Dissociating Systems and Subprocesses in Human Declarative Memory

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Dipl-Psych. Theodor Jäger

aus Chur

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Dekan:

Univ.-Prof. Dr. Jochen Kubiniok, Universität des Saarlandes

Berichterstatter:

Univ.-Prof. Dr. Axel Mecklinger, Universität des Saarlandes
Univ.-Prof. Dr. Hubert Zimmer, Universität des Saarlandes
Univ.-Prof. Dr. Matthias Kliegel, Technische Universität Dresden

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1. General introduction into human memory

1. General introduction into human memory

Remembering information from the past is one of the most essential cognitive ability and brain function of human-being, allowing an individual to mentally violate the law of irreversibility of the flow of time (Tulving, 2002). In virtually every situation of our lives, we use stored information to know what we are, what we did, what we are doing or plan to do, and how the world and our social environment are organized. The brain has evolved a complex memory system that encodes, stores, and retrieves information in multi-faceted manners. In consequence, a major goal of modern memory research has been to understand the underlying cognitive and neurophysiological organization of memory.

One important foundation of memory research is the assumption that human memory is not a single entity but is composed of several different components, which seem to be mediated by separate brain systems (Moscovitch et al., 2005; Squire et al., 1993; Squire & Zola, 1996). Some of the best and oldest evidence for distinguishing between different kinds of memory comes from the study of patients with circumscribed memory disorders, who often show large deficits in some but completely intact performance in other kinds of memory tasks (Gabrieli, 1998; Squire & Zola, 1996). More modern methods to investigate potential dissociations of different memory systems include the application of neurophysiological methods such as positron emission tomography, functional magnetic resonance imaging, or event-related brain potentials recorded using the technique of electroencephalography (EEG).

One of the oldest and most widely accepted ideas about human memory is that mnemonic abilities summarized as ‘short-term memory’ can be usefully distinguished from memory contents and processes referred to as ‘long-term memory’ (Squire et al., 1993). *Short-term memory* refers to memory processes that maintain information in an active, online form in consciousness whereby reproduction occurs without a delay or after a short delay during which the information is actively rehearsed (Buckner, 2004). By contrast, *long-term memory* refers to the memory processes which retain information over more extended periods of time (Buckner, 2004).

The strongest evidence for the view that short-term and long-term memory reflect dissociable memory processes/systems is the fact that many amnesic patients with damage in the neural structure called hippocampus within the medial temporal lobe have been reported who show fully intact short-term memory despite strongly disrupted long-term memory (Gabrieli, 1998; Moscovitch et al., 2005; cf. Study 3 of this thesis). The reverse case is relatively rare, but a few patients have been reported who show disrupted short-term memory but intact long-term memory (Shallice & Warrington, 1970). This pattern of findings (i.e., a double dissociation) can be explained by a difference between the underlying neurophysiological organization of short-term and long-term memory. To summarize the findings of a wealth of studies, it can be concluded that while long-term memory seems to be mediated mainly by the hippocampus and the surrounding medial temporal lobe cortices, a major neural mediator of short-term memory is the prefrontal cortex and other brain regions outside the medial temporal lobes (e.g., Baddeley, 2003; Fuster & Alexander, 1971; Squire et al., 1993).

In addition to this broad distinction between short-term and long-term memory, long-term memory itself has been subdivided into several memory systems. Figure 1 shows a widely accepted taxonomy of different components of long-term memory.

Figure 1

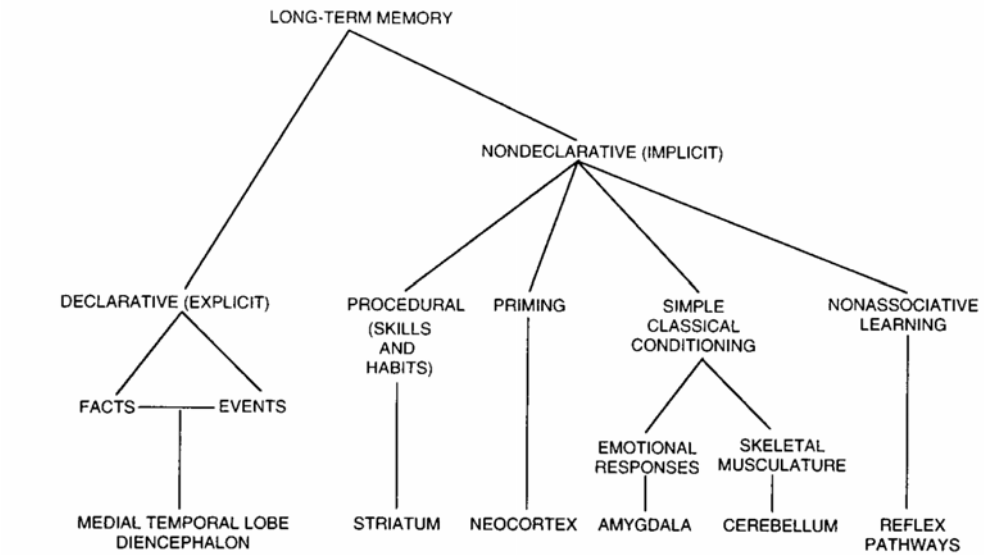


Figure 1: A taxonomy of long-term memory systems together with specific brain structures thought to be involved in each system (adopted from Squire & Zola, 1996).

The first major distinction of long-term memory is made between declarative memory and nondeclarative memory (see Figure 1). *Declarative memory* refers to forms of long-term memory able to relate diverse information that can be used flexibly and are available to conscious awareness and verbal report, such as memories for facts and events (Buckner, 2004). *Nondeclarative memory* refers to various forms of long-term memory that are less flexible, less relational, can operate outside awareness, and are expressed through performance rather than by explicit recall, such as skill and habit learning, simple classical conditioning, or the phenomenon of priming (Buckner, 2004).

Again, amnesic patients with damage to the temporal lobes provide evidence for the distinction between declarative and nondeclarative memory because these patients often show impaired declarative memory, indicating that at least some forms of declarative memory are mediated by the temporal lobe, while their nondeclarative memory processes can be completely spared and thus do not crucially depend on the temporal lobe (Gabrieli, 1998; Moscovitch et al., 2005). Thus, the two forms of

memory seem to have (at least partly) different underlying neural substrates; while declarative memory strongly depends on medial and lateral aspects of the temporal lobes, nondeclarative memory has been found to be mediated by brain systems such as the striatum, the amygdala, or the cerebellum (Squire et al., 1993, 2004; Squire & Zola, 1996).

Declarative memory itself has been subdivided into two major systems: episodic memory and semantic memory (see Figure 1; e.g., Squire et al., 1993; Tulving, 1972, 1983). *Episodic memory* refers to memory for particular autobiographical episodes or specific events that happened during the life of an individual, which includes information about both the content of the experience and the spatial and temporal context in which it occurred (Moscovitch et al., 2005). Importantly, episodic memory has been found to be critically dependent on medial aspects of the temporal lobe. By contrast, *semantic memory* refers to the noncontextual content of experience, or knowledge about the world acquired during experience, which contributes to the formation and long-term representation of concepts, categories, facts, word meanings, and so on. It even includes knowledge about ourselves (where we were born, where we lived, who our friends were, what schools we attended, what jobs we held), what some have called *personal semantics* to distinguish this memory from that for autobiographical episodes (Moscovitch et al., 2005).

Some evidence for a distinction of episodic and semantic memory is again provided by a few neuropsychological patients, who sometimes are able to accumulate semantic knowledge despite severe impairments of episodic memory (Tulving et al., 1991; Vargha-Khadem et al., 1997). Consistent with this neuropsychological dissociation, semantic memory has been found to rely more on anterior and lateral than medial temporal cortex areas (Moscovitch et al., 2005), e.g., there are findings that the severity of impaired semantic knowledge is related to the extent of lateral temporal damage (Squire et al., 2004) and that semantic memory can survive medial temporal lobe damage though it may initially benefit from the contribution of these structures (Moscovitch et al., 2005). However, the functional

and neurophysiological distinction of episodic and semantic memory is not so clear as, for instance, the distinction of short-term and long-term memory or the dissociation of declarative and nondeclarative memory processes and will thus be a continuing challenge for future memory research (Eysenck & Keane, 2000; Squire et al., 1993).

As mentioned above, episodic memory critically depends on the functional integrity of the medial temporal lobe, more specifically on the hippocampus and the surrounding entorhinal, perirhinal, and parahippocampal neocortices. The hippocampus lies at the end of a cortical processing hierarchy, and the entorhinal cortex is the major source of its cortical input. The entorhinal cortex receives much of its afferents from perirhinal and parahippocampal cortices, which in turn receive widespread projections from unimodal and polymodal areas in the brain, as is depicted in Figure 2 (Gabrieli, 1998; Moscovitch et al., 2005; Norman & O'Reilly, 2003; Squire et al., 2004; Squire & Zola, 1996). The hippocampus is proposed to have a special role in tasks that depend on relating or combining information from multiple sources, such as tasks that ask about specific events or associative memory tasks (Squire et al., 2004). Thus, it is understandable that lesions limited to the hippocampus disproportionately impair tasks of episodic and associative memory relative to tasks of semantic or single-item memory (Squire et al., 2004).

Figure 2

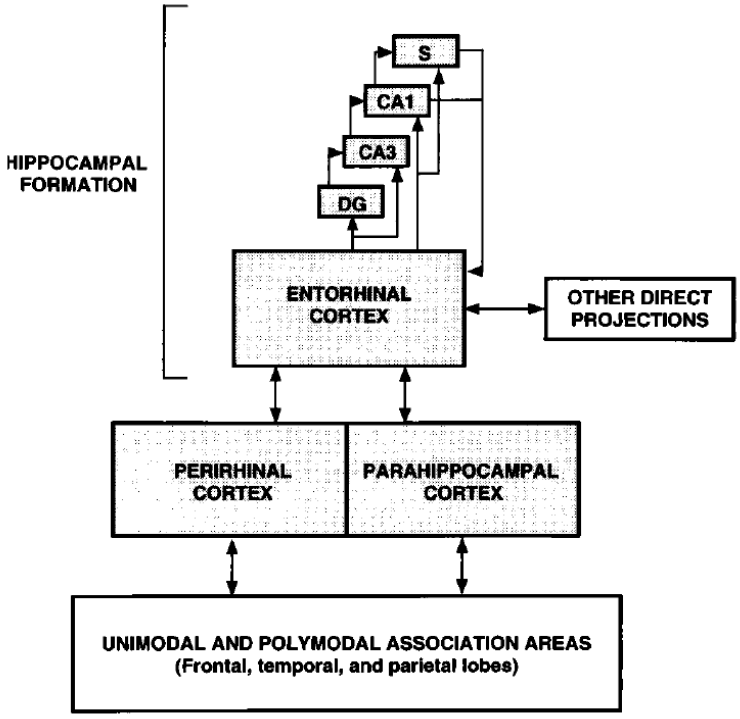


Figure 2: Schematic view of the medial temporal lobe memory system (adopted from Squire & Zola, 1996).

This general introduction into memory summarizes the main findings of modern memory research with regard to the mnemonic systems that have been differentiated within the human cognitive system. Whereas short-term memory has been distinguished from long-term memory, the latter memory system itself has been subdivided into declarative and nondeclarative memory systems. Finally, declarative memory seems to encompass two partly dissociable subsystems, namely episodic and semantic memory. The specific aim of the present thesis with regard to this theoretical framework of the organization of human memory is outlined in the next chapter.

2. Studies

2.1 The aim of the present studies

The global aim of the present studies was to further examine human memory. More specifically, the aim was to provide additional evidence for a fractionation of human memory into different systems and subprocesses – as described in the introduction of this thesis – by the means of differentiating independent memory processes. This differentiation is tried to be achieved by applying several scientific methods (e.g., studies collecting novel data versus studies analyzing the data of the existing literature), different experimental paradigms (e.g., item recognition memory tasks versus associative recognition memory tasks), different methods of investigating memory subprocesses (e.g., analyzing overall performance in memory tasks versus modelling the components underlying memory performance), and – last but not least – different study populations (e.g., students, healthy younger compared to older adults, or neurological patients with memory disorders compared to healthy controls).

Of course, the present thesis is not able to investigate all aspects of the multi-faceted memory system as outlined in the introduction (e.g., see Figure 1); thus, besides investigating memory on a systemic or 'macro' level (Study 3), a particular focus (Studies 1, 2, & 4) is given on the memory processes that subserve so-called *recognition memory*, which reflects a mnemonic ability within the broader framework of episodic long-term memory. Recognition memory is defined as the ability to decide whether or not a presented information has already been encountered some time in the past, by this enabling an individual to classify information from the environment as known or novel, respectively, regardless of whether this information consists of single items (item recognition memory) or of associations between items (associative recognition memory).

