This posterior hippocampal activity could be related to both retrieval and re-encoding (Giovanello et al., 2009). When the environment was changed by removing landmarks or blocking paths, posterior hippocampal activity was not observed.

The differences observed in MTL activation between the different way-finding conditions are not merely reflecting differences in performance but are related to task demands. Performance was similar in conditions Blocked and Without, and still the contrast Without>Blocked yielded increased hippocampal activation. However, performance measured as success rate is biased, as shown by the movement plots. Subjects were always close to the targets in

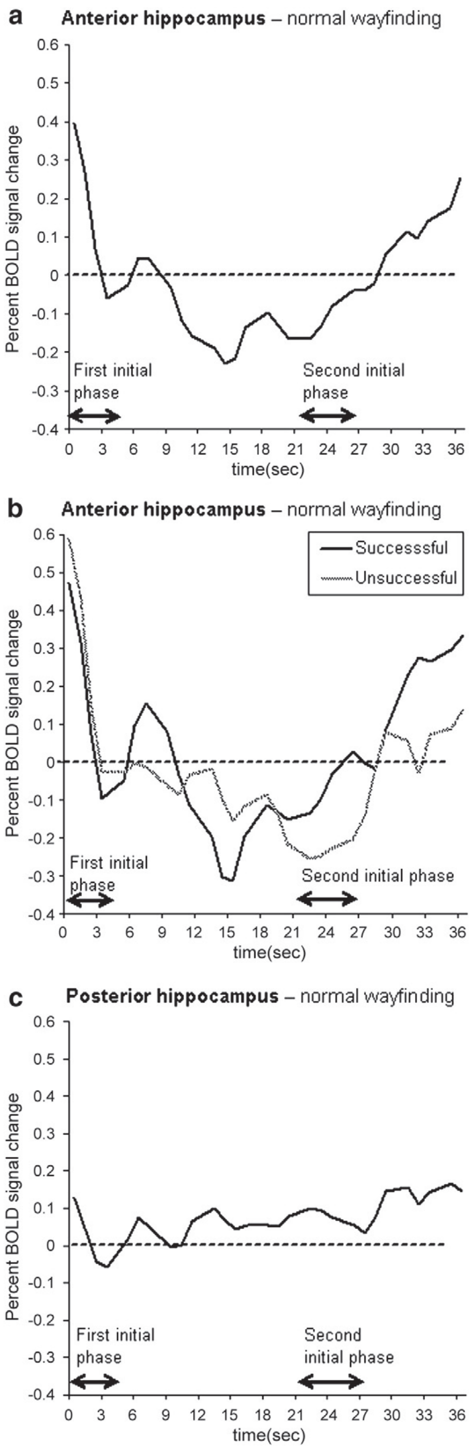

Fig. 7. Plots of the BOLD signal time course changes (% of baseline) in the hippocampus during condition Normal. The baseline signal was the average BOLD signal for all conditions in each run. (a and b) BOLD signal changes in a smoothed functional voxel in the anterior hippocampus. The voxel used in the analysis was the voxel with peak activity in the contrast initial>execution phase in condition Normal (25, −20, −18). (b) BOLD signal changes in the same smoothed functional voxel in the anterior hippocampus. Activity in the voxel in successful (black line) and unsuccessful (gray line) trials are shown. (c) BOLD signal changes in a smoothed functional voxel in the mid-posterior part of the hippocampus. The voxel used in the analysis was the voxel with peak activity in condition Normal for the entire navigation phase>Line following (baseline condition). The voxel coordinates were 29, −35, −14. The BOLD signal time course plots were similar in the posterior hippocampus in successful and unsuccessful trials, results not shown. The BOLD signal related to the initial phases appears delayed due to the lag in the BOLD response with regard to the onset of neuronal activity. The duration of the initial phase was defined based on the participants' post-scan self-reports to last 4.6 s, which was corroborated by the behavioral movement data (see Fig. 1 and Results for details).

condition Blocked, but not in condition Without, still the success rate was similar.

As noted above, condition Blocked did not have persistent hippocampal activity during navigation. The execution phase in condition Blocked resembles to some extent the Morris water maze (Morris, 1984) with visible platform since targets were visible quite early in the navigation block. It has been shown in humans that navigation under conditions similar to this does not require hippocampal activity (Shipman and Astur, 2008). An alternative interpretation is suppression of MTL activity by the rostral medial prefrontal cortex (Anderson et al., 2004; Miller and Cohen, 2003; Spiers and Maguire, 2006). The medial rostral prefrontal cortex was significantly more active during condition Blocked and accompanied by reduced MTL activity. Indeed, condition Blocked had even lower hippocampal activity than condition Without activity as clearly demonstrated in the contrast Without>Blocked. Thus, having actually seen the target but been unable to reach it led to reduced MTL activity and increased prefrontal activity.

In the current study, the anterior parahippocampal cortex was more active in the initial phase, whereas the posterior part was active throughout the navigational period in all conditions. In other words, the parahippocampal cortex displayed an anterior–posterior division of activity during the course of navigation, similar to the hippocampus. It should be noted that current evidence for functional segregation within the parahippocampal cortex is limited, and the interpretation of our findings is therefore preliminary. To date, very few neuroimaging studies of navigation have reported activity in the anterior part of the parahippocampal cortex (Parslow et al., 2005; Spiers and Maguire, 2006). Animal and human studies as well as theoretical models suggest that the parahippocampal cortex generates a representation of the environmental layout (Bird and Burgess, 2008; Moscovitch et al., 2005). Furthermore, spatial memory and associations and retrieval of indirect spatial relationships all engage the anterior parahippocampal cortex (Ekstrom and Bookheimer, 2007; Epstein, 2008; Preston et al., 2004). The increased activity in anterior parahippocampal cortex during the initial phase suggests that the anterior parahippocampal cortex provides a representation of the virtual environment at large. The posterior parahippocampus cortex was, however, active throughout navigation and in all conditions, underscoring the perceptual role of this region (Preston et al., 2004).

In summary, our results demonstrate that successful navigation requires dynamic recruitment of MTL subregions as navigation progresses from self-localization, target localization and navigational planning to execution of the navigational plan. Furthermore, the current findings support a functional segregation between anterior and posterior MTL. The anterior MTL, including the anterior hippocampus, anterior parahippocampal cortex and entorhinal cortex, was specifically engaged in the initial phase of navigation, irrespective of upcoming navigational demands. Activation in the posterior MTL, including the posterior hippocampus and posterior parahippocampal cortex, persisted throughout the entire navigational period. These results suggest that the anterior MTL engendered a mental representation of the environment as a whole, including a global sketch of current position, target position and the path between these two locations. The finding that the initial, transient anterior hippocampal activity correlated with navigational success 15–20 s later in the navigation block underscores the importance of this region in providing a map and a plan leading to the target. Regions in the posterior MTL were activated throughout the period of navigation and could be involved in keeping track of current location within the environment. The current results are consistent with the functional segregation suggested by electrophysiological recordings in the rat hippocampus and describe a similar segregation in the parahippocampal cortex. Finally, this study demonstrated a specific role for the entorhinal cortex in the initial phase of navigation. Although the spatial functions of this region have received much attention in animal studies, its role in human navigation remains to be explored further.

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PAPER 2

The Anterior Hippocampus Supports a Coarse, Global Environmental Representation and the Posterior Hippocampus Supports Fine-grained, Local Environmental Representations

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Abstract

■ Representing an environment globally, in a coarse way, and locally, in a fine-grained way, are two fundamental aspects of how our brain interprets the world that surrounds us. The neural correlates of these representations have not been explicated in humans. In this study we used fMRI to investigate these correlates and to explore a possible functional segregation in the hippocampus and parietal cortex. We hypothesized that processing a coarse, global environmental representation engages anterior parts of these regions, whereas processing fine-grained, local environmental information engages posterior parts. Participants learned a virtual environment and then had to find their way during fMRI. After scanning, we assessed strategies used and representations stored. Activation in the hippocampal head (anterior) was related to the multiple distance and global direction judgments and to the use of a coarse, global environmental representation during navigation. Activation in the hippocampal tail (posterior) was related to both local and global direction judgments and to using strategies like number of turns. A structural shape analysis showed that the use of a coarse, global environmental representation was related to larger right hippocampal head volume and smaller right hippocampal tail volume. In the inferior parietal cortex, a similar functional segregation was observed, with global routes represented anteriorly and fine-grained route information such as number of turns represented posteriorly. In conclusion, moving from the anterior to the posterior hippocampus and inferior parietal cortex reflects a shift from processing coarse global environmental representations to processing fine-grained, local environmental representations. ■

INTRODUCTION

Recent research indicates that space is processed along the entire axis of the hippocampus, but that the spatial representations differ in their nature. Findings in rodents demonstrate that hippocampal place fields increase in size when moving from posterior (dorsal) to anterior (ventral) regions and that different firing fields overlap more in the anterior than in the posterior hippocampus (Kjelstrup et al., 2008; Jung, Wiener, & McNaughton, 1994). These findings suggest that the anterior hippocampus forms a course, global representation of the environment, whereas the posterior hippocampus forms fine-grained, local representations.

Recent fMRI studies in humans support this idea. We have found that retrieving a coarse, global representation of an episode's spatial location activates the anterior hippocampus, whereas retrieving information about fine-grained spatial relations within the episode, for example, the seating arrangement of the guests in a wedding, activates the posterior hippocampus (Nadel, Hoscheidt, & Ryan, 2012). In another fMRI study, participants were shown pictures of familiar landmarks, and activation in the hippocampal head was found to increase with increasing real-world distance between landmarks (Morgan, MacEvoy, Aguirre, & Epstein, 2011). However, no human study has yet made a direct comparison between fine-grained, local and coarse, global spatial processing in the hippocampus.

The proposed distinction between anterior and posterior hippocampal representations of the environment may be a general principle of functional organization in the brain. In the visual system, the size and complexity of receptive fields increase from posterior to anterior regions, both within the occipital lobe and across other parts of the brain (Serences & Yantis, 2006). In rodents, parietal neurons have been observed to fire according to a route-centered reference frame during navigation (Nitz, 2006, 2009). It is possible that, in the human parietal cortex, the most complete route representations are processed anteriorly (Serences & Yantis, 2006), since this region is part of the dorsal visual stream (Silver & Kastner, 2009). However, this possibility remains unexplored.

A typical environmental navigation period can be divided into initial self-localization within the environment (self-localization), followed by planning how to get to the target landmark (planning), and finally moving to the target

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landmark (execution). We have previously shown that self-localization and planning result in a massive increase in anterior hippocampal activation, as well as posterior hippocampal activation, compared with the execution period (Xu, Evensmoen, Lehn, Pintzka, & Håberg, 2010). Additionally, self-localization and planning, compared with execution, have been shown to be characterized by retrieval of environmental representations (Xu et al., 2010; Spiers & Maguire, 2006). Thus, the hippocampus appears to be particularly important for the self-localization and planning periods of navigation, likely reflecting retrieval of environmental representations. The aim of this study was to investigate how spatial representations differ along the anterior–posterior axis of the human hippocampus. We also explored a possible segregation of route representations in the parietal cortex. To this end, we used fMRI of navigation; specifically comparing self-localization and planning with execution, in a learned virtual environment. The nature of representations acquired and used was evaluated by environmental tests and a questionnaire, respectively. Finally, hippocampal morphology was analyzed. We hypothesized that (a) activation and shape of the hippocampal head correlate with the use of a coarse, global environmental representation; (b) activation and shape of the hippocampal tail correlate with the use of fine-grained, local environmental representations; and (c) in the parietal cortex, posterior activation correlates with the use of fine-grained, local route representations and anterior activation correlates with the use of coarse, global route representations.

METHODS

Participants

Thirty men (19–28 years, mean = 22.8 years) participated in this study, all right-handed as ascertained with the Edinburgh Handedness Inventory (mean score = 89.7 ± 11.7%). We included only men to reduce the number of confounding factors, because gender differences have sometimes, but not always, been observed in navigation (Barra, Laou, Poline, Lebihan, & Berthoz, 2012; Ohnishi, Matsuda, Hirakata, & Ugawa, 2006; Blanch, Brennan, Condon, Santosh, & Hadley, 2004; Grön, Wunderlich, Spitzer, Tomczak, & Riepe, 2000). The participants had no history of neurological disorders, head trauma, or current DSM-IV axis I diagnosis of psychiatric illness including substance abuse. All participants provided written informed consent before participation and received 500 Norwegian Kroner as reimbursement. The study was approved by the Regional Committee for Medical Research Ethics in Midt-Norge, Norway, and adhered to the Declaration of Helsinki.

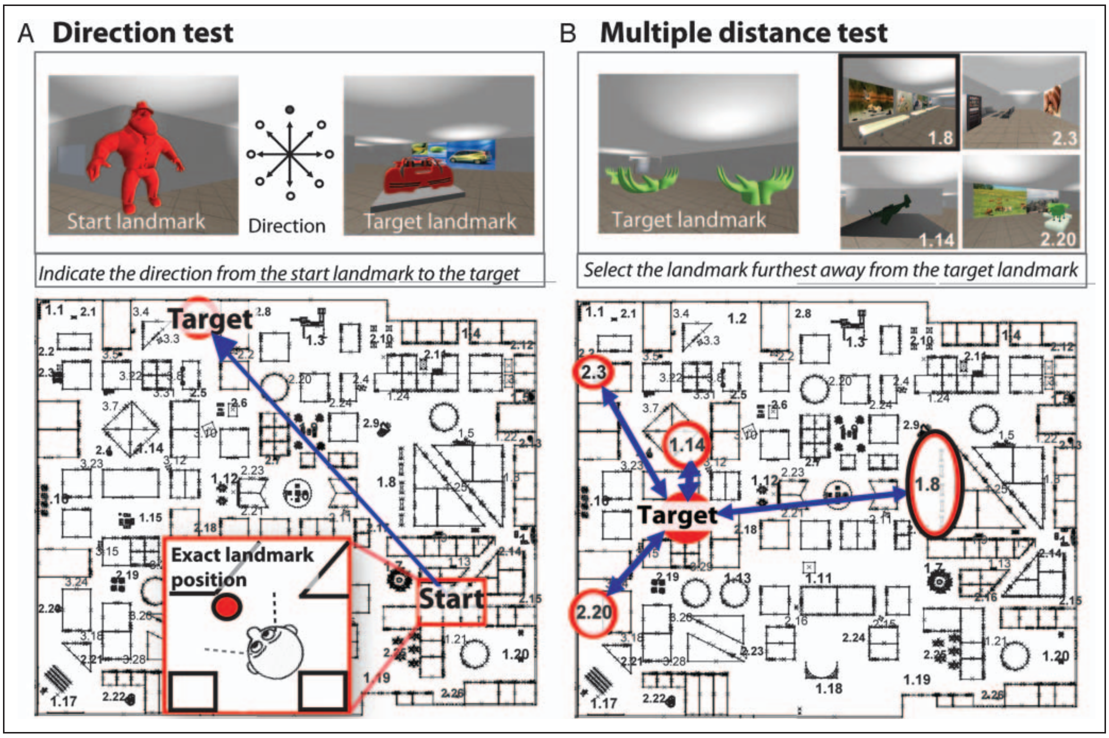
Virtual Reality Environment

The virtual reality (VR) environment was developed in collaboration with Terra Vision AS (Terra Vision, Trondheim, Norway) using the Torque game engine (Garage Games, Eugene, OR). The environment is 115.28 by 138.46 units in size, with player moving speed set to 3.73 unit/sec. It mimics the inside of a modern office building with rooms, corridors, and open areas of various sizes but lacks exterior windows. All doors inside the environment are "locked," that is, participants are only allowed to navigate through the corridors and open areas. Eighty-two distinct landmarks, made up of 240 objects and 62 pictures, were placed at various locations (Figure 1). On the basis of criteria for significance (Lynch, 1960), the landmarks were divided into three categories. "Primary landmarks" have unambiguous shapes, standing in sharp contrast to the surroundings with a prominent position within the virtual environment. "Secondary landmarks" have unambiguous shapes and stand in sharp contrast to their surroundings, but with less prominent positions. "Minor landmarks" had an unambiguous shape but were only visible from a few locations and not that easy to separate from the surroundings. The main focus in the learning phase was on primary and secondary landmarks, and in the fMRI experiment, only primary and secondary landmarks were used as targets. This was done to ensure that the participants could learn the location of all possible target landmarks well enough to plan entire routes from start to target locations in the fMRI experiment. Wall structure, ceiling, carpeting, and lighting of the interior were similar throughout the VR environment and modeled to make the environment as realistic as possible.

Prescanning

Day 1

On the initial day of the experiment, the participants completed the learning phase. First, the participants freely explored the VR environment for 2 × 10 min using a standard desktop computer and a joystick. Next, they completed three test sequences to become familiarized with the VR in its full extent and to see all landmarks at least once. In each test sequence, the participants started at a specific landmark in the environment and had to find a target landmark that was shown in the bottom center of the screen. Upon arrival at the target landmark, a new target landmark was presented. The participants were given new target landmarks in the same manner until a sequence of approximately 25 landmarks was completed. In the first sequence primary landmarks were used as targets, in the second sequence secondary landmarks were used as targets, and in the third sequence minor landmarks were used. This was done to make sure the participants had seen as much as possible of the environment before they had to find the most difficult and/or unobtrusive landmarks. After completing all three sequences, the participants were tested on their proficiency in the VR by means of 18 navigation tasks. In each task, they had to find their



Indicate the direction from the start landmark to the target

Select the landmark furthest away from the target landmark

Figure 1. Environmental tests. The top row shows an example of one of the Direction test trials (A) and an example of one of the Multiple distance test trials (B). The maps illustrate the types of representation required to complete each test type successfully. (A) In the Direction test, the participant determines the direction to the target landmark when facing the start landmark as shown in the figure. To achieve this, the participant has to first retrieve a fine-grained local representation, the exact position and orientation of the start landmark relative to the adjacent walls/architectural features in the background, and next where the target landmark was located relative to the start landmark, requiring only a coarse judgment of the landmark's locations. Two points were given for choosing the correct direction, and one point for choosing either of the two most nearby directions. (B) In the Multiple distance test, the participant has to remember which of four landmarks was farthest away from a target landmark. This required comparing interlandmark relationships in terms of Euclidian distances, in other words, a coarse, global representation of the environment. One point was given for the correct alternative.

way from a randomly selected position in the environment to one of the primary landmarks.

