Processing mechanisms of relational and non-relational memory

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ABSTRACT

This doctoral thesis addresses the issues of dissociability of relational memory (RM) and non-relational memory (NRM) and of potential similarity of spatial and non-spatial RM in humans: Whether the hippocampus and perirhinal cortex are critical in RM and NRM, respectively, or whether the hippocampus is key for both RM and NRM, is under discussion. Whether the hippocampus is crucial for general RM or for spatial RM only, is also debated. Our findings from three studies on encoding and retrieval stages of spatial and non-spatial RM as well as NRM are related to the impact of normal ageing and focal lesions on the anatomy and connections of the mediotemporal lobe, prefrontal cortex, and thalamus.

Study 1 investigated the potential impact differences of age-associated dysfunctions in memory-critical brain areas on memory during normal ageing. Thus, 106 healthy adults from age 20-76 were assessed in a consecutive age groups design. Spatial and non-spatial RM both declined in the 66-76 years group. This pattern accorded with the presumed course of hippocampal changes across normal ageing. An impairment of NRM commenced earlier in the 51-65 years group.

Study 2 analysed the time course of novelty detection on variants of the above memory tasks using event-related potentials for encoding and retrieval in 13 healthy subjects. The event-related potentials related to RM and NRM were dissociable in an early and late time window. A late old/new effect replicated the frequently reported RM-associated old/new effect. The novelty detection P3a effect did not differ in spatial vs. non-spatial RM. Event-related potentials for subsequent hits differed between RM and NRM.

Study 3 assessed the potentially differential involvement of the human thalamus in RM and NRM. Ten patients with focal ischemic thalamic lesions were compared to individualised control groups of healthy subjects matched to each individual patient on age and IQ. Six patients showed poorer RM than their respective control samples. None of the ten patients showed a significant deficit on the NRM task.

Taken together, our results support the idea of RM and NRM dissociability in terms of distinct onsets of age-related declines, differential RM and NRM-related ERPs during encoding and retrieval, and disproportionate impairment of RM after focal thalamic lesions. Our observations support the notion of a common neuronal mediator for spatial and non-spatial RM with regard to similar spatial and non-spatial RM performances in terms of onsets and courses across the four consecutive age groups and topographically and temporally indistinguishable ERPs related to spatial and non-spatial novelty detection.
1 PART 1: GENERAL INTRODUCTION

Retrieving the best route to one’s destination and recollecting where things have been placed, exemplify the importance of spatial relational memory (RM), in which spatial contextual details are at hand. Remembering that the alternative route is actually ideal due to current temporary roadwork and recalling the sequence of events illustrate the prominence of non-spatial RM, in which non-spatial contextual details can be retrieved. In contrast, non-relational memory (NRM) refers to the memory when no context is retrievable, albeit the induced feeling of familiarity, such as when one cannot recall the name while encountering a familiar person.

The mechanisms mediating spatial and non-spatial RM and NRM in humans are still debated. To better understand these memory processes, we conducted three experimental studies incorporated in this doctoral thesis. The first study investigated the course of these memory processes across the healthy adult life span (Soei and Daum, 2008). The second study focused on the neuronal mechanisms of novelty detection in these memory processes (Soei, Bellebaum and Daum, submitted). The third study examined the role of the human thalamus in RM and NRM (Soei, Koch, Schwarz and Daum, in revision for EJN).

The first part of this doctoral thesis covers the broad introduction of the issues of interest, the description of the current state of the art, and finally the outline of the aims of the studies. The second part of the thesis deals with the implications of our findings, and finally the outlook on future research. The third part covers the three studies.
1.1 Do relational and non-relational memory processes differ?

Firstly, this section covers the general evidence on the human neuronal network mediating declarative memory. Secondly, the evidence for and against the dissociability of RM and NRM is covered. Thirdly, the issue of similarity of spatial and non-spatial RM is discussed.

1.1.1 The human neural network mediating declarative memory

Numerous rodent and non-human primate studies, using electrophysiology and lesion techniques, have corroborated the accounts made in the following paragraphs. However, as the scope of this work is on human spatial and non-spatial RM and NRM, the main evidence cited in the following stems from human and non-human primate studies.

This section begins with a definition of the different declarative memory types, and then deals with the neuroanatomical regions and their interconnections within the medial temporal lobe (MTL), prefrontal cortex (PFC) and thalamus in order to facilitate a critical discussion of the behavioural, neuroimaging and lesion evidence concerning these memory processes.

In humans, declarative memory refers to memory that can be declared explicitly e.g. RM and NRM, while non-declarative memory refers to memory which is only implicit and does not require effortful remembering, e.g. procedural memory, perceptual representational memory, and classical conditioning, as advanced by Tulving et al. (2000): Procedural memory mediates the acquisition and later performance of cognitive and motor functions. Perceptual representational memory encodes and retains sensory information thought to underlie priming effects. Classical conditioning refers to associative learning. While implicit memory is not within the scope of this thesis, the subdivision of declarative memory into RM and NRM is in focus. In a long history of research since Endel Tulving (1972) introduced this subdivision to psychologists, different researchers have examined RM using synonyms such as episodic, associative, contextual, source, and recollective memory, and NRM using synonyms such as semantic, non-associative, non-contextual, item and familiarity memory (Eichenbaum et al., 2007). The main characteristics of these two memory processes can be described as follows in various dual-process views: RM is a relatively slow, effortful and threshold-like process related to remembering items within a specific spatiotemporal context whereas NRM is a faster and more automatic signal-detection process related to knowing an item without recalling the encoding context (Atkinson and Juola, 1974; Brown and Aggleton, 2001; Eichenbaum et al., 2007; Jacoby and Dallas, 1981; Mandler, 1980; Rugg and Yonelinas, 2003; Tulving, 1972; 2002; Yonelinas, 2001; 2002).
Illustrated in Figure 1 are the differential behavioural effects of experimental manipulations on RM and NRM: Firstly, manipulations of the study time during encoding and long delays during retrieval have large effects on both RM and NRM. Secondly, manipulations of attention and elaboration during encoding have large effects on RM and moderate ones on NRM, while manipulations of attention and speeding during retrieval have large effects only on RM. Thirdly, manipulations of bias and fluency have large effects during retrieval only on NRM, and manipulations of rote repetition during encoding, and perceptual match of the verbs and a brief delay during retrieval have moderate effects only on NRM. Likewise, under speeded processing conditions, participants are faster in accurately deciding whether an item has been previously studied or not, compared to when or where they have studied the item (Hintzman et al., 1998), suggesting that NRM is faster than RM (Yonelinas and Jacoby, 1994; 1996). Moreover, pharmacological manipulation has been shown to selectively impair the putative RM- but not NRM-associated brain potential (Curran et al., 2006). Thus, the experimental manipulations have rather distinct effects on RM and NRM, strongly supporting the notion of dissociable processes (Eichenbaum et al., 2007; Yonelinas, 2002).

Since the first short report on lasting memory deficits in a patient with MTL damage (von Bechterew, 1900), it has been established across human and non-human primates and rodents that the MTL is critical to memory. The first formal anatomical study of memory loss after bilateral damage of the MTL in the famous patient H.M. yielded a deficient acquisition of declarative memories without further cognitive deficits (Scoville and Milner, 1957). A later study confirmed the bilateral symmetrical damage in the medial temporal polar cortex, most of the amygdaloid complex, most or all of the entorhinal...
cortex (ERC) and approximately half of the partly atrophic hippocampal formation, sparing the perirhinal (PRH) and parahippocampal cortex (PHC), and atrophic cerebellum and mamillary nuclei (Corkin et al., 1997). Subsequent studies supported the idea of memory deficits associated with MTL lesions in humans (Lah and Miller, 2008; Spiers et al., 2001). In non-human primates, damage of the MTL was also linked to memory dysfunctions in pioneering observations (Buckmaster et al., 2004; Mishkin, 1982; Zola-Morgan et al., 1982).

However, the early reports suffered from inconsistent classification schemes regarding the neural areas and anatomical projections (subregionally, MTL-neocortically and MTL-subcortically) (Suzuki and Amaral, 2003b). Following a contemporary nomenclature of the boundaries within the primate MTL (Lavenex and Amaral, 2000; Suzuki and Amaral, 2004), the MTL encompasses broadly the PRC, PHC, ERC, and hippocampus (HC). The HC can be subdivided into the dentate gyrus, Ammon’s horn, and subiculum. Information exchange between the MTLs in both hemispheres is mainly enabled by means of the ventral hippocampal commissure between the anterior hippocampi, and the dorsal hippocampal commissure between the parahippocampal gyri (Demeter et al., 1985).

Notably, while some researchers exclude the amygdala from the MTL (Murray and Wise, 2004), others have found the same activity pattern during retrieval in the HC and the amygdala (Rutishauser et al., 2006; 2008). Further, the MTL as an entity serving primarily memory functions has been questioned recently, suggesting that each MTL area mediates distinct functions such as memory and perception. For example, the PRC has been suggested to be involved in the perceptual analysis of single items and in the binding of individual stimulus features to a coherent representation of the object, which requires perceptual and mnemonic competence (Bussey et al., 2002; 2006; Bussey and Saksida, 2005; Lee et al., 2005; Murray et al., 2007; Murray and Bussey, 1999), while other investigations have seemingly refuted this account (Levy et al., 2005; Shrager et al., 2006; Squire et al., 2006). These two issues are beyond the scope of this work and thus not covered hereafter.

Anatomically, the PRC and PHC cover the lateral bank and the fundus of the collateral sulcus in the anterior and posterior parahippocampal gyrus (PHG), respectively (Pruessner et al., 2002). Both cortices consist of numerous subdivisions (PRC (35, 36cl, 36cm, 36d, 36rl, and 36rm); PHC (TFI, TFm, and TH)) (Lavenex et al., 2004) with distinct chemoarchitectonic and cytoarchitectonic features (Suzuki and Amaral, 2003a). The incoming information has been proposed to be substantially integrated via intrinsic associational connections (Lavenex and Amaral, 2000), which are mostly intrasubdivisional in the PHC and predominantly intersubdivisional in the PRC (Lavenex
Do relational and non-relational memory processes differ? (et al., 2004). The latter has been suggested to be at a higher level than the PHC in the hierarchy of associational cortices, due to the direction of feedforward and -backward projections (Lavenex et al., 2004).

Using retrograde tracing, Suzuki and Amaral (1994a) have elucidated the cortical afferents to the PRC and PHC: The majority of neocortical afferents into the PRC originate from the unimodal visual areas TE and rostral TEO in the inferior temporal cortex, but also from the area TF in the PHC, and little from the orbitofrontal and insular cortices, processing information about the quality of the object i.e. the “what” information. The majority of neocortical afferents into the area TF in the PHC come from the V4, the more caudal TE and TEO, the retrosplenial cortex, the superior temporal sulcus, insular cortex, frontal cortex, and posterior parietal lobes processing polymodal spatial information i.e. the “where” information. Area TH receives afferents from the retrosplenial cortex and the superior temporal sulcus, but not from TE and TEO.

These “what” and “where”-information are forwarded to the ERC, situated in the medial PHG (Suzuki and Amaral, 2003a) and serving as the main interface between the PHG and the HC (Lavenex and Amaral, 2000). The subsequent information processing is largely segregated, as the PRC projects mainly to the lateral entorhinal area, while the PHC projects predominantly to the medial entorhinal area, with the projections being mostly reciprocal (Suzuki and Amaral, 1994b). Finally, these two types of information converge into the cornu ammonis 1, 2 and 3, subiculum and dentate gyrus (Witter and Amaral, 1991), again segregated as projections from the lateral entorhinal area ascend into the rostral HC, while the dorsal HC receives input from the medial entorhinal area (Witter et al., 1989b). This segregation of connectivity domains within the ERC and its interconnections with the HC subregions indicates a parallel processing mode in the ERC. In contrast, the information processing appears to be serially in both the PRC and PHC, leaving the information processed in the HC to be highly integrated, supermodal or amodal (Lavenex and Amaral, 2000). However, there are some reciprocal connections between the PRC, PHC, and lateral and medial entorhinal areas (Suzuki and Amaral, 1994b). The HC subsequently feeds the even more highly integrated, multifaceted, and abstract information back to the ERC, then PRC and PHC, and finally, to the neocortical areas from which the input into the MTL originated (Lavenex and Amaral, 2000).

The PFC, interacting with the MTL, has also been associated with memory processes (Fletcher et al., 1997; Fletcher and Henson, 2001; Simons and Spiers, 2003). As the PFC projects reciprocally to three different regions within the mediodorsal thalamic nuclei (MD), the PFC itself has accordingly three functional areas (Fuster, 1997). The first area, the dorsolateral PFC (DLPFC), receives projections from the parvocellular lateral region of the MD in the thalamus and cortical projections from the
parietal cortex. The DLPFC not only contributes to successful encoding during RM (Dolan and Fletcher, 1997; Murray and Ranganath, 2007; Staresina and Davachi, 2006) and working memory (Ghashghaei and Barbas, 2001; Wendelken et al., 2008), but is well known for mediating executive functions (Fuster, 1997). These presumably support the strategic encoding and retrieval of contextual details (Squire, 1994; Squire and Zola, 1998). The DLPFC is also part of the “dorsal visual processing stream”, which transmits the perceptual object-locations representations from the visual to the frontal cortices (Goodale et al., 2004). The second area of the PFC refers to the frontal eye fields, which receive projections from the thalamic pars paralamellaris, but have not been linked to memory. The third PFC area is the orbitofrontal cortex (OFC), which receives projections from the magnocellular medial part of the MD. It is part of the “ventral visual processing stream”, and transmits the object-detail representations from the visual to the frontal cortices (Goodale et al., 2004). The OFC receives further projections from cortical and subcortical areas associated with long-term memory and emotional processing, and autonomic functions (Ghashghaei and Barbas, 2001). The anterior PFC does not receive projections from the MD, but its activity has been found to correlate with RM (Allan et al., 2000; 2005b; Simons et al., 2005a).

The thalamus has been dubbed the major relay to the cerebral cortex, as almost all knowledge about the external world is based on visual, auditory, somatosensory, cerebellar and other input that have had to pass through the thalamus (Sherman and Guillery, 2006). The thalamus is located on each side of the midline, and entails several nuclei, each transmitting distinct afferent signals via well-defined pathways to a major neocortical area. In the following, mostly the memory-related MD and its pathways will be highlighted (Aggleton et al., 1986; Saunders et al., 2005; Witter et al., 1989a). The MD is the largest structure in the medial thalamus and is located medial to the internal medullary lamina. The ERC and PRC efferents join the ventral amygadalothalamic pathway, stria terminalis and a relay station in the bed nucleus of the stria terminalis to terminate in the medial portion of the MD, which also receives projections from the basal forebrain (Russchen et al., 1987). ERC projections also join the hippocampothalamic pathways (via the fornix and via the caudal thalamic pole) to terminate in the anterior, midline and lateral dorsal nuclei. The midline nuclei project back to the originating area (Insausti et al., 1987), while the MD projects to the PFC and the anterior and lateral dorsal nuclei project to the cingulate cortex and HC (Goldman-Rakic and Porrino, 1985; Ray and Price, 1993; Vogt et al., 1987).
1.1.2 Relational and non-relational memory in humans

It is debated, whether there is a functional subdivision of labour in the human MTL, with the HC mediating RM and the PRC subserving NRM (Eichenbaum et al., 1994) or whether the MTL functions as a unified system critical for both RM and NRM (Squire, 1994). This issue has been investigated using neuroimaging methods such as non-invasive electrophysiology to detect the time-varying electric fields at the scalp surface generated by synchronously active neuron populations, with the measure most used in memory research being the event-related potential (ERP) (section 1.2.2.1). This section focuses on evidence from another neuroimaging technique and patients studies.

Whilst non-invasive functional magnetic resonance tomography (fMRI) does not test whether a particular region is necessary for the task at hand (Logothetis, 2008), it offers fine-grained spatially-resolved localisation of the neural network, and conveys the neural correlates of cognitive task processing. Using this technique, differential activations of the HC vs. PRC / anterior PHC have been found to correlate with either RM or NRM: The HC has been suggested to play a role in RM (Davachi et al., 2003; Davachi and Wagner, 2002; Giovanello et al., 2004; Pihlajamaki et al., 2004), whereas the PRC has been assumed to support NRM (Brown and Aggleton, 2001; Henson et al., 2003; Montaldi et al., 2006; Pihlajamaki et al., 2004). A recent study showed that the PRC activity was predictive of subsequent NRM even under associative conditions where word pairs were encoded as a single conjunctive item (Haskins et al., 2008), which accords to behavioural findings (Diana et al., 2008). This is seemingly in good agreement with the notion, that the HC and adjacent cortex mediate RM and NRM, respectively (Eichenbaum et al., 1994).

However, following Kopelman et al. (2007), it may be possible, that the correlational nature of fMRI observations in healthy participants and focal lesion findings in patients point in different directions: Single and group studies of hypoxic patients with lesions affecting either the HC or of a patient with PRC resection due to intractable epilepsy, have as yet not yielded a clear picture with respect to the notion of RM and NRM dissociability. On the one hand, disproportionate impairment depending on the lesion site has been observed (Bowles et al., 2007; Giovanello et al., 2003; Holdstock et al., 2005; Mayes et al., 2004; Turriziani et al., 2004; Yonelinas et al., 2002). On the other hand, proportionate deficits on RM and NRM after critical lesions or stimulations have also been reported across a variety of material and group-matched NRM performance (Cipolotti et al., 2006; Coleshill et al., 2004; Gold et al., 2006; Kopelman et al., 2007; Kopelman and Stanhope, 1998; Manns et al., 2003; Reed and Squire, 1997; Stark et al., 2002; Stark and Squire, 2003; Wais et al., 2006; Wixted and Squire, 2004). Interestingly, the MRI volume of either the HC or PHC showed the highest correlation with both RM
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and NRM measures (Kopelman et al., 2001; 2007; Kramer et al., 2005). Thus, after early single-process theories (Gillund and Shiffrin, 1984; Hintzman, 1988; Murdock, 1982), a contemporary single-process view suggests that both memory components differ only in quantity of memory strength and are both critically mediated by the HC and adjacent cortex (Slotnick and Dodson, 2005; Squire, 1994; Squire et al., 2007; Squire and Zola, 1998; Wixted, 2007). This perspective was recently supported by an fMRI study showing that both the HC and the PRC predicted memory strength of subsequently remembered information (Shrager et al., 2008).

According to Kopelman et al. (2007), the dispute cannot be easily resolved at present, as according to Eichenbaum et al. (2007), studies with (severe) hypoxic patients may be potentially compromised by damage outside the HC. Further, present structural MRIs may not be sensitive enough to reveal all damage apparent in post-mortem histology and may lead to conflicting results (Holdstock et al., 2008; Rempel-Clower et al., 1996).

1.1.3 Spatial vs. non-spatial relational memory in humans

It is disputed, whether the human HC is confined to spatial memory and mapping of large-scale space consistent with the cognitive map theory (O'Keefe, 1999; O'Keefe and Nadel, 1978) or whether it plays a general role in RM, with spatial processing being only one aspect of RM (Cohen et al., 1997; Eichenbaum et al., 1999; 2001; 2004).

Positron emission tomography studies with healthy human subjects focusing mainly on spatial processing and navigation have supported the idea of a more important role of the HC in spatial compared to non-spatial RM processing: Right-sided activation of the HC/PHG has been found to correlate with recall of the navigation routes and recognition of object locations with landmark cues (Johnsrude et al., 1999; Maguire et al., 1997).

FMRI studies also supported the spatial processing view: Activations of the HC have been found to correlate with spatial but not social RM, and with virtual navigation based on spatial RM (Kumaran and Maguire, 2005; Rauchs et al., 2008; Ross and Slotnick, 2008). Spatial novelty detection correlated with the anterior HC activation, while posterior HC was associated with location processing in a virtual environment task (Doeller et al., 2008).

Human lesion studies focusing on spatial processing and navigation have provided supporting evidence: Holdstock et al. (2000) showed in a patient with a bilateral HC lesion that the HC is more important for consolidation of allocentric as opposed to egocentric spatial memory. Astur et al. (2002) described ten patients with unilateral removal of the HC due to medically intractable epilepsy; who were significantly slower to
find the hidden platform in a virtual Morris water maze. Moreover, after training, not a single patient employed a spatial strategy. Brandt et al. (2005) reported deficient spatial RM and navigation in a virtual Morris water maze for ten patients with chronic acquired vestibular loss resulting in HC atrophy. Maguire et al. (2006) showed in a patient that chronic bilateral HC damage impaired navigation based on remote spatial representations.

In contrast, fMRI studies with healthy human subjects, in which RM of perceptually and conceptually distinct items was assessed, have supported the hypothesis of a general role of the HC in RM: Duzel et al. and Fenker et al. (2001; 2003; 2005) showed in healthy human volunteers, and in one patient with early HC damage, that the HC plays a role in spatial, non-spatial and emotional RM. Eldridge et al. (2000; 2005) reported that the dentate gyrus, CA2 and CA3 were more active during verbal and nonverbal RM formation, while the subiculum was more active during retrieval. Kohler et al. (2005) reported that the right-sided middle HC was more active during both nonverbal spatial and non-spatial RM, while Davachi and Wagner showed that the HC proper activation correlated with relational processing of word triplets (2002).

Studies of human patients with HC lesions assessing different types of RM have also been conducted: Cave and Squire (1991) reported spatial and non-spatial RM deficits of seven patients with lesions of the hippocampal formation, suggesting that the HC is important for rapid acquisition of relational information. Kumaran (2007) found in four patients with selective HC damage similar impairments on a spatial and non-spatial configural learning task. Shrager et al. (2007) examined six patients with damage of the HC and found similarly impaired performance on tests of object location memory with and without a view-point shift between study and test. Spiers et al. (2001) reviewed the literature on the consequences of damage of the HC on anterograde amnesia, corroborating the account that the patients' RM deficits are of a general nature, as the deficits span materials like words and paired associates, sentences and stories, pictures of objects and scenes and combinations of words and pictures. This account has also been supported by rodent and non-human primate studies that were not mentioned for the sake of brevity (for extensive reviews Eichenbaum et al., 1999; Eichenbaum and Fortin, 2005; Wood et al., 1999).