Importantly, current theories of recognition memory emphasize that the ability to recognize information as 'old' (i.e., already encountered) or 'new' (i.e., novel) seems to be supported by two functionally and neurophysiologically independent memory processes termed *familiarity* and *recollection*, respectively (for reviews see Aggleton & Brown, 1999, 2006; Diana et al., 2006, 2007; Eichenbaum et al., 2007;

Jacoby, 1991; Mandler, 1980; Mecklinger & Jäger, 2009; Norman & O'Reilly, 2003; Yonelinas, 2002). These so-called 'dual-process models' stand in contrast to 'single-process models' of recognition memory. The latter posit that recognizing is based on a unidimensional scalar value of global memory strength (e.g., Donaldson, 1996; Gillund & Shiffrin, 1984; see Quamme et al., 2004; Yonelinas, 2001, for discussions). Within the dual-process framework, the process of *familiarity* is conceptualized as an acontextual, item-specific form of recognition memory, which leads an individual to have the feeling of 'knowing' an encountered item from somewhere while being unable to recall any further information on the episodic context during which the item was originally experienced. Familiarity seems to be generated by the cortex of the medial temporal lobes surrounding the hippocampus (i.e., entorhinal, perirhinal, and parahippocampal cortices). By contrast, the process of *recollection* refers to the explicit retrieval of (e.g., spatial or temporal) contextual information of the episode in which an item was encountered and thus reflects the kind of memory experience typically associated with episodic remembering. Importantly, recollection has been found to critically rely on successful processing of the hippocampal formation (e.g., Aggleton & Brown, 1999, 2006; Eichenbaum et al., 2007).

However, the existence of two (independent) memory processes subserving recognition memory is still highly controversial; thus it was an aim of the present thesis to find further experimental conditions or situations in which the two subprocesses seem to be dissociable. Specifically, this dissociation is tried to be achieved by applying two different types of associative recognition memory situations which are assumed to promote familiarity- and recollection-based retrieval, respectively (Study 1), two different participant groups of younger and healthy older adults that may differ in the profile of their efficiency of familiarity- and recollection-based recognition memory (Study 2), and two different participant groups of healthy controls and patients in a state after a short-lived but tremendous memory disturbance (i.e., transient global amnesia – TGA), who may show a selective disruption of one of the two putative processes underlying recognition memory (Study 4).

While Studies 1 and 2 investigated the subprocesses of recognition memory on a behavioral basis (i.e., only behavioral data were available), Study 4 also enabled explicitly linking the estimates of the subprocesses of recognition memory to their potential neuronal basis, as the patient group examined showed a circumscribed and small locus of disturbance in brain function. More specifically, patients were examined during the recovery phase after an attack of transient global amnesia (TGA), most of whom evidenced visible lesions lying within the hippocampal formation. By this means, it was possible to investigate whether or not familiarity and/or recollection rely on the functional integrity of the hippocampus.

Study 3 was conducted in advance to Study 4 and aimed to clarify whether or not the hippocampal lesions demonstrated by patients with TGA result in a selective impairment of episodic long-term memory (rather than, e.g., short-term or semantic memory), an assumption that is met by most researchers and clinicians. By this, Study 3 also contributed to a more general investigation of the dissociability of different memory systems such as short-term, long-term, episodic, and semantic memory. Study 4 then more specifically focused on a detailed fractionation of the subprocesses of episodic memory that may be influenced by functional disturbances of the hippocampal formation.

2.2 Study 1: Familiarity Supports Associative Recognition Memory for Face Stimuli That Can Be Unitized: Evidence From Receiver Operating Characteristics[1]

2.2.1 Rationale for Study 1

The first study of this thesis aimed to examine the dissociability of the subprocesses of recognition memory in healthy younger adults. In order to find an experimental condition that could be able to separate the contributions of familiarity and recollection to recognition memory performance, we capitalized on some recent findings which indicated that familiarity and recollection seem to contribute differentially to the retrieval of associative memories depending on the nature and characteristics of the to-be-remembered associations. Specifically, it was reported that (hippocampus-mediated) recollection is critically important for the retrieval of associations between *arbitrary* items such as the word-pair 'bullet-food', whereas familiarity is able to support associative memory given that the to-be-associated items can be 'unitized' into a coherent whole such as the word-pair 'sea-food' (e.g., Diana et al., 2008; Giovanello et al., 2006; Jäger et al., 2006; Mayes et al., 2007; Quamme, 2004; Quamme et al., 2007; Rhodes & Donaldson, 2007; Yonelinas et al., 1999).

In the light of these findings that experimental conditions which involve the retrieval of arbitrary versus unitized associations foster the contributions of either recollection or familiarity, a manipulation of the degree to which to-be-associated items can be unitized was applied in Study 1 in order to behaviourally dissociate the two putative subprocesses of recognition memory in samples of healthy younger

[1]The data reported in this study are also reported in the following article: Jäger, T. & Mecklinger, A. (2009). Familiarity supports associative recognition memory for face stimuli that can be unitized: Evidence from receiver operating characteristics. *European Journal of Cognitive Psychology, 21*, 35-60.

adults. By this, Study 1 aimed to contribute to the fractionation of the subprocesses underlying episodic (recognition) memory.

2.2.2 Introduction of Study 1

Recognition memory refers to experiences in which individuals become aware that a particular item or information has already been encountered in the past. A considerable body of evidence suggests that recognizing is subserved by two (rather than one) qualitatively distinct and independently acting processes, which are termed *familiarity* and *recollection*, respectively (e.g., Aggleton & Brown, 1999, 2006; Diana, Reder, Arndt, & Park, 2006; Jacoby, 1991; Mandler, 1980; Norman & O'Reilly, 2003; Yonelinas, 2002). Familiarity is assumed to be a fast-acting memory process of continuously varying strength, whereby a previously encountered item is perceived as "reminding us of something" without retrieving further contextual information (e.g., "*This woman looks very familiar to me but I can't remember where I met her!*"; see Yovel & Paller, 2004). By contrast, recollection refers to a threshold-like process, which, once successful, leads to the conscious and effortful retrieval of an item plus further contextual details, such as the spatio-temporal context of an episode or other related information (e.g., "*I have seen this man yesterday jogging through the park!*").

Importantly, it is assumed that familiarity and recollection cannot contribute equally to all types of recognition memory tasks. Specifically, the dual-process view predicts differential contributions of familiarity and recollection to tests of *item* and *associative recognition memory*, respectively (e.g., Yonelinas, 2001a, 2002). Whereas item recognition memory involves judgments about the old/new status of single items, associative recognition memory typically requires participants to retrieve particular pairings of items in order to distinguish between *intact* pairs (i.e., pairs of test stimuli presented identically as in the study phase) and *recombined* pairs (i.e., pairs of test stimuli that were studied but not presented as pairs in the study phase). The dual-process account proposes that familiarity as well as recollection support item recognition, as stimuli can be judged 'old' if participants recollect information about the study episode or if an item is experienced as sufficiently

familiar. By contrast, only recollection but not familiarity is assumed to support associative recognition memory, as individual stimuli are equally familiar in both intact and recombined pairs and thus familiarity cannot be diagnostic to distinguish between them. Therefore, accepting intact or rejecting recombined pairs is thought to require recollection for the particular pairings of stimuli. A considerable body of literature supports this suggestion by revealing an important role of recollection in associative recognition memory tasks with little contributions of familiarity (e.g., Donaldson & Rugg, 1998, 1999; Hockley & Consoli, 1999; Rotello & Heit, 2000; Rotello, Macmillan, & Van Tassel, 2000; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004; Yonelinas, 1997, 1999).

However, since recently there is a growing interest into the role of familiarity for associative recognition memory (Aggleton & Brown, 2006). In fact, there are some findings which challenge the view that familiarity cannot be supportive for associative recognition memory. These studies indicate that familiarity is diagnostic for associative recognition judgments given that the to-be-associated stimuli can be encoded as a coherent whole or as a 'unitized' representation. *Unitization* refers to a process by which two or more previously separate items become represented as a single unit (Graf & Schacter, 1989). Initial evidence for this suggestion is reported by Yonelinas, Kroll, Dobbins, and Soltani (1999). In this study, participants were required to memorize schematic faces and to discriminate repeated faces from faces that contained studied but rearranged features (e.g., hair, eyes, nose, head shape). The faces were either presented upright – by this allowing unitization of facial features – or upside down. Estimates of familiarity derived from receiver operating characteristics (ROCs; see below) indicated that familiarity significantly contributed to recognition judgments for associations of facial features when the features could be unitized into a coherent whole, i.e., in the upright but not in the upside down condition.

ROCs examined by Quamme (2004) revealed greater contributions of familiarity for associative recognition memory for pre-experimentally existing compound words (e.g, sea-food) compared to unrelated word-pairs (e.g., bullet-food).

In addition, Quamme applied an encoding manipulation in which participants either encoded unrelated word-pairs as if the two words referred to a single object (compound condition) or memorized word-pairs while judging each word of the word-pairs, separately (separate condition). Results revealed substantially higher contributions of familiarity (as well as recollection) in the compound condition relative to the separate condition even though the same stimuli were used in both conditions. However, it should be noted that there were substantial performance differences between conditions which may have influenced the shape of the ROCs as well.

Similar findings were obtained by Giovanello, Keane, and Verfaellie (2006), who applied the remember/know procedure (Tulving, 1985) and found substantially higher contributions of familiarity to associative recognition memory for pre-experimentally existing compound words (e.g., land-scape) compared to unrelated word-pairs (e.g., telephone-trumpet). Finally, Quamme, Yonelinas, and Norman (2007) applied a task in which unrelated word-pairs were either encoded as separate units within sentences (sentences condition) or as if the two words of each word-pair referred to a single object (compound condition). In this paradigm, three hypoxic patients previously determined to have impaired recollection together with intact familiarity showed a larger deficit in the sentences condition than in the compound condition compared to age-matched controls. This result indicates that intact familiarity processes supported associative recognition memory only given that the to-be associated stimuli were unitized during encoding.

A few studies measuring event-related brain potentials (ERPs) have revealed further evidence that familiarity can support associative recognition memory in certain situations. Importantly, ERPs are thought to provide dissociable indices of familiarity and recollection: An early, frontally pronounced ERP old/new effect is suggested to be the putative neural correlate of familiarity, whereas a somewhat later, parietally pronounced ERP old/new effect is believed to reflect recollection (e.g., Curran, 2000; Mecklinger, 2006; Rugg & Yonelinas, 2003; Woodruff, Hayama, & Rugg, 2006).

Opitz and Cornell (2006) used an encoding manipulation that required participants to memorize words while judging which word out of four did not fit in the context of the other three words (associative condition) or while judging which word out of four denotes the smallest object (relational condition). During the test phase, three of the four studied words were repeated as single item retrieval cues. Results revealed an early frontal old/new effect in the associative but not in the relational condition. In addition, the early frontal old/new effect in the associative condition was enhanced for those words for which the complete word triplet could be recognized. These results are consistent with the view that familiarity arises during the retrieval of pre-experimentally existing semantic associations. In another ERP study, Rhodes and Donaldson (2007) obtained an early frontal old/new effect for associative recognition of word-pairs rated to reflect unitized representations (e.g., traffic-jam) but not for word-pairs rated to reflect unitized representations to a low degree (e.g., prince-duke).

Finally, a recent ERP study conducted in our lab provided further evidence for the "familiarity supports associative recognition memory" view using faces as stimulus materials (Jäger, Mecklinger, & Kipp, 2006). Participants memorized pairs of face stimuli depicting two *different* persons (inter-item condition) or pairs of physically different but very similar face stimuli rated to be perceived as depicting the *same* person (intra-item condition). Given that recollection supports associations between arbitrarily paired information, we expected the inter-item condition to elicit a parietal old/new effect during associative recognition of face-pairs. Conversely, assuming that two photographs showing the same person can be unitized into a representation of a single person, we expected an early frontal old/new effect during associative recognition in the intra-item condition. Note that these associations between unitizable stimuli were formed during the experiment rather than being pre-experimentally existing unitized associations as in most of the aforementioned studies (cf., Giovanello et al., 2006; Opitz & Cornell, 2006; Quamme, 2004; Rhodes & Donaldson, 2007). As the electrophysiological data turned out to reflect the expected pattern of results, this study provided further evidence that in addition to recollection,

also familiarity can subserve associative retrieval. While recollection seems to enable the retrieval of associations between arbitrarily paired items, familiarity may support associative recognition memory in situations where the to-be-associated items can be unitized.