Day 2

On Day 2, the participants first explored the environment freely for 10 min. Next, they completed a test sequence where they had to find their way to 20 primary and 26 secondary landmarks. The primary and secondary landmarks were the same as the target landmarks in the fMRI experiment but presented in a different order. This was done to assure good performance during fMRI. Participants were excluded from the fMRI experiment if they made more than four errors of the 46 trials in the test sequence. Before fMRI the participants were given a 30-min break.

Scanning Procedure

Scanning was performed on a 3T Siemens Trio scanner with a 12-channel Head Matrix Coil (Siemens AG, Erlangen, Germany). Foam pads were used to minimize head motion. The fMRI stimuli were presented using MRI compatible LCD goggles with 800 × 600 resolution (Nordic Neuron Lab, Bergen, Norway), and the participants moved inside the environment using an MRI compatible joystick (Current Designs, Philadelphia, PA).

The participants were first allowed to familiarize themselves with the presentation equipment and joystick and then completed practice trials from the different experimental conditions. Scanning was commenced when complete task compliance was ensured.

fMRI Paradigm

The fMRI paradigm was a self-paced block design with alternating blocks of navigation (max duration = 40 ± 2 sec) and rest (cross fixation; 10 ± 2 sec).

Each navigation block consisted of three phases: Self-localization, Planning, and Execution. At the start of a navigation block, the participants were placed at a random position in the environment and instructed to figure out their current position using at least one other landmark in addition to the start landmark by turning and looking around. This phase is referred to as Self-localization. The participants were instructed to press a button when they were confident that they knew their current position. Subsequently, a target landmark was displayed in the bottom center of the screen. The participants were instructed to determine the location of this target landmark in the environment and plan as accurately as possible the path toward it. This phase is referred to as Planning. The participants pressed a button when they had finished planning and then started moving toward the target landmark. This phase is referred to as Execution. When the target was reached or the maximum allotted time had expired, the navigation block ended and the rest condition ensued.

Each participant completed three experimental runs, with 20 navigation blocks and 20 rest blocks in each run. The order of the runs was randomized between participants and the order of the blocks was randomized within each run.

Positional data capturing the participants' movements inside the environment were logged with a sampling interval of 30 msec.

Imaging Parameters

T2* weighted, BOLD-sensitive images were acquired during the navigation task using an EPI pulse sequence (repetition time = 2600 msec, echo time = 30 msec, field of view = 244 mm, slice thickness = 3.0 mm, slice number = 47, matrix = 80 × 80 giving an in-plane resolution of 3.0 × 3.0 mm). The slices were positioned as close to 90° on the anterior–posterior direction of the hippocampus as possible. Each functional run contained 449 ± 32 volumes, depending on the time needed by each individual to complete the runs. For anatomical reference, a T1-weighted 3-D volume was acquired with an MP-RAGE sequence (repetition time = 2300 msec, echo time = 30 msec, field of view = 256 mm, slice thickness = 1.0 mm, matrix 256 × 256 giving an in-plane resolution of 1.0 × 1.0 mm).

Postscanning Tests and Questionnaires

After scanning, the participants performed three computer-based tests to ascertain the level of fine-grained, local representations and coarse, global representations of the VR environment, inspired by Newcombe and Liben (1982). The first test, the *Multiple distance test*, was related to coarse, global knowledge of map distance in multiple cardinal directions between several distant landmarks in the virtual environment (see Figure 1). The participants had to decide which of four landmarks was farthest away from a target landmark. Knowledge of the distance in time when walking between the landmarks, for example, would not be sufficient to solve this problem, rather a coarse, global representation of the environment is needed. One point was given for the correct alternative. The second test, the Direction test, assessed the participants' ability to evaluate the direction between pairs of landmarks in the virtual environment. This test was divided into Local direction and Global direction. The Local direction test included pairs of nearby landmarks that were located within the same part of the environment, covering maximally one sixth of the total area. The Global direction test included pairs of distal landmarks that were located in two remote parts of the environment, stretching across at least two thirds of the total environment. Having a coarse, global representation of the environment would be especially advantageous for the Global direction test. Both the Local and Global direction tests first required evaluation of the exact position and orientation of the start landmark relative to the adjacent walls, that is, fine-grained, local information. Next, the start landmark had to be placed relative to a target landmark to be able to indicate the direction to the target landmark. The placement of the target landmark relative to the start landmark, compared with the local positioning of the start landmark, only requires a coarse representation of the environment. There were eight alternatives based on north–south and east–west directions. Two points were given for correct direction, and one was given for the two adjacent directions. In the third test, the Spatial sequence test, a more coarse, global environmental representation was assessed. The participants were shown four landmarks and had to put them in the correct order when pretending to move from one particular position to another, stretching across at least two thirds of the total environment. The sequences of landmarks were previously unexperienced and did not consist of landmarks along routes that were performed during environmental learning. Remembering the routes as previously experienced was thus insufficient to perform the task, which required information to be linked across the learned routes, representing a more coarse, global overview of the environment (Siegel & White, 1975). One point was given if all landmarks were placed in a correct sequence.

All participants completed a strategy questionnaire, which included 29 statements relating to the use of fine-grained, local environmental representations and a coarse, global representation of the environment during the Self-localization and Planning phases of navigation (see Table 1). The participants rated each statement on a 9-point scale, ranging from *strongly agree* (9) to *strongly disagree* (1).

Finally the participants were given a *Map test*. They were shown a 2-D representation of the environment that included only the outer walls and no interior architecture or landmarks and were asked to place 14 primary landmarks in correct predefined locations on this 2-D representation. The participants received one point for each landmark placed in the correct location.

In summary each individual's success in forming a coarse, global representation of the environment was tested with the Spatial sequence, Global direction, Multiple distance, and Map tests, whereas fine-grained, local representations were tested with the Local direction test. In addition, each individual's own experience of using a coarse, global representation of the environment and/or fine-grained, local environmental representation was assessed based on self-ratings of strategy use.

Data Analysis

Behavioral Data

Behavioral data were analyzed in SPSS 17.0 (SPSS, Inc., Chicago, IL). The critical performance measures include duration and distance moved in the three navigation phases of Self-localization, Planning, and Execution, the average

Table 1. Strategy Questionnaire Results Describing the Average Group Score for the Mental Strategies Used in Navigational Self-localization and Planning

		Mean + SD
Self-localization		
s1	A main landmark	7.0 ± 2.3
s2	A map like representation of the environment	6.3 ± 2.3
s3	A route or a sequence of landmarks	3.5 ± 2.0
s4	Nearby landmarks	7.5 ± 1.5
s5	Landmarks from the whole environment	4.8 ± 2.3
s6	A representation of the environment as a whole	6.1 ± 2.3
Planning		
p1	Placed the target landmark relative to nearby landmarks	6.6 ± 1.9
p2	Placed the target landmark in a representation of the environment as a whole	6.8 ± 2.0
p3	Placed the target landmark relative to start position	5.9 ± 2.5
p4	Placed the target landmark relative to other landmarks in a route or sequence	4.1 ± 2.2
p5	Direction to target landmark	8.3 ± 1.7
p6	Direction to landmarks in between	4.5 ± 2.0
p7	Distance to target landmark	5.4 ± 2.4
p8	Distance to landmarks in between	3.0 ± 1.5
p9	Sequences of landmarks	4.1 ± 1.9
p10	Exact routes	3.6 ± 2.1
p11	A map-like representation of the environment	6.0 ± 2.4
p12	A representation of the environment as whole	6.0 ± 2.6
p13	Landmarks in between	5.2 ± 2.3
p14	Number of turns	3.4 ± 2.5
p16	A set of routes	3.8 ± 2.2
p17	Rapid route following	5.3 ± 3.2
p18	Direction only?	8.5 ± 0.8
p19	I knew the environment well enough to plan	7.3 ± 1.1
p20	Mental route following over long distances	6.0 ± 2.3
p21	Mental route following over short distances	5.8 ± 2.7
p22	Direction(alone) over long distances	6.8 ± 2.1
p23	Direction(alone) over short distances	5.4 ± 2.4

Each individual was asked to rate on a scale from 1 to 9 to what extent he used the different strategies during the Self-localization and Planning phases (*SD*, standard deviation).

success rate for the navigation tasks during fMRI, and the average success rate on the postscan tests of Multiple distance, Local direction, Global direction, and Spatial sequence. The strategies participants used during navigation were inferred from the strategy questionnaire data. Here, a PCA was used to extract the main factors describing the reported strategies, separately for the questions related to Self-localization and Planning. Factors were made orthogonal using varimax rotation with Kaiser Normalization, and questions with an absolute coefficient value of less than 0.4 for a given factor were suppressed. We used factor analysis instead of simply aggregating scores regarding fine-grained environmental representations and a coarse environmental representation separately, because factor analysis is a more objective and data-driven approach. Although factor analysis is usually considered to be a technique for relatively large samples, it has been shown that sample sizes far below 50 can give reliable results (De Winter, Dodou, & Wieringa, 2009). To confirm this, correlation analyses between questionnaire scores and fMRI activity were performed with the score from the individual questions as well as with the calculated factors. Similar results were observed. The scores from the environmental tests were tested for correlation, between participants, using Spearman's rho.

MRI Data Analysis

Imaging data were analyzed using FSL 4.1.8 (Analysis Group, FMRIB, Oxford, UK). First, nonbrain tissue was removed from the T1 anatomical images, and the resulting images were transformed to the MNI standard template ($1 \times 1 \times 1$ mm; Montreal Neurological Institute, Montreal, QC, Canada) using nonlinear registration (FNIRT; reference). The fMRI data were motion corrected, smoothed with a 5-mm FWHM Gaussian filter, and temporally high-pass filtered with a cutoff at 250 sec. Each functional image series was coregistered to the corresponding anatomical T1 image and transformed into MNI space using the transformation matrix obtained with the T1 image. The statistical analysis of the fMRI data was carried out in FEAT (Smith et al., 2004). The experimental conditions (Self-localization, Planning, and Execution) were modeled according to a boxcar stimulus function convolved with a two-gamma hemodynamic response function (Boynton, Engel, Glover, & Heeger, 1996). The rest condition constituted the model's baseline. The effect of each condition was estimated with a general linear model (GLM) and averaged across participants in a mixed effects analysis (FLAME 1; Beckmann, Jenkinson, & Smith, 2003).

Medial-temporal Lobe Analysis

A brain mask was applied to investigate activation in the medial-temporal lobe (MTL) more closely. The mask was created from the probabilistic maps of the Harvard Oxford Structural Atlases (part of FSL; fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases; Flitney et al., 2007), using no probability threshold. The mask contained 76,864 (1-mm) voxels and included both the hippocampus and parahippocampal gyrus. Within this mask, specific ROIs were also identified. The entorhinal cortex and the perirhinal cortex were defined based on anatomical boundaries (Insausti et al., 1998). The hippocampus was divided into head, body, and tail (DeFelipe et al., 2007; Duvernoy, 2005).

The contrasts Self-localization > Execution and Planning > Execution were investigated within participants using paired t tests together with an initial voxel threshold of $p < .001$ and a subsequent clusterwise correction for multiple comparisons ($p < .05$).

Combined fMRI and Behavioral Data Analysis

We performed separate GLM analyses to examine possible correlations between activation in the MTL ROI and individual scores on the environmental tests and strategy questionnaire. Each individual's results on the Multiple distance, Local direction, Global direction, and Spatial sequence tests were entered as separate regressors in a mixed effects GLM analysis with MTL activation in the contrast Planning > Execution as the dependent factor. Planning and not Self-localization was used because interviews with participants in pilot experiments revealed that the distributions of fine-grained, local environmental representations and coarse, global representations were more homogenous in the Planning phase. The threshold was set at voxel $p = .005$ (uncorrected), and a minimum cluster size of 30 continuous 1-mm voxels.

Each individual's strategy questionnaire factor loadings (see above for details on factor analysis) were entered as separate regressors in two GLM analyses, one with MTL activation in the contrast Self-localization > Execution as the dependent factor and one with MTL activation in the contrast Planning > Execution as the dependent factor. In the analysis of Self-localization > Execution, the factor loadings relating to Self-localization were entered (s1–6; Table 2). In the analysis of Planning > Execution, the factor loadings relating to Planning were entered (p1–23; Table 3).

We performed an additional GLM analysis to investigate possible associations between activation in a parietal ROI (see below for further details) and different types of route representations. Here, we used all questionnaire items related to the use of route centered representations during Planning: p9 (landmark sequences), p10 (exact routes), p14 (nr of turns), and p16 (set of routes). Each individual's item ratings were entered as separate repressors in the GLM. The contrast used was Planning > Execution. The statistical threshold was voxel $p < .005$ (uncorrected) with a minimum cluster size of 30 continuous 1-mm voxels. A stricter statistical threshold was used for the parietal lobe, compared with the MTL, since the calculated t and β values are reduced for subcortical compared with cortical structures using a Siemens 3T system with a 12-channel head coil (Kaza, Klose, & Lotze, 2011). The parietal ROI consisted of 288,809 (1-mm)

Table 2. Factor Analysis of Questionnaire Items Related to Self-localization

		Local Environment Factor S1	*Environmental Coherence Factor S2*	*Route/Sequence Factor S3*
s4	Nearby landmarks	0.873		
s2	A map like representation of the environment	−0.774		
s6	A representation of the environment as a whole	−0.467	0.443	−0.433
s5	Landmarks from the whole environment		0.781	
s1	A main landmark		−0.735	
s3	A route or a sequence of landmarks			0.89

The factors were extracted from the strategy questionnaire scores using a PCA and then rotated using varimax. Questions from the strategy questionnaire with an absolute coefficient value of less than 0.4, for a given factor, were suppressed. Factor S1 was given the name "Local" because it represents the use of nearby landmarks, but not a map like representation of the environment or a representation of the environment as a whole. Factor S2, representing the use of a coherent representation of the environment as a whole, and not just an independent main landmark, and was given the name "Coherent." Factor S3 was named "Route/sequence," representing use of a route or a sequence of landmarks, but not the environment as a whole.

voxels that encompassed the parietal lobe. The mask was based on the probabilistic maps of the MNI structural atlas (part of FSL; fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases; Flitney et al., 2007), using a probability threshold of 25%.

Hippocampal Shape Analysis

The automatic segmentation tool within FSL (FIRST) was applied to the T1 images to estimate individual variations in shape and size of the right and left hippocampus. Each segmented hippocampus was transformed to a template based on the averages of all participants' common mean native space, using six degrees of freedom, thus only differences in local shape or local volumes were assessed. To investigate the use of a coarse, global representation of the environment independent of navigational phase, the questions from the strategy questionnaire most strongly related to the use of a global environmental representation for both Self-localization and Planning (s2, s5, s6, p2, p11, p12) were grouped, and an aggregate score was calculated. Likewise, the questions from the strategy questionnaire most strongly related to using fine-grained, local environmental representations for both self-localization and planning (s4, p5, p14, p18) were grouped, and an aggregate score was calculated. These scores, plus scores from the Multiple distance and Global and Local direction tests, were entered as separate regressors in a GLM. This was done to investigate the relationship between hippocampal shape and the type of environmental representation acquired and applied during navigation, as well as the level of spatial proficiency as determined by the different tests in each participant. We used a statistical threshold of $p = .0001$, uncorrected.

RESULTS

Learning Phase

Two participants were excluded from the analysis: one because he failed to meet the learning criterion and the other because of severe nausea during VR navigation in the scanner. After the learning phase on Day 1, the participants included in the final sample ($n = 28$) were able to reach 88.9 ± 7.4% of the landmarks in the environment in the prescan test, indicating they were highly familiar with the environment.

fMRI Task Performance

The Self-localization phase lasted on average 8.5 ± 2.9 sec, the Planning phase lasted 8.1 ± 2.5 sec, and the Execution phase lasted 13.2 ± 1.0 sec. There was a significant effect of phase with regard to duration ($F = 47.5, p < .001$). Post hoc comparisons revealed a significant difference between Self-localization and Execution ($t = 4.7, p < .001$) and between Planning and Execution ($t = 5.1, p < .001$), but not between Self-localization and Planning. Participants moved on average 2.7 ± 2.7 m during Self-localization, 0.27 ± 0.34 m for Planning, and 100.2 ± 5.71 m during Execution. There was a significant effect of phase with regard to distance moved ($F = 5480, p < .001$). Post hoc comparisons showed a significant difference between Self-localization and Planning ($t = 2.4, p < .0001$) and, as expected, between Self-localization and Execution ($t = 95.8, p < .0001$), and between Planning and Execution ($t = 97.8, p < .0001$). Movement plots for each trial clearly showed that the participants followed the instructions for movement in the different trial phases, that is, moving around the starting landmark during Self-localization and standing still while choosing the direction or route during Planning.

The participants were able to reach on average 82.2 ± 14.9% of the target landmarks during scanning. Visual inspection of the movement plots, combined with feedback from the participants after scanning, revealed that in most cases participants failed to reach the target because they ran out of time, and not because they did not know the way to the target landmark.