In summary, the neuroimaging and patient studies addressing not only spatial but also non-spatial and emotional RM using perceptually and conceptually distinct items in the verbal and nonverbal domain support the notion of a more general function of the HC (Cohen et al., 1997; Eichenbaum et al., 1999; 2001; 2004).
1.2 State of the art

As outlined in the previous sections, the evidence for the account that different neuronal networks are engaged in RM and NRM comes from manifold lines of investigation: Differential behavioural sequelae of damage of critical areas, dissociable effects of experimental manipulations, and distinct correlating activation patterns in neuroimaging studies. This section extends the state of the art concerning our three studies beyond the published or submitted versions of the articles.

1.2.1 Ageing and spatial and non-spatial relational and non-relational memory

The first study focused on age-related changes of spatial and non-spatial RM and NRM. In the next subsections, the scope is extended to general age-related changes in memory, associated structural changes in memory-related brain structures, and finally the caveats of existing experimental approaches.

1.2.1.1 Age-related functional changes in memory

As introduced, declarative memory comprises RM and NRM, while non-declarative memory comprises procedural memory and perceptual representational memory (section 1.1.1). These distinct memory processes are differently affected by rising age. Procedural memory and perceptual representational memory remain fairly stable across healthy ageing, while declarative memory typically declines with rising age to different extents (Balota et al., 2000). Several candidate mechanisms underlying the age-related memory decline have been proposed. The concept of general slowing and resulting deteriorated memory performance (Salthouse, 1996) is difficult to reconcile with similar patterns of fewer benefits and more costs for older adults on both free and forced recall tests and on timed and self-paced tests (Henkel, 2007). The concept of reduced processing resources or attentional capacity in ageing (Kahneman, 1973) assumes that difficult cognitive tasks require more resources than simpler tasks, but the concept has been criticised as too vague without addressing the neural correlates, and it cannot account for the entire age-related memory decline (Salthouse et al., 1988). This raises the question which additional factor may play a pivotal role, possibly a specific deficit to associate unrelated pieces of information (Naveh-Benjamin, 2000).

A long tradition of psychological research employing recall and single-item recognition tests has shown, that RM for personal experiences undergoes a more pronounced age-related decline than the relatively stable NRM for the general knowledge about the world (Balota et al., 2000; Yonelinas, 2002) as observed in extreme-group comparisons (old vs. young participants) (Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2003; 2004), or that age effects are reliably more variable in RM relative to NRM.
(Spencer and Raz, 1995). Results of studies showing that RM and NRM were proportionately reduced by healthy ageing in extreme-group comparisons (Mark and Rugg, 1998; Schacter et al., 1997) have been linked to ceiling effects (Yonelinas, 2002). However, this view has been challenged in a recent within-subjects-designed study using three different process estimation methods for RM and NRM in an extreme-group comparison (Prull et al., 2006). Two process estimation methods revealed that both RM and NRM estimates were negatively affected by ageing, while the third method found age-related decreased RM but invariant NRM estimates. All three methods confirmed the proposal of a decline of RM with ageing (Prull et al., 2006). Support for the age-related decline of RM and NRM came from a study employing the process-dissociation procedure in a large extreme-group comparison (Toth and Parks, 2006). In another extreme-group comparison, age-related significant deficits in spatial and non-spatial RM have been reported, but interpretation may have suffered from a ceiling effect in the later task (Driscoll et al., 2003). Our own ageing study across four consecutive age groups of the healthy adult life span (section 3.1) showed a differential course of decline extending the notion of age-related decrement in spatial and non-spatial RM and NRM. The last three studies are powerful as different estimation methods were employed yielding converging results and they do not suffer from ceiling effects (Prull et al., 2006; Soei and Daum, 2008; Toth and Parks, 2006).

1.2.1.2 Age-related structural changes in the relevant neural correlates

This section covers the structural and morphological impact of healthy ageing in the memory-related brain structures outlined above (section 1.1.1). Pathological ageing, such as in Parkinson’s or Alzheimer's disease, and age-related changes in the transmitter systems and electrophysiological neuronal properties are not covered for the sake of brevity.

Within the MTL, research has been mostly conducted on the HC, but less on ERC, PRH or PHC. Beginning with the HC, it has been reported that age-related HC volume losses were significant (Raz et al., 2004a; 2004b) and accelerated relative other brain regions (Jernigan et al., 2001; Schuff et al., 1999). It has been further observed that HC volume, on average, decreased annually at a faster pace, with a moderate decline in the adults < 50 years, but a twice as fast decline in the older adults (Raz et al., 2004a; Raz et al., 2004b; Raz et al., 2005). Similarly, a linear relationship for the rate of HC volume loss in healthy adults in their sixties and seventies has been reported (Cohen et al., 2006). However, stable HC volume across ageing has also been found (Sullivan et al., 2005; Van Petten et al., 2004). Studies using stereological methods suitable for estimating the total number of neurons in the brain have reported a substantial loss in the
HC subiculum (~52%), in the hilus of the dentate gyrus (~31%), but almost none in the CA1 region across the age range (West, 1993; West et al., 1994). A marker for the neuronal integrity is N-acetyl-aspartate as evident in MR spectroscopy (Barker, 2001), which levels have been shown to be decreased in the HC across the healthy adult life span (Schuff et al., 1999), and in healthy old compared to young subjects (Driscoll et al., 2003). While increased dendritic extent in the dentate gyrus in healthy old relative to middle-aged subjects has been reported (Flood et al., 1987), apical and basal dendritic branching of pyramidal neurons in the CA1 region were stable across the healthy adult life span (Hanks and Flood, 1991). Taken together, the volume of the human HC has been found to decline curvilinearly with rising age, with an accelerated decrease after age 50 to 60 (Cohen et al., 2006; Driscoll et al., 2003; Raz et al., 2004a; 2004b; 2005; Schuff et al., 1999), but conflicting results call for a cautious interpretation (Sullivan et al., 2005; Van Petten et al., 2004) as the evidence for a positive relationship between HC volume and RM performance is variable and surprisingly weak (Schiltz et al., 2006; Van Petten, 2004). Differential age-related changes across the adult life span have been reported for the number of neurons (West, 1993; West et al., 1994) and for the extent of dendrites of the HC subregions (Flood et al., 1987; Hanks and Flood, 1991). Decreased levels of N-acetyl-aspartate in the HC have also been observed in the elderly (Driscoll et al., 2003; Schuff et al., 1999).

Concerning the other MTL regions, it has been reported that the ERC volume does not change with age, and declines only in pathological but not in healthy ageing (Small et al., 2002). Further, ERC volume decreased annually on average only minimally (0.32%), with the adults < 50 years showing virtually no annual pace of decline (0.11%), unlike the more affected older adults (0.53%) (Raz et al., 2004b; 2005). However, these findings are at odds with an observation of age-related ERC volume reduction across the adult life span (Simic et al., 2005). For the PRC, a stable volume across healthy ageing has been reported (Insausti et al., 1998a; 1998b), although little is known about the functional integrity of the PRC (Burke and Barnes, 2006). With respect to the PHC, no age-related volume differences have been observed (Raz et al., 1997; Van Petten et al., 2004).

In the PFC, the DLPFC and OFC volume declined across a five-year change with a high annual percent change (0.91%, and 0.85%) (Raz et al., 2005). The inferior frontal and OFC volume declined across the adult life span as assessed via MRI (Resnick et al., 2003), and PFC volume shrinkage has been reported in a sample of healthy humans across the adult life span (Raz et al., 1998). All volumes of frontal lobe regions have been shown to be affected strongly but differentially by age using differential estimation methods (Jernigan et al., 2001; Raz et al., 1997; Tisserand et al., 2002). An average
linear decline of 5% per decade within the PFC after the year 20 has been estimated (Raz et al., 2004a). For old relative to young non-human primates, a substantial 32% reduction in neuron number in all layers of the DLPFC (BA 8A) and a conserved neuron number in BA 46 of the PFC has been reported (Smith et al., 2004). Decreased dendritic extent in the medial PFC has been reported in healthy humans across the adult middle to old life span (de Brabander et al., 1998). Successively lower synaptic density has been observed in layers I to VI particularly in the PFC and declining with age in humans (Liu et al., 1996) and non-human primates (Bourgeois et al., 1994). Driscoll et al. (2003) further observed decreased N-acetyl-aspartate levels in frontal white matter in the elderly, while volume of the frontal regions was not assessed. The greatest age-related declines in white matter integrity have been observed in the PFC in healthy humans using diffusion tensor imaging in extreme-group comparisons (Head et al., 2004; Pfefferbaum et al., 2005), across the adult life span (Bartzokis et al., 2003), although all brain regions show alterations with healthy ageing in humans (Head et al., 2004; Madden et al., 2004a; O’Sullivan et al., 2001). Increased apparent diffusion coefficients in frontal white matter have been found (Abe et al., 2002). Taken together, the volume of the human PFC has been found to decline linearly with rising age (Jernigan et al., 2001; Raz et al., 1998; 2005; Resnick et al., 2003; Tisserand et al., 2002). Age-related detrimental impact on the number of neurons (Smith et al., 2004), the extent of dendritic branching (de Brabander et al., 1998), and on the synaptic density (Bourgeois et al., 1994; Liu et al., 1996) of the PFC subregions has been reported for humans. Further, decreased white matter integrity in the PFC in elderly people has been observed (Bartzokis et al., 2003; Head et al., 2004; Madden et al., 2004a; O’Sullivan et al., 2001).

In comparison, much less is known about the thalamus, which shows a linear volumetric decline in age (Sullivan et al., 2004; Van Der Werf et al., 2001; Walhovd et al., 2005), although observations of no or little volumetric change have also been made (Jernigan et al., 1991; 2001). There was a significant increase in mean diffusity, decrease in white matter integrity and volume in the human thalamus with advancing age (Abe et al., 2002; 2008).

To further elucidate the issues of the potential dissociability of RM and NRM (section 1.1.2) and the hippocampal role in spatial RM vs. general RM (section 1.1.3), our first study linked the available volumetric observations on ageing-related changes in the brain regions relevant to RM and NRM (HC, PRC, PFC and thalamus) with a narrow-age cohort design covering the adult life span in four consecutive age groups.
1.2.1.3 Caveats of previous experimental approaches

All of the above studies used a cross-sectional approach, which might overestimate age-related changes due to possible cohort differences due to historical influences like education, culture and socioeconomic status (Hofer and Sliwinski, 2001), but they are the most labour-efficient comparisons (Hedden and Gabrieli, 2004). They can be classified into extreme-group comparisons and assessment across the adult life span:

On the one side, most of the behavioural studies on age-related impact on memory used extreme-group comparisons (Driscoll et al., 2003; Mark and Rugg, 1998; Naveh-Benjamin, 2000; 2003; Naveh-Benjamin et al., 2004; Prull et al., 2006; Schacter et al., 1997; Toth and Parks, 2006). On the other side, many of the anatomical and neuroimaging studies on age-related impact on the neural correlates of memory were assessed across the adult life span (Abe et al., 2002; 2008; Bartzokis et al., 2003; de Brabander et al., 1998; Hanks and Flood, 1991; Jernigan et al., 1991; 2001; Raz et al., 1997; 1998; 2004; 2005; Schuff et al., 1999; Simic et al., 2005; Small et al., 2002; Sullivan et al., 2005; Tisserand et al., 2002; Van Der Werf et al., 2001; Walhovd et al., 2005; West, 1993; West et al., 1994).

A better approach to infer age-related impact is the longitudinal assessment, which does not suffer from cohort differences, but in return may underestimate age-related changes, because they are potentially confounded by selective attrition at older ages. Specifically, behavioural studies may be confounded by practice effects at younger ages and/or short retest intervals (Hedden and Gabrieli, 2004). Due to the labour-consuming nature, the rare longitudinal behavioural studies also do not tap RM and NRM in greater detail (Beason-Held et al., 2008; Singer et al., 2003), and the few anatomical longitudinal studies cover less than ten year retest intervals (Raz et al., 2004b; Resnick et al., 2003).

While both approaches have their flaws, it has been proposed to use a sequential narrow-age cohort approach as a useful means for evaluating associations between ageing-related changes (Hofer and Sliwinski, 2001). Therefore, we employed a narrow-age cohort design covering the adult life span from 20-76 years in 106 healthy adults, allowing comparison of the course of progression of RM and NRM with published structural data, elucidating not only the extreme but also two intermediate age groups (Soei and Daum, 2008).
PART 1: GENERAL INTRODUCTION
State of the art

1.2.2 Electrophysiology of spatial and non-spatial relational and non-relational memory

As outlined above, the evidence for the notion that dissociable neuronal networks are engaged in RM and NRM stems from several lines of research: Dissociable behavioural sequelae after damage of relevant areas, dissociable effects of experimental manipulations, differential correlating activation patterns in neuroimaging studies, and distinct impact of healthy ageing. The second study focused on the electrophysiological correlates of novelty detection in spatial and non-spatial RM and NRM. In the following, the scope is extended to findings on ERPs of novelty detection in general, of RM and NRM, and finally the caveats of existing experimental approaches.

1.2.2.1 Electrophysiological correlates of relational and non-relational memory

Research on the ERPs of RM and NRM during retrieval has yielded topographically, functionally, and temporally dissociable potentials: The RM-associated late old/new effect typically peaks at left posterior electrode sites from 400-800 ms, whereas the NRM-associated early old/new effect (also dubbed FN400) typically peaks at mid-frontal sites from 300-500 ms post-stimulus onset (Allan et al., 1998; Donaldson and Rugg, 1998; Friedman and Johnson, Jr., 2000; Johnson et al., 2008; Paller et al., 1999; Rugg and Curran, 2007).

The RM-associated late old/new effect was found to be more positive for hits relative to correct rejections (Sanquist et al., 1980; Warren, 1980), for correct relative to incorrect RM judgements (Johnson et al., 2008; Rugg et al., 1998), and for successful relative to unsuccessful source memory classifications (Senkfor and Van Petten, 1998; Van Petten et al., 2000; Wilding and Rugg, 1996). The same ERP effect was found for Remember relative to Know responses (thought to index the participant’s subjective judgement whether the quality of the memory is rather RM- or NRM-based, respectively) (Curran, 2004; Duarte et al., 2006; Paller et al., 1999; Woodruff et al., 2006). Further, this effect has been observed to be larger for inter- than for intra-item associations (Jager et al., 2006), and to be topographically and functionally dissociated from parietal late effects related to response confidence and stimulus probability (Curran, 2004; Curran and Hancock, 2007; Rugg and Curran, 2007; Woodruff et al., 2006).

The NRM-associated early old/new effect has been shown to be more negative for correct rejections relative to hits (Curran, 2000; Curran and Cleary, 2003; Rugg et al., 1998), for Know relative to Remember responses (Curran, 2004; Woodruff et al., 2006), and to increase with confidence strength (Woodruff et al., 2006). Further, this effect has
been shown to be larger for intra- than for inter-item associations (Jager et al., 2006). NRM has also been observed to be dissociated from conceptual priming in terms of distinct ERPs (Rugg et al., 1998) and activated cortical networks (Voss et al., 2008).

RM and NRM have further been shown to be topographically dissociable in terms of subsequent memory effects during encoding, although the number of reports is minimal and neither temporally nor topographically consistent (Rugg and Curran, 2007). Subsequent NRM-based judgements were associated with a left-lateralised enhanced positivity at frontal electrode sites from 300 to 450 ms, whereas subsequent RM was associated with a right-lateralised positivity at frontal electrode sites from 300 to 450 ms and bilateral activity from 450 to 600 ms post-stimulus onset (Duarte et al., 2004). Another study yielded that subsequent face NRM was predicted by right-sided neural activity at parietal electrode sites from 600-800 ms, while subsequent face RM was predicted by bilateral slow-wave potentials at parietal electrode sites from 300 ms post-stimulus onset (Yovel and Paller, 2004). However, the latter study reported associations of both RM and NRM with bilateral, parietal-maximum brain potentials at retrieval, albeit smaller amplitudes and shorter durations for NRM.

Taken together, the ERPs of RM and NRM have been shown to be topographically, functionally, and temporally dissociable during retrieval and encoding and thus add further support to the idea of dissociable neuronal networks for RM and NRM (Eichenbaum et al., 2007).

1.2.2.2 Electrophysiological correlates of novelty detection

Novelty detection is important for updating established knowledge in the face of change and utilises previously formed memory representations (O'Keefe and Nadel, 1978). Concerning the mediating neural regions, a distributed network has been implicated for novelty processing (Halgren et al., 1998; Knight and Nakada, 1998; Nyberg, 2005; Ranganath and Rainer, 2003). Using fMRI, the HC and parahippocampal region have been proposed to be pivotal for relational and non-relational novelty detection, respectively (Duzel et al., 2003; Kohler et al., 2005; Kumaran and Maguire, 2007; Pihlajamaki et al., 2004). Recorded potentials from intracerebral electrodes prior to surgery for intractable epilepsy have revealed further regions critical in novelty processing (Baudena et al., 1995; Clarke et al., 1999a; 1999b; Halgren et al., 1995a; 1995b; 1998): The lateral PFC, inferior temporal, entorhinal, orbitofrontal regions, anterior cingulate cortex, parietal lobes, primary and extrastriate visual areas, and premotor and motor areas. While these observations stem from assessing severe epileptic brains and inference to healthy neural processes thus warrants caution,
standard ERPs and fMRI in healthy participants supported this evidence (Dudukovic and Wagner, 2007; Knight, 1984; Williams et al., 2007).

Regarding the ERPs of novelty detection in RM, the P300 potentials (Sutton et al., 1965) have been proposed to reflect the different orienting responses, through which attentional resources are automatically allocated towards the stimulus changing the memorised context (Corbetta and Shulman, 2002; Sokolov, 1963). The P300 potentials typically peak 200-500 ms post-stimulus onset with positive polarity, with the time range depending on stimulus modality, subject age, task conditions etc. Based on studies using variants of the oddball paradigm; in which infrequently presented targets have to be detected among the standard stimuli, the recorded P300 potentials are thought to index neural activities underlying revision or updating of the mental representation induced by the incoming stimuli (Donchin, 1981). After initial sensory processing of the stimuli, an attentional comparison evaluating the representation of the previous event takes place in working memory, a process distinct albeit related to the auditory or visual mismatch-negativity (Heslenfeld, 2003; Kujala et al., 2003). Subsequently, if the representation of the previous event remains unchanged, only sensory evoked potentials are elicited (N100, N200, P200), if a change is detected, attentional processes update the representational context and elicit the P300 (Polich, 2003; 2007). The P300-effects have been observed in many mammalian species (dolphins, rabbits, rats, dogs, cats, squirrel and macaques monkeys, and humans) (Paller, 1994). The P300-effects have been broadly subdivided into the P3a and P3b, with the latter being related to subsequent attentional resource activations promoting memory operations in temporal and parietal regions (Brazdil et al., 2001; 2003; Knight, 1996), and which will not be covered here, as the focus is on novelty detection.

The P3a is the potential most directly related to novelty detection (Courchesne et al., 1975; Squires et al., 1975). Polich (2007) has reviewed the available evidence on the P3a, the novelty P3 and no-go P300, and has proposed that these are all variants of the same potential, with the scalp distributions varying as a function of attentional and task demands. The P3a-effect typically peaks 200-350 ms post-stimulus onset with a positive polarity, and presumably originates from stimulus-driven frontal attention mechanisms during task processing related to detection and rapid orientation to novel events and stimuli (Fabiani and Friedman, 1997; Friedman et al., 2001; Knight and Nakada, 1998; Polich, 2007; Ranganath and Rainer, 2003; Soltani and Knight, 2000). Three characteristics of the P3a have been observed (Friedman et al., 2001): P3a responses habituate across successive presentations of novel items, i.e. the more predictable, the smaller the magnitude of the response (Courchesne et al., 1975; Sokolov, 1990). P3a
responses have been shown to be robust even when the detected deviance was task irrelevant or unattended (Courchesne et al., 1975; Friedman et al., 1998; Ranganath and Paller, 1999; Squires et al., 1975). Similar P3a responses have been observed for auditory, visual and somatosensory modalities (Comerchero and Polich, 1999; Knight, 1996; 1984). The question, whether the P3a responses are also similar for different contexts (e.g. spatial vs. non-spatial), was addressed in the second study of this thesis (section 3.2).

1.2.2.3 Limitations of previous paradigms

Although ERPs lack the spatial resolution required to localise the neural substrates of different processes, they help to determine whether neural correlates of RM and NRM differ qualitatively (indexed by ERP effects that differ in scalp distribution as opposed to simple magnitude differences), as would be expected if RM and NRM have different neural substrates (Rugg and Yonelinas, 2003). The studies discussed above have not addressed the question, whether the mechanisms underlying spatial and non-spatial RM are dissociable regarding novelty detection effects (e.g. the P3a) and the encoding phase has so far not been analysed in terms of subsequent RM and NRM effects.

1.2.3 The human thalamus in spatial and non-spatial relational and non-relational memory

As stated earlier, the support for the proposal that differential neuronal networks mediate RM and NRM comes from converging lines of investigation: Distinct behavioural sequelae of damage of mediating areas, dissociable impact of experimental manipulations, differential correlating activation patterns in neuroimaging studies, distinct impact of healthy ageing, and differential ERPs in electrophysiological studies. In this section, the behavioural sequelae of thalamic damage are introduced, as these have been shown to resemble those of lesions of the MTL (Kopelman and Stanhope, 1998; Squire et al., 2004) and the PFC (Kopelman et al., 1997; Shimamura, 1995): Human thalamic lesions were associated with impaired anterograde memory and executive dysfunctions without further cognitive deficits (Bentivoglio et al., 1997; Carrera and Bogoousslavsky, 2006; Daum and Ackermann, 1994b; Parkin et al., 1994; Van Der Werf et al., 2003a; 2003b; Zoppelt et al., 2003). Thus, the third study focused on the behavioural sequelae of focal lesions of the MD in spatial and non-spatial RM and NRM. The next subsections comprise a review of the findings concerning the role of the MD in NRM, and the role of the MD in spatial RM, and finally the methodological issues of previous studies.