In the present study, we aimed at further examining the circumstances under which familiarity can support associative recognition memory. We were also interested in whether the aforementioned ERP evidence (Jäger et al., 2006) would receive cross-validation through the application of alternative operational definitions of familiarity and recollection (cf. e.g., Yonelinas, 2001b; Yonelinas, Otten, Shaw, & Rugg, 2005 versus Woodruff et al., 2006, for comparisons of alternative measures of familiarity and recollection using the same paradigm). To examine these issues, we applied modified versions of the task employed in Jäger et al. and used the behavioral measures to derive estimates for familiarity and recollection. Specifically, participants memorized pairs of faces and made intact/recombined judgments about face-pairs during the test phase.

To investigate the relative contributions of familiarity and recollection, we examined the shapes of associative ROCs (e.g., Yonelinas, 1994, 1997). ROCs plot the proportion of hits and false alarms across a number of response criteria. The left-most point on the ROC function is created by relating hits and false alarms for the most strict response criterion, including only the most confident responses. The remaining points on the ROC reflect continuously more relaxed response criteria. With regard to the specific shape of an ROC, if performance relies exclusively on familiarity, then the dual-process model predicts a curvilinear ROC that is symmetrical along the diagonal (see e.g., Yonelinas, Dobbins, Szymanski, Dhaliwal, & King, 1996). This shape emerges when the response criterion is continuously relaxed for familiarity distributions of ‘old’ and ‘new’ items that are assumed to be Gaussian and of equal variance (e.g., Yonelinas, 1994). By contrast, if performance relies exclusively on recollection, which is assumed to be a threshold process with items falling above a given threshold being recollected and items falling below the threshold not being recollected, then the ROC should be linear and approach the point

1,1 of the coordinate system. As recollection is associated with high-confidence responses, increasing levels of recollection shift the lower left part of the ROC upward on the *y* axis, resulting in an asymmetrical ROC curve. Finally, if performance relies on both familiarity and recollection, the dual-process model predicts an ROC that is curvilinear and asymmetrical along the diagonal, because recollection pushes the ROC up at its lower left part, by this rendering the curvilinear ROC asymmetrical along the diagonal.

Capitalizing on these characteristics of ROC curves, in the present study we obtained estimates of familiarity and recollection from empirically derived ROC points. We also examined ROCs plotted in *z*-space (i.e., *z*-ROCs), because if z-ROCs turn out to be linear, recognition memory performance can be regarded as mainly relying on familiarity (Yonelinas, 1997; Yonelinas et al., 1996; Wixted, 2007). By contrast, nonlinear (i.e., U-shaped) z-ROCs are predictive for the additional contribution of a threshold-like recollection process. Consistent with our hypotheses reported above, we thus predicted a nonlinear (i.e., U-shaped) *z*-ROC for the inter-item condition, whereas a linear *z*-ROC was expected for the intra-item condition. Moreover, familiarity estimates as derived from ROC curves were predicted to be higher in the intra- than the inter-item condition. Conversely, in light of our previous findings (Jäger et al., 2006), recollection estimates were expected to be higher in the inter- than the intra-item condition.

2.2.3 Experiment 1

2.2.3.1 Methods

Participants

Twenty, mostly undergraduate students (10 females) provided informed consent to participate in return for a cash payment of 8 Euro/hour. Mean age of participants was 22.95 years (*SD* = 2.78, range = 19-30). Participants were screened for conditions of neurological or psychiatric disorders using a questionnaire, which

revealed no such conditions besides for one male participant reporting a history of attention-deficit hyperactivity disorder.

Materials and Procedure

Face stimuli. The face stimuli used in this study were the same as those of Jäger et al. (2006), except that we did not include completely novel face stimuli. The face stimuli were gray-scale photographs of unfamiliar and emotionally neutral faces taken from a picture database (Jäger, Seiler, & Mecklinger, 2005). The database contains continua of *morphed faces*, i.e., sets of two different 'parent' faces that were gradually transformed into each other resulting in intermediate morphed faces. Of the available morph-continua, we selected the 0%, 35%, 70%, and 100% morphed faces to be used in the intra-item condition. The four faces of each morph-continuum were rated in a separate study for similarity on physical and identity dimensions (Jäger et al., 2005) and we selected 60 morph-continua in which faces of neighboring morph-degrees were rated as clearly physically discriminable but still representing the same person to a high degree. Additionally, we selected a further 240 unmodified face stimuli from the same database to form 120 face-pairs for the inter-item condition. Note that morphed and unmodified face stimuli were carefully matched in physical characteristics such as picture sharpness (see Jäger et al., 2005). The face stimuli had a size of 257 pixels (9.07 cm) in width and 379 pixels (13.37 cm) in height, with an image resolution of 72 pixels/inch.

Associative recognition memory task. Participants performed 25 blocks of an associative recognition memory task, each consisting of a study phase, a distracter task, and a test phase. In 15 blocks, participants encoded face-pairs representing two different, gender-matched persons (i.e., inter-item condition). In 10 blocks, participants encoded face-pairs consisting of faces that were judged to represent the same person to a high degree (i.e., intra-item condition). This was achieved by creating face-pairs either consisting of a 35% and a 0% morphed face, or consisting of a 100% and a 70% morphed face. Participants were instructed that they would be

presented with study-test blocks in which two photographs have to be memorized that either show two different persons or twice the same person on physically different pictures (instruction [translated from German into English]: *"In this task, you have to memorize face-pairs which either show two different persons or the same person twice on different photographs."*).

In each *study phase* (see Figure 3A for illustration), participants memorized a total of 12 or 8 face-pairs for the intra- and the inter-item condition, respectively. We used slightly longer blocks in the intra-item condition because performance revealed to be higher in the intra-item condition when equal numbers of study trials have to be learned in both conditions (Jäger et al., 2006). Individual photographs of each face-pair were presented sequentially in the centre of the screen. Every novel face-pair was announced by 'next pair' (1500 ms), then a fixation cross appeared (1000 ms), and the first face of a given face-pair was presented (700 ms), followed by a fixation cross (1500 ms). Then, the second face of the face-pair was presented (700 ms), again followed by a fixation cross (1500 ms), and a blank screen (200 ms). Thereafter, the next study trial started. The face-pairs in the *inter-item condition* depicted two arbitrarily paired, but gender-matched persons. Half of the face-pairs in the *intra-item condition* were a 35% and a 0% morphed face (presented in this order), whereas the other half were a 100% and a 70% morphed face (presented in this order) from the same morph-continua.

Participants were instructed to memorize the pairings of photographs for a subsequent associative recognition memory test. Additionally, participants were required to judge the gender of each face stimulus by a button press. The sequence of study trials was pseudorandomly intermixed with the constraints that pairs with same gender did not appear more than twice consecutively, that pairs belonging to the same morph-continua were separated by at least three intervening study trials, and that in the inter-item condition, study trials in which the faces used to form recombined pairs appeared were separated by at least three intervening study trials. After the study phase, a *distracter task* was performed for 20 s in which participants had to count

aloud backwards in steps of 6, 7, 8, or 9 from a randomly presented number between 100 and 200.

In each *test phase* (see Figure 3B for illustration), half of the trials consisted of *intact* and *recombined* face-pairs, respectively. There were 6 test trials in the intra-item condition and 4 test trials in the inter-item condition. First, a fixation cross appeared (1000 ms), followed by a pair of face stimuli presented side by side. To derive ROC curves, participants were required to judge the face-pairs as 'intact' or 'recombined' on a 6-point confidence scale (instruction [translated from German into English]: *"During the test phase, you have to decide whether or not the two faces of each face-pair had been paired during the study phase"*), from *sure intact* (1) to *sure recombined* (6). Responses 1-3 were explained to reflect 'intact' responses of different confidence levels. Responses 4-6 were explained to reflect 'recombined' responses of different confidence levels. The face-pairs stayed on the screen until a response was made or for maximally 2500 ms. In the intra-item condition, intact face-pairs consisted of 35% and 0% morphed faces, whereas recombined face-pairs consisted of 35% and 70% morphed faces (see Figure 3B). By this, intact and recombined face-pairs both consisted of faces that differed by a morph-degree of 35% and thus intact/recombined decisions could not be made solely on the basis of differences in face similarity. In the inter-item condition, intact face-pairs consisted of faces that were paired in the study phase, whereas recombined face-pairs were formed by recombining two studied faces that were not presented as pairs during the study phase (see Figure 3B). For both conditions, faces initially paired with the faces used for the recombined pairs were excluded from the test phase. Before the next test trial started, a blank screen was presented for 1000 ms. The test trials were pseudorandomly intermixed with the constraints that intact or recombined faces and pairs with same gender did not appear more than twice consecutively.

Figure 3

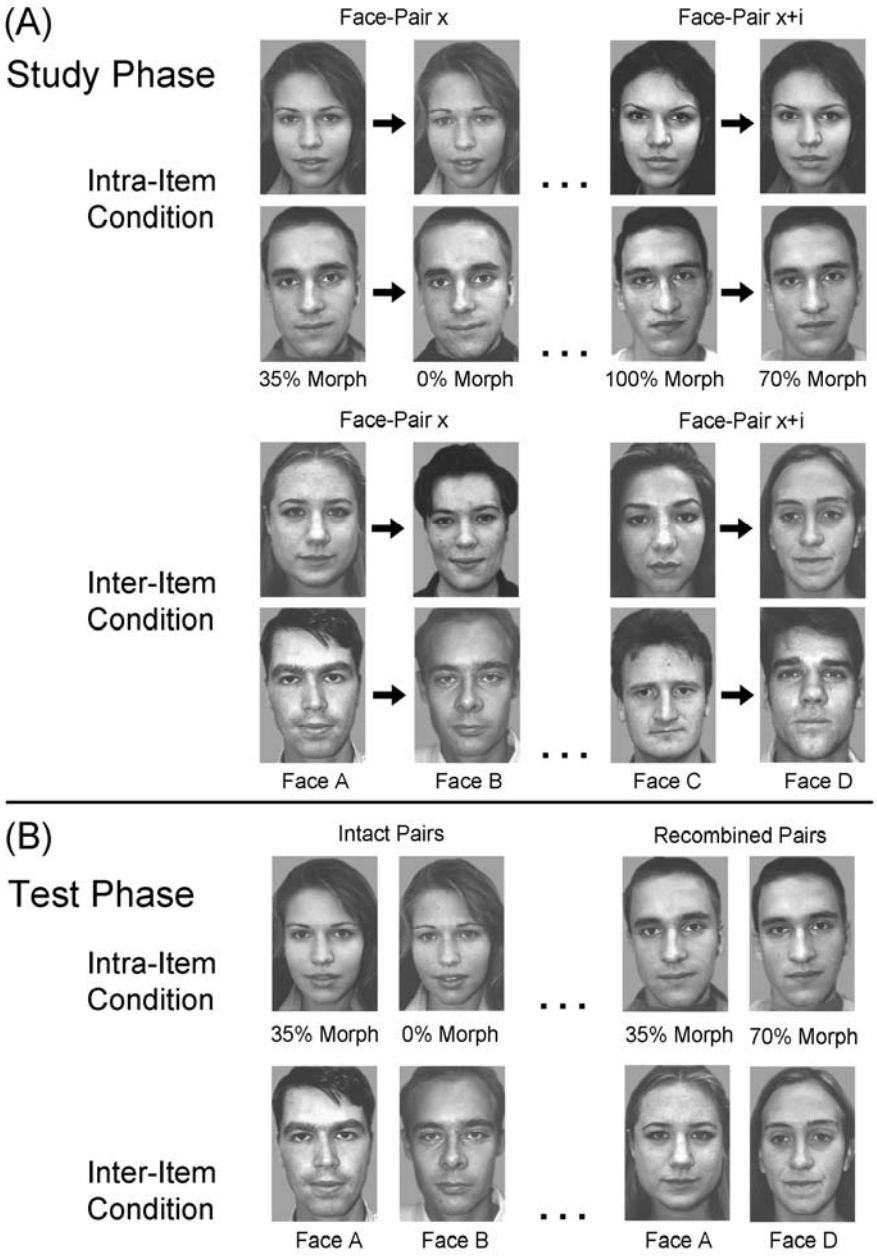


Figure 3: Illustration of the study and the test phase of the associative recognition memory task (the task as used in Experiment 1 is shown).

Across all intra- and inter-item condition blocks, half of the face-pairs were female and male, respectively. Moreover, for both intact and recombined face-pairs, the assignment of the first study faces and the second study faces to the left or right side of the screen within test face-pairs was counterbalanced within and across participants. The random assignment of the particular face-pairs to the 25 blocks was kept constant across all participants, but the sequence of blocks was pseudorandomly intermixed for every participant with the constraints that there were no more than two consecutive blocks from the same condition and that one half of participants commenced with an intra- or an inter-item block, respectively. Before starting the experiment, participants performed four practice blocks of the task using faces that did not appear during the subsequent 25 blocks. Responses were given on the computer keyboard, and the mapping of response type to response keys was counterbalanced across participants, for both the study phase and the test phase.