Table 3. Factor Analysis of Questionnaire Items Related to Planning

		Environmental Coherence Factor P1	*Sequence and Turns Factor P2*	*Direction Factor P3*	*Exact/Complete Long Routes Factor P4*	*Environmental Chunking Factor P5*	*Map Factor P6*	*Direction to Remote Landmarks Factor P7*	*Routes Factor P8*
p12	A representation of the environment as whole	0.786							
p7	Distance to target landmark	0.784							
p2	In a representation of the environment as a whole	0.774							
p14	The number of turns		0.734						
p4	Relative to other landmarks in route or sequence		0.707						
p23	Direction(alone) over short distances		−0.638						
p9	Sequences of landmarks		0.613				−0.423		
p6	Direction to landmarks in between		0.591						
p5	Direction to target landmark			0.773					
p18	Direction			0.769					
p17	Rapid route following	0.47		0.723					
p20	Mental route following over long distances				0.835				

p10	Exact routes				0.811				
p1	Relative to nearby landmarks			−0.43	−0.527				
p8	Distance to landmarks in between					0.833			
p16	A set of routes					−0.687			0.428
p21	Mental route following over short distances					0.629			
p11	A map like representation(s) of the environment						0.794		
p13	Landmarks in between					0.408	−0.633		
p22	Direction(alone) over long distances							0.762	
p19	I knew the environment well enough to plan							0.725	
p3	Relative to start position								−0.915

The factors were extracted from the strategy questionnaire scores using a PCA and then rotated using varimax. Questions from the strategy questionnaire with an absolute coefficient value of less than 0.4 for a given factor were suppressed. Factor P1 was named “Coherent representation” because it involves primarily questions indicating the use of a coherent representation of the environment. Factor P2 was given the name “Sequences and turns,” because it involves questions that indicate the use of landmark sequences and turns and direction to landmarks in between but not direction, for example, to the target landmark. Factor P3 was named “Direction,” the name is based on the fact that two of the four questions in this factor depend on the use of direction. Factor P4, was given the name “Exact long routes,” representing the use of exact routes and mental route following over long distances. Factor P5 was named “Environmental chunking,” because tabout the questions involved representation of a limited part of the environment between the start position and the target landmark. Factor P6 was given the name “Map,” because it involves using a map-like representation(s) in a third person perspective, but not parts of the environment like sequences of landmarks. Factor P7 was named “Direction to remote landmarks” because it involves using direction between the start position and remote landmarks. Factor P8 was named “Set of routes,” since it involved using a set of routes when planning, but not placing the target landmark relative to the start position.

Tests of VR Knowledge and Navigation Strategies

The average number of correct answers were as follows: on the Multiple distance test, 8.1 ± 1.7 of 10 points; on the Local direction test, 7.8 ± 1.6 of 10 points; on the Global direction test, 7.9 ± 1.9 of 10 points; on the Spatial sequence test, 5.4 ± 2.3 of 10 points; and on the Map test, 13.6 ± 1 of 14 points. The average success rate was well above chance level for all tests, which was 2.4 point for the Multiple distance test, 2.5 points for the Local direction and Global direction test, 2.5 points for the Spatial sequence test, and 1 point for the Map test. These results show that the participants knew the VR environment very well, although they did not reach all target landmarks during fMRI within the given time. The scores on the Local direction test and Global direction test were not correlated ($R = .163$, $p = .407$), nor were the scores on the Local direction test and Multiple distance test ($R = .294$, $p = .129$), the scores on the Global direction test and Multiple distance test ($R = .242$, $p = .215$), the scores on the Local direction test and the Spatial sequence test ($R = .257$, $p = .186$), or the scores on the Global direction test and the Spatial sequence test ($R = .315$, $p = .102$). However, a significant correlation was found between the score on the Multiple distance test and the score on the Spatial sequence test ($R = .573$, $p = .001$). These results support a behavioral, and possibly also neural, separation of the ability to have a highly accurate spatial (environmental) representation of individual landmarks versus a more coarse, global environmental representation.

On the basis of the factor analysis of the questionnaire, the mental representations used for Self-localization (S) could be linked to the Environmental coherence factor S2, which describes the use of a coherent representation of the environment; the Local environment factor S1, which describes the use of nearby landmarks, and the Route/sequence factor S3, which depends on positioning one's self in a more local route or sequence of landmarks (Table 2).

Planning (P) relied on eight factors, of which half can be viewed as reflecting the use of a coarse, global environmental representation and the other half the use of fine-grained, local environmental representations. The coarse, global factors included Environmental coherence (P1), which describes the use of a coherent representation of the entire environment; Exact long routes (P4), which described the use of an exact representation of the entire route to the target; Map-like representation (P6), which indicated the use of a mental map of the environment; and Direction (P7), which described the use of direction between start position and remote landmarks other than the target landmark. The factors that represented fine-grained, local environmental representations were Sequences and turns (P2), which depend on remembering and utilizing landmark sequences and number of turns to reach target; Local direction (P3), which describes using the direction from start position to target; Exact routes (P4), which indicates using an exact representation of the entire route from start position to target; Environmental chunking (P5), which describes chunking part(s) of the environment, including landmarks located between start position and target, and uses these halfway targets to find the final target; and Route (P8), which describes using a set of fixed routes. Note that the factor Exact routes (P4) is linked to the use of both a global environmental representation and fine-grained, local representations. This was because of the fact that both of the questions "Mental route following over long distances" and "Use Exact routes" load on this factor (Table 3).

fMRI Results

MTL Activation during Different Phases of Navigation

For the contrasts Self-localization > Execution and Planning > Execution, increased activation was present in the right hippocampal body, bilateral hippocampal head, and bilateral rostral entorhinal cortex (Table 4). For Self-localization > Execution, additional activations were observed in the left hippocampal body, right caudal entorhinal cortex, and bilateral parahippocampal cortex. Only the contrast Planning > Execution activated the hippocampal tail bilaterally.

The Association between MTL Activity and Multiple Distance and Direction Tests Scores

There was no association between the spatial test scores and activation in the contrast Self-localization > Execution. For Planning > Execution, there was an effect in the hippocampal tail for both Local direction and Global direction, whereas in the hippocampal head an effect was observed only for Global direction (Figure 2; Table 5). The Multiple distance test showed an effect only in the right hippocampal head. No effects were observed of the Spatial sequence test.

The Association between MTL Activity and Self-reported Navigation Strategy

The GLM revealed no significant relationship between activation in the MTL and any of the questionnaire factors when using the a priori statistical threshold. However, we did identify a number of sub-threshold activations ($p < .05$ uncorrected). Activation bilaterally in the hippocampal head correlated with all the factors related to the use of a coarse, global representation of the environment during both Self-localization and Planning. The factor Environmental coherence (S2) correlated with activation in the contrast Self-localization > Execution (Figure 2; Table 6), and the factors Exact route (P4), Map (P6), Direction to remote landmarks (P7), and Direction

Table 4. MTL Activation during Self-localization and Planning

	Coordinates of Peak Activation (MNI)					
MTL Region	*X*	*Y*	*Z*	*Cluster Number*	*Cluster Size (No. of Voxels)*	*Z Score*
Self-localization > Execution						
Hippocampal body	25	−30	−10	(1)		3.56
	−16	−31	−7	(2)		4.02
Hippocampal head	28	−16	−25	(1)		4.09
	−30	−18	−22	(2)		3.49
Entorhinal cortex (caudal)	25	−22	−24	(1)		4.03
Entorhinal cortex (rostral)	22	−5	−37	(1)		4.24
Perirhinal cortex	25	0	−36	(1)		4.68
	−30	−8	−37	(2)		4.01
Parahippocampal cortex	20	−32	−23	(1)		4.41
	−27	−29	−25	(2)		3.67
Temporal fusiform cortex	39	−10	−39	1	13281	5.16
Temporal pole	−31	8	−38	2	7101	5.53
Planning > Execution						
Hippocampal tail	13	−38	5	(1)		4.74
	−14	−40	1	(2)		4.48
Hippocampal body	−28	−27	−17	(2)		3.97
Hippocampal head	26	−16	−21	(1)		3.54
	−31	−11	−24	(2)		4.01
Entorhinal cortex (rostral)	17	2	−28	(1)		4.66
	−21	1	−30	(2)		4.52
	−25	−11	−34	(2)		3.69
Perirhinal cortex	32	−4	−34	(1)		4.46
Temporal fusiform cortex	39	−11	−38	1	9900	5.08
Temporal pole	−29	8	−38	2	11473	4.88

The analysis was carried out using an MTL mask and voxel based thresholding, $p = .001$ uncorrected, and a cluster threshold, $p = .05$ corrected. MNI 152 brain template has a voxel resolution of 1 mm^3. The cluster number is given in parenthesis for secondary peaks within the respective clusters. R = right; L = left.

(P3) correlated with activation in the contrast Planning > Execution (Figure 2; Table 7). Hippocampal tail activation correlated with factors related to fine grained local environmental representations: Sequence and turns (P2), Exact routes (P4), and Direction (P3) (Figure 2; Table 6) for Planning > Execution.

The Association between Parietal Cortex Activity and Type of Mental Route Representations

A positive relationship was observed between the questionnaire items that indicate use of different types of route representations and activity in the inferior parietal cortex in the contrast Planning > Execution (Figure 3). More complete mental route representations were observed in anterior compared with posterior inferior parietal cortex. Most posteriorly, at the parietal-occipital junction, activation in left hemisphere was associated with the use of number of turns ($[-34\ -86\ 36], z = 3.52$). More anteriorly, the use of sequences of landmarks was associated with activity in the right inferior parietal cortex ($[41\ -66\ 28], z = 3.47$) and the use of complete routes with activity even more anteriorly in left inferior parietal cortex ($[-52\ -53\ 42], z = 5.18$).

Hippocampal Shape Analysis

In the right hippocampal head, larger local volume correlated with self-reported use of a coarse, global representation of the environment, both during Self-localization

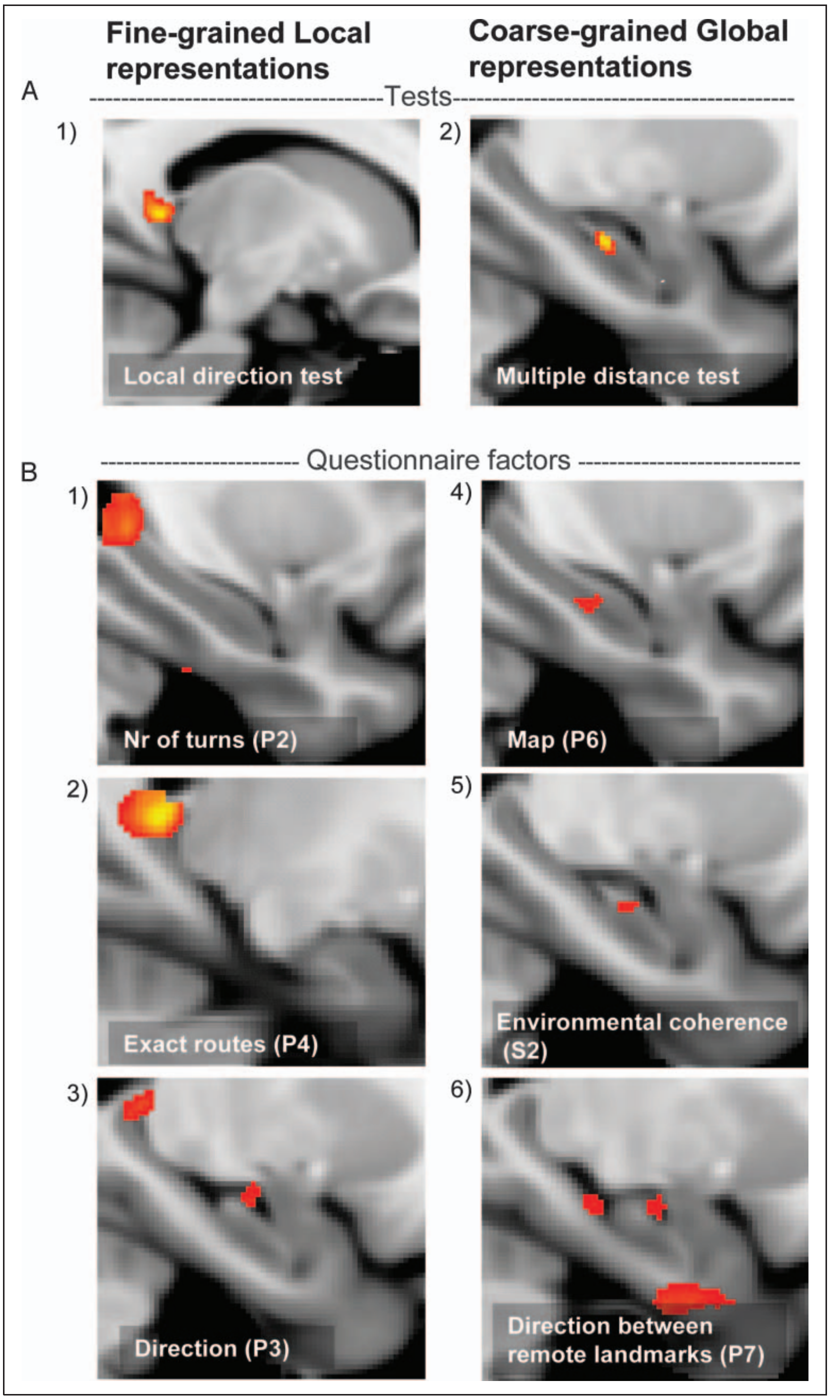


Figure 2. Fine-grained, local representations in posterior hippocampus and a coarse, global environmental representation anteriorly. Regions in MTL that correlated with scores on Local direction and Multiple distance test (A) and strategy factors (B), for either Self-localization > Execution or Planning > Execution. (A1) shows areas correlating with the Local direction test, which tested the ability to evaluate the exact position of the landmark within the proximate surrounding walls to be able to tell the direction to a nearby landmark. The images in the left column, B1–B3, represent analysis of MTL activity related to more exact knowledge of the position of the landmarks within the environment. B1–B3 show areas positively correlated with the strategy factors from the factor analysis of the strategy questionnaire, representing the use of details from a more local part of the environment. The images in the right column (A1) show MTL regions that correlated with the Multiple distance test (A2), which tested if the participants were able to decide the relative distance between several remote landmarks in the environment and (B4–B6) show MTL regions that correlated with strategy factors, indicating the use of a coarse, global representation of the environment. Voxel-based thresholding was applied at the level of $p = .05$ uncorrected for the factor GLM and $p = .005$ uncorrected for test score GLM. These images are all from the right hemisphere. Activations are superimposed on the MNI 152 brain template.

Table 5. The Relationship between the Spatial Accuracy and Multiple Distance Test Scores and MTL Activation during Planning

	Coordinates of Peak Activation (MNI)					
MTL Region	*X*	*Y*	*Z*	*Cluster Number*	*Cluster Size (No. of Voxels)*	*Z Score*
Global Direction Test						
Hippocampal tail	23	−42	4	1	5399	4.58
	−25	−41	7	2	2588	3.53
Hippocampal head	27	−15	−15	3	141	3.10
	−25	−14	−15	(1)		3.41
Parahippocampal cortex	28	−34	−18	(1)		3.06
Entorhinal cortex, caudal	−20	−17	−31	4	2559	3.95
	28	−21	−27	(5)		3.15
Perirhinal cortex	11	−11	−23	5	1899	3.61
	24	8	−33	6	186	3.3
	−29	6	−30	7	1306	3.63
	−35	−16	−36	8	167	3.48
Local Direction Test						
Hippocampal tail	12	−38	7	1	603	3.51
Multiple Distance Test						
Hippocampal head	26	−16	−17	1	35	2.78
Spatial Sequence Test						
n/a						

For an explanation of the tests, see Methods. The analysis was carried out using an MTL mask and voxel based thresholding, $p = .005$ uncorrected. Only clusters with a cluster size of >30 voxels were reported. MNI 152 brain template has a voxel resolution of 1 mm^3. The cluster number is given in parenthesis for secondary peaks within the respective clusters. R = right; L = left.

Table 6. The Relationship between Factors of the Strategy Questionnaire and MTL Activation during Self-localization

	Coordinates of Peak Activation (MNI)					
MTL Region	*X*	*Y*	*Z*	*Cluster Number*	*Cluster Size (No. of Voxels)*	*Z Score*
Local (S1)						
n/a						
Environmental Coherence (S2)						
Hippocampal head	−30	−15	−18	1	47	2.05
	24	−14	−17	2	39	2.05
Perirhinal cortex	−31	6	−39	3	823	3.54
	24	10	−26	4	219	2.74
Route (S3)						
n/a						

The analysis was carried out using an MTL mask and voxel based thresholding, $p = .05$ uncorrected. Only clusters with a cluster size of >30 voxels were reported. MNI 152 brain template has a voxel resolution of 1 mm^3. R = right; L = left.

Table 7. The Relationship between Factors of the Strategy Questionnaire and MTL Activation during Planning

MTL Region	Coordinates of Peak Activation (MNI) X	Y	Z	Cluster Number	Cluster Size (No. of Voxels)	Z Score
Environmental Coherence (P1)						
n/a						
Sequence and Turns (P2)						
Hippocampal tail	33	−42	−1	1	744	2.38
	31	−38	0	(1)		2.33
Hippocampal body	−31	−32	−5	2	43	1.94
Entorhinal cortex, caudal	−14	−25	−19	3	562	2.32
Perirhinal cortex	−32	−4	−28	4	280	2.39
Direction (P3)						
Hippocampal tail	16	−42	5	1	794	2.64
	22	−35	4	(1)		2.04
Hippocampal body	−33	−27	−7	2	1552	2.89
Hippocampal head	29	−14	−14	3	210	1.94
	−26	−16	−10	(2)		2.58
Parahippocampal cortex	34	−35	−15	4	192	2.09
Perirhinal cortex	−29	6	−28	5	308	2.28
Exact Long Routes (P4)						
Hippocampal tail	−12	−38	7	1	1754	2.83
	14	−35	8	2	1189	2.60
Hippocampal head	−31	−7	−22	(3)		2.52
Entorhinal cortex, rostral	18	4	−27	4	112	2.32
	−24	−14	−37	3	46	2.25
Perirhinal cortex	−35	−18	−33	5	3138	2.76
	33	−24	−28	6	381	2.21
	28	7	−39	7	378	2.36
	−27	6	−39	8	49	1.94
Environmental Chunking (P5)						
n/a						
Map (P6)						
Hippocampal head	25	−16	−8	1	241	2.27
	30	−19	−18	2	47	1.81
Direction to Remote Landmarks (P7)						
Hippocampal body	39	−35	−7	1	430	2.38
	20	−24	−14	2	87	1.91
	15	−34	−8	3	46	1.87
	16	−28	−11	4	32	1.83

Table 7. (*continued*)

MTL Region	*Coordinates of Peak Activation (MNI)*			*Cluster Number*	*Cluster Size (No. of Voxels)*	*Z Score*
	X	*Y*	*Z*			
Hippocampal head	18	−12	−15	5	314	2.51
	−33	−19	−12	6	266	1.96
Entorhinal cortex, rostral	18	−8	−37	7	1626	3.07
Amygdala	24	−2	−24	8	73	1.92
Routes (P8)						
n/a						

The analysis was carried out using an MTL mask and voxel based thresholding, $p = .05$ uncorrected. Only clusters with a cluster size of >30 voxels were reported. MNI 152 brain template has a voxel resolution of 1 mm^3. R = right; L = left.

and Planning (Figure 4). In the right hippocampal tail, smaller local volume was associated with the same measure (Figure 4). For the left hippocampus, there was no relationship between local volume and spatial representation. There were no significant relationships between local hippocampal volume and any of the test scores.