1.2.3.1 The mediodorsal thalamic nuclei and non-relational memory

Memory impairments are frequent after thalamic lesions (Bentivoglio et al., 1997), which can result from various causes, such as ischemic infarctions, hemorrhages, traumatic injuries, and neoplastic processes. They can also stem from necrosis-associated thiamine deficiency related to chronic alcoholism in Wernicke-Korsakoff syndrome (Kopelman, 1995). As the impairments resemble deficits after MTL lesions (Squire et al., 2004), an anatomical model for RM has been proposed (Aggleton and Brown, 1999; 2006; Aggleton and Saunders, 1997; Vann and Aggleton, 2004), in which the mamillary bodies, the fornix and the anterior thalamic nuclei are regarded as functional extensions of the HC in humans. NRM has been suggested to be mediated by a loop involving the PRC and the MD. The proposal accords with some tracing studies reporting reciprocal projections from the HC to the anterior thalamic nuclei (Aggleton et al., 1986; Amaral and Cowan, 1980) and unidirectional projections from the PRC to the MD via the inferior thalamic peduncle and rostral thalamus (Aggleton et al., 1986; Saunders et al., 2005).

The evidence for the proposed extension of the division of labour from the MTL-level to the thalamus (Aggleton and Brown, 1999) has been mixed. Contrary to the predictions of the model were the following observations: A patient with lesions in the left anterior thalamic nuclei and fornix was reported to have normal RM and NRM levels (Hanley et al., 2001). A group study comparing patients with and without lesions in the MD suggested its contribution in RM with a possible involvement of the medial MD in NRM (Zoppelt et al., 2003), as the failure to retrieve contextual information may be due to dysfunctional MD-PFC projections (Van Der Werf et al., 2000). Memory for temporal relations (i.e. RM) was impaired after an MD lesion (Shuren et al., 1997). A patient with lesions bilaterally in the dorsolateral thalamic nuclei and left-sided in the MD had impairments in RM and preserved NRM (Edelstyn et al., 2006). Recently, one patient with damage to the right anterior and dorsolateral thalamic nuclei and mamillo-thalamic tract but not the MD had deficient NRM, and the remaining patient with damage to the right MD but spared anterior thalamic nuclei and mamillo-thalamic tract had impaired RM (Cipolotti et al., 2008). In a group study, patients with lesions affecting either the MD or the ventrolateral (VL) thalamic nuclei showed deficient RM, but neither MD nor VL lesions led to significant deficits in NRM (Soei et al., in revision for EJN). The results of a patient with lesions in both anterior and medial thalamic parts and deficits in both RM and NRM do not unequivocally support the model (Kishiyama et al., 2005). In accordance with the model, a patient with bilateral lesions of the anterior thalamic nuclei was deficient in RM and spared in NRM (Carlesimo et al., 2007). Following Cipolotti et al. (2008), these
results raise the possibility that allocation of RM and NRM to separate thalamic nuclei may not fully capture the role of thalamic sub-regions in memory function, and warrant further research.

1.2.3.2 The mediodorsal thalamic nuclei and spatial relational memory

As mentioned above (section 1.1.1), the different PFC subregions are critical in declarative memory, especially for retrieval or post-retrieval RM processes (Henson et al., 1999). In non-human primates, the PFC was involved in acquisition of spatial RM (Wilson et al., 2007), and both the dorsolateral PFC and MD showed spatial coding properties (Funahashi et al., 2004; Tanibuchi and Goldman-Rakic, 2003). The MD projects reciprocally to the dorsolateral PFC (Goldman-Rakic and Porrino, 1985).

This agrees well with a recent observation in non-human primates: Lesions of the magnocellular MD (the medial MD in humans (Bentivoglio et al., 1997)) led to deficient acquisition but not to impaired retention or retrieval for object-in-place scene memory, i.e. spatial RM (Mitchell and Gaffan, 2008). The authors did not assess NRM, but the results by Soei et al. (in revision for EJN) tentatively suggest a stronger MD involvement in the acquisition of spatial RM rather than NRM. This is consistent with ablation studies showing that the PFC is required for acquisition of spatial RM (Baxter et al., 2007; Wilson et al., 2007). These two findings are at odds with patient observations with group-matched NRM performance that spatial RM was not impaired after focal frontal and diencephalic lesions (Kopelman et al., 1997). However, a patient with right-sided MD damage had impaired RM on spatial memoranda (human faces and topography) (Cipolotti et al., 2008). No other study to date has focused on spatial vs. non-spatial RM after focal MD lesions. Together, these findings are generally in line with the MD-PFC-striatal connections (Alexander et al., 1986; Cavada et al., 1995; Cummings, 1993; Goldman-Rakic and Porrino, 1985), supporting the idea of a role of the MD in spatial RM, and offering an explanation for the resemblance of the impairments after thalamic and PFC lesions.

1.2.3.3 Methodological issues concerning the previous research

All studies discussed above were single case studies except one (Zoppelt et al., 2003), which reported results on nine patients with thalamic lesions in the MD or VL and nine age-, IQ and handedness-matched healthy controls. The number of the healthy controls ranged from five (Shuren et al., 1997) to nine (Edelstyn et al., 2006) per patient, which is modest (Crawford and Garthwaite, 2005). As it is not uncommon for neuropsychological test scores of controls to depart from normality, small numbers of controls bear the potential risk of misdiagnosing a patient’s deficit. Further, these healthy
controls cited above were only age-matched (Cipolotti et al., 2008; Kishiyama et al., 2005), age and educational background-matched (Hanley et al., 2001; Shuren et al., 1997), or knowledge-matched (Edelstyn et al., 2006), thus none of the studies controlled ideally for IQ, sex, and age at the same time. In contrast, our study compared ten patients with thalamic lesions in the MD or VL to ten age-, sex- and IQ-matched healthy controls on the group level, then each patient was individually compared to 15 or 16 age- and IQ-matched healthy participants on the single-case level (Soei et al. in revision for EJN). This was particularly important; given the differential changes of RM and NRM across the healthy adult life span (Soei and Daum, 2008). The strategy allowed the comparison of each patient with the other patients on the same RM and NRM tasks.

1.3 Hypotheses

The motivation for and the hypotheses of the experimental studies included in these doctoral studies are summarised as follows.

1.3.1 Study 1: Course of relational and non-relational memory across the adult lifespan

The first study was conducted to elucidate the course of spatial and non-spatial RM and NRM across the adult life span in healthy humans (Soei and Daum, 2008) and was motivated by the following issues: Human memory declines during normal ageing (section 1.2.1.1) which has been linked to age-associated dysfunctions of MTL structures, such as the HC and the PRC (section 1.2.1.2). Further, whether the HC is critical for human general RM or for spatial RM only is still disputed (section 1.1). The human PRC is thought to be critically involved in NRM, but another view postulates a critical role for the HC in both RM and NRM (section 1.1.2).

Examining whether there is a differential impact of ageing on spatial and non-spatial RM and NRM may lead to a better understanding of these issues. Thus, 106 neurologically and psychiatrically healthy adults were enrolled in a consecutive age groups design involving a range from age 20-76. They performed variants of tasks that elicited specific activations in the HC and PRC in a recent fMRI study (Kohler et al. 2005), which allowed the separate assessment of the memory processes in question. The cross-sectional design, despite its known caveats (Hedden et al. 2004), allowed the estimation of the course of the progression of RM and NRM across ageing and may mirror the course of the presumed age-associated changes in different brain regions. Specifically, it was hypothesised that the presumed curvilinear changes in hippocampal function may be paralleled by a late-life decline in RM. Similar changes in spatial and non-spatial RM would point to a more general role of the HC in mediating RM. If the PRC
alone played a critical role in NRM, its estimates should remain relatively invariant despite rising age. A critical involvement of the HC in NRM would yield a similar decline of RM and NRM.

1.3.2 Study 2: Relational and non-relational memory: electrophysiology of novelty detection

The second study aimed at elucidating the mechanisms of novelty detection in RM and NRM (Soei, Bellebaum and Daum, in revision for EJN) and was motivated by the following issues: The potential dissociability of the ERPs related to RM and NRM during both encoding and retrieval remains elusive (section 1.2.2). A common neuronal involvement in spatial RM vs. general RM is disputed (section 1.1.3). Lastly, the mechanisms of novelty detection in spatial and non-spatial RM and NRM during retrieval are unclear (section 1.2.2). Although the issues overlap partly in the first and second study, the experimental approach employed here differed and yielded complementary insights.

Examining whether the temporal and topographical scalp distributions elicited by RM and NRM are distinct or similar may shed further light on these issues. The time courses and underlying brain areas for these memory processes were examined electrophysiologically by means of electroencephalograms (EEG) and electrooculograms (EOG). These were recorded during encoding and retrieval on three memory tasks in 13 healthy human subjects. Maximal ERP peak amplitudes entered LORETA source analysis. Detection of spatial and non-spatial novelty in RM and novelty in NRM was separately assessed in a variation of the experimental paradigm by Kohler et al. (2005). Specifically, it was hypothesised, that dissimilarity of the courses of ERPs related to RM and NRM during encoding and retrieval would support the account of dissociable neural mediators. Similarity of the courses of ERPs related to novelty detection in spatial and non-spatial RM would support the account of a common mediator of RM.

1.3.3 Study 3: Involvement of the human thalamus in relational and non-relational memory

The third study was conducted to investigate the role of the human thalamus in RM and NRM (Soei, Koch, Schwarz and Daum, in revision for EJN) and was motivated by the following issues: While damage of the human thalamus has been associated with anterograde memory deficits, examinations of patients with selective lesions of thalamic nuclei have yielded controversial results, as most studies have been single-case studies or did not entail a well-matched control sample (section 1.2.3.3). Whether lesion location
within the human thalamus (i.e. involvement of MD) would be associated with different profiles of memory impairments was a further issue of interest (section 1.2.3).

Comparing patients with thalamic lesions to individualised healthy control groups on spatial and non-spatial RM as well as NRM may further elucidate these issues. Ten patients with focal ischemic thalamic lesions in the MD or VL were compared to individualised control groups of healthy subjects matched to each individual patient on age and IQ, using the same paradigm as in the ageing study of Soei and Daum (2008). It was hypothesised that disruption of the PRC-MD projections might be associated with disproportionate NRM deficits, while disruption of MD-PFC-striatal circuits should be linked to disproportionate spatial RM impairments. Disruptions of non-MD regions were expected to spare RM and NRM.
PART 2: GENERAL DISCUSSION

In the discussion, the findings and their implications are summarised in the light of the relevant theoretical issues and some future research directions are provided.

2.1 Implications of the findings

Before addressing the implication of our results, the findings are summarised as follows.

2.1.1 Summary of the findings

All three studies aimed to elucidate the mechanisms underlying spatial and non-spatial RM and NRM using different experimental approaches. The individual research questions were “Do these memory processes undergo similar changes across healthy ageing?”, “Do the temporal and topographical patterns and sources of these memory processes differ during encoding and retrieval phase?” and finally, “Does the MD contribute selectively to these memory processes?”

The individual findings have been summarised and discussed in depth in each article (section 3.1-3). In this section, the main evidence is grouped to provide arguments for the overarching two main findings of this thesis (section 1.1):

Relational and non-relational memory are seemingly dissociable processes

- **Support:** Unlike spatial and non-spatial RM, NRM showed an earlier decline in overall memory performance across healthy ageing, with subjects in the 51-65 years age range showing a significant deficit relative to the youngest group. Further, there was also no significant difference between the two oldest groups (Study 1).
- **Support:** The behavioural patterns of the hit rates across ageing were strikingly similar for spatial and non-spatial RM, and differed for NRM (Study 1).
- **Support:** The ERPs related to hits and correct rejections in RM vs. NRM differed significantly in the early and late time windows during retrieval (Study 2).
- **Support:** Single case analyses based on individualised IQ and sex-matched control samples yielded a significant RM impairment in six thalamic patients, while NRM was not significantly impaired in any of the patients (Study 3).
Spatial and non-spatial relational memory are processed similarly

- **Support:** The decline of overall memory performance in both spatial and non-spatial RM had a strikingly similar late onset, as the 66-76 years group was significantly outperformed by all younger age groups (Study 1).

- **Support:** The decline of correct rejections in both spatial and non-spatial RM had a strikingly similar late onset, as the 66-76 years group was significantly inferior to all younger age groups (Study 1).

- **Support:** Spatial and non-spatial RM correlated significantly across the adult life span (Study 1).

- **Support:** The ERPs related to novelty detection, i.e. correct rejections, in spatial and non-spatial RM did not differ significantly in the early and late time windows during retrieval (Study 2). This is particularly interesting in light of the significant ERP differences for topographical and temporal patterns and brain sources related to novelty detection in horizontal vs. inverted NRM (Study 2).

- **Non-support:** There was evidence of stronger MD involvement in spatial than in non-spatial RM: Three of the five MD patients were significantly impaired in spatial RM, while only one MD patient was significantly impaired in non-spatial RM (Study 3).

Despite the caveat of unequal task difficulty in all RM and NRM tasks, the results patterns were consistent across our three studies and agree well with previous research. The following two sections relate the separate findings to the broad context of dissociability of RM and NRM and similarity of spatial and non-spatial RM.

### 2.1.2 Relational and non-relational memory - dissociable or not?

Our first study showed that RM and NRM both declined in overall memory performance across four consecutive healthy age groups, but with different onsets of the declines (Soei and Daum, 2008). The courses of both RM tasks seem to mirror neuroimaging data of a late-onset decline of hippocampal volume with a delay (Cohen et al., 2006; Raz et al., 2005) (section 1.2.1.2). This highlights the possibility that the loss of functional integrity required in this task followed only after a substantial loss of hippocampal volume. Despite the distinct onsets, the age-related decline of NRM as such accords more with the perspective that the HC is critical for both RM and NRM (Slotnick and Dodson, 2005; Squire, 1994; Squire et al., 2007; Squire and Zola, 1998; Wixted, 2007). The decline replicated and extended a recent extreme-group comparison (Prull et al., 2006): Using three different methods to estimate RM and NRM, RM was consistently found to be reduced in older compared to younger subjects,
irrespective of the analysis method. Two of the three methods did, however, also yield NRM deficits in older adults. Age-related impairment of RM and NRM was also reported in other extreme group studies (Driscoll et al., 2003; Toth and Parks, 2006), but parts of the interpretation of the former study may have suffered from a ceiling effect (Driscoll et al., 2003). However, our own ageing study across four consecutive age groups of the adult life span, did not suffer from ceiling effects, and showed a differential course of decline offering novel insights into the issue of age-related decrement in RM and NRM.

Our second study showed that our ERPs for hits and correct rejections in RM and NRM differed significantly in the early and late time windows during retrieval. We replicated the RM-associated late old/new effect, but found an NRM-associated early old/new effect in opposite direction (Allan et al., 1998; Donaldson and Rugg, 1998; Friedman and Johnson, Jr., 2000; Johnson et al., 2008; Paller et al., 1999; Rugg and Curran, 2007). Possibly, our novel variant of NRM, used exclusively in this study, induced an additional non-NRM-related effect through the stimuli inversion (section 3.2). This limits the interpretation of the ERP differences in terms of RM and NRM dissociability. Notably, our NRM-associated early old/new effect in opposite direction has no consequence for interpretation of the results from the first and third study, as the NRM condition entailed a change not employed in those studies (section 3.1 and 3.3). Along similar lines, the topographically dissociable subsequent memory effects during encoding of our RM and NRM tasks add evidence to the small number of studies (Rugg and Curran, 2007). However, the behavioural results in this sample of healthy young adults replicated the results obtained in the youngest healthy age group in the first study. This along with the finding of the replicated RM-associated late old/new effect, confirmed that both the spatial and non-spatial RM tasks actually tap RM, and enhance the value of our results in light of the discussion concerning the similarity of spatial and non-spatial RM in the intact human brain (section 2.1.3).

Our third study entailed single case analyses based on individualised IQ and sex-matched control samples and we reported a significant RM impairment in six patients, while NRM was not significantly impaired in any of the patients. The patients with selective thalamic lesions were significantly impaired in both RM and NRM relative to the controls, supporting the view of a critical involvement of the thalamus in human memory formation (Bentivoglio et al., 1997). The finding that lesions affecting the MD were associated with impaired RM (spatial and non-spatial) but spared NRM is in good agreement with the hypothesis of a failure to accurately remember contextual information, due to MD-PFC-striatal disconnection (Zoppelt et al., 2003). Furthermore, the evidence of stronger impairment in spatial compared to non-spatial RM accords
well with the notion that the medial MD might be more important for the acquisition of spatial RM rather than NRM (Mitchell and Gaffan, 2008). This added an interesting aspect to the spatial vs. non-spatial RM discussion (section 2.1.3), as it showed that a focal lesion in a critical region could have a stronger impact on one but not the other RM process, which warrants further research. However, the finding that neither MD nor VL lesions led to significant deficits in NRM offers only weak support for the model proposed by Aggleton and Brown (1999), since RM was more impaired than NRM after MD lesions (only the results of one patient were compatible with that model).

Taken together, the evidence for the notion that differential neuronal networks mediate RM and NRM (Eichenbaum et al., 1994; Eichenbaum, 2000; 2003; Eichenbaum et al., 2007; Eichenbaum and Fortin, 2003; 2005) comes from converging investigation lines: Distinct behavioural sequelae of damage of mediating areas (section 1.1.1), dissociable impact of experimental manipulations and differential correlating activation patterns in neuroimaging studies (section 1.1.2). Our own research lines add to this body of evidence by showing dissociable RM and NRM in terms of distinct onsets of age-related declines (sections 1.2.1 and 3.1), differential RM and NRM-related ERPs, albeit a possible non-NRM-effect in the NRM task (sections 1.2.2 and 3.2), and disproportionate impairment of RM after focal thalamic lesions (sections 1.2.3 and 3.3).

2.1.3 Spatial and non-spatial relational memory draw on similar processes

Our first study showed that the declines of overall memory performance across four consecutive healthy age groups in both spatial and non-spatial RM had a strikingly similar late onset and course (Soei and Daum, 2008). The declines in absolute numbers of correct rejections in both spatial and non-spatial RM had a strikingly similar late onset and course, concurring well with the results of the second study (see next paragraph). Spatial and non-spatial RM correlated highly significantly across the adult life span. The pattern across ageing accords well with a hippocampal mediation of both spatial and non-spatial memory (section 1.1.3 and 2.13) and its late life dysfunction (section 1.2.1.2). The data do not accord with the hypothesis that hippocampally mediated relational processing disproportionately affects spatial relationships (O'Keefe 1999). So far, only one study assessed age-related effects on spatial and non-spatial RM previously, reporting significant deficits in spatial and non-spatial RM, but interpretation may be limited by a ceiling effect in the later task (Driscoll et al., 2003). Our results were free of ceiling effects and offer novel insights into the course of spatial and non-spatial RM during healthy ageing.
Our second study focused on novelty detection in a sample of healthy young adults. The ERPs related to correct rejections in spatial and non-spatial RM did not differ significantly in the early and late time windows. The issue of spatial and non-spatial RM has not yet been addressed so far using electrophysiology (section 1.2.2.2), thus the results again offer novel insights, and accord well with the findings from the first study, as both the course across healthy ageing and the temporal and topographical patterns of spatial and non-spatial RM were similar.

Our third study yielded evidence of stronger MD involvement in spatial than in non-spatial RM, as assessed in patients with focal thalamic lesions. This appears to be contrary to the findings from the first two studies, but highlights the need to investigate more thoroughly the issue of spatial and non-spatial RM and focal lesions in critical brain areas. The finding itself is in good accordance with the observation that the MD is reciprocally connected to the OFC and DLPFC (Cavada et al., 1995; Goldman-Rakic and Porrino, 1985). The OFC has been shown to be involved in acquisition of spatial RM (Baxter et al., 2007; Browning et al., 2005) and associated with successful performance in spatial tasks in rodents (Kolb et al., 1983). This agrees well with the observation that the OFC is connected to the medial part of the MD in non-human primates (Cavada et al., 1995). Baxter et al. (2007) suggested that the OFC may contribute to strategies aimed at maximising learning in spatial RM tasks or allocating cognitive resources to scenes ought to be remembered. Further, both the dorsolateral PFC and the MD showed spatial coding properties (Funahashi et al., 2004; Tanibuchi and Goldman-Rakic, 2003). This also agrees well with the observation that lesions of the MD led to impaired acquisition but not to deficient retention or retrieval of spatial RM (Mitchell and Gaffan, 2008). Interestingly, a patient with right-sided MD damage had impaired RM on spatial memoranda (human faces and topography) (Cipolotti et al., 2008). No other study to date has focused on spatial RM after MD lesions, thus our findings also offer novel insights in this matter.

Taken together, the evidence for the notion that the HC has a general role in RM, i.e. spatial processing is only one aspect of RM (Cohen et al., 1997; Eichenbaum et al., 1999; 2001; 2004) comes from converging research lines: Similar behavioural sequelae of damage of mediating areas and activation patterns in neuroimaging studies (section 1.1.3). Our own investigation lines, which were not compromised by unequal task difficulty, support this growing body of evidence by showing similar spatial and non-spatial RM performances in terms of onsets and courses across the four consecutive age groups (sections 1.2.1 and 3.1), and topographically and temporally indistinguishable ERPs related to spatial and non-spatial novelty detection (sections 1.2.2 and 3.2). Our finding of stronger MD involvement in spatial than in non-spatial RM
seems at odds with our two previous main findings, but can be reconciled with retrograde tracing, electrophysiological and patient studies (sections 1.2.3 and 3.3).

2.2 Outlook on future research

In general, a caveat of the experimental paradigms in all three studies was the higher level of difficulty in the NRM tasks. Thus, future research using these tasks in healthy participants should ideally aim for equated levels of difficulty between the RM and NRM tasks, by either reducing the study time in each study block or number of study block repetition for RM, thus making the RM task more difficult. Reducing the number of stimuli in NRM could lead to lower trial numbers available for ERP analysis, and thus should be avoided. Notably, this caveat only affected the issue of RM and NRM dissociability, but not the issue of spatial and non-spatial RM similarity. Before addressing three potential experimental approaches using novel variants of the tasks reported in this doctoral thesis, four general future prerequisites in this field are highlighted.