Associative recognition memory performance was measured by the proportion of hits (i.e., the proportion of responses 1-3 for intact pairs), the proportion of correct rejections (i.e., the proportion of responses 4-6 for recombined pairs), the area under the ROC curve (A_z; i.e., a bias-free measure of recognition sensitivity; cf. Quamme et al., 2007), and recognition decision times for hits and correct rejections.

ROC analysis

To test our specific predictions regarding the contributions of familiarity and recollection to associative recognition judgments across conditions, a formal dual-process model including the processes of familiarity and recollection was fitted to the empirically obtained ROC points (i.e., the proportions of hits and false alarms across confidence levels) in order to obtain behavioral estimates of familiarity and recollection (see Arndt & Reder, 2002; Yonelinas, 1999, 2001a; Yonelinas et al., 1996). This model conceptualizes familiarity as a Gaussian equal-variance signal-detection process whereby the probability of accepting an item depends upon sensitivity (*d'*, the distance between the means of the old and new distributions,

which provides a measure of familiarity) and response criterion (c_i). If performance only relies on familiarity, the probability that an old item's familiarity exceeds the response criterion is $P(\text{'yes'}|\text{old})_i = \Phi(d'/2 - c_i)$ and the probability that a new item is sufficiently familiar to be incorrectly accepted as ‚old' is $P(\text{'yes'}|\text{new})_i = \Phi(-d'/2 - c_i)$.

By also taking into account the potential contributions of recollection, the model assumes that the probability of a hit is $P(\text{'yes'}|\text{old})_i = R_o + (1 - R_o) * \Phi(d'/2 - c_i)$. This equation reflects the assumption that a hit occurs when an old item is either recollected [i.e., R_o] or accepted on the basis of familiarity given that the item is not recollected [i.e., $(1 - R_o)*\Phi(d'/2 - c_i)$]. Importantly, findings show that in associative recognition memory tasks participants can also sometimes recollect new items as 'new' (R_n) (Rotello & Heit, 2000; Rotello et al., 2000). For example, given that face-pairs A+B and C+D were encoded, an individual may recollect a recombined pair A+C as 'new' (i.e., 'recombined') because he/she can recollect that A was paired with B. Thus, in the formal dual-process model we allowed the possibility that new (i.e., recombined) items can be recollected as 'new'. In consequence, false alarms only occur when a new item is sufficiently familiar to be judged as 'old' in the absence of recollection that the item is new. Hence, the probability of a false alarm is $P(\text{'yes'}|\text{new})_i = (1 - R_n)*\Phi(-d'/2 - c_i)$. Note that this formal dual-process model also includes the possibility that only one of the processes (i.e., familiarity or recollection) contributes to associative recognition memory, as the process estimates can also have values of zero.

To summarize, the final equations of the applied dual-process model are: $P(\text{'yes'}|\text{old})_i = R_o + (1 - R_o) * \Phi(d'/2 - c_i)$ and $P(\text{'yes'}|\text{new})_i = (1 - R_n)*\Phi(-d'/2 - c_i)$. Each point on the ROC is described by these equations. Assuming that memory (i.e., R_o, R_n, & d') remains constant across the ROC and only response criterion c_i varies, then the equations can be used to derive estimates for the parameters of the model. This was done using Microsoft Excel's Solver (see Dodson, Prinzmetal, & Shimamura, 1998) to find the best fitting parameters for the equations by minimizing the sum of squared errors between observed and predicted values (cf. Yonelinas et al., 1996).

2.2.3.2 Results

Study phase performance

Participants accurately judged the gender of both the first and the second faces of each face-pair (96.2% and 98.8% correct judgments, respectively). An analysis of variance (ANOVA) examined decision times for gender judgments (see Table 1) using the within-subjects factors of Condition (intra- vs. inter-item condition) and Face (first vs. second face). There was no statistically significant main effect of Condition, $F(1,19) = 4.17$, $p = .055$, but a significant main effect of Face, $F(1,19) = 7.19$, $p = .015$, reflecting faster responses for the second than the first faces. There was also a reliable Condition by Face interaction, $F(1,19) = 13.27$, $p = .002$, reflecting faster response times for the second study faces in the intra- compared to the inter-item condition.

Table 1

	Experiment 1		Experiment 2	
	Intra-Item Condition	Inter-Item Condition	Intra-Item Condition	Inter-Item Condition
Decision Times for Gender Judgments 1st Study Faces [ms]	729 (38)	734 (39)	--	--
Decision Times for Gender Judgments 2nd Study Faces [ms]	656 (49)	699 (52)	--	--
Proportion of Hits	.71 (.02)	.57 (.02)	.74 (.03)	.58 (.03)
Proportion of Correct Rejections	.46 (.03)	.55 (.03)	.58 (.02)	.66 (.02)
Area Under the ROC (A_z)	.65 (.03)	.60 (.03)	.72 (.02)	.68 (.02)
Recognition Decision Times for Hits [ms]	1678 (97)	1859 (102)	2002 (108)	2053 (97)
Recognition Decision Times for Correct Rejections [ms]	1981 (86)	1907 (89)	2444 (161)	2307 (133)

Table 1: Study phase and test phase performance and decision times for Experiments 1 and 2.

Note. Standard errors of the means are presented in parenthesis.

Associative recognition memory performance

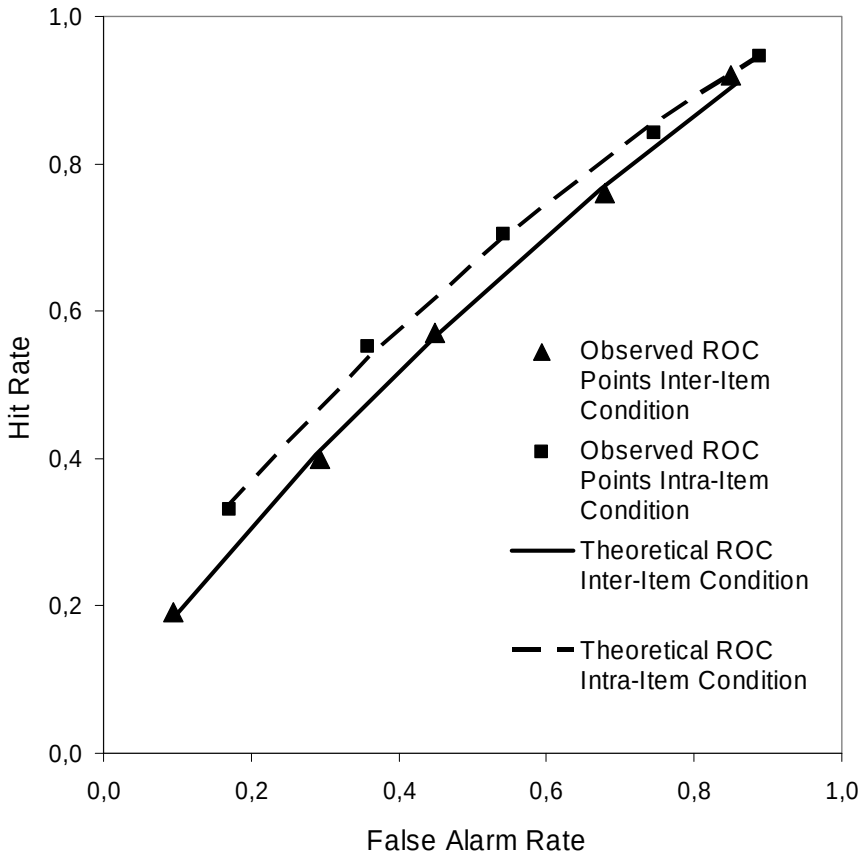
Table 1 presents the proportion of hits and correct rejections, the area under the ROC curve (A_z-values), and recognition decision times. The proportion of hits was higher in the intra- than the inter-item condition, $F(1,19) = 34.54$, $p < .001$. Conversely, the proportion of correct rejections was higher in the inter- than the intra-item condition, $F(1,19) = 9.70$, $p = .006$. Importantly, A_z -values did not differ significantly between conditions and were only slightly higher in the intra- than the inter-item condition, $F(1,19) = 2.66$, $p = .119$, indicating comparable associative recognition memory performance across conditions. Analyses of recognition decision times revealed that hits occurred faster in the intra- than the inter-item condition, $F(1,19) = 13.64$, $p = .002$, whereas no difference in recognition decision times emerged for correct rejections, $F(1,19) = 2.26$, $p = .149$.

ROC analyses

First, we calculated the empirical ROC points for cumulated responses across participants. Observed proportions of hits and false alarms across response criteria are shown in Figure 4 (upper row). Next, *z*-ROC curves were derived from the empirical ROCs and are also shown in Figure 4 (lower row). We then examined the shape of the *z*-ROCs to determine whether they were linear or curvilinear. Because *x*- and *y*-axes in (*z*-)ROCs are arbitrary, *x* was regressed onto *y* in a first regression, and *y* was regressed onto *x* in a second regression (cf. Yonelinas, 1999; Yonelinas et al., 1999). For the inter-item condition, both regressions revealed that the *z*-ROC had a significant linear term (first regression: $t = 42.67$, $p = .001$, second regression: $t = 42.32$, $p = .001$), and a marginally significant quadratic term (first regression: $t = 3.07$, $p = .092$, second regression: $t = -3.56$, $p = .071$; cf. Experiment 2 for evidence that these trends truly reflect statistically significant quadratic terms in the inter-item condition). Hence, the *z*-ROC for the inter-item condition appeared to be curvilinear rather than linear. For the intra-item condition, both regressions revealed that the *z*-ROC had a significant linear term (first regression: $t = 32.23$, $p = .001$, second

regression: t = 18.07, p = .003), but no quadratic term (first regression: t =.69, p = .563, second regression: t = -.78, p = .518). Hence, the z-ROC for the intra-item condition appeared to be linear rather than curvilinear.

Figure 4



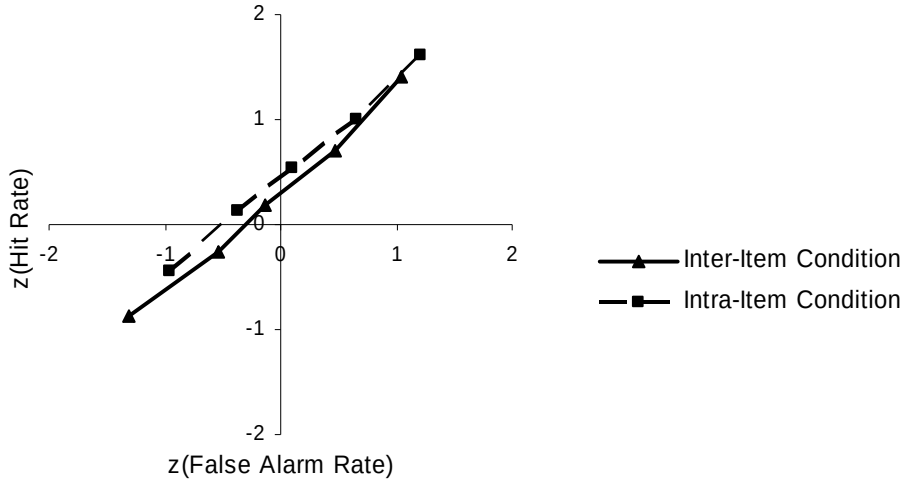


Figure 4: Observed ROC points and fitted theoretical ROC curves (upper row) and corresponding *z*-ROC curves (lower row) from Experiment 1.

Notes: Triangles and squares represent (z-transformed) observed proportions of hits and false alarms across response criteria. In the ROC diagram (upper row), lines represent the fitted theoretical ROC curves derived from the formal dual-process model.

Fitting the dual-process model. In the next step, we fitted the dual-process model as described above to the empirical ROC points. The model was used to derive estimates for familiarity (*d*'), recollection for intact pairs (R_o), and recollection for recombined pairs (R_n) from both cumulated and individual ROC curves. Model-generated curves for cumulated ROC points are shown as lines in Figure 4 (upper row). As can be seen in Figure 4, there was an accurate fit of the model to the empirical ROC points in both conditions. Minimizing the sum of squared error terms for the difference between observed and expected values on the cumulated ROCs revealed the parameter estimates shown in Figure 5. As can be seen in Figure 5, familiarity (*d*') was substantially higher in the intra-item condition compared to the inter-item condition. By contrast, there were only small differences for recollection, such that recollection for intact pairs (R_o) was slightly higher for the intra- than the inter-item condition, whereas recollection for recombined pairs (R_n) was slightly higher for the inter- than the intra-item condition.