DISCUSSION

In this study, we tested the hypothesis that anterior hippocampus supports a coarse, global environmental representation whereas posterior hippocampus supports fine-grained, local representations. We used a virtual environment combined with fMRI to describe how localization of functional activation and hippocampal shape related to the level of coarse, global and fine-grained, local spatial representations of the virtual environment, measured with both objective tests and self-report. Our main finding was that activation in the hippocampal head was positively related to measures reflecting coarse, global environmental representations, whereas activation in the

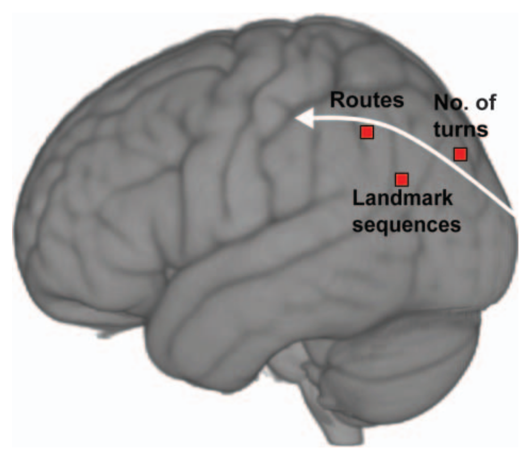


Figure 3. The route representation becomes more complete in the anterior part of the inferior parietal lobe. This figure shows the peak voxels in the inferior parietal lobe when correlating activation for condition Planning > Execution with route related questions from the strategy questionnaire. The original x coordinate of the peak voxels is presented as located to one hemisphere to visualize the relative position of each peak voxel along the anterior–posterior axis. Activation peaks are superimposed on the MNI 152 brain template.

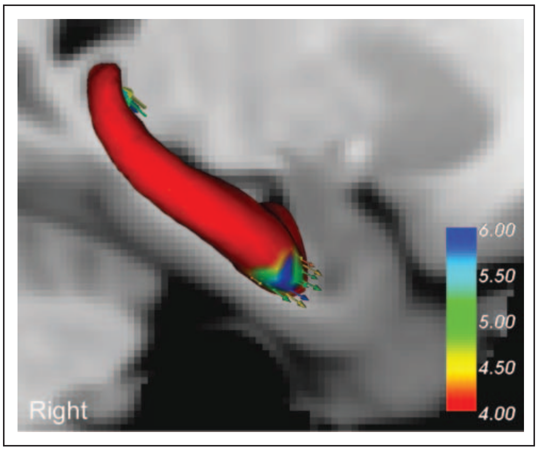


Figure 4. The relationship between hippocampal shape and the ability to use a coarse, global representation of the environment from an aggregate score, based on the strategy questionnaire (s5, s6, p2, and p12). Arrows pointing outward indicate increased local volume (enlargement), and arrows pointing inward indicate reduced local volume (reduced volume). Right hippocampal tail volume correlated negatively and right hippocampal head volume positively with this aggregated coarse, global score. To investigate local changes within the hippocampus, each segmented hippocampus was transformed to a common mean native space, using six degrees of freedom, whereas global changes from each hippocampus were removed. Threshold used was $p = .0001$ uncorrected. The color bar illustrates what z value the colors in the volumetric image represent.

hippocampal tail was positively related to measures reflecting fine-grained, local representations. This is in line with the suggested functional segregation along the anterior–posterior axis of the hippocampus from animal studies of hippocampal function (Kjelstrup et al., 2008; Jung et al., 1994), but to our knowledge, this hypothesis has never before been tested in humans.

The behavioral data support the idea of two systems of spatial representation, one related to a coarse and global overview and another related to fine-grained, local environmental representations. The strategies that participants used during self-localization and navigational planning were reduced to 11 main factors that reflect the use of coarse, global environmental representations or fine-grained, local environmental representations. An example of a coarse, global environmental factor is Map, reflecting the use of an environmental map of the environment when planning how to reach the target. An example of a fine-grained, local factor is Sequence and turns, which involved evaluating landmarks and turns between the start position and the target landmark when planning how to reach the target. The idea of two spatial systems is supported by the observation that individual scores on the Local direction test were uncorrelated with the test scores that reflect processing of a coarse, global environmental representation, that is, Global direction, Multiple distance, and Spatial sequence test scores. This is consistent with a previous navigation study, where the representations of individual rooms were more accurate than and separate from a coarse, global representation of the environment (Colle & Reid, 2000). Although two separable spatial systems appear to exist, they are likely to interact. For example, people have been shown to switch between the two types of representations during navigation (Wang & Brockmole, 2003). We identified one factor, Exact long routes, that seems to reflect the use of both fine-grained, local environmental representations and a coarse, global environmental representation, also suggesting that the two systems interact.

The fMRI data show that representation of a coarse, global representation relies most strongly on the hippocampal head. The Multiple distance test score was only related to activation in the hippocampal head. Importantly, activation in the hippocampal head was associated with the Global direction test, but not the Local direction test. Moreover, activation in the hippocampal head was related to the questionnaire factor Environmental coherence during Self-localization and to the factors Map and Exact long route during Planning. These factors are all considered to reflect the use of a coarse, global representation of the environment. The activation in the hippocampal head did not correlate with the Spatial sequence test. This might be because of low performance on this test, or that this test is not an equally sensitive measure of a coarse, global environmental representation. During Planning, activation in the hippocampal head was also associated with the Direction factor. The region in the hippocampal head that was related to the Direction factor was also related to Direction to remote landmarks. This indicates that the hippocampal head is important when direction is evaluated using a global environmental frame. In summary, we find the hippocampal head to be especially important for supporting a coarse, global representation of the environment. Although previous fMRI studies have not investigated this issue explicitly, several studies are consistent with the current findings. For example, activation in the hippocampal head has been observed to increase with increasing distance between real world landmarks (Morgan et al., 2011) and in persons who use relative distance to more than two landmarks to reach four target landmarks (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003). These findings indicate that the hippocampal head is sensitive to large-scale features of the environment and supports the ability to form a coarse, global environmental representation during learning.

Our structural image analysis also supported a role for the hippocampal head in representation of a coarse, global representation. Specifically, we found that use of a coarse, global representation of the environment during Self-localization and Planning correlated with a larger right hippocampal head and smaller right hippocampal tail. Hence, involvement of the hippocampal head in a coarse, global environmental representation was not only reflected in the level of activity, but also in its structure. The fact that the hippocampal tail was smaller in participants who reported greater use of a coarse, global environmental representation, strengthens the claim that the coarse, global environmental representation in the hippocampal head is independent of the fine-grained, local representations in the hippocampal tail. Supporting this, blind individuals were observed to have a larger hippocampal head and an increased ability to recognize a global overview representation of learned environments (Leporé et al., 2009; Fortin et al., 2008). We found no relationship between the spatial tests and local hippocampal shape. This is similar to a study of London taxi drivers, where no relationship was found between hippocampal shape and the ability to judge landmark proximity (Woollett & Maguire, 2011). The reason for the lack of relationship in this and in our study is not clear. However, one could speculate that strategy questionnaire factors are more sensitive to personality traits than test scores. Personality traits are known to influence the shape of brain structures (Gardini, Cloninger, & Venneri, 2009).

Our findings confirmed the prediction that fine-grained, local representations are processed in the hippocampal tail. During Planning, activation in the hippocampal tail correlated with the Local and Global direction test scores, but not with the Multiple distance scores. The main difference between the direction tests and the distance test is that the former required a fine-grained mental representation (of the exact position and orientation) of the landmarks' position relative to the adjacent walls, whereas the latter required a coarse, global representation of the environment with the different parts of the environment merged and oriented relative to one another. Thus, our finding indicates that the hippocampal tail is important for fine-grained, local environmental representations. The behavioral analysis showed that activation in the hippocampal tail correlated with the questionnaire factors Sequence and turns and Direction during Planning, but not with the factors Direction to remote landmarks or Map. The first two factors reflect the use of fine-grained representations of the local environment. The results are consistent with the observation that the hippocampal tail is important for the exact representation of an individual object's location (Baumann, Chan, & Mattingley, 2010; Rodriguez, 2010; Doeller, King, & Burgess, 2008). Other studies have linked activation in the hippocampal tail to choosing the optimal environmental path (Hartley, Maguire, Spiers, & Burgess, 2003) and to the amount of details recalled or imagined from past and future events (Addis & Schacter, 2008). Furthermore, there is evidence that the hippocampal tail represents local parts of the environment (Xu et al., 2010; Janzen & Weststeijn, 2007; Peigneux et al., 2004), such as decision point objects (Janzen & Weststeijn, 2007). Our study extends these findings by providing the first direct evidence that the human hippocampal tail represents the local environment most precisely, as previously shown in rats (Kjelstrup et al., 2008; Jung et al., 1994).

The volume in the hippocampal tail did not correlate positively with use of fine-grained, local environmental representations. This could be related to a smaller variance being observed for the fine-grained, local aggregate score (range = 15–49) than the coarse, global aggregate score (range = 17–34). The inferior parietal lobe appeared to have a similar posterior–anterior segregation based on the self-reported use of a fine-grained, local route representation and/or a global route representation. During Planning, increased activation of the left inferior parietal lobe was observed in one anterior and one posterior cluster. The posterior activation was associated with relying on number of turns between the start position and target landmark, and the anterior cluster with the use of complete routes. In the right hemisphere, activation in the posterior inferior parietal lobe was related to using sequences of landmarks. These findings suggest that the inferior parietal cortex supports route-centered representations by processing fine-grained, local route representations posteriorly and a global route representation anteriorly. Activation in the inferior parietal cortex has previously been associated with spontaneous route planning (Spiers & Maguire, 2006) and correlated with the ability to tell the spatial relationship between landmarks in a route centered reference frame (Wolbers, Weiller, & Büchel, 2004). Our results add to these findings by suggesting a functional specialization within the inferior parietal cortex that reflects the completeness of environmental route representations. Past research has only provided indirect support for such a distinction. For example, the posterior inferior parietal cortex has been associated with object-specific responses (Konen & Kastner, 2008a) and saccadic eye movements (Konen & Kastner, 2008b). Sacccadic eye movements are necessary to remember local details from images (Loftus, 1972), but not overviews of spatial scenes and objects (Potter, 1976).

In conclusion, our study shows that a coarse, global representation of the environment is established in the hippocampal head, whereas the hippocampal tail supports fine-grained, local environmental representations. The anterior part of the inferior parietal cortex supports a coarse, global route-representation, whereas fine-grained, local route representations are found posteriorly. Further studies focusing on a functional segregation along the anterior–posterior axis both in the hippocampus and parietal cortex as well as in other regions of the brain will be important, not only to understand the nature of neural processing in these regions but also to elucidate fundamental organizational principles of the human brain.

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PAPER 3

Variations in the granularity of environmental representations along the human hippocampal anterior-posterior axis

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SUMMARY

In rodents, representation of environmental positions follows a granularity gradient along the hippocampal and entorhinal anterior-posterior axis; with fine-grained representations most posteriorly. To investigate if such a gradient exists in humans fMRI data was acquired during environmental learning. Activation in the hippocampal tail (posterior) and the hippocampal body (intermediate) was highest for Fine-grained and Medium-grained representations, respectively. Additionally, hippocampal tail activation correlated with granularity in positions encoded. For the hippocampal head (anterior) no activation differences were observed between the different granularity representations, but when permitting a coarse representation activation correlated with number of environments encoded. Activation in posterior entorhinal cortex correlated with granularity for the positions encoded, and activation in posterior and intermediate entorhinal cortex increased for Medium-grained representations. This demonstrates that positional granularity is represented in a graded manner along the anterior-posterior axis of the human hippocampus, and to some extent entorhinal cortex, with most Fine-grained representations posteriorly.

RUNNING TITLE

Granularity variations along hippocampal long-axis

HIGHLIGHTS

- The exactness of map positioning varies along the hippocampal a-p axis
- A less clear environmental granularity variation exists along the entorhinal a-p axis
- The coarse representations in the hippocampal head supports finer encoding

INTRODUCTION

Several different schemes for functional segregation along the hippocampal anterior-posterior axis have been proposed (Hüfner et al., 2011; Lepage et al., 1998; Murty et al., 2010; Poppenk et al., 2010; Ryan et al., 2009). A recent review of human evidence suggests that the segregation along the anterior-posterior axis of the hippocampus is based on the granularity of the environmental representation, with the posterior hippocampus supporting fine-grained local representations, while the anterior hippocampus supports coarse, global representations (Poppenk et al., 2013). The role of the intermediate human hippocampus is less clear, though there are some indications that it serves a role in-between that of the posterior and anterior hippocampus (Poppenk et al., 2013).

This evidence from humans corresponds to findings in rats where it has been observed that neurons in the hippocampal tail, the most posterior (or dorsal) hippocampus, have small "place" fields that seemingly represent fine-grained versions of the environment (Jung et al., 1994; Kjelstrup et al., 2008; Maurer et al., 2005). The finding in rats that lesions to posterior hippocampus impair discrimination for close, but not distant, positions further supports the hippocampal tail as specifically involved in fine-grained representations of space (McTighe et al., 2009). Additionally, the environmental representations for place cells in the hippocampal tail have been observed to be nearly orthogonal both within an environment and between environments, while the environmental representations for place cells in the hippocampal head are strongly correlated within an environment and orthogonal between environments (Kjelstrup et al., 2008). This suggests that the fine-grained environmental representations in posterior hippocampus are local and the coarse-grained environmental representations in anterior hippocampus are global.

A recent study with humans, involving navigation through a large virtual environment, provided evidence that the hippocampal tail represents fine-grained local representations and the hippocampal head a coarse, global representation of the environment. This included both functional magnetic resonance imaging (fMRI) and structural data (Evensmoen et al., 2013). In other fMRI studies of navigation, hippocampal tail activation has been associated with an accurate representation of individual landmarks' positions (Baumann et al., 2010; Doeller et al., 2008; Rodriguez, 2010). On the other hand, activation in the hippocampal head correlates with increasing distance between the presented landmarks (Morgan et al., 2011). For episodic memories, the hippocampal head has been associated with a coarse, global spatial representation, i.e. the location in which a specific event took place, but not details within the episode, e.g. the specific seating arrangement (Nadel et al., 2012). Similarly, activation in the hippocampal head was present during retrieval of a coarse overview of an episodic memory, but not with later elaboration of details (Addis and Schacter, 2008; Holland et al., 2011).

Increased activation in the hippocampal body, i.e. the intermediate hippocampus, has been observed for overlapping routes (Brown et al., 2010), and when retrieving information related to distance evaluation between relatively close, but not remote, landmarks (Hirshhorn et al., 2012). Electrophysiological recordings in place cells implies that the hippocampal body engenders medium-grained environmental representations (Kjelstrup et al., 2008). These findings imply that the hippocampal body is involved in medium sized spatial representations in-between that of the fine-grained environmental information suggest to be supported by the posterior hippocampus (tail) and the coarse, global representation of the environment supported by the anterior hippocampus (head).

The entorhinal cortex is also thought to represent spatial information, via the so-called "grid cells", in a graded manner along the anterior-posterior axis. In rats, the scaling or the inter-node distance in the grid cells' firing fields increases approximately linearly from the posterior to anterior end of the entorhinal cortex, mirroring the hippocampal place cells. Moreover, when moving anteriorly in the entorhinal cortex the connectivity is shifted toward the anterior hippocampus (Brun et al., 2008). One interpretation of this anatomical arrangement is that the observed shift in granularity along the hippocampal anterior-posterior axis reflects graded entorhinal input (Moser et al., 2008).

Based on previous studies we hypothesize that activation in the hippocampal tail should peak when the positional representations are fine-grained, activation in the hippocampal body should peak with medium-grained positional representations, and activation in the hippocampal head with coarse-grained representations. We further hypothesized that a similar activation pattern should be present in the posterior, intermediate, and anterior entorhinal cortex. We tested these predictions by implementing fMRI during navigation through 35 small virtual environments, each involving five objects and an outer wall. A subsequent recall of objects' positions on a 2d map was used to define the encoding of each environment as Fine-grained, Medium-grained or Coarse-grained.

In fMRI increased hippocampal activity, blood oxygen level dependent (BOLD) response seems to be particularly related to encoding in the post-stimulus period. For example, hippocampal activation in the post-stimulus and not the stimulus presentation period, predicts successful encoding of episodic movie clips and emotional pictures (Ben-Yakov and Dudai, 2011; Mackiewicz et al., 2006). Similarly, in a delayed match-to-sample study, successful encoding of two faces was accompanied by increased hippocampal and entorhinal activation in the post-stimulus delay period, and not in the stimulus presentation period (Olsen et al., 2009). Based on these studies we predicted that the post-stimulus presentation period will be most sensitive for detecting activity related to successful encoding, and that location of the activity along the anterior-posterior axis of the hippocampus and entorhinal cortex will reflect variations in granularity of the encoded information.

RESULTS

Environmental encoding

The average number of environments in which the positional score was Fine-grained was 11.3 ± 6.4, Medium-grained 11.7 ± 4.0, Coarse-grained 5.2 ± 2.9, and Failed 7.8 ± 5.6 (Figure 2). A repeated measure general linear model showed significant effect of number of environments for each granularity ($F = 9.47$, $p = 0.005$). Post-hoc comparisons showed that the number of Coarse-grained environments was significantly different from both number of Fine-grained environments ($p = 0.004$) and number of Medium-grained environments ($p < 0.0001$), and further that the number of Failed environments was significantly different from the number of Medium-grained environments ($p = 0.037$).