Firstly, one measure (e.g. NRM) must be equated across patients and controls, before it can be determined whether the other measure (i.e. RM and vice versa) is disproportionately disrupted in the patients. This matching of NRM or RM in the patients’ and controls’ performance as closely as possible could be accomplished by extending the exposure time for the patients for one measure to avoid possible ceiling and floor effects, as exemplified by Hirst et al. (1988) and promoted and modified by Kopelman et al. (2007; 1998).

Secondly, one caveat of contemporary experimental approaches relates to differences in the amount of information remembered between RM and NRM tasks, potentially hindering a straightforward interpretation. Thus, an experimental approach that equates the amount of information remembered between RM and NRM conditions is favourable yielding two possible outcomes: The modern dual-process view would predict HC activity correlating with RM and PRC activity correlating with NRM. The contemporary single-process perspective would anticipate that both HC and PRC activity would correlate and predict both RM and NRM.

Thirdly, Burwell and Furtak (2008) further raised the issue of different confidence levels in current RM and NRM paradigms: Only if an experimental approach would allow high confidence RM ratings similar in strength to high confidence NRM ratings, the two views could be directly compared with each other. The contemporary dual-process view would predict HC activity correlating with RM confidence ratings and PRC activity correlating with NRM confidence ratings. The modern single-process
perspective would anticipate that both HC and PRC activity would correlate and predict both RM and NRM.

Fourthly, given the correlational nature of fMRI evidence (section 1.1.2), comparing many patients with focal lesions either in the HC, PRC, dorsolateral PFC, MD or anterior thalamic nuclei and individualised control groups on the same task would further elucidate the issue of the interplay of the critical brain regions: This strategy would allow the comparison of each patient with the other patients and thus the effects of the damage of key regions could be directly compared on the same RM and NRM tasks.

2.2.1 Relational and non-relational memory in the nonverbal and verbal domain

The first study revealed intriguing relationships between spatial and non-spatial RM and NRM, and nonverbal short-term-memory and working memory, respectively: In short, the groups did not differ significantly on verbal short-term memory and working memory. However, the oldest group had poorer nonverbal short-term memory and working memory compared to the two youngest groups. Age alone significantly predicted performance in spatial RM and NRM. Non-spatial RM performance was predicted by age combined with verbal short-term memory and IQ. In light of this issue it is interesting, that the NRM task seemed to place higher demands on perceptual processing and also did not easily benefit from verbal mediation, semantic processing or screen position cues as was the case for the RM tasks. Additionally, the observation that older adults showed increased thalamic activation during verbal encoding, presumably reflecting enhanced attentional processing relative to younger peers (Madden et al., 1999; 2004b) raises the question, whether the results and inferences (section 2.1) can be replicated in verbal variants of the existing experimental tasks, with equated levels of difficulty. Instead of object pairs, nouns could be paired and used as in the known spatial and non-spatial RM tasks. As for the NRM task, the novelty in the word pairs could manifest as changes in the font size or type. This latter aspect would presumably resolve indirectly the issue of equating the task difficulty, as the perceptual processing demands in NRM in terms of attending to horizontal changes in the views would be significantly reduced if novelty in the visual appearance of the word pairs needed to be detected. These future results would be interesting in light of a recent fMRI study demonstrating that PRC activity was increased when pairs of words were processed as a single unit and that this activity predicted subsequent NRM-based associative memory (Haskins et al. 2008), which, however, did not differentiate between spatial and non-spatial RM. Nevertheless, future studies should also include
additional tasks tapping on verbal and nonverbal short-term and working memory processes.

2.2.2 The attentional demands modulating relational and non-relational memory

A possible scenario in the first study (section 3.1, page 48) raised the possibility that the reduction of NRM might be linked to the high attentional demands due to the higher difficulty of the NRM task (sections 2.1 and 3.1-3) which might induce the joint recruitment of the PRC and the thalamus. The activity of the latter brain region has not only been associated with declarative memory processes (section 1.2.3 and 3.3), but has also been suggested to reflect enhanced attentional processing: Relative to younger subjects, older adults showed increased thalamic activation during verbal encoding or visual target detection (Madden et al., 1999; 2004b). Interestingly, the volume of the thalamus was found to decrease linearly with rising age (Walhovd et al., 2005), which thus could have led to compromised thalamic activation serving higher-order visual feature processing in general (Huettel et al., 2001), resulting in the NRM decline observed across healthy ageing (Soei and Daum, 2008). This issue could be addressed via a parametric modulation of the level of difficulty in an fMRI study with healthy participants, with a highly spatially resolved field of view covering the PFC, MTL and thalamus. The original study by Kohler et al. (2005) entailed a field of view covering the longitudinal axis of the HC, so an fMRI study may reveal the collaboration of the neural correlates which are crucial to spatial and non-spatial RM and NRM under manipulation of attentional demands. This approach would also benefit from a nonverbal and verbal version for the reasons highlighted in the previous section. A group study of patients with selective lesions in the key regions would yield complementary insights into this issue (section 2.2): The PFC involvement in strategic encoding and retrieval processes (Squire, 1994; Squire and Zola, 1998), the suggested thalamic involvement in attentionally demanding tasks, and the reciprocal connections between the PFC and thalamus (Cavada et al., 1995; Goldman-Rakic and Porrino, 1985), would predict pronounced and correlating PFC and thalamic activation patterns in the fMRI or disproportionate deficits of PFC and thalamic patients compared to the other patients. This would further point to the importance of MD-PFC-striatal connections in RM (Alexander et al., 1986; Cavada et al., 1995; Cummings, 1993; Goldman-Rakic and Porrino, 1985; Van Der Werf et al., 2000; Zoppelt et al., 2003).
2.2.3 Course of relational and non-relational memory across the developmental life span

Structural MRI studies showed that the brain volume remains stable between ages 4-18 (Giedd et al., 1996a). Gray matter volume generally increases before puberty and decreases thereafter (Giedd et al., 1996a; 1999; Giedd, 2004; Jernigan et al., 1991; Sowell et al., 2001b), while white matter volume increases between adolescence and adulthood (Giedd, 2004; Jernigan et al., 1991; Pfefferbaum et al., 1994; Reiss et al., 1996). Adolescence marks the beginning of adult-level cognitive control supported by myelination, synaptic pruning, axonal/dendritic collateralisation and collaborative brain function (Luna and Sweeney, 2004), but the different brain regions mature at different paces (Jernigan et al., 1991; Pfefferbaum et al., 1994). The frontal lobe matures initially posteriorly and then anteriorly, with the PFC maturing last (Gogtay et al., 2004) and the dorsolateral PFC maturing at age 20 (Casey et al., 2000; Giedd, 2004). As for the HC, significant volume increases between the ages 4-18 of the right-sided HC were only observed in females but not in males (Giedd et al., 1996b), which accords well with previous studies in rats indicating hormonal responsivity of MTL structures (Gould et al., 1991; Morse et al., 1986). The thalamus has been found to mature most in the first two years in a paediatric healthy sample of 1 month - 17 years (Zhang et al., 2005), and it was also reported to have a greater proportional volume in females relative to males (Sowell et al., 2002).

With respect to cognitive performance, working memory capacity has been shown to improve with increasing processing speed and capacity in the course of healthy childhood, adolescence and adulthood (Anderson et al., 2001; Diamond and Doar, 1989). It has been shown in healthy children and adolescents, that frontal lobe gray matter thinning strongly predicted delayed verbal and nonverbal memory functioning (Sowell et al., 2001a). However, the course of spatial and non-spatial RM and NRM has not been specifically addressed to date in a comparison of healthy females and males from early childhood to adulthood, which would yield interesting insights into maturational and gender-specific aspects of declarative memory.

Following Sowell et al. (2002), this approach would also benefit from structural MRIs enabling estimation of the correlation between the volume estimates and memory performance. As electrophysiology offers temporally-resolved information in the range of milliseconds, assessing the ERPs in healthy participants of narrow age-cohorts of developmental, adult, and ageing samples could uncover a presumably U-shaped pattern of processing speed mirroring the behavioural reaction times. Further, the analysis of the development of the RM and NRM-associated ERP effects (section 1.2.2.1) could yield interesting insights into the issue of dissociability of RM and NRM: The contemporary dual-process view predicts that one of the processes would reach
sooner or later a mature level, mirroring the structural and functional development of the key brain regions. The modern single-process perspective would anticipate that both processes would mature at the same pace.
3 PART 3: ARTICLES


I contributed to this article the idea on the variant of the task by Kohler et al. (2005), the stimuli preparation, the independent programming of the task from scratch using Presentation, the collection and analysis of the data, and the writing of the paper. Prof. Dr. Irene Daum supervised the project and corrected the drafts of the article. Sabine Bierstedt helped me with the figure preparation.
Course of relational and non-relational recognition memory across the adult lifespan

Soei E and Daum I

Course of relational and non-relational recognition memory across the adult lifespan

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Human recognition memory shows a decline during normal ageing, which is thought to be related to age-associated dysfunctions of mediotemporal lobe structures. Whether the hippocampus is critical for human general relational memory or for spatial relational memory only is still disputed. The human perirhinal cortex is thought to be critically involved in non-relational memory, but another view postulates hippocampal involvement in both relational and non-relational memory. Investigating whether there is a differential impact of ageing on these memory processes may shed further light into these issues. Thus, in the present study, 106 healthy adults performed three recognition memory tasks in a consecutive age groups design involving a range from age 20 to 76. This allowed the separate assessment of spatial and nonspatial relational memory as well as non-relational memory. Both spatial and nonspatial relational memory declined in the 66-76 yr group. This pattern is consistent with the presumed course of hippocampal changes across normal ageing and points to the hippocampal role in relational memory in general. An impairment of non-relational memory commenced earlier in the 51-65 yr group. This finding is discussed in relation to perceptual/attentional mediation of memory and its potential brain correlates in ageing.
Introduction

There is an ongoing debate about the contribution of the HC to RM (Eichenbaum, 2004) as compared to spatial relational processing consistent with the cognitive map theory (O'Keefe, 1999). Studies of hippocampal lesions in humans and fMRI studies generally support the hypothesis of a general role of the HC in RM (Eldridge et al., 2005; Fenker et al., 2005; Kumaran et al., 2007; Spiers et al., 2001) Right HC activation correlated with novelty-detection of both spatial and non-spatial relations of stimulus pairs, but not with novelty-detection of single stimuli, which in turn correlated with PRC activation (Kohler et al., 2005). In contrast, animal lesion studies and human fMRI studies focusing mainly on spatial localisation and navigation (Burgess et al., 2002; Kumaran and Maguire, 2005; Lavenex et al., 2006; Maguire et al., 1997; 1998; O'Keefe, 1999) have supported the idea of a more important role of the HC in spatial compared to non-spatial relational processing.

RM has generally been linked to recollection, i.e. episodic memory for event features within a specific context whereas item or NRM is thought to rely on familiarity, i.e. the feeling of knowing an item without remembering the study context (Aggleton and Brown, 2006; Rugg and Yonelinas, 2003; Yonelinas, 2002). Evidence for the dissociability of RM and NRM stems from fMRI studies of differential HC vs. PRC/anterior PHC activations associated with the two types of memory (Daselaar et al., 2006; Kohler et al., 2005; Montaldi et al., 2006; Pihlajamaki et al., 2004). Studies of patients with hippocampal lesions have as yet not yielded a clear picture with respect to the dissociability of RM and NRM (Manns et al., 2003; Mayes et al., 2004; Wais et al., 2006; Wixted, 2007; Wixted and Squire, 2004; Yonelinas et al., 2002). Interestingly, single-unit recordings in human epilepsy patients demonstrated that hippocampal neurons show a familiarity response in absence of successful RM, but notably also in absence of successful NRM (Rutishauser et al., 2006). Thus, whether the HC is involved in RM only or in both RM and NRM remains to be clarified. The PRC was shown to be involved in the perceptual analysis of single items and in binding of individual stimulus features into a coherent representation of an object, which requires perceptual and mnemonic competence (Buckley, 2005; Bussey et al., 2002; 2005). It may support relational processing under some circumstances, such as unitising two features of the same kind to one single item or merged unity representation, but not spatiotemporal relational associations (Jager et al., 2006; Mayes et al., 2004; Norman and O'Reilly, 2003). The HC, on the other hand, mediates associations of the same kind such as object-object associations (Kesner and Hopkins, 2006).

To further clarify the issues of hippocampal involvement in spatial RM vs. general RM and the potential dissociability of RM and NRM, this study investigates
effects of healthy ageing on different memory processes. Hippocampal volume has been found to decline in a curvilinear manner with rising age, with an accelerated decrease after age 50 to 60 (Cohen et al., 2006; Raz et al., 2005). The volume of the HC remains relatively stable across age (Insausti et al., 1998a; 1998b). Consistent with these findings, RM showed a more pronounced age-related decline than the relatively stable NRM in previous studies (Cabeza et al., 2004; Grady et al., 1994; Yonelinas, 2002). However, this pattern has been challenged in a recent study (Prull et al., 2006). Using three different methods to estimate RM and NRM, RM was consistently found to be reduced in older compared to younger subjects, irrespective of the analysis method. Two of the three methods did, however, also yield NRM deficits in older adults. Support for an age-related decline of both memory components also came from another recent study involving 144 young and old participants (Toth and Parks, 2006). The reasons for these conflicting findings are as yet unresolved. The ageing studies carried out so far were exclusively based on extreme group comparisons of one young and one older group, a procedure which entails the known problems of cohort effects. A consecutive age groups design might be better suited to elucidate the course of progression of RM and NRM across ageing.

To address the aforementioned issues, spatial and non-spatial RM as well as NRM were studied in a consecutive age groups design, involving healthy subjects ranging in age from 20-76 years. A variant of a task which yielded specific HC and PRC activations in a recent fMRI study was used (Kohler et al., 2005). Despite the known limitations of cross-sectional investigations (Hedden and Gabrieli, 2004), the design allows an estimation of the course of the progression of memory across age and may mirror the course of the presumed age-associated changes in different brain regions. For instance, the presumed curvilinear changes in hippocampal function may be paralleled by a late-life decline in RM. The separate assessment of spatial and non-spatial RM should add to our knowledge about the generality of the hippocampal mediation of RM. If the PRC was critical for NRM, its estimates should remain relatively stable with rising age. A critical involvement of the HC in NRM, on the other hand, would yield a similar decline of RM and NRM.

Results

The data for neuropsychological screening are summarised in Table 1. The age groups differed significantly in estimated intellectual ability (IQ) ($F[3,102]=3.48$, $p=.019$), with better performance of the 66-76 years group ($p=.046$) and the 51-65 years group ($p=.037$) compared to the 20-35 years group. The groups did not differ significantly on verbal short-term memory (both $F\leq2.29$). There were, however,
significant age differences for non-verbal memory. The group difference in non-verbal short-term memory ($F[3,102]=11.47, p<.001$) was due to the poorer performance of the 66-76 group compared to the 20-35 years group ($p<.001$) and the 36-50 years group ($p<.001$). Analysis of non-verbal working memory also yielded significant age differences ($F[3,102]=12.34, p<.001$), with lower scores of the 66-76 years group compared to the 20-35 years ($p<.001$) and the 36-50 years groups ($p<.001$), and lower scores of the 51-65 years group compared to the 20-35 years group ($p=0.006$). The four age groups did neither differ on depression ($F=1.70$) nor the dementia screening score (MMST, $F=2.09$). Taken together, the data suggest typical patterns observed in healthy ageing samples.

Table 1 shows the neuropsychological data (M = means and SEs = standard errors) for the four age groups.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>20-35 years</th>
<th>35-50 years</th>
<th>51-65 years</th>
<th>66-85 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IQ</strong></td>
<td>107.02 (.99)</td>
<td>111.00 (.83)</td>
<td>112.69 (1.21)</td>
<td>112.72 (2.60)</td>
</tr>
<tr>
<td><strong>Verbal STM</strong></td>
<td>7.96 (.37)</td>
<td>8.31 (.38)</td>
<td>7.58 (.36)</td>
<td>7.00 (.32)</td>
</tr>
<tr>
<td><strong>Verbal WM</strong></td>
<td>7.00 (.33)</td>
<td>7.14 (.40)</td>
<td>6.23 (.34)</td>
<td>6.00 (.33)</td>
</tr>
<tr>
<td><strong>Non-verbal STM</strong></td>
<td>8.93 (.25)</td>
<td>8.93 (.29)</td>
<td>7.85 (.28)</td>
<td>6.83 (.35)</td>
</tr>
<tr>
<td><strong>Non-verbal WM</strong></td>
<td>8.54 (.32)</td>
<td>8.10 (.33)</td>
<td>7.00 (.30)</td>
<td>5.96 (.32)</td>
</tr>
<tr>
<td><strong>BDI</strong></td>
<td>4.79 (.74)</td>
<td>5.34 (.81)</td>
<td>4.12 (.61)</td>
<td>6.67 (1.03)</td>
</tr>
<tr>
<td><strong>MMST</strong></td>
<td>28.71 (.25)</td>
<td>29.07 (.19)</td>
<td>29.08 (.13)</td>
<td>28.43 (.24)</td>
</tr>
</tbody>
</table>

Abbreviations: STM = Short-term memory, WM = Working memory, BDI = Beck Depression Inventory, MMST = Mini-Mental-Status-Test

Table 1 shows the neuropsychological data (M = means and SEs = standard errors) for the four age groups.

**Spatial relational memory in the four age groups comparison**

ANOVA yielded significant age differences in discrimination indices ($F[3,102]=11.01, p<.001$, Figure 1). Post-hoc Bonferroni-corrected tests yielded the following results, and no other group differences reached significance. The 66-76 group showed poorer discrimination than each of the younger groups (20-35 years group ($p<.001$), 36-50 years group ($p=.001$), 51-65 years group ($p=.010$)). Separate analysis of the hit rates yielded the same pattern (Figure 2, overall group difference $F[3,102]=10.58, p<.001$, 66-76 group vs. 20-35 years group ($p<.001$), vs. 36-50 years group ($p=.001$), vs. 51-65 years group ($p=.020$)). The significant age group difference for false alarm rates ($F[3,102]=4.19, p=.008$) was due to higher error rates in the 66-76 years group compared to the youngest group ($p=.004$, Figure 2). Analysis of response bias did not yield significant age group differences (Table 2, $F=.79$).

RTs associated with hits (Figure 3) yielded significant age differences ($F[3,102]=9.58, p<.001$), with the 20-35 years group responding faster than each of the
other groups (36-50 years group ($p=.036$), 51-65 years group ($p=.025$), 66-76 years group ($p<.001$)), and the 36-50 years group responding faster than the 66-76 years group ($p=.047$). The significant RT difference on false alarm trials ($F[3,102]=3.26$, $p=.025$) was due to faster responses of the youngest compared to the oldest group ($p=.028$).

Non-spatial relational memory in the four age groups comparison

As in the spatial task, analysis of the discrimination indices for non-spatial memory (Figure 1) indicated a significant age difference ($F[3,102]=8.47$, $p<.001$), with the 66-76 years group showing poorer memory performance than each of the younger groups (20-35 years group ($p<.001$), 36-50 years group ($p=.002$), and the 51-65 years group ($p=.006$)). Analysis of hit rates yielded the same pattern (overall group difference $F[3,102]=7.85$, $p<.001$, 66-76 group vs. 20-35 years group ($p<.001$), vs. 36-50 years group ($p=.001$), vs. 51-65 years group ($p=.001$)). Similar to the spatial task, the false alarm group difference ($F[3,102]=3.98$, $p=.010$), was due to higher false alarm rates in the 66-76 years group compared to the youngest group ($p=.005$) (Figure 2). Response bias estimates did not differ between age groups (Table 2, $F=.51$).

The significant RT difference on hits trials (Figure 3, $F[3,102]=8.02$, $p<.001$), was due to slower responses in the 66-76 years relative to the two youngest age groups (20-35 years group ($p<.001$), 36-50 years group ($p=.021$)). The group difference for RTs on false alarms trials ($F[3,102]=7.01$, $p<.001$) was due to faster RTs of 20-35 years group compared to the 66-76 years group ($p<.001$) and the 36-50 years group ($p=.019$).

Non-relational memory in the four age groups comparison

The significant age group difference for the discrimination index ($F[3,102]=11.01$, $p<.001$), was due to a poorer performance of the 66-76 years group relative to the two youngest age groups (vs. 20-35 years group ($p<.001$), vs. 35-50 years group ($p=.001$)). The difference between the 66-76 years and 51-65 year groups approached but did not reach significance ($p=.055$). In addition, the discrimination index of the 51-65 years group was lower than the index of the youngest group ($p=.023$) (Figure 1). Analysis of hit rates also yielded an overall group difference ($F[3,102]=4.15$, $p=.008$), with lower hit rates of the 66-76 group compared to the two youngest age groups (vs. 20-35 years group ($p=.012$), vs. 36-50 years group ($p=.025$), Figure 2). The significant age difference in false alarm rates ($F[3,102]=7.81$, $p<.001$) was due to higher rates of the 66-76 years group relative to the 20-35 years group ($p<.001$) and the 36-50 years group ($p=.026$). In addition, the false alarm rates of the
51-65 years group were higher than those of the 20-35 years group ($p=.011$). Response bias estimates did not differ between groups (Table 2, $F=.79$).

The significant RT difference for hits trials (Figure 3, $F[3,102]=5.19, p=.002$) was related to slower responding of the 66-76 years group compared to the two youngest groups (vs. 20-35 years ($p=.001$), vs. 36-50 years ($p=.030$)). The RT on false alarm trials did not differ between groups ($F=2.45$).

Figure 1

![Figure 1](image1.png)

Figure 1 shows the discrimination indices (M = means and SEs = standard errors) of spatial and non-spatial RM and NRM estimates in the four age groups. Lines indicate significant paired group differences (Bonferroni-corrected).