To test the statistical significance of these observations, the model was next fit to individual ROCs in order to obtain parameters for every participant. The mean estimates for d', R_o, and R_n derived from individual ROCs are presented in Figure 5 and were of comparable magnitude as the parameter values derived from cumulated ROCs. These estimates were subjected to a Condition (inter- vs. intra-item condition) by Estimate (d', R_o, R_n) ANOVA, which revealed significant main effects of Condition, $F(1,19) = 4.92$, $p = .039$, and of Estimate, $F(2,38) = 12.24$, $p < .001$, but most importantly a significant Condition by Estimate interaction, $F(2,38) = 10.07$, $p = .001$. The interaction supported our expectation that the three estimates were differentially modulated by the condition factor. Planned comparisons (using one-tailed p-values because of our directional hypotheses) revealed that familiarity (d') was significantly higher for the intra- than the inter-item condition, $t(19) = 3.30$, $p = .002$. Conversely, recollection for recombined face-pairs (R_n) was significantly larger for the inter- than the intra-item condition, $t(19) = 2.14$, $p = .023$. By contrast, there was no difference between conditions for recollection of intact face-pairs (R_o), $t(19) = .07$, $p = .472$.

Figure 5

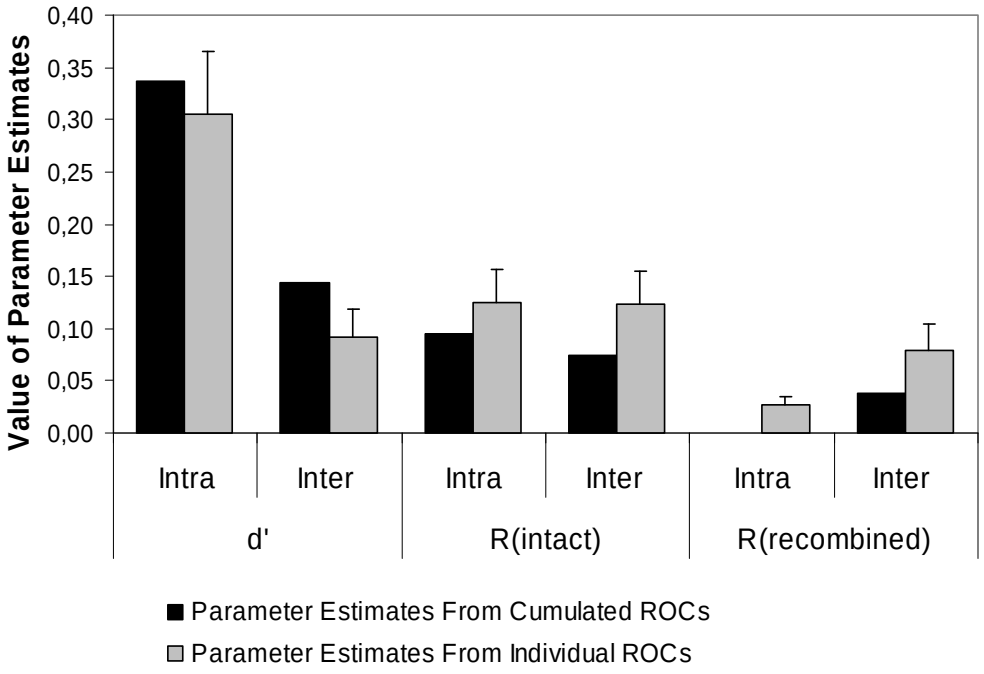


Figure 5: Parameter estimates for cumulated and individual ROCs for Experiment 1.

Notes: Parameter estimates were derived using the formal dual-process model. Error bars represent standard errors of the means. In the intra-item condition, the value of *R*(recombined) is zero for parameter estimates from cumulated ROCs.

2.2.3.3 Discussion of Experiment 1

Experiment 1 revealed several results that were consistent with our hypotheses. The main findings were that familiarity estimates as derived from ROC curves were higher in the intra- than the inter-item condition. Conversely, recollection estimates for recombined pairs were higher in the inter- than the intra-item condition. Before discussing the findings in detail, two objections against the interpretation of these results in light of dual-process models of recognition memory have to be addressed. First, associative recognition memory performance was relatively low in both conditions, which might have influenced the estimates of

familiarity and recollection in different ways. Second, the study and test phases were separated by a relatively short (20 s) retention interval that is shorter than retention intervals used in other tasks examining episodic long term memory (e.g., Giovanello et al., 2006), although we believe that despite the short retention interval, the task can be considered as tapping episodic long-term memory because of the large amount of to-be-remembered information and the presence of a distracting activity that prevents actively rehearsing the information during the 20 s delay

To address these two issues, a second experiment was conducted. In this experiment, task performance was enhanced by presenting the face-pairs longer and simultaneously rather than sequentially, and the retention interval was increased from 20 to 40 s.

2.2.4 Experiment 2

2.2.4.1 Methods

Participants

Thirty-two, mostly undergraduate students (16 females) provided informed consent to participate in return for cash payment of 8 Euro/hour. Participants were screened for conditions of neurological or psychiatric disorders using a questionnaire, which revealed no such conditions. Four participants were excluded from analyses because of their poor associative recognition memory performance (these participants produced more false alarms than hits); the data from one participant were incomplete due to computer breakdown. Thus, data from 27 participants were included in the following analyses. Mean age of the 27 participants was 24.93 years (*SD* = 3.57, range = 20-35).

Materials and Procedure

Face stimuli. The same face stimuli were used as in Experiment 1.

Associative recognition memory task. The same task as in Experiment 1 was used with the following modifications: (1) The gender judgment task was omitted in order to reduce the cognitive demands during encoding. (2) The presentation and timing of study phase stimuli was altered as follows: Each study trial started with a fixation cross (500 ms). Thereafter, the two face stimuli of each face-pair that had to be associated were presented side by side (3000 ms) instead of sequentially. A blank screen was presented (1000 ms), after which the next study trial started. (3) Between the study and the test phase, a distracter task highly similar to the one in Experiment 1 was performed (i.e., participants had to count aloud backwards in steps of 6, 7, 8, or 9 from a randomly presented number between 300 and 400), but the duration of the task was increased to 40 s. (4) The presentation and timing of test phase stimuli was altered as follows: Each test trial started with a fixation cross (500 ms). Thereafter, a pair of face stimuli was presented side by side (50% intact and 50% recombined face-pairs, respectively). The face-pairs stayed on the screen until a response was made or for maximally 3000 ms. Before the next test trial started, a blank screen was presented for 1000 ms.

2.2.4.2 Results

Associative recognition memory performance

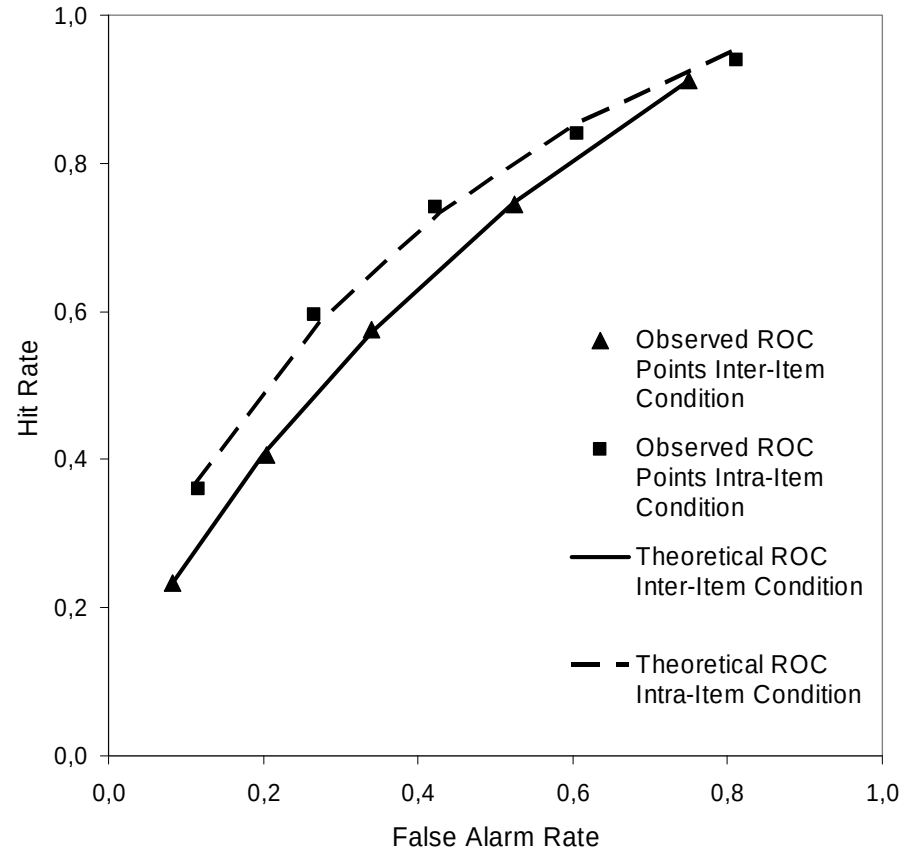
Table 1 presents the proportion of hits and correct rejections, A_z-values, and recognition decision times for Experiment 2. Consistent with Experiment 1, the proportion of hits was higher in the intra- than the inter-item condition, $F(1,26) = 50.08$, $p < .001$. Conversely, the proportion of correct rejections was higher in the inter- than the intra-item condition, $F(1,26) = 16.43$, $p < .001$. The area under the ROC (A_z) did not differ significantly between conditions and was only slightly higher in the intra- than the inter-item condition, $F(1,26) = 3.07$, $p = .091$, indicating comparable associative recognition memory performance across conditions. Analyses of recognition decision times revealed no condition differences for hits, $F(1,26) =$

1.10, $p = .303$, whereas correct rejections occurred faster in the inter- than the intra-item condition, $F(1,26) = 8.70$, $p = .007$.

ROC analyses

Observed proportions of hits and false alarms across response criteria (i.e., empirical ROC points for cumulated responses across participants) are shown in Figure 6 (upper row). The derived empirical *z*-ROCs are also shown in Figure 6 (lower row). The shape of the *z*-ROCs was again examined by applying regression analyses. For the inter-item condition, both regressions revealed that the *z*-ROC had a significant linear term (first regression: $t = 76.05$, $p < .001$, second regression: $t = 76.95$, $p < .001$) as well as a significant quadratic term (first regression: $t = 5.03$, $p = .037$, second regression: $t = -4.85$, $p = .040$). Hence, consistent with Experiment 1, the *z*-ROC for the inter-item condition appeared to be curvilinear rather than linear. For the intra-item condition, both regressions revealed that the *z*-ROC had a significant linear term (first regression: $t = 29.51$, $p < .001$, second regression: $t = 18.19$, $p = .003$), but no quadratic term (first regression: $t = -1.96$, $p = .189$, second regression: $t = 2.10$, $p = .171$). Hence, consistent with Experiment 1, the *z*-ROC for the intra-item condition appeared to be linear rather than curvilinear.

Figure 6


1,0
0,8
0,6
0,4
0,2
0,0
Hit Rate
0,0
0,2
0,4
0,6
0,8
1,0
False Alarm Rate
Observed ROC Points Inter-Item Condition
Observed ROC Points Intra-Item Condition
Theoretical ROC Inter-Item Condition
Theoretical ROC Intra-Item Condition

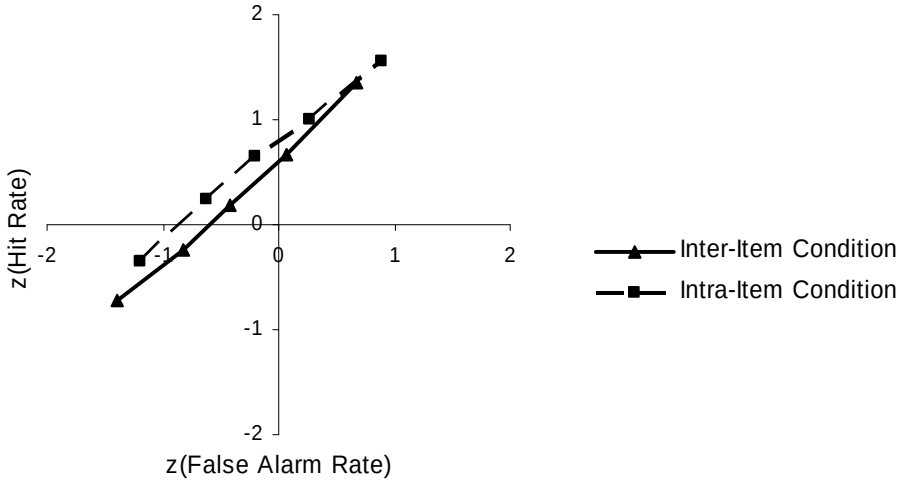

2
1
0
-1
-2
z(Hit Rate)
-2
-1
0
1
2
z(False Alarm Rate)
Inter-Item Condition
Intra-Item Condition

Figure 6: Observed ROC points and fitted theoretical ROC curves (upper row) and corresponding *z*-ROC curves (lower row) from Experiment 2.