Hippocampal and entorhinal activity related to positional granularity within subjects

For the hippocampal tail, increased activation was observed in the post-stimulus encoding phase for contrasts Fine-grained > Coarse-grained ($t = 6.16$, $p < 0.0001$) and Medium-grained > Coarse-grained ($t = 3.98$, $p = 0.0003$). Additionally, using an uncorrected threshold revealed increased activation in the hippocampal tail for contrast Fine-grained > Medium-grained ($t = 2.06$, $p = 0.049$) (Figure 3A; see also Figure S1A for results from the Stimulus presentation period). With Odd-even as the implicit baseline, increased activation was observed in the hippocampal tail for Fine-grained ($t = 7.21$, $p < 0.0001$) and Medium-grained ($t = 4.13$, $p = 0.002$) representations, but not for Coarse-grained representations. In the hippocampal tail the BOLD signal was found to increase linearly from negative activity for Coarse-grained representations, positive activity for Medium-grained, and then peaking for Fine-grained representations ($R= 0.98$) (Figure 3A). For the hippocampal body, increased activation was present for Medium-grained > Coarse-grained representations ($t = 3.72$, $p = 0.005$), while decreased activation was found for Fine-grained > Medium-grained representations ($t = -5.28$, $p < 0.0001$). When using Odd-even as the implicit baseline, increased activation was observed in the hippocampal body for Medium-grained representations ($t = 6.38$, $p < 0.0001$), but not Fine-grained or Coarse-grained representations. For the hippocampal head, none of the contrasts were associated with increased activity. However, when comparing Coarse-grained representations with Failed trials, using an uncorrected p-value, increased activation was observed ($t = 2.14$, $p = 0.04$). While, still using an uncorrected p-value, for contrast Medium-grained representations > Failed decreased activation was observed in the hippocampal head ($t = -2.339$, $p = 0.027$), and for contrast Fine-grained representations > Failed no difference in activation was observed for the hippocampal head ($t = -1.652$, $p = 0.110$).

Activation in posterior entorhinal cortex was present for Medium-grained representations ($t = 4.07$, $p = 0.002$) and for Fine-grained representations when using Odd-even as implicit baseline and an uncorrected p-value ($t = 2.31$, $p = 0.028$) (Figure 3B; see also Figure S1B for results from the stimulus presentation period). No differences in posterior entorhinal activation were observed between Fine-grained, Medium-grained, and Coarse-grained representations. For the intermediate entorhinal cortex, increased activation was observed for contrast Medium-grained > Coarse-grained representations ($t = 4.65$, $p = 0.0004$) and decreased activation for contrast Fine-grained > Medium-grained representations ($t = 2.92$, $p = 0.04$). When using Odd-even as implicit baseline, increased activation in the intermediate entorhinal cortex was observed only for Medium-grained representations ($t = 3.28$, $p = 0.018$).

For the anterior entorhinal cortex no differences in activation were observed between Fine-grained, Medium-grained, and Coarse-grained representations. In an additional analysis, it was observed that anterior entorhinal cortex showed decreased activation for Fine-grained representations > Failed ($t = -3.15$, $p = 0.008$), but not for Coarse-grained representations > Failed ($t = -1.087$, $p = 0.572$) and Medium-grained representations > Failed ($t = -1.172$, $p = 0.502$).

The main conditions

For the contrast Post-stimulus encoding> Stimulus presentation increased activation was observed in the hippocampal tail, hippocampal body, hippocampal head, and perirhinal cortex (Table 1, Figure 4). For contrast Stimulus presentation >Post-stimulus encoding no increased activation in the medial temporal lobe was observed.

The time-course analysis showed that the activation in the hippocampus and entorhinal cortex decreased in the Stimulus presentation period, increased during the Poststimulus encoding period, and then decreased slightly but stayed above the average BOLD activity during the Odd-even period (Figure 5).

Correlations with variations in positional granularity between subjects

The BOLD signal correlated negatively with the positional granularity measure, i.e. activity was increased for the lower granularity measures which represented the most accurate reproduction of the positions.in the hippocampal tail (R = 0.385, p = 0.032) and posterior entorhinal cortex (R = 0.439, p = 0.013). Similar correlations were not found in the hippocampal body (R = 0.278, p = 0.13), intermediate entorhinal cortex (R = 0.231, p = 0.212), hippocampal head (R = 0.179, p = 0.34) or anterior entorhinal cortex (R = 0.227, p = 0.219). For the positional granularity measure threshold analysis with cut off at 4 000, activation in the hippocampal tail (R = 0.385, p = 0.032) and posterior entorhinal cortex (R = 0.394, p = 0.028) was positively correlated. No significant activity associated with positional accuracy < 4 000 was detected in the hippocampal body (R = 0.241, p = 0.192), intermediate entorhinal cortex (R = 0.218, p = 0.24), hippocampal head (R = 0.092, p = 0.62) or anterior entorhinal cortex (R = 0.180, p = 0.33). Using the coarse grained cut off at 16 000 gave positively correlated activation in the hippocampal head (R = 0.362, p = 0.046). Hippocampal tail (R = 0.345, p = 0.058) and hippocampal body (R = 0.256, p = 0.164) activity did not correlate with coarse positional granularity. For the entorhinal cortex, posterior entorhinal cortex (R = 0.481, p = 0.0060), but not intermediate entorhinal cortex (R = 0.242, p = 0.19) or anterior entorhinal cortex (R = 0.229, p = 0.215), correlated with the Coarse-grained cut off at 16 000. Moreover, the correlation for the hippocampal head was significantly stronger when demanding only a coarse representation (cut off at 16 000) of the objects' positions compared to when demanding a Fine-grained representation (cut off at 4 000) (Z=2.638, p=0.008) (Figure 6). No similar differences in correlations were observed for the hippocampal tail (Z=0.411, p=0.681), hippocampal body (Z=0.148, p=0.883), or any of the entorhinal subregions.

DISCUSSION

The current study confirmed our hypothesis concerning graded spatial representations along the human hippocampal and entorhinal anterior-posterior axis, with Fine-grained representations most posteriorly. This functional segregation is similar to that observed with electrophysiological methods in rats, and also supported by other structural and functional findings in humans. We observed the highest activation in the hippocampal tail for Fine-grained representations, and in the hippocampal body for Medium-grained representations, while hippocampal head activation did not significantly differ across fine-, medium- or Coarse-grained representations. However, hippocampal head activity was significantly correlated with the number of coarse environmental representations encoded, and showed increased activation, using an uncorrected p-value, for Coarse-grained representations compared to Failed. For activation in the entorhinal cortex, Medium-grained representations revealed significant effects in posterior and intermediate entorhinal cortex, and Fine-grained representations, using an uncorrected p-value, in the posterior entorhinal cortex only. The activation in anterior entorhinal cortex increased for Failed compared to Fine-grained representations. Between subjects, activation in both posterior hippocampus and posterior entorhinal cortex correlated with the level of Fine-grained granularity of the encoded objects' positions.

A granularity gradient along the hippocampal anterior-posterior axis

The most posterior part of the hippocampus, the hippocampal tail, is involved in generating Fine-grained representations of the environment. This was demonstrated directly in the within subject analysis, which showed that activation in the hippocampal tail was highest for Fine-grained representations, compared to both Medium-grained and Coarse-grained representations. Additionally, activation in the hippocampal tail correlated positively, between subjects, with how Fine-grained the encoded representations were. These effects were only observed for the hippocampal tail. In fMRI studies of virtual navigation, the hippocampal tail has been associated with Fine-grained local representations (Evensmoen et al., 2013), and with tasks involving a Fine-grained representation of a landmark’s position (Baumann et al., 2010; Doeller et al., 2008; Rodriguez, 2010). In rats, place cells in the hippocampal tail represent the environment in a Fine-grained fashion (Jung et al., 1994; Kjelstrup et al., 2008).The hippocampal tail is the part of the hippocampus that receives most of the projections, via entorhinal cortex, from both perirhinal and parahippocampal cortex, which together constitute the main environmental input to the hippocampus (Lavenex and Amaral, 2000; Witter et al., 1989). This anatomical arrangement suggests that the hippocampal tail receives the most Fine-grained environmental information, and that this region, through its dense environmental input is, as predicted by our hypothesis, most important for Fine-grained representations of environmental positions.

The most anterior part of the hippocampus, the hippocampal head, represents the environment in a Coarse-grained manner. In the within subject analysis activity in the hippocampal head was increased, using an uncorrected threshold, for Coarse-grained compared to Failed trials. Furthermore, activation in the hippocampal head was significantly correlated only with a Coarse-grained representation of the objects‘ positions. In a previous navigation study, hippocampal head activity was associated with the use of a coarse, global representation during initial self-localization and planning (Xu et al., 2010). Additionally, individuals using global representations during navigation have larger hippocampal heads than individuals relying on environmental details (Evensmoen et al., 2013). In other navigational fMRI studies, hippocampal head activation has been demonstrated to correlate with increasing distance between landmarks (Morgan et al., 2011), and when requiring recall of the internal relationship between landmarks (Ekstrom et al., 2011; Iaria et al., 2003). For episodic memories, the hippocampal head has been associated with a coarse global representation, but not Fine-grained spatial relationships of elements within the episode (Nadel et al., 2012). Taken together these results indicate that the hippocampal head supports a coarse representation of the material to be recalled. The activation in the hippocampal head did not show increased activation for Coarse-grained representations compared to Fine-grained and Medium-grained ones. One interpretation of this is that the coarse representations stored in the hippocampal head are somehow linked to the more Fine-grained representations of the environment generated elsewhere. Supporting this, activation in the hippocampal head correlated with the positional granularity score, a score that reflects all granularity levels. However, the finding that none of the granularity levels were associated with increased hippocampal head activation with Odd-even as an implicit baseline weakens this interpretation. It is possible that the encoding processes continued in the hippocampus during the Odd-even period, and that the hippocampal head is particularly engaged in this. This possibility is supported by the finding that similar hippocampal head activity was observed for the contrast Poststimulus encoding > Stimulus presentation and the contrast Odd-even > Stimulus presentation, although at a less strict statistical threshold for the latter ($p<0.001$, uncorrected).The hippocampal head supports a Coarse-grained representation of the environment as predicted by our hypothesis. Still, the results also support a role of this Coarse-grained representation and of the hippocampal head, for Fine-grained and Medium-grained representations.

Activation in the intermediate hippocampus, hippocampal body, was increased for Medium-grained representations compared to both Fine-grained and Coarse-grained representations. The hippocampal body has been associated with more local representations of the environment (Xu et al., 2010), and retrieval of hallway segments (Brown et al., 2010). The hippocampal body seems to position itself somewhere in between the hippocampal tail and head. Supporting this anatomical studies in both humans and monkeys have shown that the hippocampal body has an extrinsic connectivity pattern that is a mixture of what is observed for the hippocampal tail and head (Libby et al., 2012; Mohedano-Moriano et al., 2007; Zarei et al., 2013). However, our results show that the activation in the hippocampal body is more similar to that in the hippocampal tail than in the hippocampal head. Activation in the hippocampal tail and body was highest for Fine-grained and Medium-grained representations, respectively. For the hippocampal head, on the other hand, activation did not differ between the different granularity representations. This indicates that representations in the hippocampal body more closely resemble representations in the hippocampal tail than those in the hippocampal head. Previous studies also support the notion that the hippocampal body is more similar to the hippocampal tail than the hippocampal head, as activation in the hippocampal body has been associated with more Fine-grained, but not Coarse-grained, spatial representations (Hirshhorn et al., 2012; Nadel et al., 2012). The hippocampal head has been shown to have a relatively smaller dentate gyrus volume than the tail and body regions (Malykhin et al., 2010). Since the dentate gyrus is associated with pattern separation, one might speculate that the smaller dentate gyrus volumes restrict pattern separation in the head, while the process may be enhanced in the tail and body. Taken together, the hippocampal body involves Medium-grained, possibly more separate, environmental representations which resemble the Fine-grained representations in the hippocampal tail.

A less clear granularity gradient along the entorhinal anterior-posterior axis

Posterior entorhinal cortex appeared most important for fine- and medium-grained representations, and the intermediate entorhinal cortex for Medium-grained representations. The anterior entorhinal cortex did not seem to process granularity. We found activation in posterior, but not intermediate or anterior, entorhinal cortex to be correlated between subjects with the level of Fine-grained granularity. The activation in posterior entorhinal cortex was increased for Medium-grained representations and, when using Odd-even as an implicit baseline and an uncorrected p-value, for Fine-grained representations. These results imply that the intermediate entorhinal cortex is especially important for Medium-grained representations, i.e. increased activation was observed in the intermediate entorhinal cortex for Medium-grained representations compared to both Fine-grained representations, Coarse-grained representations and the implicit baseline. In the anterior entorhinal cortex variations in granularity did not elicit differences in activity, but Failed trials compared to Fine-grained did. This was not seen for Failed trials compared to Medium-grained or Coarse-grained representations. One interpretation of this is that anterior entorhinal cortex is important for the most Coarse-grained representations, because Failed trials, involving trials with the largest positional granularity measures, not only involves Failed trials but also the most Coarse-grained representations. Supporting this, the difference was observed only when comparing the Failed trials with Fine-grained representations. The findings in the entorhinal cortex thus s replicated to some degree the overall findings in the hippocampus with fine-medium grained representations in the posterior segment and Medium-grained representations in the intermediate segment, and possibly the most Coarse-grained representations in the anterior entorhinal cortex. However, these results are only somewhat similar to the hippocampal results. One possible explanation for this is that the environmental gradient is finalized within the hippocampus. Alternatively, the less convincing granularity gradient in the entorhinal cortex may be related to this region being more vulnerable to susceptibility artifacts than the hippocampus (Olman et al., 2009). In rats, entorhinal grid cells show a scaling gradient along the anterior-posterior axis, comparable to that observed for hippocampal place cells (Brun et al., 2008). Our results lend some support to a comparable granularity gradient along the anterior-posterior entorhinal axis in humans, at least for the posterior and intermediate entorhinal cortex, similar to that observed for the hippocampus, with Fine-grained positional representation in the posterior entorhinal cortex and Medium-grained representations in intermediate entorhinal cortex. Thus, in line with our hypothesis, a somewhat similar positional granularity gradient does appear to be present already in the entorhinal cortex, the main input to the hippocampus.

Conclusions

This study confirms that a granularity gradient exists along the human hippocampal anterior-posterior axis, from Fine-grained environmental representations in the most posterior hippocampus, Medium-grained representations in the intermediate hippocampus, and Coarse-grained representations in the most anterior hippocampus. These anterior Coarse-grained representations appear to also be engaged when fine- and Medium-grained representations are encoded. For the entorhinal cortex a similar gradient was demonstrated for the posterior and intermediate, but not the anterior, subregion. This suggests that while functional segregation related to positional granularity occurs upstream in the medial temporal lobe hierarchy, some aspect of the segregation observed in hippocampus depends on processing within the hippocampus itself.

EXPERIMENTAL PROCEDURES

Subjects

Thirty-one men (18 - 27 years**,** mean 21 years) with no history of neurological disorders, head trauma, or current DSM-IV axis I diagnosis of psychiatric illness including substance abuse were recruited. They were all right handed, ascertained with the Edinburgh Handedness Inventory (Oldfield, 1971), with mean score of 88.4 % (± 29.7). All subjects provided written informed consent prior to participation and received 1000 Norwegian Kroner as reimbursement. The study was approved by the Regional Committee for Medical Research Ethics in Midt-Norge, Norway.

Virtual Reality Environment

The VR-environments were developed in collaboration with Terra Vision AS (Terra Vision, Trondheim, Norway) using the Torque game engine (Garage Games, Eugene, Oregon, US). The environments were between 50 and 90 m^2, with player moving speed set to 2 m/s (Figure 1 A).The environments consisted of five unique objects (Figure 1 B). Each object was positioned in one of 16 possible squares, together forming a unique positional pattern. The individual objects were additionally assigned to one of five possible sub-squares within each square (Figure 1). Each environment was enclosed by one of 10 differently shaped outer walls.

Scanning Procedure

Scanning was performed on a 3T Siemens Trio scanner and a 3T Siemens Skyra scanner which replaced the Trio, for the last seven subjects, with a 32-channel Head Matrix Coil (Siemens AG, Erlangen, Germany). Foam pads were used to minimize head motion. The fMRI stimuli were presented using a LCD monitor with 1280 x 1024 resolution, and the subject moved inside the environment using a MRI compatible joystick (Current Designs, Philadelphia, US).

The subjects were first allowed to familiarize themselves with the presentation equipment and joystick, and then completed practice trials from the different experimental conditions. Scanning was commenced when complete task compliance was ensured.

fMRI paradigm

The fMRI paradigm used a blocked design. It consisted of a Stimulus presentation period (30sec), a Post-stimulus encoding period (15sec) and a period with Odd-even judgments (15sec). In the Stimulus presentation period, the subjects explored the virtual environments freely from a first person perspective. For the Post-stimulus encoding period a cross fixation was shown for15 sec, and the subjects were instructed to memorize the positions of the five objects. The Odd-even task involved pushing the right joystick button when a random even number (<100) appeared and the left joystick button when a random odd number (<100) appeared.

The subject completed seven experimental runs, with 5 Stimulus presentations, Post-stimulus encoding- and Odd-even blocks in each run. The order of the runs was randomized between subjects, and the order of the blocks was randomized within each run. Between each run, while still lying in the scanner, the subjects were tested on their ability to position the objects from a 2d overview perspective for each environment (Map test) (Figure 1).

In the Map test, the subjects had to position the five objects on a 2d overview representation of the environment (Figure 1). From this test a “positional granularity” measure was calculated. The positional granularity” measure is an estimate of the exactness of the relative positing of the objects. This was obtained from the sum of squares of the error in the objects’ positions after removing translation, rotation and scaling differences between the positional pattern of the objects placed by the participant and the true positional pattern of the objects. This estimate reflects a pure positional measure. In other words, only the positions of the objects, and not their relationship with the outer wall were estimated (Figure 2).

The score on the positional granularity measure was divided into Fine-grained, Medium-grained and Coarse-grained representations depending on the level of accuracy of the reproduced spatial representation. A Fine-grained representation required a positional granularity measure < 4 000, i.e. the objects' positioning were typically within one-fourth of a square (corresponding to $0.9x0.9m^2$). A Medium-grained representation had a positional granularity measure between 4 000 and 10 000, i.e. the objects' positioning were typically within one square (corresponding to $1.8x1.8m^2$). For a Coarse-grained representation the positional granularity was between 10 000 and 16 000, i.e. the objects' positioning were between one square and one and a half square. The environmental representations were considered as Failed for a positional granularity measure > 16 000, i.e. the objects' positioning were > one and a half square. However, since accuracy was calculated as a sum for all the positions within one environment, there might be cases where for example the positioning of one of the objects deviated more than the positioning of the others. For optimal positioning of the objects, the environments were piloted in order to try and obtain an even distribution of environments across the different representations of granularity.