Figure 2

![Figure 2](image2.png)

Figure 2 shows the hits and false alarm rates (M = means and SEs = standard errors) of spatial and non-spatial RM and NRM estimates in the four age groups. Lines indicate significant paired post-hoc tests for group differences (Bonferroni-corrected).
Figure 3 shows the RTs (M = means and SEs = standard errors) for spatial and non-spatial RM and NRM in the four age groups. Lines indicate significant paired post-hoc tests for group differences (Bonferroni-corrected).

Table 2 shows the response biases (M = means and SEs = standard errors) for the four age groups.

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>20-35 years</th>
<th>36-50 years</th>
<th>51-65 years</th>
<th>66-85 years</th>
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<td>0.56 (.03)</td>
<td>0.54 (.04)</td>
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<td>Response bias index non-spatial relational memory</td>
<td>0.59 (.04)</td>
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<tr>
<td>Response bias index non-relational memory</td>
<td>0.62 (.03)</td>
<td>0.65 (.03)</td>
<td>0.69 (.04)</td>
<td>0.63 (.04)</td>
</tr>
</tbody>
</table>

Table 2 shows the response biases (M = means and SEs = standard errors) for the four age groups.

**Direct comparison of spatial and non-spatial relational and non-relational memory in the four age groups**

An ANOVA with repeated measures including the discrimination ability in the three memory tasks as the within-subjects factor and age group as the between-factor yielded a main effect of task ($F(2,102)=55.84$, $p<.001$), as performance in the NRM task is generally lower than in both RM tasks. There was also a main effect of age group
(F[3,102]=15.86, p<.001), showing decreasing discrimination ability with increasing age. However, there was no memory task x age group interaction (F[3,102]=.51).

Relationship between age, neuropsychological data and discrimination indices of spatial and non-spatial relational and non-relational memory across the adult life span

Correlation analyses, corrected for multiple testing, were conducted with all 106 participants to elucidate the relationship between the neuropsychological data and memory indices across the adult life span, and not only between age groups. They yielded negative correlations between age and spatial RM (R=-.47, p<.001), non-spatial RM (R=-.40, p<.001), and NRM (R=-.47, p<.001), respectively. Spatial and non-spatial RM correlated positively (R=.60, p<.001), as did spatial RM and NRM (R=.61, p<.001) and to a relatively lesser extent non-spatial RM and NRM (R=.50, p<.001). The same analysis conducted separately for each age group, corrected for multiple testing, did not yield any statistically significant correlation in any of the groups.

All stepwise regression analyses, also conducted across the adult life span, yielded significant results, with age alone being a predictor for spatial RM (F[1,104]=28.86, p<.001, R²=.22, Beta-coefficient=-.47, T=-5.37, p<.001) and NRM (F[1,104]=28.93, p<.001, R²=.22, Beta-coefficient=-.47, T=-5.38, p<.001). For non-spatial RM, age combined with verbal short-term memory and IQ were included as predictors (F[3,102]=11.29, p<.001, R²=.25, Beta-coefficient[age]=-.41, T[age]=4.46, p<.001, Beta-coefficient[verbal short-term memory]=.20, T[verbal short-term memory]=2.29, p=.024, Beta-coefficient[IQ]=.20, T[IQ]=2.17, p=.032).

Discussion

The aim of the present study was to assess the course of spatial and non-spatial RM and NRM across the adult age range in healthy subjects ranging in age from 20 to 76 years. In summary, the declines of discrimination ability in both spatial and non-spatial RM had a strikingly similar late onset, as the 66-76 years group was outperformed by all younger age groups (Figure 1). Additionally, spatial and non-spatial RM correlated highly across the adult life span. Taken together, the analyses of the four age groups and correlational analyses across the life span add evidence to the idea that the HC mediates general RM processing. NRM showed an earlier commencing decline, with subjects in the 51-65 years age range also showing a discrimination ability deficit relative to the youngest group and there was also no difference between the two oldest groups (Figure 1). This appears consistent with the account of a hippocampal role in both RM and NRM. A closer inspection of hit and false alarm rates revealed that the earlier commencing decline of NRM was mainly due
to the high false alarm rates of the two oldest groups relative to the youngest group (Figure 2). The patterns of the hit rates across ageing were strikingly similar for spatial and non-spatial RM, but somewhat different for NRM, which speaks in favour of the dissociability of RM and NRM. However, age correlated with and predicted (solely and jointly) performance in all three tasks across the adult life span. With respect to the lack of a statistically significant task x age group interaction, one has to bear in mind that the RM and NRM tasks were a) designed to aim at differential memory processes and b) the NRM task was confounded by a higher level of difficulty, and thus the interpretation of lacking interaction between non-comparable memory performances is not straightforward. Taken together, the implications concerning the issue of dissociability of RM and NRM vs. the issue of hippocampal involvement in NRM may be potentially complicated and this will be discussed in the second part of the Discussion.

**Spatial and non-spatial relational memory indices were affected similarly across ageing**

The relatively late onset of the discrimination impairment for spatial and non-spatial RM was based on both lower hit rates and higher false alarm rates in the 66-76 years group, with relatively stable performance in all younger groups. The question arises as to whether the course of memory changes with rising age would fit with what is known about their neuronal mechanisms and changes with normal ageing. The observed performance pattern appears to mirror neuroimaging data of a late-onset decline of hippocampal volume with a latency (Cohen et al., 2006; Raz et al., 2005). This points to the possibility that the loss of functional integrity required in this task followed only after a substantial loss of hippocampal volume. However, it should be noted that correlations between hippocampal volume and RM indices have not been consistently observed (Schiltz et al., 2006). The reduced ability to remember object-location-associations in older adults has been convincingly linked to reduced anterior hippocampal function (Mitchell et al., 2000). The data do not support the hypothesis that hippocampally mediated RM processing disproportionately affects spatial relationships (O'Keefe, 1999). The NRM task used in the present study addressed visuospatial processing to some degree, although clearly less so than the spatial RM task, as the participants were instructed to memorise the views of the objects and to later detect changes in the view. These links were illustrated by the findings of the regression analysis across the adult life span, with age alone being a strong predictor of the discrimination indices in spatial RM and NRM and the high correlation between both types of memory. The courses of both spatial and non-spatial RM across ageing were, however, strikingly similar, both reflecting a late life onset of a significant
impairment. Taken together, the finding of a strikingly similar course of spatial and non-spatial RM across the human adult life span supports the idea of a general role of the HC in RM processes (Eichenbaum, 2001; 2004; Kesner and Hopkins, 2006; Kohler et al., 2005; Kumaran et al., 2007; Rolls and Kesner, 2006; Spiers et al., 2001) and adds to increasing evidence from experimental animal studies (Gilbert and Kesner, 2004; Kesner et al., 2002) and human ageing studies using extreme group comparisons (Prull et al., 2006; Toth and Parks, 2006).

The non-relational memory index declined earlier across ageing

A somewhat surprising finding is the relatively early commencing decline of memory and more specifically of the ability to reject non-targets in NRM. This problem was already present in the 51-65 years group as compared to the youngest group (Figure 1), and there were no statistically significant differences in the abilities to discriminate, detect targets and reject non-targets between the two oldest groups as in RM. The present age-related reductions of NRM extend recent evidence of age-associated familiarity deficits in older participants (Prull et al., 2006; Toth and Parks, 2006). The two familiarity memory studies were based on extreme groups comparisons ([young group age range=18-28 vs. older group range=63-81 (Toth and Parks, 2006)] and [young group range=18-22 vs. older group range=60-82 (Prull et al., 2006)]), and thus do not provide information about the course of the age-related changes. The decline of discrimination indices on the NRM task (Figure 1) and the lack of memory task x age group interaction at hand is inconsistent with a previously reported age-associated dissociation of impaired RM/stable NRM (Cabeza et al., 2004; Grady et al., 1994; Yonelinas, 2002) and accords more with the view that the HC plays a role in both RM and NRM processing (Wais et al., 2006; Wixted and Squire, 2004). However, it should be stressed that our NRM task was clearly more difficult than NRM based on familiarity of single items, as illustrated on the basis of hit and false alarm rates (Figure 2) and RTs (Figure 3) (see below for thorough discussion), which limits the comparability of the rates of decline. An important question in this regard is whether NRM of an object consisting of two or more features of the same kind may also depend upon RM to some degree (Yonelinas, 2002). This is unlikely for the present task, since Norman et al. (2003) argued that associating two features to one item, but not spatiotemporal relational associations can be supported by a familiarity-type process, and selective hippocampal lesions spare the recognition for items and also associations between items of the same kind (e.g. word-word or face-face pairs) (Mayes et al., 2004). Still, the current NRM task clearly supported unitisation to a lesser degree than e.g. encoding of arbitrary word pairs in RM vs. NRM conditions (Quamme
et al., 2007). In this study, the strategy to encode arbitrary words pairs as compounds appeared to be clearly related to NRM. The alternative strategy to encode the words as segregated words in a sentence relied on recollection. In our task, the subjects were not instructed to use specific encoding strategies. In the NRM task, they were simply told to memorise the views, and this may not have sufficed to promote unitisation. In summary, this task seemed to place disproportionately high demands on perceptual processing and also did not easily benefit from verbal mediation, semantic processing or screen position cues as was the case for the RM tasks. The NRM task required the precise perceptual analysis of the conjunctions of features of the two objects as one merged stimulus representation to distinguish the view during recognition. This process has been linked to the PRC (Buckley, 2005; Bussey and Saksida, 2005).

It follows that linking the course of memory changes with rising age in NRM to potential underlying brain mechanisms is more difficult than in the RM task. If the present results had been found with equated levels of difficulty between the RM and NRM, three possible competing scenarios would arise. Firstly, the results would have to be interpreted in favour of the account that the HC is also critical for NRM. Specifically, the decline of the discrimination indices in NRM and the lacking memory task x age group interaction could be explained by an ageing-related disruption of hippocampal function. Secondly, the results might be due to an age-associated decline in the functional integrity of the perirhinal cortical circuits despite their stable volume across ageing, which remains to be investigated (Burke and Barnes, 2006; Insausti et al., 1998a; 1998b). Unfortunately, the major caveat of the present study is the between-task difference in difficulty, which limits the implications of the results with respect to the first two competing accounts.

A third scenario raises the possibility that the reduction of NRM might be linked to the high attentional demands of the task which might induce the joint recruitment of the PRC and the thalamus. There are several lines of evidence which indicate that the NRM task appeared to be more difficult than a simple NRM task based on the familiarity of individual items. It also appeared to be more difficult than the RM tasks, an effect which was not observed in pilot studies. The lower discrimination ability indices for the NRM task were mainly attributable to the higher false alarm rates which increased with each age group (Figure2). The RTs for false alarms were considerably longer for the NRM compared to the RM task; this difference is particularly pronounced for the youngest group, confirming the high level of difficulty (Figure3). It therefore may have recruited additional attention-related brain mechanisms which do not play a role in a NRM task using single items, and the brain imaging correlates of the single-item NRM task by Kohler et al. (2005) may not have direct implications for the current study.
In the Kohler et al. (2005) study, novel items in the NRM task were not encountered in the study phase, as opposed to the novel items in the RM tasks, which were studied objects in recombined arrangements. In the current version, we aimed to create similar levels of work load and novelty levels in the RM and NRM tasks. Taken together, our task also placed higher demands on discriminability, as all NRM pairs were equally familiar with respect to object co-occurrence and spatial layout and familiarity of spatial orientation was the key feature for old/novel judgement; hence the subjects were more inclined to endorse even changed pairs. Given the necessity of recruiting increased perceptual and attentional resources during the NRM task, the question arises whether a recruitment of the thalamus might have been needed in addition to the PRC. Familiarity-type recognition has been associated with a circuit linking the PRC and the thalamus (Aggleton and Brown, 1999). Interestingly, the volume of the thalamus was found to decrease linearly with rising age (Walhovd et al., 2005). Relative to younger subjects, older adults showed increased thalamic activation during verbal encoding or visual target detection, presumably reflecting enhanced attentional processing (Madden et al., 1999; 2004b). Higher activation in the thalamus might serve to compensate the reduced occipital activations of older adults showed in response to novel stimuli (Madden et al., 2004b) and higher-order visual feature processing in general (Huettel et al., 2001). The age-related posterior-thalamic shift of brain activations may enhance target-relevant features relayed for visual processing of the spatial orientation of the NRM items (Madden et al., 2004b). By contrast, RM could be supported by memorising the relationships of the gist of the objects, without reference to the actual view (i.e. perceptual details) of the objects. Thus, it is possible that the necessity of recruiting increased perceptual and attentional resources during the NRM task might be associated with recruitment of the thalamus. The relatively early NRM deficit (slowly beginning in the 51-65 years group) might be linked to a dysfunction of this mechanism (Raz et al., 2005; Walhovd et al., 2005).

Potential alternative interpretations of the age-associated memory deficits might relate to differences in general level of intellectual status, response speed or response bias/motivation. Careful matching and estimating IQ, years of education, MMST, BDI, overall neutral memory biases and a lenient reaction time window make these explanations unlikely.

In summary, RM and NRM were both significantly affected by age, with a late life onset of RM deficits and an earlier onset of NRM impairment. The pattern across ageing is consistent with a hippocampal mediation of both spatial and non-spatial memory and its late life dysfunction and thus strongly supports the account of a hippocampal role in general RM (Eichenbaum, 2001). A caveat of this study was the
unequal task difficulty regarding the RM vs. NRM, thus the current evidence as for the NRM can be interpreted in terms of favouring either one of the following views. NRM based on perceptually difficult and attention-demanding processes may lead to memory deficits commencing earlier in life which might be linked to either the critical involvement of the HC in RM and NRM (Wais et al., 2006; Wixted and Squire, 2004), loss of functional changes of the PRC despite structural changes, or insufficient recruitment of the thalamus.

Materials and Methods

Participants.

One hundred and six healthy participants were recruited by advertisement and private contact and gave written informed consent to take part in the study. Half of the participants of the youngest age group were undergraduate psychology students and received course credit for participation. The study was conducted in accordance with the requirements of the local ethics committee. Exclusion criteria were a history of neurological, psychiatric, head trauma or substance abuse, a Mini-Mental Status Test (MMST) Score below 27, a Beck Depression Inventory (BDI) score above 15, misunderstanding of task instructions as assessed in a post-experimental debriefing or abnormally long reaction times (>2500 ms).

The remaining participants were assigned to one of four age groups: 20-35 years (N=28, 18 females, \( M=23.89, \ SD=.78 \)), 36-50 years (N=29, 16 females, \( M=42.72, \ SD=.75 \)), 51-65 years (N=26, 17 females, \( M=55.85, \ SD=.81 \)) and 66-76 years (N=23, 12 females, \( M=69.61, \ SD=.89 \)).

The proportion of males and females did not differ significantly between groups (all \( \chi^2<2.46 \)). Screening of neuropsychological status entailed estimation of general intellectual ability by a short German version of the Wechsler Adult Intelligence Scales (Dahl, 1972). Verbal and non-verbal short-term and working memory were assessed by the German version of the digit and block span tests of the Wechsler Memory Scale-Revised (Wechsler, 1987).

Assessment of relational and non-relational memory

The memory assessment procedure of this study was based on a computerised memory test used in a recent fMRI study (Kohler et al., 2005). In brief, subjects had to encode a series of line drawings of object pairs which were presented in distinct spatial layouts (Figure 4a). In the test phase, old and novel item pairs were presented, and subjects had to indicate for each pair whether it was previously encountered or novel.
Novel items were systematically manipulated versions of the studied pairs involving new object-location (Figure 4b) or object-object relationships (Figure 4c).

NRM was assessed in a variation of the original task. We aimed to develop merged unity representations of object pairings without the need for relational processing. Kohler et al. (2005) used individual objects for the NRM task, which led to ceiling effects in memory performance. The procedure of the present study aimed to avoid such ceiling effects. The stimuli consisted of two objects presented centrally on the screen (Figure 4d). Novel items were horizontally flipped versions of the individual objects of the studied pairs, whilst all test items were intact pairs with regard to their studied spatial layouts (Figure 4e). Thus, both the object-location and the object-object relationships were held constant. Critically, as opposed to the two RM tasks, the prior occurrence or familiarity of the spatial orientation determined NRM. In the two RM tasks the spatial orientation of the individual objects never changed. Familiarity of the spatial orientation of the individual objects could thus not contribute to performance. Instead, the prior spatial layout or co-occurrence of the objects had to be remembered for successful task performance. Using paired stimuli rather than individual objects, the general processing load was more comparable in the RM and NRM tasks. The level of novelty of the distractor items was also more comparable to the RM tasks than in the original version, where the distractors of the NRM task – unlike the RM task – had not been encountered before. In both the RM and NRM tasks, the novel items were thus systematically altered versions of previously encountered stimuli. The NRM procedure was intended to tap into a merged representation of a single stimulus consisting of two object-features.

The number of items in each task and the number of repetitions of the study phase (N=4) were determined on the basis of extensive piloting. The stimulus pairs were based on 144 grey-level texture line drawings of objects presented against a white background, the stimuli were derived from a database (standardised according to naming agreement, familiarity, complexity and imagery judgements) (Rossion and Pourtois, 2004). For each participant, 72 drawings were randomly allocated to the RM task, the remainder to the NRM task. In the RM tasks (Figures 4a-c), successful RM required the formation and recollection of object-location or object-object relationships between the separate spatial or non-spatial components of an episode. In the NRM task (Figures 4d-e), successful performance did not require the memory of relations, but could be accomplished on the basis of the familiarity of the spatial orientations of items.
Relational Memory

Study Phase (Figure 4a): For each participant, 72 objects were randomly paired to create the 36 study items. These 36 item pairs were shown in one of 18 distinct spatial configurations in an invisible 8 x 6 grid. Following the original study, each spatial configuration was used twice in two different objects pairings, which allowed altering the object-object relationships without a simultaneous change in object-location relationships. The participants were asked to memorise the object-object and object-location relationships of each pair and were shown examples of old and new test items in the spatial and non-spatial RM conditions, so that they would be able to focus on the relevant features. Each item was displayed for 2000 ms each with ISIs of 3000 ms. The 36 items were presented in blocks of four (30 sec between-block intervals), each pair appeared only once within a block. The memory test followed immediately after the fourth repetition of the study phase.

Test of spatial relational memory (Figure 4b): Each of the 36 old and 18 novel items were randomly presented for 2500 ms with an ISI of 3000 ms. Old and new items were made up of the same object pairs. In old items, the spatial arrangement of the two objects was identical to the study phase; in novel items the spatial positions of the objects were swapped. Participants were asked to indicate by button-presses whether an item was old or novel. The discrimination index $P_r$ and bias index $B_r$ of the Two-High-Threshold Model ($P_r=$ hit rate - false alarm rate, and $B_r=$false alarm rate/[1-(hit rate
- false alarm rate)) were calculated to estimate spatial RM. The Two-High-Threshold Model with Pr and Br as a dependent measure was chosen, because it was reported to be more sensitive than the signal-detection theory discrimination measure (Snodgrass and Corwin, 1988). RTs were also recorded.

Test of non-spatial relational memory (Figure 4c): The 36 old and 18 novel items were presented in random order, items were presented for 2500 ms each, with ISIs of 3000 ms. All items retained the same locations on the screen as in the study phase, but they differed with respect to non-spatial pairing: Old items entailed the same object pairs as in the study phase, whereas novel items involved new object combinations, with each object keeping its spatial location from the study phase. Participants had to indicate by button presses whether an item was old or novel, and discrimination and bias indices as well as RTs were assessed.

Non-relational Memory

Study Phase (Figure 4d): 36 item pairs were presented at the central location of the screen. Subjects were asked to memorise the object-object-relationships and the views from which the objects were displayed and were shown examples of old and new test items, so that they would be able to attend to the relevant features. As in the RM tasks, items were presented for 2000 ms with ISIs of 3000 ms.

Test of non-relational memory (Figure 4e): The 36 old and 18 new items were presented in random order, each item was shown for 2500 ms with ISIs of 3000 ms. All object pairs were shown at the same location as in the study phase. Old items preserved the view from which the objects were depicted. In novel items the objects were shown from a different view. Subjects had to indicate by button presses whether an item was old or novel, and discrimination and bias indices and RTs were analysed.

The order of the RM and NRM tasks was randomised across subjects. There was only one study phase for the two RM tasks (see above), and the order of the spatial and non-spatial RM phases was also randomised. Stimuli and responses were displayed, recorded and analysed using the Presentation software (Neurobehavioral Systems Inc, Albany, California, http://www.neurobs.com/), and statistical analyses were performed via SPSS 15.0.
3.2 Study 2: Soei, Bellebaum and Daum (in press, EJN). Relational and non-relational memory: electrophysiological correlates of novelty detection, repetition detection and subsequent memory.

I contributed to this article the idea on the other variant of the task by Kohler et al. (2005), the stimuli preparation, the basic programming of the task using Presentation, the collection and analysis of the EEG data via Vision Analyzer software, and the writing of the paper. Dr. Christian Bellebaum helped me with adding EEG-specific details in the program, analysis of the EEG-data and corrected drafts of the article. Prof. Dr. Irene Daum supervised the project and corrected the drafts of the article. Sabine Bierstedt helped me with the EEG set up and the figure preparation.
Relational and non-relational memory: 
Electrophysiological correlates of novelty detection, repetition detection and subsequent memory

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Abstract

The dissociability of novelty detection in RM and NRM is currently under debate. To further address the time course and underlying brain correlates of novelty detection, ERPs were analysed for encoding and retrieval on three memory tasks in healthy subjects. Spatial and non-spatial RM as well as NRM were assessed separately. The ERPs related to RM and NRM were dissociable for hits and correct rejections in an early and late time window. An early old/new effect was observed for NRM. A late old/new effect replicated the frequently reported recollection-associated old/new effect in terms of direction and amplitudes. Four different novelty types (spatial RM, non-spatial RM, horizontal NRM and inverted NRM) were examined. The P3a related to novelty detection differed in horizontal vs. inverted distractors in NRM but not in spatial vs. non-spatial RM. Event-related potentials for subsequent hits differed between RM and NRM. These findings are discussed in relation to potential brain correlates in memory during encoding and retrieval.
Introduction

Relational memory refers to recollection, i.e. memory for episodic features within a specific context whereas NRM refers to familiarity, i.e. the feeling of knowing an item without recalling the specific context (Yonelinas, 2002). Evidence for the dissociability of RM and NRM stems from neuroimaging studies of differential HC vs. parahippocampal region (PHR) activations associated with the two types of memory ((Eichenbaum et al., 2007; Kohler et al., 2005; Winters et al., 2008)), and from studies of distinct ERPs elicited by RM and NRM (Rugg and Curran, 2007). However, studies of patients with hippocampal lesions have yielded conflicting results concerning the dissociability of RM and NRM (Wixted and Squire, 2004; Yonelinas et al., 2002).