Notes: Triangles and squares represent (z-transformed) observed proportions of hits and false alarms across response criteria. In the ROC diagram (upper row), lines represent the fitted theoretical ROC curves derived from the formal dual-process model.

Fitting the dual-process model. In the next step, we fitted the dual-process model as in Experiment 1 to the empirical ROC points. Model-generated curves for cumulated ROC points are shown as lines in Figure 6 (upper row). As can be seen in Figure 6, there was an accurate fit of the model to the empirical ROC points in both conditions. Minimizing the sum of squared error terms for the difference between observed and expected values on the cumulated ROCs revealed the parameter estimates shown in Figure 7. As can be seen in Figure 7, familiarity (*d*') was higher in the intra-item condition compared to the inter-item condition. By contrast, there were only small differences for recollection, such that recollection for intact pairs (R_o) was slightly higher for the intra- than the inter-item condition, whereas recollection for recombined pairs (R_n) was slightly higher for the inter- than the intra-item condition.

To test the statistical significance of these observations, the model was next fit to individual ROCs in order to obtain parameters for every participant. The mean estimates for *d*', R_o, and R_n derived from individual ROCs are presented in Figure 7. These estimates were subjected to a Condition (inter- vs. intra-item condition) by Estimate (*d*', R_o, R_n) ANOVA, which revealed significant main effects of Condition, $F(1,26) = 4.98$, $p = .034$, and of Estimate, $F(2,52) = 17.75$, $p < .001$. Most importantly and consistent with Experiment 1, there was a significant Condition by Estimate interaction, $F(2,52) = 5.48$, $p = .007$. The interaction supported our expectation that the three estimates were differentially modulated by the condition factor. Planned comparisons (using one-tailed *p*-values because of our directional hypotheses) revealed that familiarity (*d*') was significantly higher for the intra- than the inter-item condition, $t(26) = -2.40$, $p = .012$. Conversely, recollection for recombined face-pairs (R_n) was significantly larger for the inter- than the intra-item

condition, $t(26) = 2.53$, $p = .009$. By contrast, there was no difference between conditions for recollection of intact face-pairs (R_o), $t(26) = -.42$, $p = .388$.

Figure 7

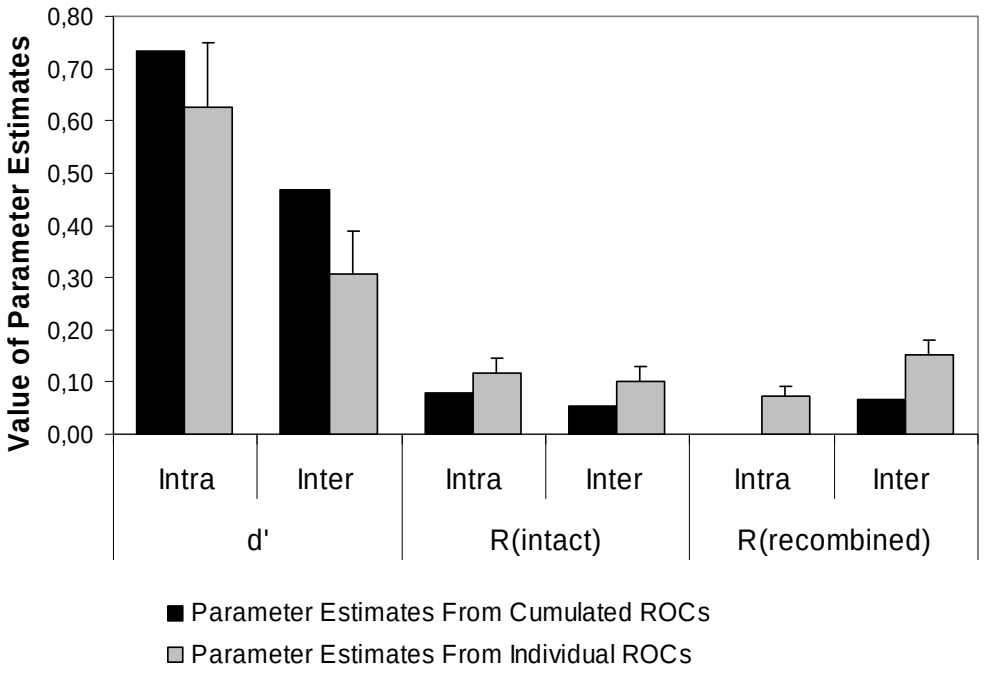


Figure 7: Parameter estimates for cumulated and individual ROCs for Experiment 2.

Notes: Parameter estimates were derived using the formal dual-process model. Error bars represent standard errors of the means. In the intra-item condition, the value of *R*(recombined) is zero for parameter estimates from cumulated ROCs.

2.2.4.3 Discussion of Experiment 2

Experiment 2 revealed results that were essentially the same as those of Experiment 1. Importantly, the findings of Experiment 1 could be replicated in the second experiment by using a task that allowed a higher level of associative recognition memory performance and by introducing longer retention intervals between the study and the test phases (i.e., 40 s instead of 20 s). These results indicate

that the findings of Experiment 1 were not significantly influenced by the low level of memory performance or the length of the retention interval.

2.2.5 General Discussion of Study 1

In the present experiments, we compared two types of associative recognition memory situations: Participants either memorized face-pairs depicting two different, arbitrarily paired persons (inter-item condition) or pairs of physically different photographs that were perceived as representing the same person (intra-item condition). Besides these differences in face similarity within face-pairs, the length of study blocks was adjusted to obtain similar associative recognition memory performance across both conditions. Indeed, A_z-values reflecting associative recognition sensitivity did not differ significantly across conditions, although they were slightly higher in the intra- compared to the inter-item condition (Table 1). The main aim of our study was to examine whether familiarity can support associations between unitizable stimuli. In line with previous studies revealing that familiarity may support associative recognition memory if the to-be-associated items can be integrated into a coherent whole, a bound or unitized representation (Jäger et al., 2006; Opitz & Cornell, 2006; Quamme, 2004; Quamme et al., 2007; Rhodes & Donaldson, 2007; Yonelinas et al., 1999; see also Eichenbaum, 1997), we expected a significantly higher contribution of familiarity in the intra- relative to the inter-item condition.

Across both experiments, regression analyses revealed a linear *z*-ROC for the *intra-item condition*, indicating that mainly familiarity contributed to intact/recombined judgments whereas recollection seemed to play a less prominent role (Figures 4 & 6). Indeed, applying the formal dual-process model to individual ROCs revealed a significantly higher estimate of familiarity for the intra- compared to the inter-item condition in both experiments (Figures 5 & 7). Hence, this result provides further evidence for the hypothesis that familiarity can support associative recognition memory judgments in situations where the to-be-associated items are

unitized or integrated into a coherent whole. The greater contribution of familiarity in the intra-item condition may have produced the significantly higher proportion of hits in the intra- compared to the inter-item condition.

By contrast, consistent with the assumption that associative recognition memory for unrelated stimuli mainly relies on recollection, results from regression analyses suggested that the *z*-ROC obtained in the *inter-item condition* was curvilinear (i.e., U-shaped) rather than linear (Figures 4 & 6). This result suggests the additional contribution of recollection in the inter-item condition. (Note that we do not wish to claim that there is *no* contribution of familiarity in the inter-item condition. Rather, we tested the hypothesis that the contribution of recollection is *greater* in the inter- than the intra-item condition.) Applying the formal dual-process model to individual ROC curves revealed that although recollection for intact pairs (R_o) did not differ across conditions, across both experiments there was a significantly higher contribution of recollection for the rejection of recombined pairs (R_n) in the inter- compared to the intra-item condition (Figures 5 & 7). This latter finding is consistent with the expectation that participants can recollect recombined face-pairs as 'recombined' to a higher degree in the inter- compared to the intra-item condition, because recollection is assumed to break down when the overlap between to-be-associated information is too high, such as in the present intra-item condition (McClelland, McNaughton, & O'Reilly, 1995; Schacter Norman, & Koutstaal, 1998). In consequence, the significantly greater proportion of correct rejections in the inter-item condition may be accounted for by the fact that recollection supported the rejection of recombined pairs to a higher degree in the inter- compared to the intra-item condition.

Although recollection for intact face-pairs could be expected to be higher in the inter- compared to the intra-item condition because recollection is thought to support associations between unrelated stimuli and may break down when the overlap between to-be-associated stimuli is too high (cf. Jäger et al., 2006), there were no condition differences in recollection for intact face-pairs. This result may have arisen from the fact that estimates for recollection were generally relatively low in both

conditions, perhaps providing little space for differences between conditions. Another argument may be that intact/recombined decision performance was slightly (but non-significantly) poorer in the inter- compared to the intra-item condition, which may have further lowered recollection in the inter-item condition. However, the fact that recollection for the rejection of recombined face-pairs was present to a significantly higher degree in the inter- relative to the intra-item condition supports the conclusion that recollection plays a more important role in associative recognition judgments for arbitrarily paired faces.

In sum, the present findings provide empirical evidence that familiarity contributes to associative judgments to a higher degree in the intra-item condition – because here the to-be-associated stimuli can be unitized – than in the inter-item condition, in which to-be-associated stimuli are arbitrarily paired and nonoverlapping. Our results extend the results of previous studies by using a different paradigm, different materials (i.e., face-pairs rather than words or facial features), and different operational definitions of familiarity and recollection (i.e., behavioral rather than electrophysiological measures of these processes). Moreover, in contrast to most other studies we used a task in which associations between unitizable stimuli were formed during the experiment rather than being pre-experimentally existing associations in semantic memory. However, the present study also has several limitations. First, the conclusions were exclusively drawn from the analyses of ROC curves. Hence, additional evidence beyond ROC analyses is needed to firmly establish that familiarity plays a greater role for the retrieval of intra- than inter-item associations. However, we would like to point to findings of other studies that converge with the present results by providing support for the "unitization hypothesis" that familiarity can contribute to associative recognition memory given that the stimuli can be unitized (for patient data, see Giovanello et al., 2006; Quamme et al., 2007; for electrophysiological evidence using a similar task as in the present study, see Jäger et al., 2006; see also Rhodes & Donaldson, 2006).

A second limitation is that the present results are constrained by specific model assumptions on the nature of familiarity and recollection as proposed by

Yonelineas and colleagues (e.g., Yonelinas et al., 1996). However, there exist several models which conceptualize recollection as a continuous, normally distributed memory process (see Wixted, 2007), by this raising the possibility that the specific model assumptions included in the present study may have produced invalid results. Again, we would like to refer to studies that used alternative operational definitions of familiarity and recollection and revealed converging evidence for the "unitization hypothesis" without relying on specific model assumptions (for patient data, see Giovanello et al., 2006; Quamme et al., 2007; for electrophysiological evidence, see Jäger et al., 2006; Rhodes & Donaldson, 2006). A third limitation is that the present experiments used relatively short time intervals between study and test (i.e., 20 or 40 s). Hence, future studies should investigate whether our findings generalize to retention intervals of hours, days, or even longer. A final limitation is that the picture database used for the present experiments did not contain enough face stimuli to enable the creation of two sets of stimuli that could be used with equal probability across the intra- and the inter-item condition. Hence, we were constrained to use different face stimuli across conditions.

In light of the findings supporting the "unitization hypothesis", the question arises about the particular mechanisms through which familiarity can support associative episodic memory. One possibility could in part be derived from the neurocomputational dual-process model put forth by Norman and O'Reilly (2003; see also Aggleton & Brown, 1999). The model assumes that the hippocampal formation is critical for recollection because the hippocampus can establish connections between arbitrarily paired items represented in medial temporal lobe cortex (MTLC). Specifically, the hippocampus creates pattern-separated representations of to-be-associated stimuli in region CA3. At test, pattern-completion enables recollecting the complete studied pattern in response to a partial cue. By this, the hippocampus plays an important role in establishing and retrieving associations between non-overlapping MTLC representations such as the arbitrarily paired faces in the inter-item condition. This mechanism is illustrated in Figure 8, showing how non-overlapping MTLC

representations A and B are linked to each other through sparse, pattern-separated representations in hippocampus.