From the positional granularity measure a positional granularity score was calculated. This was done by setting a threshold for the positional granularity measure, e.g. 4 000 and 16 000, and calculate the number of environments with a positional granularity measure below this threshold. This was used to compare brain activity correlated with encoded representations which were only Fine-grained or allowed to be Coarse-grained between subjects.

Imaging parameters

T2* weighted, blood-oxygen-level-dependent (BOLD) sensitive images were acquired during the spatial encoding task using a 2D echo-planar imaging pulse sequence (TR = 2110.8 ms, TE = 28 ms, FOV = 220 mm x 220 mm, slice thickness = 1.9 mm (no gap), number of slices= 40, matrix = 116x116 giving a voxel size of $1.9x1.9x1.9mm^3$). For the last seven subjects the 2D echo-planar imaging parameters differed slightly (TR = 2253.2 ms, TE = 28 ms, FOV = 220 mm x 220 mm, slice thickness = 2.0 mm (no gap), slice number = 40, matrix = 116x116 giving a voxel size of 1.9x1.9x2.0mm^3). The slices were positioned as close to 90° on the anterior-posterior direction of the hippocampus as possible. GRAPPA acceleration was used with a factor four. Each functional run contained 143 volumes, and for the last seven subjects 134 volumes. For anatomical reference a T1 weighted (T1W) 3D volume was acquired using a MPRage sequence (TR = 2300 ms, TE = 2.94 ms, FOV = 256 mmx 256 mm x 192 mm, matrix 256x256x192 giving an resolution of 1.0x1.0x1.0 mm^3).

Analysis of environmental encoding data

The positional granularity scores from the Map test were extracted using in-house developed MATLAB (7.9.0, Mathworks) scripts, before the statistical analyses were conducted in SPSS 20 (IBM Corporation, NY).

The number of environments associated with Fine-grained, Medium-grained, Coarse-grained representations, and Failed trials were compared using a general linear model followed by t-tests for the pairwise comparisons in SPSS.

fMRI data analysis

Imaging data were analyzed using FSL 5.0.2 (Analysis Group, FMRIB, Oxford, UK). First, non-brain tissue was removed from the T1-weighted anatomical images using BET 2 with robust center estimation (Brain Extraction Tool, FMRIB, Oxford, UK). The resulting images were transformed to the MNI 1x1x1mm^3 template (Montreal Neurological Institute, Montreal, QC, Canada) nonlinearly with FNIRT (FMRIB, Oxford, UK). The fMRI data weremotion corrected using MCFLIRT, with the median volume of each run as reference. Then each functional run was co-registered to the anatomical T1W image, before it was transformed into MNI space by using the transformation matrix obtained with the T1W image. The functional data were smoothed with a 3mm full-width at half-maximum Gaussian filter, and temporally high-pass filter with a cutoff time of 100 seconds.

The statistical analysis of the fMRI data was carried out in FEAT (FEAT, FMRIB, Oxford, UK). Granularity representations, and conditions in a separate analysis, were modeled according to a boxcar stimulus function convolved with a single gamma hemodynamic response function. The effect of each granularity representation, or condition, was estimated with GLM using FLAME 1+2 (FMRIB's Local Analysis of Mixed Effects) and automatic outlier detection.

A brain mask was applied to investigate activation in the medial temporal lobe (MTL) only. The mask was created from the probabilistic maps of the Harvard Oxford Structural Atlases (part of FSL; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) (Flitney et al., 2007), using no probability threshold. The mask contained 76,864 1-mm voxels, and included both the hippocampus and parahippocampal gyrus. Within this mask, specific regions of interest (ROIs) were also identified. The entorhinal cortex was defined based on anatomical boundaries (Insausti et al., 1998). The hippocampus was divided into head, body and tail (DeFelipe et al., 2007; Duvernoy, 2005; Poppenk et al., 2013).The entorhinal cortex was divided into posterior entorhinal cortex, i.e. the posterior-third, intermediate entorhinal cortex, i.e. the mid-third, and anterior entorhinal cortex, i.e. the anterior-third.

Within subject analysis of positional granularity

The individual runs were merged, and the contrasts Fine-grained > Medium-grained, Fine-grained > Coarse-grained, and Medium-grained > Coarse-grained positional granularity were investigated for the anatomical ROIs of the hippocampal tail, hippocampal body, hippocampal head, and posterior, intermediate and anterior entorhinal cortex. In these analyses both Post-stimulus encoding and Stimulus presentation were investigated. For the hippocampal head in rats, place cells with place fields covering the whole environment has been observed (Kjelstrup et al., 2008). In a supplementary analysis, we therefore compared hippocampal head activation for Coarse-grained representations, and as a control Fine-grained and Medium-grained representations, against Failed trials. This analysis was also completed for the anterior entorhinal cortex, a region that in rats has grid cells with coarse place fields oriented towards the environment as a whole (Brun et al., 2008; Stensola et al., 2012). In an additional analysis, the Odd-even task was used as an implicit baseline for Fine-grained, Medium-grained, and Coarse-grained representations during Post-stimulus encoding and Stimulus presentation, in order to investigate linear trends across the granularity representations. Within each anatomical ROI the average BOLD signal change and standard deviation were calculated using Featquery in FSL. The significance for each contrast was evaluated with a one-sample t-test. The coefficient R was calculated between the granularity representations to explore whether a linear trend was present (SigmaPlot, Systat Software Inc., Richmond, CA).

Two of the subjects were excluded due to a lack of either Fine-grained or Failed trials. To test for significance a 2-tailed p-value of 0.05 was used, corrected for multiple comparisons by dividing the significance level with the number of hippocampal and entorhinal ROIs involved in the analysis.

Analysis of the main conditions

The contrasts Post-stimulus encoding> Stimulus presentation and Stimulus presentation >Post-stimulus encoding were investigated with paired t-tests. The threshold used was voxel based with an uncorrected $p > 0.0001$ and cluster size > 160 voxels. The time-course of the fMRI data was plotted for anatomical ROIs of the hippocampus and entorhinal cortex using PEATE (Perl Event-related Average Timecourse Extraction) v2.61 (http://www.jonaskaplan.com/fmritools.html) on each individual's data output from the MTL analysis and then averaged over all participants. The average BOLD signal across all conditions was used as a baseline.

Correlation between fMRI data and Positional granularity between subjects

Featquery in FSL was used to calculate max Z-value for bilateral individual anatomical ROIs of the hippocampal tail, hippocampal body, hippocampal head, posterior entorhinal cortex, intermediate entorhinal cortex, and anterior entorhinal cortex, for contrast Post-stimulus encoding > Stimulus presentation. In order to evaluate the activation correlating with the encoded granularity in the hippocampal and entorhinal cortical regions the max Z value was correlated with the positional granularity measure for contrast Post-stimulus encoding > Stimulus presentation.

In a second analysis this was then evaluated, by correlating max Z-value for the individual bilateral anatomical ROIs with the positional granularity score. For this analysis, the upper threshold for the positional granularity measure was first set to a low value, 4 000, requiring a Fine-grained representation of the objects' positions in order for an environment to be described as successfully reproduced, and then a high value, 16 000,only requiring a Coarse-grained representation of the objects' positions. One point was given for each environment with a positional granularity measure below the given threshold of either 4 000 or 16 000. In SPSS, the Pearson correlation coefficient was calculated between the hippocampal and /or (?) entorhinal activations and the Positional granularity score for the high and low threshold value separately. The resulting R values were then compared in order to look for differences between the high and low threshold values (Meng et al., 1992). A two-tailed p-value of 0.05 was used to test for significance.

Secondly, the threshold value was varied from 4 000 to 16 000, creating a range of positional granularity scores and then correlated with max Z value in the hippocampal tail and head ROIs, using Pearson correlation coefficient. These correlation values were plotted to illustrate the positional granularity that yielded the highest BOLD signal in the hippocampal tail and head. The limits of 4 000 and 16 000 were set in order to avoid floor and ceiling effects.

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TABLES

Table 1. The Stimulus presentation and Poststimulus encoding period

MTL region	**Coordinates of peak activation** (MNI)			**Cluster number**	**Cluster size**	**Z score**
	X	**Y**	**Z**		(no. of voxels)	
Stimulus presentation >Poststimulus encoding						
n/a						
Poststimulus encoding> Stimulus presentation						
Hippocampal tail	-32	-40	-3	1	1141	5.34
	-30	-40	-4	(1)		5.13
	20	-40	3	2	829	4.75
Hippocampal body	-27	-24	-18	3	537	5.13
	35	-23	-14	4	312	4.90
Hippocampal head	22	-10	-27	5	611	5.26
	-27	-13	-26	(3)		4.29
Perirhinal cortex	24	-2	-36	(5)		4.56

The analysis was carried out using a medial temporal lobe mask and voxel based thresholding, p=0.0001 uncorrected, and cluster size > 160 voxels. MNI, Montreal Neurological Institute 152 brain template, which has a voxel resolution of 1 mm^3. R, right; L, left. The cluster number is given in parenthesis for secondary peaks within the respective clusters.

FIGURES

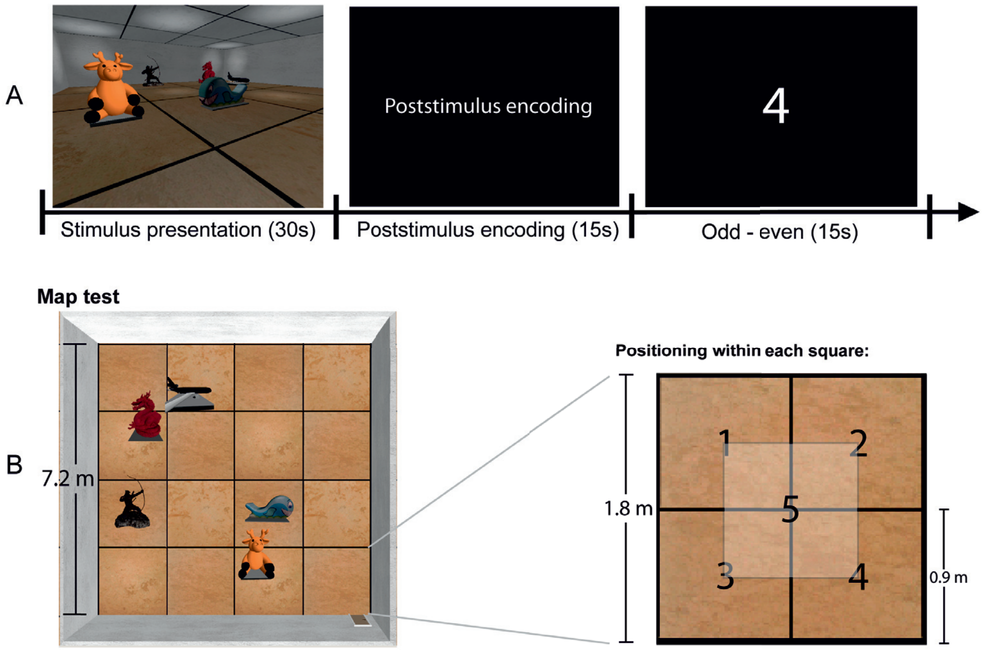

Figure 1. fMRI paradigm, virtual environment and map test. **A**. The fMRI paradigm consisted of a Stimulus presentation period lasting 30 seconds, in which the subjects moved freely while exploring the environment from a first person perspective. The subjects were instructed to move at least once along the outer wall. This was followed by 15 seconds with Post-stimulus encoding in which the subjects were instructed to memorize the environment. Finally, the subjects completed Odd-even judgments for 15 seconds. **B**. After having learned five environments the subjects completed a map-test while lying in the scanner, as illustrated in the image to the left. In this test the subjects viewed the environment from a 2d overview and positioned all five objects, as accurately as possibly. For all environments, the objects were placed within an area of 7.2 x 7.2 m, divided into 16 squares (1.8 x 1.8 m). Each object was positioned in one of five possible sub-squares (0.9 x 0.9 m) within each of these squares, as illustrated in the figure to the right. From the positioning of the objects the Positional granularity measure was calculated.

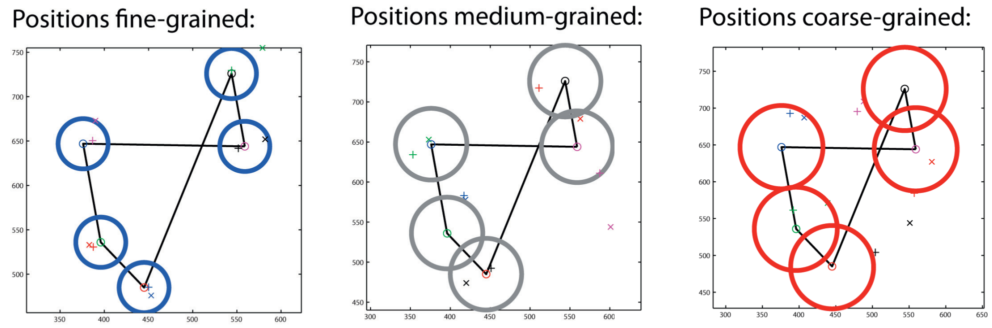

Figure 2. Positional granularity categories. The objects positions were defined as Fine-grained, Medium-grained or Coarse-grained depending on the sum of squares of the residuals after removing translation, rotation and scaling effects from the subjects' representation of the positions. In the figure to the left the Positional granularity measure is Fine-grained, i.e. below 4000 corresponding to positioning of each object typically within one fourth of a square (0.9x0.9m^2). The middle figure shows a Medium-grained representation with Positional granularity measure between 4000 and 10000, i.e. the positioning of each object typically within one square (1.8x1.8m^2).The figure to the right shows a Coarse-grained representation with Positional granularity measure above 10000, i.e. the positioning of each object typically similar to or coarser than one square. The size of the circles in each figure indicates the granularity of the representations for the Fine, Medium and Course-grained representation, respectively. The Xs represents the placement of the objects by the subject; the +s the positions of the objects after pattern fitting; and O, the correct position of the objects. The symbol's color indicates the object identity.

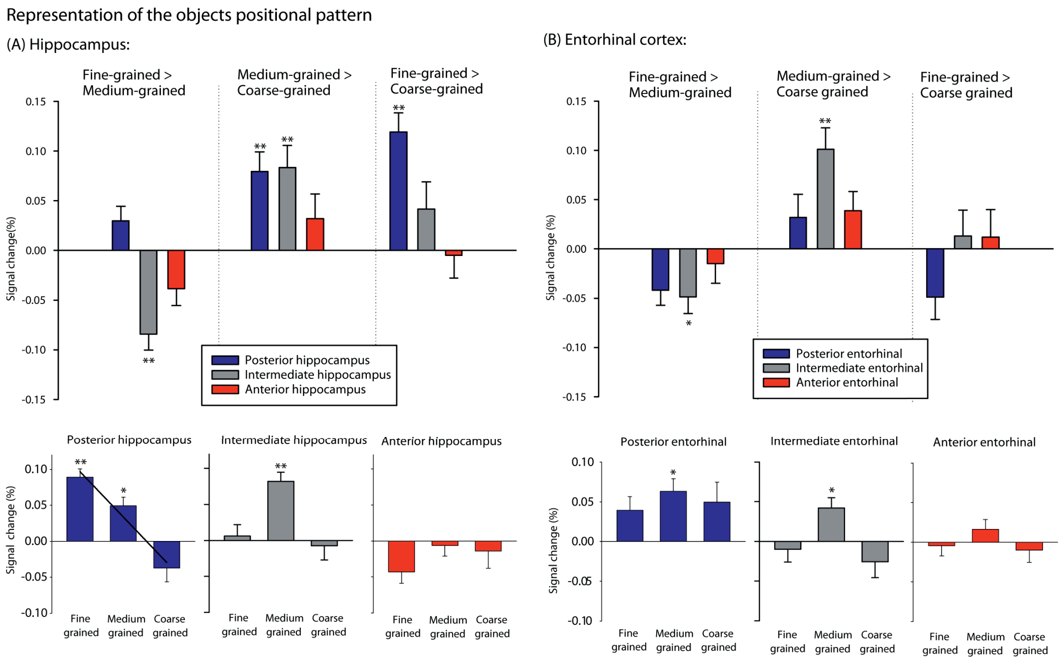

Figure 3. A positional granularity gradient along the anterior-posterior axis of the hippocampus (A) and entorhinal cortex (B). The mean percentage signal increase with standard error was calculated for each of the bilateral anatomical ROIs for the Poststimulus encoding period. The figures in the top row show results for the Fine-grained>Medium-grained, Medium-grained>Coarse-grained, and Fine-grained>Coarse-grained representations. The bottom row figures show the activation in the posterior hippocampus (hippocampal tail) or posterior entorhinal cortex (left), hippocampal body or intermediate entorhinal cortex (middle) and anterior hippocampus (hippocampal head) or anterior entorhinal cortex (right) for Fine-grained, Medium-grained and Coarse-grained representations with Odd-even as an implicit baseline. The hippocampal tail was defined as posterior hippocampus (blue), hippocampal body as intermediate hippocampus (grey) and hippocampal head as anterior hippocampus (red). The color coding of the anterior-posterior axis is similar for the entorhinal cortex. * $p < 0.05$; ** $p < 0.001$ (corrected for multiple comparisons) (see also Figure S1).

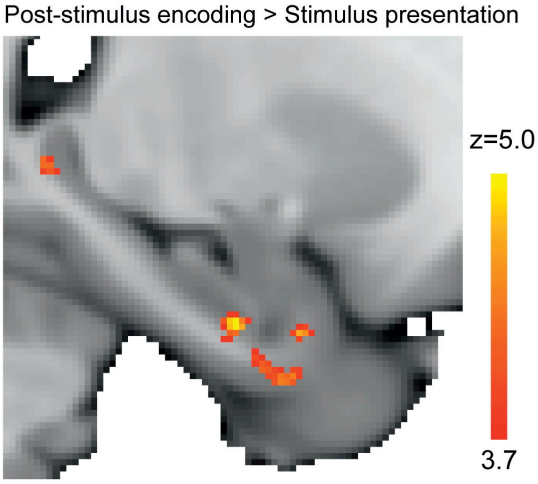

Figure 4. Increased activation in the medial temporal lobe for the Post-stimulus encoding compared to the Stimulus presentation period. No increased activation was observed for contrast Stimulus presentation > Poststimulus encoding. Statistical threshold was p = 0.0001 uncorrected and cluster size > 160 voxels. The Medial temporal lobe mask was applied. Activations are superimposed on the MNI, Montreal Neurological Institute 152 brain template.