A related issue refers to novelty detection, which is important for updating established knowledge in the face of change (O'Keefe and Nadel, 1978), drawing upon previously formed memory representations. It has been linked to the HC and PHR, depending on its relational or item-specific nature (Duzel et al., 2003; Kohler et al., 2005; Kumaran and Maguire, 2007; Pihlajamaki et al., 2004), but novelty detection may also involve the PFC and inferior temporal regions (Dudukovic and Wagner, 2007; Knight, 1984; Nyberg, 2005). The HC showed novelty-related activations in both spatial and non-spatial RM (Kohler et al., 2005). Whether the novelty detection in RM differs from that of novelty responses in NRM, in which the items themselves are familiar, but not their spatial orientations, is unclear. Human lesion and neuroimaging studies focusing mainly on spatial localisation and navigation (Burgess et al., 2002; Maguire et al., 1998) have supported the idea of a dominant role of the HC in spatial compared to non-spatial processing consistent with the cognitive map theory (O'Keefe, 1999). However, studies of the sequelae of HC lesions in patients and with healthy humans (Eldridge et al., 2005; Ryan et al., 2008; Soei and Daum, 2008; Spiers et al., 2001) generally support the hypothesis of a more general role of the HC in RM (Eichenbaum, 2004), and assessment of the processes involved in spatial and non-spatial RM and spatially-based NRM may further clarify this issue.

To elucidate the issues of the potential dissociability of novelty detection in RM and NRM, ERPs associated with encoding and retrieval on distinct memory tasks were analysed in healthy subjects. Recollection-associated late old/new effects peak over parietal electrode sites at 400-800 ms, and familiarity-associated early old/new effect peak over frontal sites at 300-500 ms post-stimulus onset (Rugg and Curran, 2007). A study comparing recollection and familiarity during encoding and retrieval (Duarte et al., 2004) reported dissociable ERPs related to the different memory stages.
Presently, variants of memory tasks yielding HC and PHR neuroimaging activations associated with novelty detection were administered (Kohler et al., 2005). Analysis of the time course of ERP patterns and their neuronal generators related to RM and NRM should shed elucidate the issue of parallels and differences in the mechanisms underlying these memory processes.

Materials and Methods

Subjects

Fifteen healthy human subjects participated in the experiment. The data of two subjects were discarded because of a low number of artefact free trials in some response conditions, the results are thus based on 13 subjects (mean age=22.7 years, SD=4.7 years, six females). All subjects were right-handed and had normal or corrected to normal vision. All procedures were approved by the ethics committee of the Ruhr-University Bochum and all subjects gave written consent prior participation. The study conforms to the Code of Ethics of the World Medical Association (Declaration of Helsinki) (Rickham, 1964).

Stimuli and Material

Memory was assessed as reported previously ((Soei and Daum, 2008), based on a task described by Kohler et al. (2005)). The item pairs comprised 120 grey-level texture line drawings of objects against a white background. The stimuli were taken from a standardised database (Rossion and Pourtois, 2004). Prior piloting (with a different subject sample of n=12) ensured that half of those stimuli led to comparable behavioural performance when displayed from an inverted view as well as from left- and rightward mirrored views. Extending the procedure applied by (Soei and Daum, 2008), those 60 objects were allocated to the NRM task for each participant and the remainder to the RM task.

Assessment of relational and non-relational memory

Relational memory encoding phase (Figure 1a): For each subject, 60 objects were randomly paired to create the 30 study items. These 30 item pairs were presented in one of 15 distinct spatial configurations in an invisible 8 x 6 grid. Each spatial configuration was used twice in two different objects pairings allowing a change of object-object relationships without simultaneously altering object-location relationships. The subjects were instructed to memorise the object-object and object-
location relationships of each pair. Initially, the subjects were trained on examples of old and novel test items in the spatial and non-spatial conditions to help the subjects focusing on the relevant features. The stimulus presentation was as follows: The 30 items were presented in four blocks; each pair appeared once per block. Stimulus duration = 2000 ms, ISI = 3000 ms, and between-block interval = 30 s. Memory performance was assessed after the fourth repetition of the study blocks.

Relational memory retrieval phase (Figures 1b and b): 30 old, 15 spatially novel, and 15 non-spatially novel items were shown in random order. In old items, the spatial configuration and pairing of the two objects was identical to the one during the RM encoding phase (Figure 1a). In spatially novel items the spatial configurations were exchanged (Figure 1b), whereas non-spatially novel items involved new object pairs, with each object retaining its spatial location from the RM encoding phase (Figure 1b). Subjects had to indicate by button presses (second, third, and fourth finger of the right hand) whether an item was old, spatially novel, or non-spatially novel (the order of buttons was counterbalanced across subjects). Stimulus presentation was terminated upon the subject’s response, with a maximum of 3500 ms; ISI was randomly set at 2500, 3000 or 3500 ms.

Non-relational memory encoding phase (Figure 1d): 30 item pairs were presented at the central location of the screen. Subjects had to memorise the object-object-relationships and the views from which the objects were presented. Initially, the subjects were trained on examples of old, horizontally mirrored novel items, and inverted (vertically mirrored) novel items to help them attending to the relevant features. The stimulus presentation was identical to the RM encoding phase.

Non-relational memory retrieval phase (Figures 1e and f): 30 old, 15 horizontally mirrored novel items, and 15 inverted novel items appeared in random order. All items consisted of the identical object pairing and each object retained its spatial location from the NRM encoding phase. In old items, the spatial view of the objects was identical to the NRM encoding phase (Figure 1d). Horizontally mirrored novel items showed the objects horizontally flipped (Figure 1e), whereas inverted novel items showed the objects vertically flipped (Figure 1f). Subjects had to indicate by button presses whether an item was old, horizontally mirrored novel, or inverted novel (second, third, and fourth finger of the right hand) (the order of buttons was counterbalanced across subjects). The stimulus presentation was identical to the RM retrieval phase.
Figure 1

Schematic overview of the RM and NRM conditions (black and white background, respectively). 1a) Examples of original items from the encoding phase of the RM task which serve also as old items in the RM retrieval phase. 1b) Example of a spatially novel item in the RM retrieval phase. 1c) Example of a non-spatially novel item in the RM retrieval phase. 1d) Example of an original item the encoding phase of the NRM condition which serves also as an old item in the NRM retrieval phase. 1e) Example of a horizontally mirrored novel item in the NRM retrieval phase. 1f) Example of an inverted novel item in the NRM retrieval phase.

Taken together, successful RM required forming and recollecting object-location or object-object relationships between the separate spatial or non-spatial features of an item, while the spatial orientation of the individual object remained constant. Familiarity of the spatial orientation of the individual objects could thus not facilitate performance. Successful NRM (Figures 1d-f) did not require the memory of relations, as both the object-location and the object-object relationships were held constant. Instead, successful recognition could be achieved based on the familiarity of the spatial orientations of items. The NRM task was designed to tap into a merged representation of a single stimulus consisting of two object-features (Soei and Daum, 2008). The novel items in all tasks were systematically manipulated versions of previously encountered stimuli.

The order of the RM and NRM tasks was counterbalanced across subjects. To ensure sufficient trials in each response classification and to exclude guessing trials, the retrieval phase was repeated after the first retrieval phase (stimuli in randomised order), and only trials yielding consistent responses across both retrieval phases entered analysis. Following Snodgrass et al. (1988), the memory performance index Pr and the bias index Br of the Two-High-Threshold Model (Pr=hit rate - false alarm rate, and Br=false alarm rate/[1-(hit rate - false alarm rate)]) were determined to estimate memory performance. Stimuli and responses were processed using the Presentation software (Neurobehavioral Systems Inc, Albany, California, http://www.neurobs.com/), statistical analyses were performed using SPSS 15.0.
Data recording

Throughout the encoding and retrieval phases, the EEG was recorded from 30 scalp sites according to the International 10-20 system (F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, TP7, CP3, CPz, CP4, TP8, P7, P3, Pz, P4, P8, PO7, PO3, POz, PO4, PO8), referenced to linked mastoids. Silver-silver chloride electrodes were fixed using an elastic cap. Subjects were seated at a distance of 60 cm in front of a 21” computer monitor in a dark room. The electrooculogram (EOG) was recorded from electrodes below and above the left eye and at the outer canthi of both eyes. A Neuroscan Synamps System and the appropriate software were used for recording. All data were sampled at a rate of 500 Hz, the impedance was kept below 5 kΩ.

Procedure

Subjects were told that the study aimed to assess brain activity related to memory processes. After subjects had signed informed consent forms, the electrodes were attached. The subjects were given standardised written and verbal instructions and practiced the encoding and retrieval phases of both experimental tasks before the experiment started.

Analysis of encephalogram data

Following the procedure adopted by Bellebaum and Daum (2006), the data were analysed off-line using the Brain Vision Analyzer Software Package. The EEG and EOG raw data underwent filtering (low cut-off: 0.1 Hz, high cut-off: 40 Hz). Segments were created based on the response categories, covering 1500 ms after stimulus onset: 1) RM hits (to old items), 2) spatial RM correct rejections (CR), 3) non-spatial RM CR, 4) spatial and non-spatial RM CR, 5) NRM hits, 6) horizontally mirrored NRM CR, 7) inverted NRM CR, and 8) horizontally and inverted NRM CR. Additionally, segments relative to subsequent hits on RM and NRM during encoding were created, covering 1400 ms after stimulus onset. Local DC detrending was applied, and ocular artefacts were corrected (Gratton et al., 1983) based on horizontal and vertical EOGs. Trials with blink artefacts were excluded based on vertical EOGs. Trials with EEG-artefacts were excluded automatically when the maximal difference between the highest and lowest data point exceeded 150 µV at one or more electrode sites. Baseline correction was carried out relative to the 100 ms preceding stimulus onset. Specified global maxima were defined within automatic peak detection (for determination of the distinct time windows and polarity see Results). A minimum of 16
artefact-free trials were required from each subject for each response category for inclusion in analysis. The grand averages were created and exported for further analysis using SPSS. Following previous reports (Donaldson and Rugg, 1998; Hayama et al., 2008; Wilding and Rugg, 1996), consecutive time windows post stimulus onset (500-800 ms and 800-1100 ms in the retrieval phases; 500-800 ms and 800-1200 ms in the encoding phase) were selected for each subject for SPSS analysis.

Statistical analysis

Mean amplitudes in the time windows specified above entered repeated measures ANOVAs with the within-subject factors ANTPOST (F3, F4 vs. P3, P4), LEFTRIGHT (F3, P3 vs. F4, P4), and one of the following CONDITION categories: TASK (RM vs. NRM), RESPONSE (hits vs. CR), CRTYPE (spatial vs. non-spatial CR in RM, or horizontal vs. inverted CR in NRM). Data from the electrode sites F3, F4, P3, and P4 entered analyses. In accordance with Donaldson and Rugg (1998), only significant F values are shown and as interest lies solely in differences between the ERPs associated with each CONDITION category, only significant main effects of CONDITION are reported.

Analysis of low resolution brain electromagnetic tomography

Maximal ERP peaks entered LORETA (low resolution brain electromagnetic tomography) source analysis (Pascual-Marqui et al., 1994). While this method is clearly inferior to neuroimaging methods such as fMRI in terms of spatial resolution and the capacity to provide exact neuroanatomical localisations, multi-channel EEGs contain sufficient information to determine an estimation of the source distribution. For all 13 subjects, LORETA-images were generated for the peaks of ERP components specified above. The images were converted (http://www.ihb.spb.ru/~petlab/L2S/L2SMain.htm) and further analysed using SPM99 (http://www.fil.ion.ucl.ac.uk/spm/), following the procedure adopted by Polezzi et al. (2008). The level of significance was set to p=0.01, unless specified differently. The coordinates of the foci of significant differences between conditions were transformed into Talairach coordinates using an appropriate algorithm (http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml). The Talairach Daemon was then used to identify the brain structures involved (Lancaster et al., 2000).
Results

Behavioural analysis

For behavioural performance, repeated measures ANOVAs with factors TASK and RESPONSE were performed on response frequency and RTs (Table 1 for means and SEMs). There were significantly more hits and CRs on RM relative to NRM ($F(1,12)=17.29, p=0.001$), and more hits than CRs regardless of the task ($F(1,12)=32.67, p<0.001$). The TASK X RESPONSE interaction was significant ($F(1,12)=18.77, p=0.001$), as hits and CRs did not differ significantly in RM, while the difference was significant for NRM. RTs were slower in RM compared to NRM ($F(1,12)=56.22, p<0.001$), and faster for hits compared to CRs ($F(1,12)=46.93, p<0.001$). The interaction did not reach significance ($p=0.077$). The subjects had neutral response biases in both memory conditions, which did not differ significantly ($p=0.41$).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Hits</th>
<th>CRs</th>
<th>Hit RT</th>
<th>CR RT</th>
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<tr>
<td></td>
<td>M (SEM)</td>
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<td>M (SEM)</td>
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<td>M (SEM)</td>
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<tr>
<td><strong>Relational memory</strong></td>
<td>56.4 (0.7)</td>
<td>54.3 (1.1)</td>
<td>1438.8 (58.0)</td>
<td>1747.4 (45.9)</td>
<td>0.5 (0.1)</td>
</tr>
<tr>
<td><strong>Non-relational memory</strong></td>
<td>55.1 (0.9)</td>
<td>48.5 (1.2)</td>
<td>1236.1 (73.9)</td>
<td>1404.7 (57.7)</td>
<td>0.5 (0.0)</td>
</tr>
</tbody>
</table>

Table 1 lists the means and SEMs of hits, CRs, Hit RT, CR RT, and Br for RM and NRM.

ERPs of hits vs. CR during RM and NRM retrieval

Mean number of trials (SD) contributing to the grand averages were 55.0 RM hits (3.27), 24.38 spatial RM CRs (4.89), 26.69 non-spatial RM CRs (3.25), 51.08 RM CRs (4.86), 52.85 NRM hits (4.58), 19.77 horizontal NRM CRs (4.30), 25.0 inverted NRM CRs (4.04), and 44.62 NRM CRs (5.58).

Figure 2a illustrates the ERPs for hits and CRs from the electrode sites F3, F4, P3, and P4. The ERPs for the time windows 500-800 ms post-stimulus entered repeated measures ANOVAs with the following factors: LEFTRIGHT, ANTPOST, TASK, and RESPONSE. ERPs related to RM and NRM were dissociable, as the factor TASK was significant ($F(1,12)=59.44, p<0.001$). The direction of old/new effects depended on the TASK type, as the interaction TASK X RESPONSE was significant ($F(1,12)=15.65, p=0.002$). Post-hoc paired samples t-tests, with the factors averaged
PART 3: ARTICLES

Study 2

across the four electrode sites, yielded the following significant differences:

Comparison of RM vs. NRM CRs \((T(12)=-8.14, p<0.001)\) led to a stronger dissociation than the one of RM vs. NRM hits \((T(12)=-3.33, p=0.006)\). Comparison of NRM hits vs. CRs \((T(12)=-3.21, p=0.007)\) yielded a stronger dissociation in opposite direction compared to RM hits vs. CRs \((T(12)=2.63, p=0.022)\).

The ERPs for the time windows 800-1100 ms underwent the same analysis and led to comparable results: TASK \((F(1,12)=7.32, p=0.019)\), and TASK X RESPONSE \((F(1,12)=12.69, p=0.004)\). Post-hoc comparisons: RM vs. NRM CRs \((T(12)=-4.47, p=0.001)\), RM vs. NRM hits (unlike in the 500-800 ms time window not significantly different \(p=0.76\)), NRM hits vs. CRs \((T(12)=-5.29, p<0.001)\), and RM hits vs. CRs \((T(12)=2.17, p=0.051)\).

Maximal ERP peaks entered LORETA source analysis (Figure 2b). Peaks were defined as follows: the early old/new effect (300-500 ms, negative polarity), and the late old/new effect (500-800 ms, positive polarity), as they are linked to familiarity-driven recognition and recollection of specific information (Rugg and Curran, 2007). The significant difference between the RM and NRM for the early old/new effect was driven by the contrast NRM > RM, yielding sources in the right-sided superior temporal gyrus \((p=0.005, BA 22, [X,Y,Z]=66,-44,16)\). The significant difference between the RM and NRM for the late old/new effect was driven by the contrast NRM > RM, yielding a right-sided source in the inferior temporal gyrus \((p=0.01, BA 20, [X,Y,Z]=45, -19, -28)\).
Figure 2a shows the ERPs for RM hits (black bold line) vs. RM CRs (black dotted line) vs. NRM hits (grey bold line) vs. NRM CRs (grey dotted line) during retrieval for the electrode sites F3, F4, P3, and P4. Figure 2b illustrates the LORETA sources for the early old/new effect (contrast NRM > RM, right-sided superior temporal gyrus), and late old/new effect (contrast NRM > RM, right-sided inferior temporal gyrus).
ERPs related to novelty detection during retrieval of RM and NRM

In a separate analysis, different types of novelty detection were explored. As the categorisation spatial vs. non-spatial CR in RM does not directly correspond to horizontal vs. inverted CR in NRM, separate ANOVAs were performed for RM and NRM. Figure 3 illustrates the ERP for CRs of novel items in spatial and non-spatial RM from sites F3, F4, P3, and P4. ERPs for the time windows 500-800 ms and 800-1100 ms post-stimulus entered repeated measures ANOVAs with the following factors: LEFTRIGHT, ANTPOST, TASK, and CRTYPE. The ERPs related to novelty detection in spatial and non-spatial RM did not differ significantly in either time windows (\(F(1,12)=0.001, p=0.98\) and \(F(1,12)=3.68, p=0.08\)).

Figure 3
Figure 3 shows the ERPs for spatial RM CRs (black line) and non-spatial RM CRs (grey line) during retrieval for the electrode sites F3, F4, P3, and P4.

Figure 4a illustrates the ERP for CRs of novel items in horizontal and inverted NRM from sites F3, F4, P3, and P4. ERPs for the time windows 500-800 ms and 800-1100 ms post-stimulus entered repeated measures ANOVAs with factors LEFTRIGHT, ANTPOST, TASK, and CRTYPE. The ERPs related to novelty detection in horizontal and inverted RM were significantly different in the earlier time window ($F(1,12)=27.35$, $p<0.001$ and $F(1,12)=3.68$, $p=0.08$), but not in the later window ($p=0.09$).

Maximal ERP peaks entered LORETA source analysis (Figure 4b). Peaks were defined as follows: the P3a effect (200-350 ms, positive polarity), as it is linked to novelty-driven responses (Ranganath and Rainer, 2003). The P3a effect within NRM was driven by the contrast inverted > horizontal CRs, yielding left-sided activations in the inferior frontal, and superior frontal gyrus (both $p=0.001$, BA 47, 11, [$X,Y,Z$]= -17,23,-18; and -17,50,-19).
Figure 4 shows the ERPs for horizontal (black dotted line) and inverted (grey dotted) CRs in NRM during retrieval for the electrode sites F3, F4, P3, and P4. Figure 4b illustrates the LORETA sources for the P3a effects in the contrasts inverted NRM CR > horizontal NRM CR (left-sided inferior and superior frontal gyrus).
Subsequent memory effects: Event-related potentials during encoding to subsequent hits in relational and non-relational memory

The mean number of trials (SD) contributing to the grand averages were 108.54 subsequent hits during RM encoding (16.23), and 100.92 subsequent hits during NRM encoding (19.75).

Figure 5a depicts the grand averages for subsequent in the RM and NRM tasks from the electrode sites F3, F4, P3, and P4. The ERPs for the time windows 500-800 ms and 800-1200 ms post-stimulus, respectively, entered repeated measures ANOVAs with the following factors: ANTPOST, LERFTRIGHT, and TASK. The TASK main effect was significant in both time windows ($F(1,12)=59.19, p<0.001$, $F(1,12)=23.81, p<0.001$, and $F(1,12)=48.71, p<0.001$).

Maximal peaks entered LORETA source analysis (Figure 5b). Peaks were defined as follows: the positive peak (PE) (300-400 ms, positive polarity), and the negative peak (NE) (250-350 ms, negative polarity). The contrast PE, with NRM > RM, yielded a source in the right-sided fusiform gyrus ($p=0.003$, BA 20, [X,Y,Z]=46,-25,-21]). The contrast NE, with NRM > RM, yielded a source in the left-sided middle temporal gyrus ($p<0.001$, BA 39, [X,Y,Z]=−51,-71,17]).
Figure 5a shows the ERPs for subsequent hits in RM (black dotted line) vs. NRM (grey dotted line) during encoding for the electrode sites F3, F4, P3, and P4. Figure 5b illustrates the LORETA sources for the PE effect (right-sided fusiform gyrus) and NE effect (left-sided middle temporal gyrus).
Discussion

*Behavioural results*

Memory accuracy was poorer on the NRM relative to the RM task, suggesting between-task differences in difficulty which would necessitate a cautious interpretation of the results. The electrophysiological findings are, however, not likely to be due to difficulty effects, since the absolute numbers of hits and CRs were high and the number of misses was low in both conditions (RM performance index $P_r=0.86$ with $SD=0.02$, and NRM $P_r=0.78$ with $SD=0.03$). Importantly, the neutral response biases did not differ between the RM and NRM conditions. Furthermore, the faster RTs on hits relative to CRs on both RM and NRM is consistent with Donaldson & Rugg (1998). Not surprisingly, the subjects responded significantly faster in NRM compared to RM. This effect is presumably linked to lower spatial search time, as the objects were displayed at central positions and not located at unexpected spatial locations.