By contrast, hippocampal recollection is presumed to break down when the overlap between to-be-associated information is too high, since the hippocampus cannot create pattern-separated representations in this case (McClelland et al., 1995; Schacter et al., 1998). Importantly, this could occur for highly overlapping stimuli such as the faces of the intra-item condition. For such intra-item associations, the MTLC (i.e., perirhinal, entorhinal, and parahippocampal cortices), which is thought to be able to generate familiarity signals (Gonsalves, Kahn, Curran, Norman, & Wagner, 2005; Henson, Cansino, Herron, Robb, & Rugg, 2003; Norman & O'Reilly, 2003), may play a critical role. The MTLC is suggested to assign similar representations to similar stimuli. Thus, in the intra-item condition, MTLC representations of faces of each face-pair can be expected to overlap substantially, by this resulting in a connection between the two stimuli in the form of a unitized representation that involves enhanced activation of overlapping features and reduced activation of nonoverlapping ones (a process termed "sharpening"; Norman & O'Reilly, 2003). While the exact nature of these MTLC connections remains unclear, this proposed mechanism is consistent with findings that familiarity supports associative retrieval of items that can be integrated into a coherent whole, a bound or unitized representation (Jäger et al., 2006; Opitz & Cornell, 2006; Quamme, 2004; Quamme et al., 2007; Rhodes & Donaldson, 2007; Yonelinas et al., 1999; see also Eichenbaum, 1997). Figure 8 shows how MTLC familiarity may connect highly overlapping representations B and D through a unitized representation, whereas this association likely cannot be formed via hippocampal pattern-separation (note that the mechanism of MTLC familiarity to support associative memory through unitization of representations is not explicitly included in the model of Norman & O'Reilly, 2003).

Figure 8

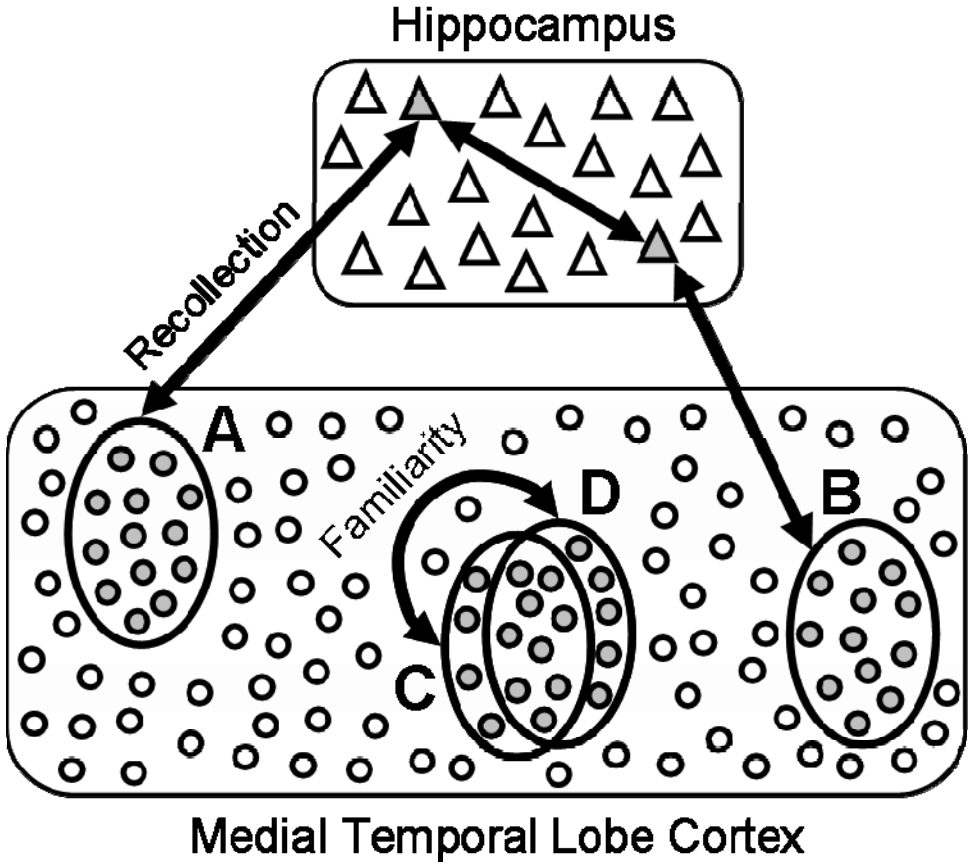


Figure 8: Hypothetical model how familiarity may support associative recognition memory.

Notes: Hippocampus is suggested to support associations between non-overlapping medial temporal lobe cortex (MTLC) representations A and B by connecting sparse, pattern-separated hippocampal representations of the stimuli (gray triangles). Pattern-completion results in recollection of stimulus B when stimulus A is presented at test. MTLC assigns highly overlapping representations to similar stimuli C and D. In this case, hippocampus has difficulty establishing pattern-separation and the recollection mechanisms breaks down. By contrast, MTLC familiarity may support associations between highly overlapping stimuli C and D. *Legend*: ellipses = representations of individual faces in MTLC (i.e., A, B, C, D); triangles = individual units of hippocampus; small circles = individual units of MTLC.

In conclusion, there is growing evidence from various studies challenging the proposal that associative recognition memory relies exclusively on recollection

without benefiting from familiarity. Some of these studies used pre-experimentally associated word-pairs and found that familiarity can support associative recognition memory of such bound representations (i.e., Giovanello et al., 2006; Quamme, 2004; Rhodes & Donaldson, 2007). Other studies using newly learned word-pairs (Quamme, 2004; Quamme et al., 2007), facial features (Yonelinas et al., 1999), or pairs of faces (Jäger et al., 2006) revealed that unitization of stimuli established during the experiment can also render associative recognition memory to benefit from familiarity. The present findings add to this growing body of literature investigating the subprocesses underlying associative recognition memory by indicating that familiarity and recollection may subserve distinct types of associative retrieval: While recollection seems to enable retrieval of associations between arbitrarily paired, non-overlapping items (such as photographs from two different persons), familiarity may support associative recognition memory in situations where the to-be-associated items are unitized or integrated into a coherent whole (such as two physically different photographs depicting the same person), even in situations in which the stimuli are not pre-experimentally associated in semantic memory.

2.2.6 Conclusions of Study 1

Study 1 applied two experimental conditions that reliably differentiated the contributions of familiarity and recollection to associative recognition memory performance (cf. Jäger et al., 2006). Importantly, Experiment 2 indicated that the findings of Experiment 1 were not confounded or influenced by low levels of associative recognition memory performance, by the particular presentation of the face stimuli (sequentially or simultaneously), or by the length of the retention interval between study and test. By this, Study 1 provided further support for the unitization hypothesis of associative recognition memory (Quamme, 2004) and for a distinction of two recognition memory subprocesses as proposed by dual-process theories (Yonelinas, 2002).

A further aspect of Study 1 that is worth noting is that the ERP evidence of Jäger et al. (2006; cf. Mecklinger & Jäger, 2009), which revealed that – using a very similar experimental paradigm as in Study 1 – intra- and inter-item associations can reliably dissociate the putative electrophysiological correlates of familiarity and recollection, received (at least partial) cross-validation through the application of an alternative operational definition of familiarity and recollection by the use of the ROC method. In consequence, the findings derived from purely neurophysiological data (Jäger et al., 2006) could be replicated across two independent experiments using a behavioral measure of familiarity and recollection (Study 1).

2.3 Study 2: Associative Recognition Memory for Faces: More Pronounced Age-Related Impairments in Binding Intra- Than Inter-Item Associations[2]

2.3.1 Rationale for Study 2

As Study 1, Study 2 was based on the finding that intra- and inter-item associations between unitizable or arbitrary face-pairs seem to promote familiarity- and recollection-based retrieval, respectively, and thus seem to reflect two situations with partly different underlying memory processes. Thus, Study 2 investigated the research question of whether the cognitive changes associated with normal aging results in a selective performance reduction in one of the two conditions as a result of relative disruption/preservation of familiarity and recollection in old age. In light of previous findings, which indicated a disruption of recollection but relative preservation of familiarity in normal cognitive aging (e.g., Bastin et al., 2003; Daselaar et al., 2006; Howard et al., 2006; for reviews see Light et al., 2000; Prull et al., 2006), it could be expected that intra- and inter-item associations dissociate familiarity and recollection in that older adults should be disproportionately impaired in their memory for arbitrary inter-item associations compared with younger adults.

However, it should be noted that no study has thus far explicitly investigated performance of older adults in memory for unitizable associations and that the literature of age effects on familiarity and recollection is still inconsistent (e.g., Duarte et al., 2006; Li et al., 2004), by this weakening the empirical fundament of the research hypothesis that older adults should show greater impairments in their memory for inter- compared to intra-item associations. In consequence, Study 2 explored whether older adults show more or less of a deficit when to-be-associated

[2]The data reported in this study are also reported in the following article: Jäger, T., Mecklinger, A., & Kliegel, M. (in press). Associative recognition memory for faces: More pronounced age-related impairments in binding intra- than inter-item associations. *Experimental Aging Research*.

items can be unitized into a single representation during encoding. By this, Study 2 aimed to contribute further evidence for the view that recognition memory involves more than one mnemonic subprocesses that can be dissociated in certain situations.

2.3.2 Introduction of Study 2

Recognition memory refers to the ability of becoming aware that a currently presented item or information has already been encountered some time in the past. Dual-process models propose that in general recognition memory is subserved by two qualitatively distinct processes termed *familiarity* and *recollection* (Aggleton & Brown, 2006; Jacoby, 1991; Mandler, 1980; Yonelinas, 2002). Familiarity is conceptualized as an item-specific, non-contextual memory process that seems to be generated by the cortex of the anterior medial temporal lobe (e.g., Henson, Cansino, Herron, Robb, & Rugg, 2003; Norman & O'Reilly, 2003). By contrast, recollection-based recognition is thought to enable the retrieval of contextual information, such as the spatio-temporal context in which an item was encountered, and is assumed to be strongly dependent on the hippocampal formation (e.g., Montaldi, Spencer, Roberts, & Mayes, 2006; Yonelinas, Otten, Shaw, & Rugg, 2005).

Within the field of cognitive aging, some studies revealed that older adults show smaller deficits in familiarity than in recollection (e.g., Bastin & Van der Linden, 2003; Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006; Howard, Bessette-Symons, Zhang, & Hoyer, 2006). However, it should be noted that the pattern of age differences in familiarity and recollection is still highly controversial (see e.g., Davidson & Glisky, 2002; Duarte, Ranganath, Trujillo, & Knight, 2006; Li, Morcom, & Rugg, 2004; Toth & Parks, 2006), as different studies, different theoretical assumptions on the relationship between familiarity and recollection, and different operational definitions for both processes have produced inconsistent results (for reviews see Light, Prull, LaVoie, & Healy, 2000; Prull, Dawes, Martin, Rosenberg, & Light, 2006). For instance, Duarte et al. (2006) provided combined behavioral and electrophysiological evidence that familiarity, rather than recollection,

is more sensitive for the deleterious effects of normal aging in a recognition memory paradigm using pictorial stimuli. Li et al. (2004) found that in one of their conditions older adults achieved equal performance as younger adults in source recognition memory judgments despite poorer performance in item recognition memory, indicating that the older adults evidenced reduced familiarity but intact recollection for the applied pictorial stimuli.

The present work examines age effects on *associative* recognition memory, which requires individuals to retrieve particular pairings of stimuli rather than purely judging the old/new status of single items as in *item* recognition memory tasks. Importantly, recollection is thought to be imperatively needed for the retrieval of item-pairings as is the case in associative recognition memory tasks (e.g., Yonelinas, 1997, 2002). In contrast, due to its proposed item-specific and non-contextual character, familiarity is not assumed to support associative recognition memory.

However, the claim that associative recognition memory is only supported by recollection without benefiting from familiarity has been challenged. Yonelinas, Kroll, Dobbins, and Soltani (1999) postulated that familiarity can contribute to associative retrieval given that the to-be-associated stimuli are encoded as a coherent whole and form a bound or 'unitized' representation. *Unitization* refers to conditions in which two or more previously separate items become represented as a single unit (Graf & Schacter, 1989). Thus, the unitization hypothesis posits that associations can be retrieved independently from recollection given that the associations have been unitized and by this support familiarity-based memory (Quamme, 2004). This has indeed been found to be possible for to-be-associated items that are perceived as a coherent entity (e.g., facial features that are holistically perceived as forming a face; Yonelinas et al., 1999), for pairs of items that frequently co-occur and thus share strong pre-experimental associations (e.g., word-pairs such as *sea-food* or *traffic-jam*; Giovanello, Keane, & Verfaellie, 2006; Quamme, 2004; Rhodes & Donaldson, 2007), for pairs of unrelated stimuli that are encoded as if they referred to a single object (Quamme, 2004; Quamme, Yonelinas, & Norman, 2001), or for pairs of words rated to reflect unitized representations to a high degree (Rhodes & Donaldson, 2007).