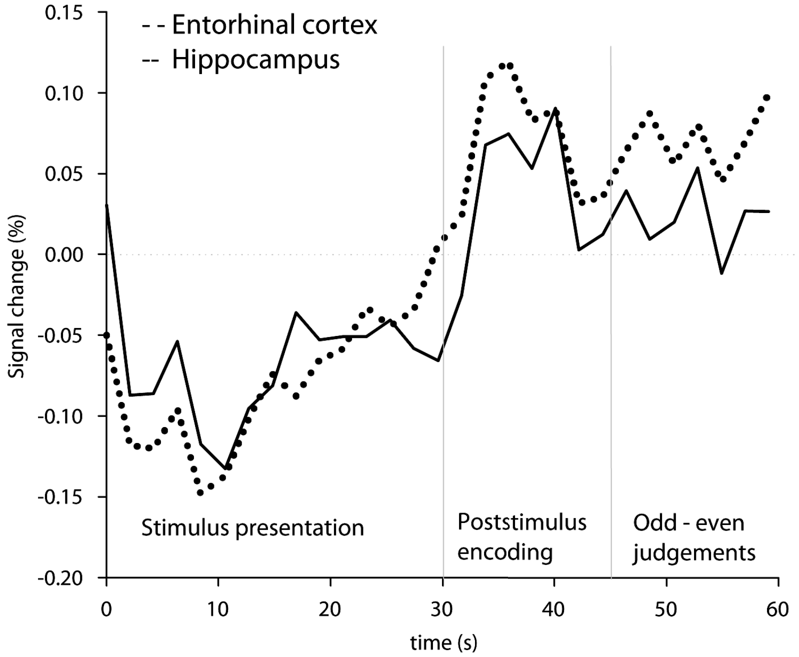

Figure 5. The average percentage BOLD signal change within the entire hippocampus and entorhinal cortex masks across all trials. The BOLD signal is shown for the Stimulus presentation period, in which the subjects moved freely within the virtual environment, the Poststimulus encoding period, and the Odd-even judgment period. The average BOLD signal across all conditions was used as baseline.

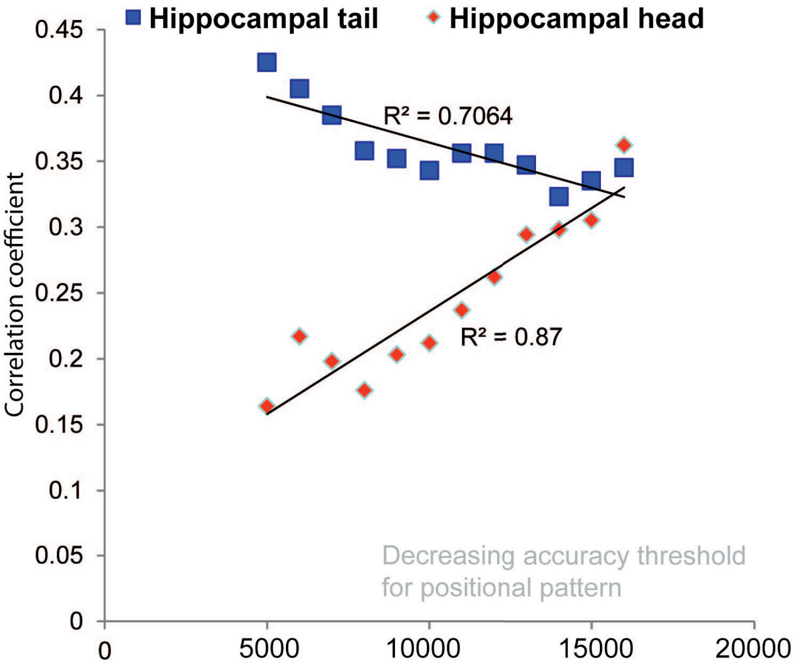

Figure 6. Plot of max z value in the hippocampal head ROI (red diamonds) and in the hippocampal tail ROI (blue squares) correlated across all individuals with accuracy in positions reproduced. Decreasing accuracy in the object positioning when moving toward the right on the horizontal axis.

SUPPLEMENTARY MATERIAL

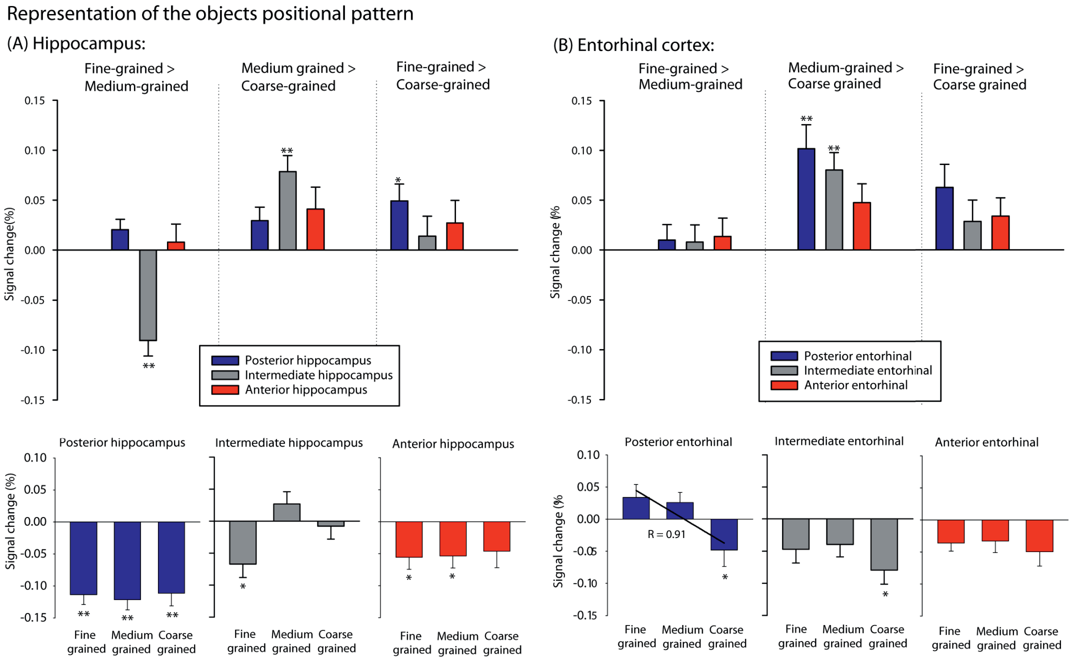

Figure S1, related to Figure 3. A positional granularity gradient along the anterior-posterior axis of the hippocampus (A) and entorhinal cortex (B) for the Stimulus presentation period. The mean percentage signal increase with standard error was calculated for each of the bilateral anatomical ROIs for the Stimulus presentation period. The figures in the top row show results for the Fine-grained>Medium-grained, Medium-grained>Coarse-grained, and Fine-grained>Coarse-grained representations. The bottom row figures show the activation in the posterior hippocampus (hippocampal tail) or posterior entorhinal cortex (left), hippocampal body or intermediate entorhinal cortex (middle) and anterior hippocampus (hippocampal head) or anterior entorhinal cortex (right) for Fine-grained, Medium-grained and Coarse-grained representations with Odd-even as an implicit baseline. The hippocampal tail was defined as posterior hippocampus (blue), hippocampal body as intermediate hippocampus (grey) and hippocampal head as anterior hippocampus (red). The color coding of the anterior-posterior axis is similar for the entorhinal cortex. * $p< 0.05$; ** $p < 0.001$ (corrected for multiple comparisons) (see also Figure S1).

PAPER 4

Proximal and distal landmarks are integrated in the human hippocampal head

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ABSTRACT

Proximal and distal landmarks are important elements in our surroundings. The neural correlates of either proximal or distal landmarks in separate environments have been thoroughly investigated in both rodents and humans. However, the neural correlates of the integration of proximal- and distal landmarks have, to our knowledge, never been investigated directly. In this study, the participants first learned a large virtual environment which involved both proximal and distal landmarks. The participants then had to find their way through the environment with only proximal landmarks (Proximal), only distal landmarks (Distal), or both proximal and distal landmarks (Proximal&Distal). Finally, a questionnaire regarding the level of integration of proximal and distal landmarks was completed. Activation in the hippocampal head increased in the contrast Proximal&Distal > Proximal + Distal. The activation in the hippocampal head correlated positively with increased level of integration between the proximal and distal landmarks, and with the number of target landmarks reached, but not with having the proximal and distal landmarks either grouped into separate representations or treat the proximal and distal landmarks as one. Integrating proximal and distal landmarks correlated with number of target landmarks reached. These findings indicate that the hippocampal head is especially important for an integration of proximal and distal landmarks, an integration which enhances wayfinding abilities. The activation in the hippocampal tail correlated with excess distance moved during wayfinding, suggesting that this region represents individual local parts of the environment.

INTRODUCTION

Proximal landmarks, which are visible only in certain locations of an environment, and distal landmarks, visible from nearly every position in the environment, are important aspects of our surroundings. The distal landmarks are typically used for orientation within the environment while the proximal landmarks are used for identification of more local parts (Lynch, 1960; O'Keefe and Nadel, 1978).

Not much is known about the integration of proximal and distal landmarks in humans. In one behavioral study using a virtual environment, with both proximal and distal landmarks, 12 out of 32 subjects reported a conflict when the local landmarks were rotated so that the proximal and distal landmarks no longer pointed in the same direction (Steck and Mallot, 2000). This indicates that proximal- and distal landmarks are integrated when humans construct representations of their surroundings, but that the level of integration varies substantially between subjects. Several fMRI studies have investigated the separate contributions of proximal landmarks (Maguire et al., 1998; Spiers and Maguire, 2006; Doeller et al., 2008; Xu et al., 2010) or distal landmarks (Iaria et al., 2003; Shipman and Astur, 2008; Iglói et al., 2010; Marsh et al., 2010) in navigation abilities and their neuronal correlates. One study combined proximal and distal landmarks, where the former were rotated relative to each other, and the latter, i.e. mountains in the background, remained fixed. Increased activation in the hippocampal head was detected only when proximal and the distal landmarks were in their original position (Doeller et al., 2008). This result indicates that the hippocampal head might be important for an integrated representation of proximal and distal landmarks. The hippocampal head has previously been demonstrated to engender an overview and large-scale environmental representation, integrating all parts of the environment, while the hippocampal tail support fine-grained local representations (Xu et al., 2010; Poppenk et al., 2013; Evensmoen et al., submitted). In rats, the hippocampal place cells' environmental representations are correlated in the hippocampal head, but nearly orthogonal in the hippocampal tail which suggest that different environmental representations are integrated in the hippocampal head but maintained as separate representations in the tail (Kjelstrup et al., 2008).

Furthermore, fMRI studies using non-spatial tasks also suggest a particular role of the hippocampal head in integrating separate/unique representations. In a source memory study, activation in the hippocampal head was increased in an object-color coding tasks when objects and colors were discontiguous, in particular when the object and the color were separated in both time and space (Staresina and Davachi, 2009). This finding was interpreted as the hippocampal head "bridging representational gaps in our experience". Another fMRI study found increased activation in the hippocampal head when previously experienced movie scenes were associated together in the correct temporal order (Lehn et al., 2009). To sum up, the hippocampal head seems to be important for the integration between separate representations, including environmental representations, while the hippocampal tail is important for more local representations. Supporting this, the hippocampal tail has been found to have the largest proportion of dentate gyrus (~38.6%), associated with pattern separation, and the hippocampal head the smallest (~25%) (Malykhin et al., 2010; Yassa and Stark, 2011).

The aim of this study was to investigate the neuronal correlates to integration of proximal and distal landmarks using a learned virtual environment. We hypothesized that the activation in the hippocampal head would correlate with integrating proximal- and distal landmarks, while the activation in the hippocampal tail would correlate with using more local representations.

MATERIALS AND METHODS

Participants

18 men (18-28 years, mean=23.4 years) with no history of neurological disorders, head trauma or current diagnosis of psychiatric illness were recruited from the university campus (of NTNU (Trondheim, Norway)). 17 subjects were right-handed (mean score 88.4 %) and 1 was left-handed (score of 43.2 %), ascertained by the Edinburgh Handedness Inventory (Oldfield, 1971). All participants provided written informed consent prior to participation and received 500 NOK as reimbursement. The study was approved by the National Committee for Medical Research Ethics of Midt-Norge (Central Norway).

Virtual Environment

The virtual environment was developed in collaboration with Terra Vision AS (Terra Vision, Trondheim, Norway) using Torque game engine (Garage Games, Eugene, Oregon, USA). The environment is 115.28 by 138.46 units of size, which corresponds to 62 by 74 meters in “real life”. Player moving speed was fixed at 2 m/s. The environment mimics the inside of a modern office building with rooms, corridors and open areas of various sizes, but it lacks exterior windows. All doors inside the environment are “locked”, i.e., subjects are only allowed to navigate through the corridors and open areas. The environment includes 76 proximal and 6 distal landmarks. Each proximal landmark is made up of a distinct group of objects and/or pictures. The proximal landmarks are located throughout the interior of the environment. The subject can walk right through all proximal landmarks. Based on criteria for the significance of landmarks (Lynch, 1960), the proximal landmarks were divided into three categories. “Primary proximal landmarks” have unambiguous shapes, standing in sharp contrast to the surroundings with a prominent position within the virtual environment. “Secondary proximal landmarks” have unambiguous shapes and standing in sharp contrast to their surroundings, but with less prominent positions. “Minor proximal landmarks” have an unambiguous shape, but were only visible from a few locations and not that easy to separate from the surroundings. The main focus in the learning phase was on primary and secondary proximal landmarks, and in the fMRI experiment only primary and secondary proximal landmarks were used as targets. This was done to ensure that the participants could learn the location of all possible target landmarks well enough to plan the entire routes from start to target locations in the fMRI experiment. The distal landmarks were skyscrapers, located in all cardinal directions of the horizon, visible to the subject through the glass ceiling (Figure 1).

Pre-scanning

Day 1

On the first day of the experiment, the participants completed the learning phase. First, the participants freely explored the virtual environment for 5 minutes using a standard desktop computer and a joystick. Later the participants completed another 2x10 minutes with free exploration of the environment. Next, the participants completed three standardized navigation sequences designed to familiarize the participants with the entire environment, and see all landmarks at least once. In each navigation sequence, the participants started at a specific landmark in the environment and had to find a target proximal landmark that was shown in the bottom center of the screen. Upon arrival at the target landmark, a new target landmark was presented. The participants were given new target landmarks in the same manner until one sequence of approximately 25 landmarks was completed. In the first navigation sequence Primary proximal landmarks were used as targets, in the second sequence Secondary proximal landmarks were used as targets, and in the third sequence Minor proximal landmarks. This was done to make sure the participants had seen the entire environment before they had to find the most difficult and/or unobtrusive landmarks.

Day 2

On day two, the participants first explored the environment freely for 5 minutes. Next, they completed a test sequence where they had to find their way to 20 primary and 26 secondary landmarks. The primary and secondary landmarks were similar to the target landmarks in the fMRI experiment, but presented in a different order and with different start positions. This was done to assure good performance during fMRI. Participants were excluded from the fMRI experiment if they made more than four errors out of the 46 trials in the test sequence. Before fMRI the participants were given a 30-min break.

Scanning Procedure

Scanning was performed on a 3T Siemens Trio scanner with a 12-channel Head Matrix Coil (Siemens AG, Erlangen, Germany). Foam pads were used to minimize head motion. The fMRI stimuli were presented using MRI compatible LCD goggles with 800 x 600 resolution (Nordic Neuron Lab, Bergen, Norway) and the participants moved inside the environment using a MRI compatible joystick (Current Designs, Philadelphia, US).

The participants were first allowed to familiarize themselves with the presentation equipment and joystick, and then completed practice trials from the different experimental conditions. Scanning was commenced when complete task compliance was ensured.

fMRI paradigm

The fMRI paradigm was a self-paced block design with alternating blocks of navigation (max. duration 40±2 sec) and rest (cross fixation; 10±2 sec). Navigation took place with both proximal and distal cues being present (Proximal&Distal), with only proximal cues (Proximal) or only distal cues present (Distal).

Each participant completed three experimental runs, with 20 navigation blocks and 20 rest blocks in each run. The order of the runs was randomized between participants, and the order of the blocks was randomized within each run.

Position data of the participants' movements inside the environment was logged with a time interval of 30 ms.

Imaging parameters

T2* weighted, blood-oxygen-level-dependent (BOLD) sensitive images were acquired during the navigation task using an echo-planar imaging pulse sequence (TR = 2600 ms, TE = 30 ms, FOV = 244 mm, slice thickness = 3.0 mm, slice number =47, matrix = 80x80 giving an in-plane resolution of 3.0x3.0 mm). The slices were positioned as close to 90° on the anterior-posterior direction of the hippocampus as possible. Each functional run contained 449±32 volumes depending on the time needed by each individual to complete the runs. For anatomical reference a T1 weighted (T1W) 3D volume was acquired with an MPRage sequence (TR = 2300 ms, TE = 30 ms, FOV = 256 mm, slice thickness = 1.0 mm, matrix 256x256 giving an in-plane resolution of 1.0x1.0 mm).

Post-scanning

After MRI, the subjects were given navigational tasks from each of the three task conditions (Proximal&Distal, Proximal or Distal) and instructed to focus on which strategies and types of spatial representations they used in each condition. Then the subjects were given a Study Specific Strategic Questionnaire (SSSQ), to report their navigational strategies, especially with regard to use of proximal, distal and proximal & distal landmarks during each of the three navigation conditions. The questionnaire had a nine point scale, ranging from ‘‘strongly agree” (nine points) to ‘‘strongly disagree” (one point). The number of questions for condition Proximal&Distal was 22, for condition Proximal 20 and condition Distal 14.