*Event-related potentials during retrieval*

The current results offer support to the idea of dissociable neuronal mechanisms for RM and NRM (Eichenbaum *et al.*, 2007). ERPs related to RM and NRM in the 500-800 ms and 800-1100 ms time windows were dissociable with respect to both hits and CRs, with CRs yielding a stronger dissociation than hits. This is in line with fMRI studies showing differential HC vs. PRC/anterior PHC activations associated with the two types of memory (Kohler *et al.*, 2005; Ranganath *et al.*, 2004; Yonelinas, 2002; Yonelinas *et al.*, 2005) and studies reporting dissociability of ERPs elicited by RM and NRM (Duarte *et al.*, 2004; Rugg and Curran, 2007; Woodruff *et al.*, 2006).

A related issue concerned the old/new effects which reflect processing differences between hits and CRs, and the strength and direction of their effects depended on whether the task tapped NRM or RM. On the one hand, the early old/new effect (time window 300-500 ms) is in opposite direction of the previously reported familiarity-associated old/new effect (Rugg and Curran, 2007). The condition of inverted novel items in NRM has not been used in previous studies which were based on similar tasks (Kohler *et al.*, 2005; Soei and Daum, 2008). It is possible, despite the prior piloting of the stimulus material, that the inverted novel items in NRM did not induce a familiarity-related effect in the contrast hits vs. CRs, overshadowing the familiarity-related effect of horizontal novel item relative to original ones. Consistent with this hypothesis, the mean numbers of trials (SD) contributing to the grand averages of the horizontal and inverted NRM CRs differed: 19.77 (4.30), and 25.00 (4.04), respectively. For comparison, the means (SD) for spatial and non-spatial RM were as follows: 24.38 (4.89) and 26.69 (3.25). Seemingly, the CRs to inverted
mirrored NRM items may have been more comparable in absolute terms to the spatial and non-spatial RM CRs. However, the mean RTs (SD) of the spatial RM, non-spatial RM and horizontal NRM CRs were comparable: 1746.31 ms (202.83), 1748.44 ms (105.03), and 1643.26 ms (256.68), respectively. Thus, the lower number of horizontal NRM CRs might reflect the perceived higher difficulty (Soei and Daum, 2008). Additionally, the mean RT (SD) of the inverted NRM CRs was significantly shorter: 1166.10 ms (198.19). More probably, the inverted item view classification was only partly accomplished by mental rotation and comparison of the displayed spatial orientations with the to-be-remembered original ones: in the time window 500-1100 ms post-stimulus (Figure 4a), the ERPs of inverted NRM CRs, as compared to the horizontal ones, had high positive amplitudes. Thus, in some trials, inverted NRM CRs may have been based on the faster classification upright vs. inverse displayed items and was therefore not solely based on the familiarity of the spatial orientations of the items. This is consistent with the shorter RTs of inverted CRs, and also with the sources found for the novelty-related P3a effect (200-350 ms post-stimulus) in NRM (see below). The early old/new effect was driven by the contrast NRM > RM, yielding sources in the right-sided superior temporal gyrus. The activity of the superior temporal gyri has been shown to be positively correlated with strength of familiarity (Montaldi et al., 2006) and to be person voice familiarity-related (Shah et al., 2001). However, the issue of a possible non-familiarity-related effect through the inversion in the NRM condition limits the interpretation of the ERP differences in terms of familiarity. Hits cannot be compared with horizontal CRs alone due to highly unequal cell sizes.

The late old/new effect (time window 500-800 ms) replicated the frequently reported recollection-associated old/new effect in terms of direction and amplitudes (Donaldson and Rugg, 1998; Friedman and Johnson, Jr., 2000; Johnson et al., 2008; Paller et al., 1999; Rugg and Curran, 2007). Surprisingly, this significant late old/new effect was not linked to the contrast RM > NRM, but to the NRM > RM contrast, yielding a right-sided source in the inferior temporal gyrus. Familiarity has been associated with activity in the inferior temporal gyrus via electrophysiological studies in the non-human primate (Fahy et al., 1993; Li et al., 1993; Xiang and Brown, 1998). A subsequent familiarity effect, as indexed by verbal recognition confidence, has been reported for the left-sided inferior temporal gyrus (Ranganath et al., 2003). Its activity has also been shown to decrease with familiarity confidence in a verbal recognition memory task (Yonelinas et al., 2005). The non-verbal material and the predominantly spatial demands (e.g. mental imagery of the swapped locations, mentally recombination, and rotation of the spatial orientations of the objects) in the current study have possibly yielded a right-sided source of the inferior temporal gyrus.
A further issue of interest was the effect of novelty type on ERPs during retrieval. The current results yielded a dissociability of distractor types in novelty detection in NRM but not in RM. ERPs related to CRs of horizontal and inverted novel items in NRM were significantly different in the earlier time window and point to distinct neuronal mechanisms underlying novelty detection within NRM as assessed in the current task. Thus, the novelty-related P3a effect (200-350 ms, positive polarity) (Squires et al., 1975) was examined, which is thought to originate from stimulus-driven frontal attention mechanisms during task processing related to detection and rapid orientation to novel events and stimuli (Polich, 2007; Ranganath and Rainer, 2003; Soltani and Knight, 2000). Congruent with this idea, the P3a effect within NRM was driven by the contrast inverted > horizontal NRM CRs, yielding left-sided activations in the inferior frontal, and superior frontal gyrus. Distinguishing between two-dimensional horizontal i.e. upright and inverted item views has presumably necessitated mental rotation of the spatial orientations of the original items in a screen plain. Three-dimensional mental rotation has been associated with activation changes of the bilateral inferior frontal (Hugdahl et al., 2006) and left-sided superior frontal gyrus (Vingerhoets et al., 2001). Two-dimensional mental rotation, in contrast, has been associated with right-sided superior parietal lobe activation changes (Kawamichi et al., 2007). This apparent discrepancy suggests that inverted NRM CRs may have been based more on the faster i.e. earlier classification upright vs. inverse displayed items and less on the familiarity of the spatial orientations of the items. Thus, the novelty-related P3a could have been linked to the contrast inverted vs. horizontal i.e. upright, eliciting stimulus-driven frontal attention mechanisms during task processing related to detection and rapid orientation to unexpected inverse displayed novel items relative to expected upright ones. The shorter RTs of inverted CRs is in good agreement with the early latency of the P3a effect in the current study corroborating the idea that these inverted novel items may have rapidly modulated cognitive processing (Ranganath and Rainer, 2003).

ERPs related to CRs of spatial vs. non-spatial novel items in RM did not differ significantly, adding some support to the idea of a common mediator of spatial and non-spatial RM (Cohen et al., 1997; Eichenbaum et al., 1999; Eichenbaum, 2004). Support stems from reports of hippocampal lesions in humans (Eldridge et al., 2005; Kumaran et al., 2007; Ryan et al., 2008; Spiers et al., 2001) and an ageing study with healthy human participants (Soei and Daum, 2008).

A subsidiary issue of interest related to the dissociability of the RM and NRM subsequent memory effects during encoding, which was clearly supported by the
current findings. However, while the differential effect for RM vs. NRM as such is consistent with a previous study (Duarte et al., 2004), the direction of the effects differed. This is most likely related to differences in the experimental procedures as the ERPs subsequent to “Remember” and “Know” responses were retrieved within one block (Duarte et al., 2004), while the current data are recorded from two separate tasks. The NRM>RM contrast for PE (time window 300-400 ms) yielded a source in the right-sided fusiform gyrus. Encoding-related activity in the right-sided fusiform gyrus has been associated with specific/detailed object memory (Garoff et al., 2005; Kelley et al., 1998). The NRM>RM contrast for NE (time window 250-350 ms) yielded a source in the left-sided middle temporal gyrus. This is consistent with previous reports of N400 correlates during word encoding in the left middle temporal gyrus (Elger et al., 1997; Mangels et al., 2001). In an fMRI study, increased activity in the left-sided middle temporal gyrus has also been associated with subsequent word recognition success (Reber et al., 2002). These findings of dissociable ERPs for subsequent hits would also add further support to the idea of dissociable neuronal networks for RM and NRM (Eichenbaum et al., 2007).

Conclusion

The current study assessed the neurophysiological correlates of novelty detection in spatial vs. non-spatial RM and NRM. The main findings are as follows. Firstly, the ERPs related to RM and NRM were dissociable for both hits and CRs in early and late time windows. Secondly, the early old/new effect for NRM was in opposite direction to the previously reported familiarity-associated old/new effect. The late old/new effect replicated the previously described recollection-associated old/new effect in terms of direction and amplitudes. Thirdly, the ERPs related to spatial vs. non-spatial RM novelty detection did not differ from each other. In contrast, the ERPs related to horizontal vs. inverted NRM novelty detection were clearly dissociable. Fourthly, the ERP correlates of the subsequent memory effect were dissociable for RM and NRM, yielding further support for dissociable memory mechanisms.
3.3 Study 3: Soei, Koch, Schwarz and Daum (in press, EJN). Involvement of the human thalamus in relational and non-relational memory.

I contributed to this article in the same manner as in the first study (Soei and Daum, 2008). Dr. Benno Koch and Prof. Dr. Michael Schwarz provided the patient referral and lesion diagnostic based on their scans. Prof. Dr. Irene Daum supervised the project and corrected the drafts of the article. Sabine Bierstedt helped me with the figure preparation.
Involvement of the human thalamus in relational and non-relational memory

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Abstract

Damage of the human thalamus has been associated with selective anterograde declarative memory impairments. In recent views, declarative memory has been subdivided into RM and NRM. The aim of the present study was to assess the potentially differential involvement of the human thalamus in RM and NRM. Ten patients with focal ischemic thalamic lesions were compared to individualised control groups of healthy subjects matched to each individual patient on age and IQ. Six patients showed poorer RM than their respective control samples. None of the ten patients showed a significant deficit on the NRM task. These observations suggest an involvement of the thalamus in RM and are discussed in terms of disruption of mediotemporal-thalamic and thalamic-fronto-striatal circuits.
Human thalamic lesions were associated with impaired anterograde memory and executive dysfunctions without further cognitive deficits (Bentivoglio et al., 1997; Carrera and Bogousslavsky, 2006; Daum and Ackermann, 1994a; 1994b; Parkin et al., 1994; Van Der Werf et al., 2003a; Van Der Werf et al., 2003b; Zoppelt et al., 2003). These deficits resembled those after lesions of the prefrontal cortex (PFC) (Shimamura, 1995), and the mediotemporal lobe (MTL) (Squire et al., 2004).

Memory can be subdivided into recollection, linked to relational memory (RM) as event features are associated together within a spatiotemporal context, and familiarity, linked to non-relational memory (NRM) without contextual reference (Yonelinas, 2002). Within the MTL, the perirhinal cortex (PRC) and hippocampus (HC) may mediate NRM and RM, respectively (Eichenbaum et al., 2007), but questions were raised (Squire et al., 2007). Further, the HC may process both spatial and non-spatial RM (Eichenbaum, 2004). The resemblance of impairment following thalamic and MTL damage concurs with the disconnection of the projections between the thalamus and the MTL (Saunders et al., 2005). Specifically, a related model extended the PRC to the mediodorsal thalamic nuclei (MD), with both being critical in NRM (Aggleton and Brown, 1999). In addition to the MTL, the PFC may also be involved in RM (Henson et al., 1999), supporting the strategic encoding and retrieval of contextual details (Squire, 1994; Squire and Zola, 1998). In non-human primates, the dorsolateral PFC (DLPFC) is connected to the lateral MD (Goldman-Rakic and Porrino, 1985), and both areas showed spatial coding properties (Funahashi et al., 2004; Tanibuchi and Goldman-Rakic, 2003). The orbitofrontal cortex (OFC), receiving projections from the medial MD (Cavada et al., 1995), has been associated with visual memory formation (Frey and Petrides, 2000; 2002) and specifically with spatial RM (Baxter et al., 2007). Thus, the similarity of the deficits after thalamic and PFC lesions may be linked to disruption of MD-PFC-striatal circuits (Alexander et al., 1986).

Single cases comparing RM vs. NRM yielded a complex pattern of impaired RM and preserved NRM after dorsolateral thalamic and MD damage (Edelstyn et al., 2006), and deficits in RM and NRM after an anterior thalamic and MD lesion (Kishiyama et al., 2005). A group study of with damage suggested an MD contribution to RM, and a possible involvement of the medial MD to NRM (Zoppelt et al., 2003). Recently, a patient with intact MD had impaired NRM, while another patient with MD damage had deficient RM (Cipolotti et al., 2008).

To examine the role of the thalamus, patients with selective thalamic lesions were compared to individualised healthy control groups on spatial and non-spatial RM as well as NRM (based on Kohler et al., 2005). Another issue of interest was whether...
lesion location within the thalamus (i.e. involvement of MD) would be associated with different profiles of memory impairments. Disruption of the PRC-MD projections might be associated with disproportionate NRM deficits (Aggleton and Brown, 1999), while disruption of MD-PFC-striatal circuits might be linked to disproportionate spatial RM impairments. Disruptions of non-MD regions are expected to spare RM and NRM.

Materials and Methods

Patients and healthy controls

Ten patients with focal ischemic lesions (nine unilateral and one bilateral) in the MD or ventrolateral thalamic nuclei (VL) and a sample of 63 healthy control participants participated in this study: On a group level, the patients and 10 age-, sex- and IQ-matched controls were compared on the RM and NRM tasks and an extended neuropsychological screening battery (see below). In addition, each patient was individually compared to 15 or 16 age- and IQ-matched participants on RM and NRM (see Table 1 for the allocation of each patient to individualised control samples).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=15)</th>
<th>Group 2 (n=16)</th>
<th>Group 3 (n=16)</th>
<th>Group 4 (n=16)</th>
<th>Group 5 (n=16)</th>
<th>Group 6 (n=15)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>IQ</td>
<td>Age</td>
<td>IQ</td>
<td>Age</td>
<td>IQ</td>
<td>Age</td>
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<tr>
<td>M</td>
<td>106.87</td>
<td>59.93</td>
<td>112.84</td>
<td>52.50</td>
<td>111.40</td>
<td>45.81</td>
</tr>
<tr>
<td>SD</td>
<td>8.57</td>
<td>6.95</td>
<td>4.68</td>
<td>5.11</td>
<td>5.22</td>
<td>6.77</td>
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<tr>
<td>T1</td>
<td></td>
<td></td>
<td>118.5</td>
<td>55</td>
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<tr>
<td>T2</td>
<td></td>
<td></td>
<td>116</td>
<td>56</td>
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<td></td>
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<tr>
<td>T3</td>
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<td>T4</td>
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<td>T6</td>
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<td>T8</td>
<td>90</td>
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<td>T9</td>
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<td>T10</td>
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</tbody>
</table>

Table 1 shows the allocation of each of the ten patients to their individualised healthy control samples (n=15-16) based on IQ and age. T1, T2, T3, and T4 are medial MD patients. T5 and T6 are lateral MD patients. T7, T8, T9, and T10 are VL patients.

Healthy control participants were selected from a large pool of volunteers recruited by advertisement and private contact at the Department of Neuropsychology to match the patients as a group. All participants gave written informed consent to take
part in the study. The study was conducted according to the requirements of the local ethics committee. The study conforms to the Code of Ethics of the World Medical Association (Declaration of Helsinki) (Rickham, 1964). Exclusion criteria for the healthy participants were a history of psychiatric, neurological, head trauma or substance abuse, a Mini-Mental Status Test Score < 27, a Beck Depression Inventory score > 15, and misunderstanding of task instructions as assessed in post-memory task interviews or abnormally long RTs (>2500 ms, longest RT of a patient=2295 ms).

All patients (six females, age range = 27-73 years, one left-handed) were outpatients of the Department of Neurology of the Klinikum Dortmund. Thalamic lesions were documented with MRI via a standard three-dimensional T1-weighted sequence for coronal sections and a standard three-dimensional T2-weighted sequence for transverse sections (1 mm x 5mm x 5 mm voxel size). Based on the visual analysis of each section obtained in neuroradiological assessment, the affected thalamic nuclei were determined for each individual patient by two experienced neurologists (M. S. and B.K) using recent atlases (Mai et al., 2004; Morel, 2007) in accordance with the procedure adopted in previous studies of focal subcortical lesions [Bellebaum et al. 2005; 2006; 2008]. Each section was also visually inspected for extra-thalamic damage. The mean lesion-test interval (in months) between lesion onset and memory assessment was 78.2 months (SD=37.4). All patients were tested in the post-acute stage, with a minimum lesion-test interval of 11 months. None of the patients had a history of psychiatric problems. Figure 1 illustrates transverse and coronal MRI sections, laterality of lesions, affected thalamic nuclei, affected extra-thalamic areas, and lesion-test intervals (in months) for the ten patients.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Transverse MRI image</th>
<th>Coronal MRI image</th>
<th>Diagnostic</th>
</tr>
</thead>
</table>
| T1      | ![MRI Image](image1.png) | ![MRI Image](image2.png) | Laterality of lesion: B  
Affected thalamic nuclei: Medial MD  
Affected extra-thalamic area: None  
Lesion-test interval: 67 |
| T2      | ![MRI Image](image3.png) | ![MRI Image](image4.png) | Laterality of lesion: L  
Affected thalamic nuclei: Medial MD  
Affected extra-thalamic area: None  
Lesion-test interval: 78 |
| T3      | ![MRI Image](image5.png) | ![MRI Image](image6.png) | Laterality of lesion: L  
Affected thalamic nuclei: Medial MD  
Affected extra-thalamic area: None  
Lesion-test interval: 122 |
| T4      | ![MRI Image](image7.png) | ![MRI Image](image8.png) | Laterality of lesion: R  
Affected thalamic nuclei: Medial MD  
Affected extra-thalamic area: None  
Lesion-test interval: 25 |
| T5      | ![MRI Image](image9.png) | ![MRI Image](image10.png) | Laterality of lesion: L  
Affected thalamic nuclei: Medial and lateral MD  
Affected extra-thalamic area: None  
Lesion-test interval: 14 |

Figure 1 (to be continued on page 80)
Figure 1 shows the transverse and coronal MRI sections, laterality of lesions, affected thalamic nuclei, affected extra-thalamic areas, and lesion-test interval in months for the ten patients.
Neuropsychological screening

Several neuropsychological screening tasks were administered to all participants. General intellectual ability was estimated by the subtests Picture Completion and Similarities from the short German version of the Wechsler Adult Intelligence Scales (Dahl, 1972). Verbal and non-verbal short-term and working memory was assessed by the digit and block span tests of the Wechsler Memory Scale-Revised (Wechsler, 1987).

The ten patients and their matched ten control participants also completed further tasks. Visuoconstructive ability and nonverbal long-term memory were examined by copy and free recall of a complex geometrical figure after a delay of 30 min (Osterrieth, 1944). Verbal memory was assessed by immediate and delayed recall (after 30 min) of a prose passage (Wilson et al., 1989). Verbal fluency was examined by asking the subject to produce as many exemplars as possible within one minute for a phonemic category, a semantic category and for a condition which required alternation between two semantic categories (Daum et al., 1994).

Assessment of relational and non-relational memory

Recognition memory was assessed using a procedure described previously ((Soei and Daum, 2008) which was based on tasks initially used by Kohler et al. (2005)). The stimulus pairs consisted of 144 grey-level texture line drawings of objects displayed on a white background. The stimuli were taken from a database (standardised according to naming agreement, familiarity, complexity and imagery judgements) (Rossion and Pourtois, 2004). For each participant, 72 objects were randomly allocated to the RM task and the remaining ones to the NRM tasks.

Figure 2
Figure 2 shows the schematic overview of the tasks for spatial and non-spatial RM (black background) and NRM (white background). 2A) Examples of original study items in spatial and non-spatial RM that serve also as old items in both spatial and non-spatial RM tests. 2B) Example of a novel item in spatial RM test. 2C) Example of a novel item in non-spatial RM test. 2D) Example of an original item from the study phase of the NRM task that serves also as an old item in NRM test. 2E) Example of a novel item in NRM test.

Relational memory

Study phase relational memory (see Figure 2A): For each participant, 72 objects were randomly paired to create the 36 study items. These 36 item pairs were presented in one of 18 distinct spatial layouts in an invisible 8 x 6 grid. Each spatial layout was used twice in two different objects pairings, which allowed changing the object-object relationships without simultaneously altering the object-location relationships. The participants were asked to memorise the object-object and object-location relationships of each pair and they were initially presented with examples of old and novel test items in the spatial and non-spatial conditions to help them focus on the relevant features. The stimulus presentation was as follows: The 30 items were presented in four blocks; each pair appeared once per block. Stimulus duration = 2000 ms, ISI = 3000 ms, and between-block interval = 30 s. Memory performance was assessed after the fourth repetition of the study blocks.

Test phase of spatial relational memory (Figure 2B): 36 old and 18 novel items were shown in random order. Old and new items involved the same object pairs. In old items, the spatial configuration of the two objects was identical to the one during the study phase RM; in novel items they were exchanged. The stimulus presentation was as follows: stimulus duration = 2500 ms, ISI = 3000 ms.

Test phase of non-spatial relational memory (Figure 2C): The 36 old and 18 new items were randomly displayed. All items retained the original locations on the screen from the study phase RM, but they altered with respect to non-spatial pairing: Old items contained the same object pairs as during study, whereas novel items involved new object pairings, with each object keeping its spatial location from the study phase. The stimulus presentation was identical to the one in the test phase of spatial RM.

Non-relational memory

Study phase non-relational memory (see Figure 2D): 36 item pairs were shown centrally on the screen. Participants were asked to memorise the object-object-relationships and the views from which the objects were presented. They were shown examples of old and novel test items, to instruct them to attend to the relevant features. The stimulus presentation was identical to the one in the study phase RM.

Test of non-relational memory (Figure 2E): The 36 old and 18 new items were randomly displayed. All object pairs were presented at the same location as during the
study phase RM. Old items retained the original view from which the objects were shown. In novel items, the objects were displayed from a different view. The stimulus presentation was identical to the one in the test of spatial RM.

Taken together, in the RM tasks (Figures 2A-C) successful recognition required the formation and recollection of object-location or object-object relationships between the separate spatial or non-spatial components of an item, while the spatial orientation of the individual object remained constant. Familiarity of the spatial orientation of the individual objects could thus not facilitate performance. In the NRM task (Figures 2D-E), successful recognition did not require the memory of relations, as both the object-location and the object-object relationships were held constant. Instead, recognition success could be accomplished based on the familiarity of the spatial orientations of items. The NRM procedure aimed to tap into a merged representation of a single stimulus consisting of two object-features (see Soei and Daum, 2008). In all tasks, all novel items were systematically changed versions of previously encountered stimuli.

The order of the NRM and RM tasks was counterbalanced across participants. There was only one study phase for the two RM tasks (Kohler et al., 2005; Soei and Daum, 2008), and the order of the spatial and non-spatial recognition memory tests was counterbalanced. In all three tests, participants had to indicate by button-presses whether an item was old or new. Hits, false alarms and RTs were recorded. The memory performance index \( P_r \) and the bias index \( B_r \) of the Two-High-Threshold Model (\( P_r = \text{hit rate} - \text{false alarm rate} \), and \( B_r = \text{false alarm rate}/[1-(\text{hit rate} - \text{false alarm rate})] \)) were calculated to estimate memory performance on each task. The Two-High-Threshold Model with the indices \( P_r \) and \( B_r \) as dependent measures was chosen since the discrimination parameters are as sensitive as those of signal-detection theory but the bias assessment has advantages compared to signal-detection theory (Snodgrass and Corwin, 1988).

Following an established statistical testing procedure for single-case analysis (Crawford and Garthwaite, 2005), the mean and standard deviation of the individualised control groups were treated as sample statistics. The \( t \) distributions (with \( n-1 \) df) were then used to estimate the deviation of the patient score relative to his/her control sample. Two-tailed probability is used throughout. For descriptive purposes, \( z \)-scores are reported and illustrated in the figures. The single-case statistics were calculated using a program accompanying the description of the method by Crawford and Garthwaite (2005). To control for multiple testing, the significance threshold (0.05)
was divided by three (i.e. the number of recognition memory tests in each subject),
corresponding to a threshold z-score of -2.13 and 2.13.

Stimuli and responses were displayed, collected and analysed using the
Presentation software (Neurobehavorial Systems Inc, Albany, California,
http://www.neurobs.com/), and statistical analyses were performed using SPSS 15.0.

Results

Group comparisons

Neuropsychological screening

As shown in Table 2, the two groups (both n=10) did not differ significantly on
the following variables: age, years of education, visuoconstructive ability, estimate of
general intellectual ability, verbal and nonverbal short-term and working memory,
immediate story recall and verbal fluency in phonemic and semantic categories (all
p>0.083). The patient group was, however, impaired relative to the control group on
nonverbal delayed recall (F(1,18)=63.80, p<0.0001), verbal delayed recall
(F(1,18)=6.33, p=0.022), and verbal fluency when alternating between two categories
(F(1,18)=5.43, p=0.032).

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=10)</th>
<th>Patients (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52.10 (3.79)</td>
<td>54.60 (4.03)</td>
</tr>
<tr>
<td>Years of education</td>
<td>10.30 (0.77)</td>
<td>10.00 (0.58)</td>
</tr>
<tr>
<td>General intellectual ability</td>
<td>105.85 (1.67)</td>
<td>106.65 (3.36)</td>
</tr>
<tr>
<td>Digit spans forward</td>
<td>6.80 (0.55)</td>
<td>6.70 (0.65)</td>
</tr>
<tr>
<td>Digit spans backward</td>
<td>6.70 (0.54)</td>
<td>5.70 (0.63)</td>
</tr>
<tr>
<td>Block spans forward</td>
<td>7.90 (0.62)</td>
<td>7.70 (0.40)</td>
</tr>
<tr>
<td>Block spans backward</td>
<td>7.50 (0.50)</td>
<td>7.10 (0.72)</td>
</tr>
<tr>
<td>Phonemic fluency</td>
<td>13.90 (2.20)</td>
<td>10.80 (1.22)</td>
</tr>
<tr>
<td>Alternating fluency*</td>
<td>14.80 (1.65)</td>
<td>10.00 (1.23)</td>
</tr>
<tr>
<td>Semantic fluency</td>
<td>15.20 (1.36)</td>
<td>11.40 (1.56)</td>
</tr>
<tr>
<td>Immediate story recall</td>
<td>8.65 (1.08)</td>
<td>8.10 (0.72)</td>
</tr>
<tr>
<td>Delayed story recall*</td>
<td>8.45 (1.10)</td>
<td>5.50 (0.40)</td>
</tr>
<tr>
<td>Figure Copy</td>
<td>35.70 (0.21)</td>
<td>34.35 (0.74)</td>
</tr>
<tr>
<td>Figure delayed recall*</td>
<td>28.10 (1.25)</td>
<td>11.25 (1.70)</td>
</tr>
</tbody>
</table>

Table 2 shows the neuropsychological background data (means and SEMs) for the patient and control groups. * denote statistically significant differences in ANOVA.
Relationships between measures of nonverbal and verbal long-term memory, executive function, lesion-test interval, and relational and non-relational memory

Correlation analyses were performed separately for the group of controls (n=10) and thalamic patients (MD and VL combined, n=10) to assess the relationship between neuropsychological variables and spatial RM, non-spatial RM, and NRM, respectively. Analyses did not yield any significant correlations in either group.

Relational and non-relational memory

The data of patient T5 had to be excluded from analysis of false alarm related variables in the spatial RM task, because of technical problems in response registration.

Repeated measures ANOVAs with GROUP (patients vs. controls) and MEMORY TASK (spatial RM, non-spatial RM, and NRM) as factors and the recognition memory performance index P_r as dependent variable yielded a significant GROUP effect, reflecting a general deficit of the patients ($F(1,17)=11.09, p=0.004$). The significant TASK effect ($F(2,34)=6.66, p=0.003$) reflected a higher level of difficulty of the NRM compared to the RM tasks (Figure 3), the interaction was not significant ($p=0.42$).

Separate repeated measures ANOVAs of hits and false alarm rates yielded a significant GROUP effect for hits ($F(1,17)=7.13, p=0.016$), reflecting lower hit rates in the patients compared to the controls, whereas the TASK effect and the interaction were not significant (both $p>0.35$). Analysis of false alarm rates also yielded a significant GROUP effect, with higher false alarm rates in the patients ($F(1,17)=4.78, p=0.042$) and a significant TASK effect ($F(2,34)=7.93, p=0.001$), representing higher false alarm rates in the NRM compared to both RM tasks. Analysis of response bias indices did not yield any significant effects (all $p>0.21$).
Figure 3 shows the group differences between the thalamic patients and controls in the three memory tasks (means and SEs). * denote statistically significant differences in ANOVA.

**Analysis of individual performance**

Response bias comparisons did not yield significant differences for any of the patients in any of the three recognition memory tasks (-1.14<all z<1.23), except that T9 was marginally more conservative than her control sample in non-spatial RM (z=-2.18, T(15)=-2.11, p=0.005). The memory performance indices P_r of the individual patients relative to performance of the respective controls in terms of z-scores are illustrated in Figure 4A-C.

**Spatial relational memory.** Three of the five MD patients (T5 was excluded, see above) showed significantly poorer recognition memory relative to their control sample (Figure 4A): T1 (z=-2.33, T(15)=-2.27, p=0.039), T2 (z=-5.20, T(15)=-5.04, p<0.001), and T3 (z=-3.42, T(15)=-3.32, p=0.005). Two of the four VL patients also showed significant impairments relative to their controls: T8 (z=-3.94, T(15)=-3.83, p=0.002), and T10 (z=-4.18, T(14)=-4.05, p=0.001). Separate analysis of hits and false alarms yielded significantly lower hit rates in two of the six MD patients: T1 (z=-2.69, T(15)=-2.61, p=0.020), and T2 (z=-5.16, T(15)=-5.01, p<0.001) and in one of the four VL patients, T10 (z=-3.83, T(14)=-3.71, p=0.002). Analysis of the false alarm rates did not
yield significant effects in any of the MD patients (0.29<all z<1.99), while two of the four VL patients showed significantly elevated false alarm rates, T8 (z=4.98, T(14)=4.83, p<0.001), and T10 (z=2.23, T(14)=2.16, p<0.050).

**Non-spatial relational memory.** As illustrated in Figure 4B, only patient T2 in the MD group was significantly impaired on the index P, (z=-2.74, T(15)=-2.66, p=0.018), while a significant deficit emerged in two of the four VL patients, T7 (z=-2.25, T(15)=-2.18, p=0.046) and T8 (z=-4.25, T(15)=-4.13, p<0.001). Analysis of hit rates yielded a significant deficit in MD patient T2 (z=-5.06, T(15)=-4.91, p<0.001) and VL patient T7 (z=-2.63, T(15)=-2.55, p<0.022). A significantly elevated false alarm rate was observed in VL patient T8 (z=5.67, T(14)=2.16, p(two-tailed)<0.050). None of the MD patients showed evidence of significantly higher false alarm rates (0.07<all z<1.40).

**Non-relational memory.** As illustrated in Figure 4C, none of the patients showed a significant deficit on the recognition memory performance index P, (-2.11<all z>-0.20). MD patient T2 (z=-3.17, T(15)=-3.07, p=0.008) and VL patient T10 showed significantly lower hit rates than their control groups (z=-2.23, T(14)=-2.16, p<0.050). Analysis of the false alarm rates revealed that only VL patient T7 had a significantly higher false alarm rate than his control sample (z=2.63, T(14)=2.55, p=0.022). None of the MD patients had significantly higher false alarm rates (-0.59<all z<1.50).

**Discussion**

We investigated the role of the thalamus in RM and NRM by analysing the performance of patients with selective thalamic lesions affecting the MD and/or VL on a group and single case level. As a group, the thalamic patients were impaired on both...
RM and NRM relative to healthy controls, corroborating the view of a critical involvement of the human thalamus in recognition memory. Single case analyses based on individualised on IQ and sex-matched control samples yielded a significant RM impairment in six patients, based on data averaged across spatial and non-spatial RM.

Focusing on lesion location, our results provided some evidence of stronger MD involvement in spatial than in non-spatial RM: Three of the five MD patients were impaired in spatial RM, while only one MD patient was impaired in non-spatial RM. Two of the four VL patients were impaired in spatial or non-spatial RM, respectively. Interestingly, NRM was not significantly impaired in any of the patients in the single-case comparisons, although the group comparisons and an earlier ageing study (Soei and Daum, 2008) indicated that this task was generally clearly more difficult than the two RM tasks.

It should be noted, however, that the NRM performance of three patients (patients T4, T7 and T10) was far below the normal range and approached the significance level (z>-2.11). Interestingly, patients T7 and T10 still showed impaired RM (on at least one of the subtests), relative to NRM in quantitative terms (Figure 4). The lesion location and laterality differed (Figure 1): patient T7 had impaired non-spatial RM, while patient T10 had impaired spatial RM. Only the data from the right-sided medial MD patient, T4, who was clearly impaired in NRM, compared to both RM conditions, offered support for a stronger involvement of the MD in NRM relative to RM (Aggleton and Brown, 1999).

Three patients with MD lesions had poorer RM (either spatial or non-spatial), relative to NRM: Both the bilateral MD patient, T1, and the left-sided MD patient, T2, showed poorer spatial and non-spatial RM. The left-sided MD patient, T3, had poorer spatial RM relative to both non-spatial RM and NRM. Together, these three medial MD lesion patients offer support for the MD-PFC-striatal disconnection hypothesis (see below).

Disproportionate impairment of relational vs. non-relational memory after mediodorsal and ventrolateral thalamic nuclei lesions

As concerns the sequelae of MD lesions, the finding of more pronounced RM compared to NRM deficits resembles recent studies on recollection/familiarity with nonverbal (Cipolotti et al., 2008) and verbal material (Zoppelt et al., 2003). One of the patients of Cipolotti et al. (2008) had a right-sided MD lesion, but spared anterior thalamic nuclei and mammillo-thalamic tract and showed impaired nonverbal recollection estimates. In agreement with van der Werf et al. (2000), Zoppelt et al. interpreted the
verbal recollection deficits after MD lesions in terms of a failure to accurately retrieve contextual information about the target, due to MD-PFC-striatal disconnection (Cavada et al., 1995; Goldman-Rakic and Porrino, 1985; Zoppelt et al., 2003). The present nonverbal RM deficits would also be consistent with this interpretation. The observations offer only weak support for the model proposed by Aggleton and Brown (1999), since RM was more impaired than NRM after MD lesions (only the data of patient T4 are compatible with that model), and there was evidence of a similar pattern of impairment after VL damage. However, due to the small sample size, the present observations provide only preliminary evidence for a direct rejection of the model.

It is important to note that the caveat of unequal task difficulty favouring the RM over the NRM tasks (Soei and Daum, 2008) also applies to the current study, given the results of the group comparisons. An important implication is, however, that the reported lack of a significant NRM deficit in thalamic lesion patients at single case level cannot simply be attributed to a lower level of task difficulty.

For NRM – which shares some features with familiarity – a separate comparison of the effects of MD lesions with medial and lateral involvement might be of interest, following Zoppelt et al. (2003). Exploratory analysis using a more lenient statistical threshold (z-score=-1.64, corresponding to p<.05) yielded evidence of poorer performance of the four patients with MD lesions affecting the medial part (T1, T2, T3, T4), compared to the two patients with MD damage affecting both medial and lateral parts (T5 and T6) (Figure 4 C). T6 performed within the normal range on all three tasks (Figure 4 A-C). Patients with medial MD lesions generally showed reduced memory in all three tasks, which would support the assumption that the medial MD is critical for anterograde diencephalic amnesia (Bentivoglio et al., 1997). The disconnection of the projections between the PRC and the medial MD (Aggleton and Brown, 1999; Russchen et al., 1987; Saunders et al., 2005) might explain this result, but this is rather speculative, given the lenient statistical threshold and small sample size.

As concerns the findings for VL lesions, the more pronounced deficits in RM compared to NRM extend the findings of a previous study (Zoppelt et al., 2003), which emphasised the functional sequelae of disruption of fronto-striatal circuits after VL lesions (Cummings, 1993): poor self-elaboration of encoding and retrieval strategies. Using a more lenient statistical threshold, two VL patients (T7 and T10) were impaired in NRM, which is consistent with a reported mild familiarity deficit after VL damage (Zoppelt et al., 2003). Notably, the VL patients T7 and T10 showed evidence of enlarged ventricles, while the lesions of T9 and T10 also partly extended to the anterior pulvinar complex. Recently, a patient with an anterior pulvinar lesion showed spatial but not temporal attention deficits (Arend et al., 2008), which might explain the larger
deficit in spatial compared to non-spatial RM in T9 and T10. Altogether, these extra-thalamic lesions make the interpretation of the VL findings less straightforward than in the case of MD lesions, as these features might have had an additional detrimental impact on the memory performance (Van Der Werf et al., 2003b).

Taken together, the present memory performance patterns of thalamic lesion patients support the view that RM and NRM are at least partly dissociable (Eichenbaum et al., 2007). They are in good agreement with complementary studies using similar experimental procedures: In a functional neuroimaging study, which did not address thalamus activations, a dissociation of the neuronal activation pattern emerged, since spatial and non-spatial RM correlated with HC activation, whereas NRM correlated with PRC activation (Kohler et al., 2005). Similarly, a cross-sectional ageing study indicated a differential impact of healthy ageing: Both RM tasks started to decline late in life, while NRM declined earlier (Soei and Daum, 2008). The findings for the RM were comparable across all three studies, suggesting a critical role of the HC and related thalamic regions. The findings for NRM are difficult to compare across our and Kohler et al.’s tasks, as they entailed different levels of cognitive processing load and novelty (for detailed discussion see (Soei and Daum, 2008)).

The disproportionate impairment of spatial vs. non-spatial relational memory after lesions of the mediodorsal thalamic nuclei

The three significantly impaired MD patients (T1, T2, and T3) showed evidence of a more pronounced impairment of spatial compared to non-spatial RM. Patients T4 and T6, who were not significantly impaired, showed the same pattern of a larger deficit of spatial compared to non-spatial RM. In all these cases, lesions affected the medial part of MD. Only patient T6 had an MD lesion which affected both the medial and lateral parts, with the latter being connected with the DLPFC (Goldman-Rakic and Porrino, 1985). This would concur with the spatial coding properties of the lateral MD and DLPFC in a spatial memory task in non-human primates (Tanibuchi and Goldman-Rakic, 2003). As mentioned above, a patient with right-sided MD damage showed impaired RM on spatial memoranda (human faces and topography) (Cipolotti et al., 2008), but the location within the MD was not specified. Interpretation must remain tentative, however, since patient T6 performed within the normal range.

Based on four patients (T1, T2, T3, and T6), the finding that more medial MD lesions were associated with disproportionate impairment of spatial compared to non-spatial RM concurs well with a recent report on non-human primates: Lesions of the magnocellular MD in non-human primates (the medial MD in humans (Bentivoglio et al., 1997)) led to impaired acquisition but not to impaired retention or retrieval for
object-in-place scene memory, i.e. spatial RM (Mitchell and Gaffan, 2008), extending previous findings (Gaffan and Parker, 2000). They did not assess NRM, but the current observations (note the discussion on unequal task difficulty below) tentatively suggest a stronger medial MD involvement in the acquisition of spatial RM rather than NRM. This concurs with ablation studies showing that the OFC is required for acquisition of spatial RM in non-human primates (Baxter et al., 2007; Browning et al., 2005) and successful performance in spatial tasks in rodents (Kolb et al., 1983), as the OFC is connected to the medial part of the MD in non-human primates (Cavada et al., 1995). Baxter et al. (2007) suggested that the OFC may contribute to strategies aimed at maximising learning in spatial RM tasks or allocating cognitive resources to scenes ought to be remembered.

In summary, the hypothesis of a failure to accurately remember contextual information (Zoppelt et al., 2003) due to disconnection of MD-PFC-striatal circuits (Alexander et al., 1986; Cavada et al., 1995; Cummings, 1993; Goldman-Rakic and Porrino, 1985), yields the following possibilities: The lateral MD and DLPFC show both spatial coding properties (Tanibuchi and Goldman-Rakic, 2003), which would be consistent with the impaired spatial RM after a lesion affecting the lateral MD. The observed spatial RM deficit after MD lesions with medial involvement suggests that the medial MD-OFC circuit might be more important for the acquisition of spatial RM compared to NRM (Baxter et al., 2007; Gaffan and Parker, 2000; Mitchell and Gaffan, 2008).

The lack of a significant association between lesion laterality, neuropsychological profile, and memory performance

Left thalamic damage was to some degree associated with a disproportionate impairment in non-spatial RM, presumably because memory processing in this task benefited to some degree from verbal mediation. There were no clear associations between laterality and performance on the other tasks, a finding which has been frequently observed in human subjects with unilateral thalamic lesions (Hanley et al., 2001; Wallesch et al., 1983; Zoppelt et al., 2003). However the two most affected patients (T2 and T8) showed essentially the same behavioural pattern of impaired RM and spared NRM, although the lesion site in the left thalamus differed.

The lack of correlations between nonverbal and verbal long-term memory, executive function measures, and lesion-test interval must be interpreted with caution because of the small sample size. As ‘executive function’ is a multidimensional concept and was only tapped by one measure (verbal fluency), the non-significant correlations in a small sample cannot be considered as strong evidence against an explanation in
terms of disrupted MD-PFC-striatal connectivity. The lack of a significant correlation between lesion-test interval and memory performance is consistent with observations of lasting cognitive impairments after lesion-test intervals up to 24 years (Van Der Werf et al., 2003b).

Interestingly, the patients T4 (medial MD lesion, age=60 years, lesion-test interval 25 months, IQ=95) and T6 (medial and lateral MD lesion, age=42 years, lesion-test interval 110 months, IQ=121), as well as T9 (VL and pulvinar damage, age=49 years, lesion-test interval 88 months, IQ=118) all performed in the normal range in all three memory tasks. Neither relatively young age, nor superior IQ, return to work life or long lesion-test interval were variables common to all three patients. These rare cases add to the two published single case reports of normal memory performance after bilateral paramedian infarctions, which affected the MD (Khoiny et al., 2006; Krolak-Salmon et al., 2000). Why MD and VL patients with seemingly similar lesions show distinct performance patterns is unclear, and following Holdstock et al. (2008) on a related issue, this stresses the need for more sensitive structural neuroimaging in future studies if the role of specific thalamic nuclei is to be clarified.

Summary

Patients with selective thalamic lesions were significantly impaired in both RM and NRM on the group level. Single case analyses yielded a more complex pattern of impaired and spared memory performance. Lesions affecting the MD were associated with evidence of more pronounced deficits in spatial compared to non-spatial RM. These findings are consistent with MD-PFC-striatal disconnections and also support the ideas of a role of the medial as well as lateral MD in spatial RM. VL lesions were associated with deficits in both spatial and non-spatial RM. Although NRM was generally poorer in the patients compared to the controls, neither MD nor VL lesions led to significant deficits in single case analyses based on the comparison of individualised strictly matched healthy control groups. Interestingly, there were also three cases with focal thalamic lesions who showed intact memory performance. We agree with Cipolotti et al. (2008), that these findings altogether point to the possibility that fractionation of RM and NRM to separate thalamic nuclei may not fully capture the role of thalamic sub-regions in memory function. Overall, the findings offer further support to the idea RM and NRM are at least partly dissociable (Eichenbaum et al., 2007).
4 GENERAL BIBLIOGRAPHY


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5 DECLARATION

I certify herewith that the dissertation at hand was completed and written independently and without external assistance. The “Guidelines for Good Scientific Practise” according to §9, Section 3, were adhered to. This work has never been submitted in this or similar form at this or any other domestic or foreign institution of higher learning as a dissertation.

Eleonore Soei Bochum, 09 December 2008
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