Data Analysis

Behavioral data

Behavioral data were analyzed in SPSS 17.0 (SPSS Inc., Chicago, Illinois, USA). In order to compare number of targets reached and distance moved for successful trials across condition Proximal&distal, condition Proximal and condition Distal, a GLM followed by paired t-tests for within subjects comparisons was used. All values are given as Mean ± SD.

The scores from the questionnaire regarding the use of proximal landmarks were aggregated for each condition. These scores were then compared between conditions using paired t-tests. This was repeated for the distal landmarks.

Finally, number of target landmarks reached during wayfinding was correlated using Spearman`s correlation coefficient with the scores from the questionnaire; question (1) I thought about the proximal and distal landmarks as two completely separate entities, (2) I thought about the proximal and distal landmarks as one, and (3) I grouped proximal- and distal landmarks together into new, separate representations. Both positive and negative correlations were investigated.

Distance moved and time to completion was calculated for each task from the log files using in-house software written in Python (Python Software Foundation).

MRI data analysis

Imaging data were analyzed using FSL 4.1.8 (Analysis Group, FMRIB, Oxford, UK). First, non-brain tissue was removed from the T1-weighted anatomical images using BET 2 with robust center estimation (Brain Extraction Tool, FMRIB, Oxford, UK). The resulting images were transformed to the MNI 1x1x1mm template (Montreal Neurological Institute, Montreal, QC, Canada) nonlinearly with FNIRT (FMRIB, OXFORD UK). The fMRI data was motion corrected using MCFLIRT, with the median volume of each run as reference. Then each functional run was co-registered to the corresponding anatomical T1W image and transformed into MNI space by using the transformation matrix obtained with the T1W image. The functional data was smoothed with a 5mm full-width at half-maximum Gaussian filter, and temporally high-pass filter with a cutoff time of 250 seconds. The statistical analysis of the fMRI data was carried out in FEAT (FEAT, FMRIB, Oxford, UK). Conditions were modeled according to a boxcar stimulus function convolved with a two-gamma hemodynamic response function. The effect of each condition was estimated with GLM using FLAME 2 (FMRIB's Local Analysis of Mixed Effects) and automatic outlier de-weighting.

A whole brain analysis was performed for contrast Proximal&Distal > Proximal + Distal, Proximal + Distal > Proximal&Distal, Proximal > Distal and Distal > Proximal using a voxel based thresholding of $p = 0.05$ corrected. Only clusters larger than 30 voxels were reported.

Combined fMRI and behavioral data analysis

The number of landmarks reached in condition Proximal&Distal minus average total number of landmarks reached for condition Proximal and condition Distal combined were added as a separate regressor in the mixed effects GLM analysis, with contrast Proximal&Distal > Proximal + Distal as the dependent factor. This was done in order to identify regions of activation that correlated with being able to find the target when both proximal and distal landmarks were present correcting for possible differences in success between conditions. For condition Proximal&Distal, an average based on distance moved for each successful trial divided by the shortest path to the target was added as a separate regressor. This was done in order to investigate activity that represents local parts of the environment as the subject moved through it.

The effect on brain activity of the use of different mental representations of proximal and distal landmarks were assessed using scores from the SSSQ as separate regressors in the mixed effects GLM analysis with contrast Proximal&Distal > Proximal + Distal as a dependent factor. For question (1), (2), and (3), both the positive and the negative correlations were investigated.

A brain mask was applied to investigate the activation in medial temporal lobe (MTL) more closely. The mask was created from the probabilistic maps of the Harvard Oxford Structural Atlases (part of FSL; http://www.fmrib.ox.ac.uk/fsl/fslview/atlas-descriptions.html#ho) (Flitney et al., 2007) using no probability threshold. In total, the mask encompassed 73 352 1mm voxels. The entorhinal cortex and the perirhinal cortex were segregated based on anatomical boundaries (Insausti et al., 1998). Moving along the anterior-posterior axis, the last coronal slice with the uncal apex still visible was defined as the posterior limit of the hippocampal head. The coronal slice where the fimbria and fornix connect was defined as the anterior limit of the hippocampal tail. The part of hippocampus that fell between these two points was defined as the hippocampal body. Thresholding was voxel based with an uncorrected voxel threshold set to p=0.005, and a minimum cluster size of 30 continuous 1mm voxels.

Novelty analysis of the fMRI data

In order to look for novelty effects within the medial temporal lobe, the activation in the navigation blocks from the first part of each run was compared with the activation in the navigation blocks from the second part of each run for contrast Proximal&Distal > Proximal + Distal. The MTL mask was used together with a low statistical threshold, set to p=0.05, and a minimum cluster size of 30 continuous 1mm voxels.

RESULTS

Behavioral results

The study specific questionnaire showed that proximal (mean score for all six proximal questions: 29.1±2.4) and distal landmarks (mean score for all six distal questions: 29.2±2.9) were used to the same extent for condition Proximal&Distal. Proximal landmarks were used to a larger extent in condition Proximal (mean score question for all six proximal questions: 34.6±5.0) compared to condition Proximal&Distal (mean score for all six proximal questions: 29.1±16.9) (p=0.02). Distal landmarks were used to a larger extent for condition Distal (mean score for all six distal questions:

37.3±4.8) compared to condition Proximal&Distal (mean score for all six distal questions: 29.2±12.8) (p=0.0001).

The participants reached 17.8±3.6 of the 22 target landmarks in condition Proximal&Distal, 16.6±4.5 in condition Proximal, and 16.1±4.7 in condition Distal. There was not a significant effect of condition with regard to number of landmarks reached (F=0.723, p=0.493).

For the successful tasks, participants moved 32.5±3.4 meters in condition Proximal&Distal, 33.5±4.8 meters in condition Proximal, and 30.9±2.7 meters in condition Distal. There was no significant effect of condition with regard to distance moved for successful trials (F=3.015, p=0.062).

For condition Proximal&Distal a significant correlation was observed between number of target landmarks reached and the score on question 1; integrating distal and proximal landmarks (R=0.464, p=0.047), but not between number of landmarks reached and question 2; thinking about the proximal and distal landmarks as one representation (R=0.306, p=0.144), or question 3; grouping proximal and distal landmarks into separate representations (R=0.295, p=0.153).

Activation for conditions Proximal&Distal, Proximal and Distal

For the contrast Proximal&Distal > Proximal + Distal increased activation was observed in the frontal pole bilaterally, left superior frontal gyrus, left insula, and bilateral hippocampal head (Fig. 2; Table 1). For the contrast Proximal + Distal > Proximal&Distal increased activation was observed in the anterior cingulate cortex, precentral gyrus, primary somatosensory cortex, supramarginal gyrus, the superior parietal lobe, precuneus, visual cortices, and cerebellum.

For contrast Proximal > Distal increased activation was observed in secondary visual cortex (Table 1). Contrast Distal > Proximal did not show any increase in activation.

Correlations between strategy measures and medial temporal lobe activity for condition Proximal&Distal

Activation in the hippocampal head (coordinates: 23 -12 -25, z = 3.28) correlated positively with integrating proximal and distal landmarks for contrast Proximal&Distal > Proximal + Distal (Fig. 3). No correlation was observed between brain regions in the medial temporal lobe and having the proximal and distal landmarks grouped together in separate representations or thinking about the proximal and distal landmarks as one representation for contrast Proximal&Distal > Proximal + Distal.

Activation in the hippocampal head correlated positively with number of landmarks reached for contrast Proximal&Distal > Proximal + Distal (coordinates: -26 -19 -14, z = 3.17; coordinates: 27 -18 -16, z=3.06), and overlapped with the activity in the hippocampal head related to the integration of proximal and distal landmarks. Activity in the anterior entorhinal cortex correlated positively with number of landmarks reached for contrast Proximal&Distal > Proximal + Distal (coordinates: -20 -2 -34, z = 4.0).

The activation in the hippocampal tail, perirhinal cortex, fusiform cortex, and lingual gyrus correlated with excess distance moved for contrast Proximal&Distal > Proximal and Distal (Table 2).

Novelty effects in the medial temporal lobe

A comparison of the navigation blocks from the first half of each run with navigation blocks from the last half for contrast Proximal&Distal > Proximal and Distal, did not show any increase in activation in the medial temporal lobe.

DISCUSSION

The current findings demonstrate that the hippocampal head is especially important for the integration of proximal and distal landmarks. This integration gives an advantage during wayfinding. In contrast, the hippocampal tail seems to represent a more local part of the environment.

Increased activation was observed in the hippocampal head for condition Proximal&Distal> Proximal + Distal. This activation correlated with integrating proximal and distal landmarks, represented as two separate entities, as well as with number of target landmarks reached. The activation in the hippocampal head did not correlate with grouping proximal and distal landmarks into local representations or with thinking about the proximal and distal landmarks as one representation. Taken together these results suggest that the hippocampal head integrates a separate new global representation of the proximal and distal landmarks based on individual proximal and distal representations. Previously, increased activation in the hippocampal head has been related to bridging gaps between separate representations related to source and temporal memory (Lehn et al., 2009; Staresina and Davachi, 2009). In rats, the hippocampal head has been shown to integrate environmental representations (Kjelstrup et al., 2008). The fact that the hippocampal head has the lowest dentate gyrus to cornu ammonis ratio (Malykhin et al., 2010), most likely bias this region towards pattern completion (Yassa and Stark, 2011). The current findings, together with electrophysiology results in rats, the previously described role of the hippocampal head in source and temporal memory and the subfield distribution, supports a unique role of the hippocampal head in linking separate representations, spatial as well as non-spatial.

The activation in the hippocampal tail correlated with excess distance moved for contrast Proximal&Distal > Proximal + Distal. This suggests that the hippocampal tail represents local parts of the environment. A local part of the environment could be either a route like representation or individual locations within the environment not linked together across time or space. Excess distance moved did not correlate with using a route like representation for condition Proximal&Distal (r= -0.151, p=0.551). This indicates that the hippocampal tail represents individual local environmental locations being observed as the subject moves though the environment. Supporting this, activation in the perirhinal cortex, fusiform cortex and lingual gyrus, areas typically associated with processing of item details and item recognition (Grill-Spector et al., 1999; Eichenbaum et al., 2007; Staresina et al., 2012), also correlated with excess distance moved. In our previous fMRI studies we observed that the hippocampal tail was important for fine-grained local environmental representations (Xu et al., 2010; Evensmoen et al., submitted). In another fMRI study, the activation in the hippocampal tail increased when viewing objects from decision points within a learned route (Janzen and Weststeijn, 2007). Taken together these results strongly indicate that the hippocampal tail represents separate local parts of the environment not only in rats (Jung et al., 1994; Kjelstrup et al., 2008), but also in humans.

The environment used in condition Proximal and condition Distal could be argued to be new to the participants, while condition Proximal&Distal was identical to the learned environment. Hence, the effect observed in the hippocampal head for contrast Proximal&Distal > Proximal + Distal could result from increased cortical reinstatement for condition Proximal&Distal compared to condition Proximal and condition Distal (Alvarez and Squire, 1994). However, when directly comparing the navigation blocks from the first half of each run with the navigation blocks from the last half, for contrast Proximal&Distal > Proximal + Distal, activation in the hippocampal head was similar, even at lower statistical thresholds. Further, the success rate and distance moved did not differ between the three conditions. This indicates that the participants experienced the environment as the same for all three conditions.

At the whole brain level more anterior regions in the prefrontal cortex were activated during intergration of proximal and distal landmarks as seen in the contrast Proximal&Distal > Proximal + Distal. This region has been argued to be more important for processing of abstract concepts, including complex relations and contexts, than the posterior prefrontal cortex (Badre, 2008; Barbey and Patterson, 2011).

For contrast Proximal + Distal > Proximal&Distal increased activation was observed in the visual cortices. In another fMRI study we did a similar observation, increased activation in the primary visual cortices being observed both when proximal landmarks were removed and roadblocks added to a learned environment (Xu et al., 2010). This may be related to the fact that removing either the proximal or the distal landmarks alters the visual input slightly, leading to increased processing of local details in the primary and secondary visual cortices.

CONCLUSIONS

To sum up, the hippocampal head appears to engender a more global integration of individually represented proximal and distal landmarks. This leads to improved performance during wayfinding. The hippocampal tail was shown to represent local parts of the environment.

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TABLES

Table 1. Activation for condition Proximal&Distal, condition Proximal and condition Distal

MTL region	**Coordinates of peak activation** (MNI)			**Cluster number**	**Cluster size** (no. of voxels)	**Z score**
	X	**Y**	**Z**			
Proximal&Distal > Proximal + Distal						
Frontal pole	-1	57	15	1	1571	6.47
	17	40	45	2	129	6.18
	7	60	27	3	34	5.20
Superior frontal gyrus	-15	29	52	4	92	5.65
Insula	-17	-4	45	5	214	6.20
	-37	-24	3	6	92	5.81
Hippocampal head	-21	-11	-20	7	112	5.76
	22	*-9*	*-18*	*8*	*13*	*5.19*
Proximal + Distal > Proximal&Distal						
Cingulate gyrus, anterior	1	10	43	1	486	6.55
Precentral gyrus	-53	0	32	2	394	6.11
	49	2	29	3	61	5.88
Primary somatosensory cortex	39	-20	49	4	2364	6.87
Supramarginal gyrus	44	-38	38	5	109	5.84
	-52	-29	35	6	57	5.81
Superior parietal lobe	-35	-50	51	7	31	5.73
Precuneus	-9	-50	47	8	178	6.67
	12	-45	43	9	281	6.60
Occipital pole	-25	-92	18	10	44999	12
Primary visual cortex	5	-93	-1	(10)		11.50
Secondary visual cortex	-18	-59	-3	11	164	6.72
	-10	-63	-1	12	112	6.22
Cerebellum	-32	-50	-27	13	191	5.80
	35	-49	-26	14	101	6.83
	0	-74	-39	15	96	5.71
Proximal > Distal						
Secondary visual cortex	-27	-99	-16	1	742	6.36
	39	-93	-11	2	231	6.01
Distal > Proximal						
n/a						

The analysis was carried out using voxel based thresholding, p=0.05 corrected. Only clusters with a cluster size > 30 voxels were reported. MNI, Montreal Neurological Institute 152 brain template, has a voxel resolution of 1 mm^3. The cluster number is given in parenthesis for secondary peaks within the respective clusters. The activations written in italic are below the minimum cluster size.

Table 2. MTL ROI activity during condition Proximal&Distal>Proximal + Distal correlating with excess distance moved.

MTL region	Coordinates of peak activation (MNI)			Cluster number	Cluster size (no. of voxels)	Z score
	X	Y	Z			
Hippocampal tail	26	-39	4	1	784	5.28
Perirhinal cortex	-32	-24	-29	2	646	4.62
Fusiform cortex	32	-33	-28	3	63	4.00
Lingual gyrus	16	-43	-9	4	38	3.83

The analysis was carried out using a medial temporal lobe mask and voxel based thresholding, p=0.005 uncorrected. Only clusters with a cluster size > 30 voxels were reported. MNI, Montreal Neurological Institute 152 brain template, has a voxel resolution of 1 mm^3.

FIGURES


Proximal & Distal

Proximal

Distal

Figure 1. Wayfinding conditions Proximal&Distal, Proximal, and Distal. Distal landmarks, marked by blue squares, were high buildings placed in all cardinal directions outside the office building and visible from all positions in the environment. Proximal landmarks, marked by red circles, were positioned within the office landscape. The target landmark was shown as a small image at the bottom of the screen.

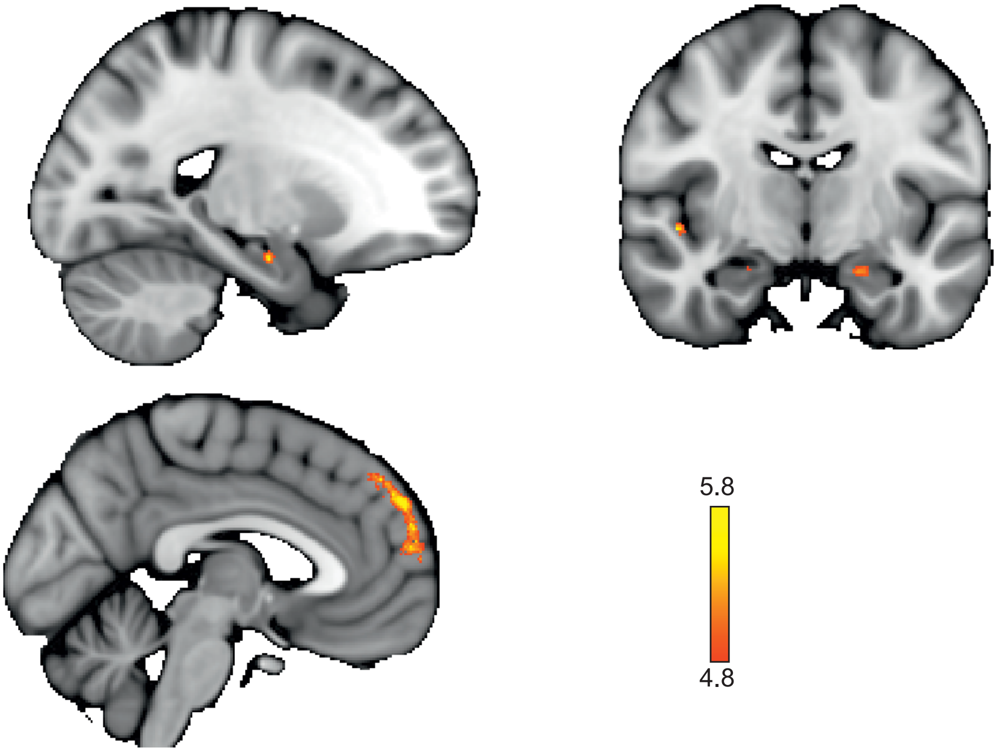

Figure 2. Increased activation for wayfinding condition Proximal&Distal > Proximal + Distal. Threshold used was p = 0.05 corrected. The color bar illustrates the activations' z- values. Activations are overlaid on the MNI, Montreal Neurological Institute 152 brain template.

Figure 3. Activation in the MTL correlating with integrating the distal and proximal landmarks for condition Proximal&Distal > Proximal + Distal. Threshold used was p = 0.005 uncorrected. The color bar illustrates the activations' z-values. Activations are superimposed on the MNI, Montreal Neurological Institute 152 brain template.