Further support for the unitization hypothesis was provided in an event-related brain potentials (ERP) study on associative recognition memory for face-pairs conducted in our lab (Jäger, Mecklinger, & Kipp, 2006). In a first condition, participants memorized *inter-item associations*, i.e., associations between pairs of face stimuli depicting two *different* persons. In a second condition, participants memorized *intra-item associations*, i.e., associations between pairs of physically different faces that were highly similar and thus perceived as depicting the *same* person, which enables the unitization of stimuli into the representation of a single item (i.e., person). Consistent with the assumptions of the dual-process account, we found that performance in the *inter*-item condition mainly relied on *recollection* without benefiting from familiarity. By contrast, in line with the unitization hypothesis, we found evidence that the retrieval of *intra*-item associations was supported by *familiarity* without the contribution of recollection. In terms of ERP correlates, we revealed that the retrieval of *intra*-item associations elicited the putative ERP correlate of familiarity, namely the *early frontal old/new effect*, whereas there was no putative ERP correlate of recollection, namely the *late parietal old/new effect*, indicating that memory for intra-item associations mainly relied on familiarity. Conversely, in the *inter*-item condition, we observed a strong late parietal old/new effect but no early frontal old/new effect, indicating that memory for inter-item associations exclusively relied on recollection and was not subserved by familiarity.

Within respect to the effects of cognitive aging on the memory for associations between items, it has been found that normal aging is associated with a substantial deficit in associative recognition memory for different types of arbitrary associations (Bastin & Van der Linden, 2006; Castel & Craik, 2003; Naveh-Benjamin, 2000; Naveh-Benjamin, Brav, & Levy, 2007; Naveh-Benjamin, Guez, Kilb, & Reedy, 2004; Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003). This age deficit is assumed to result from a reduction of recollection due to a disproportionally large loss of hippocampal volumes in old age (Raz et al., 2005). However, it should be noted that in some situations older adults may successfully compensate their lower memory performance for unrelated associations by recruiting strategic cognitive

processes (Cabeza, Anderson, Locantore, & McIntosh, 2002; cf. Naveh-Benjamin et al., 2007; see Buckner, 2004, for a review) such as effective encoding strategies that older adults seem to apply as efficiently as younger adults do (see Hertzog & Dunlosky, 2004, for a review). By contrast, there is so far no direct test of whether older adults also show disrupted memory performance for associations between stimuli *that can be unitized* at the time of encoding and thus may benefit from familiarity-based recognition at the time of retrieval.

In consequence, the present study examined whether healthy older adults show differential impairments in memory for intra- versus inter-item associations. Although most studies revealed that older adults show smaller deficits in familiarity than in recollection (see above), the pattern of age differences in familiarity and recollection is still highly controversial, with some studies reporting even stronger age effects on familiarity than on recollection (e.g., Duarte et al., 2006; Li et al., 2004). In spite of the inconsistencies in the literature, on the basis of the assumption that older adults may show smaller deficits in familiarity than in recollection, it could be expected that older adults exhibit only mild impairments in the formation and retrieval of (intra-item) associations between unitizable face stimuli. On the other hand, unitization during memory formation at encoding and familiarity-based recognition at retrieval are no isomorphic cognitive processes. Hence, unitization processes at encoding may be affected by old age even if the process of familiarity-based recognition is spared by cognitive aging. Thus, it is conceivable that older adults are specifically impaired in their memory for intra-item associations due to deficits in forming unitized associations at encoding. Applying a similar associative recognition memory task for unrelated and unitizable face-pairs as in our previous study (Jäger et al., 2006), we expected older adults to demonstrate reliable impairments in memory for inter-item associations. Due to the inconsistent findings in previous aging studies, it was an open issue if and how age may modulate memory performance for intra-item (i.e., unitized) associations.

2.3.3 Methods

Participants and Design

A total of 40 participants provided informed consent to participate in return for cash payment of 8 Euro/hour. There were 20 younger adults (12 females), mostly undergraduate students who had a mean age of 24.75 years (*SD* = 3.60, range = 20-31) and 20 older adults (10 females), who were community-dwelling volunteers and had a mean age of 66.05 years (*SD* = 3.41, range = 62-76). Older adults showed higher verbal abilities in a German vocabulary test (*Mehrfachwahl-Wortschatztest MWT-B*; Lehrl, 1977) than younger adults (IQ-scores [*M* ± *SE*]: younger adults: 110.85 ± 2.58; older adults: 125.40 ± 2.20; $t(38) = 4.29$, $p < .001$). In contrast, the two age groups did not differ in degree of education as measured on a 5-point scale ($t(38) = .15$), number of years of formal education ($t(38) = .59$), self-rated health as measured on a 5-point Likert scale ($t(38) = .92$), and number of currently taken medication ($t(38) = 1.77$, $p = .088$).

Several neuropsychological tests were applied to characterize the participants' cognitive status: (1) The *DemTect* battery (Kalbe et al., 2004) was used to screen participants for mild cognitive impairments, (2) the *digit-symbol substitution task* of the Wechsler-Adult-Intelligence-Scale Revised (Wechsler, 1981) was used to assess processing speed, (3) a paper-and-pencil version of the *Stroop task* was used to assess inhibitory control (Oswald & Fleischmann, 1997), and (4) a computerized *operation span task* was used to assess working memory (Conway & Engle, 1996). Results for these screening tests indicated that none of the participants showed signs of mild cognitive impairments, as all DemTect total transformed scores were at least 3 points above the cut-off score for the diagnosis of mild cognitive impairment. However, older adults evidenced slower speed of processing (digit-symbol substitution task: younger adults [*M* ± *SE*]: 71.25 ± 2.36; older adults: 45.95 ± 1.75; $t(38) = 8.61$, $p < .001$), poorer inhibitory control (Stroop task: younger adults: 8.80 ± .93; older adults: 15.35 ± 1.48; $t(38) = 3.76$, $p < .01$), and reduced working memory capacities (operation span task: younger adults: 22.85 ± 2.21; older adults: 14.95 ± 1.64; $t(38) = 2.87$, $p < .01$).

The design of this study involved a manipulation of the factors Age Group (younger vs. older adults) and Condition (intra- vs. inter-item condition), varied between and within subjects, respectively.

Materials

Face stimuli. Face stimuli were gray-scale photographs of unfamiliar and emotionally neutral faces drawn from a picture database (Jäger, Seiler, & Mecklinger, 2005). Among other variables, the database contains continua of *morphed faces*, i.e., sets of two different 'parent' faces that were gradually transformed into each other resulting in intermediate morphed faces. Of the available morph-continua, we selected the 0%, 35%, 70%, and 100% morphed faces to be used in the intra-item condition (see Figure 9 for illustration). Every morph-continuum was rated in a separate study for similarity on physical and identity dimensions (Jäger et al., 2005). For the intra-item condition we selected 36 morph-continua in which faces of neighboring morph-degrees were rated as clearly physically discriminable but still representing the same person to a high degree (see Jäger et al., 2005, 2006). Additionally, we selected 144 unmodified face stimuli from the picture database to form 72 face-pairs for the inter-item condition.

Figure 9

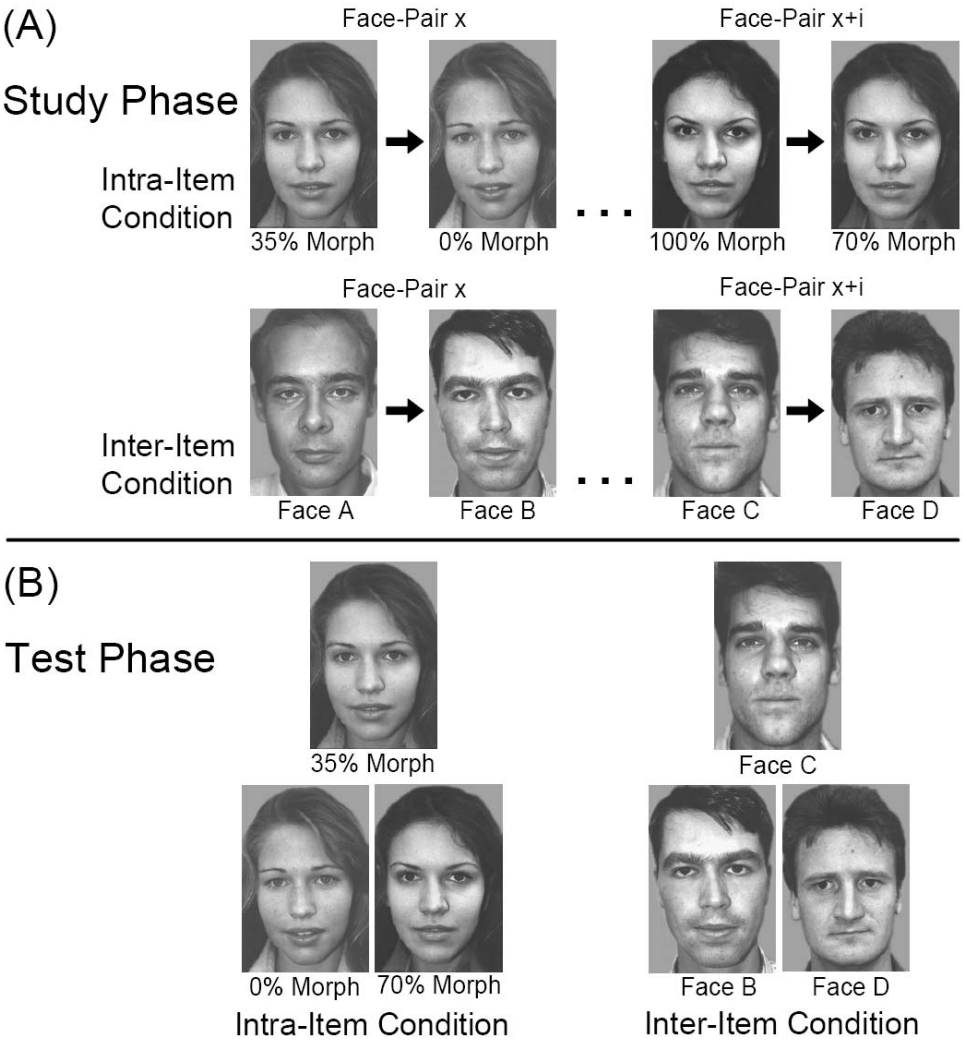


Figure 9: Illustration of the study and the test phase of the associative recognition memory task.

Associative recognition memory task. The associative recognition memory task was similar to the task used in Jäger et al. (2006), except that no novel faces were presented during the test phase. There were a total of 15 study-test blocks (6 blocks for the intra- and 9 blocks for the inter-item condition). In the *inter-item condition*, participants encoded face-pairs representing two different, but gender-matched persons. In the *intra-item condition*, participants encoded face-pairs

consisting of faces that were judged to represent the same person to a high degree. This was achieved by creating face-pairs consisting of a 35% and a 0% morphed face, and face-pairs consisting of a 100% and a 70% morphed face from the same morph-continuum. Participants were instructed that they would be presented with study-test blocks in which two photographs have to be memorized that *either* show two different persons (inter-item condition) *or* twice the same person on physically different pictures (intra-item condition). Each block consisted of a study phase, a distracter task, and a test phase.

For the *study phases*, participants were instructed to memorize particular pairings of faces for a subsequent associative recognition memory test. Participants memorized a total of 12 or 8 face-pairs in the intra- and the inter-item condition, respectively (we used longer blocks in the intra-item condition because performance can be expected to be slightly higher for intra- than for inter-item associations; see Jäger et al., 2006).

The study phase procedure was as follows (see Figure 9A for illustration): Photographs of each face-pair were presented sequentially. Every novel face-pair was first announced by the words ‘next pair’ (1500 ms), which were followed by a blank screen (200 ms). Then, the first face of a given face-pair was presented (1500 ms for younger; 1800 ms for older adults. To account for age-related slowing, presentation times of study and test face stimuli were increased by 20% for older adults (see e.g., Naveh-Benjamin et al., 2003, 2007, for similar procedures). Thereafter, a fixation cross appeared (700 ms for younger; 840 ms for older adults). Then, the second face of the face-pair was presented that had to be associated with the first face (1500 ms for younger; 1800 ms for older adults). Again, a fixation cross appeared thereafter (700 ms for younger; 840 ms for older adults) followed by a blank screen (200 ms). After this, the next study trial started.

After the study phase, a *distracter task* had to be performed for 20 s in which participants counted aloud backwards in steps of 2, 3, or 4 from a randomly drawn number between 100 and 200. After the distracter task was concluded, the *test phase* started.

In each trial of the test phase (see Figure 9B for illustration), a *single test face* was first presented at the top of the screen (1000 ms for younger; 1200 ms for older adults). The single test faces were faces that were presented as the first faces within study face-pairs (in the intra-item condition the studied single test faces were always the 35% morphed faces). While the single test faces remained on the screen, two additional faces that were both studied were then presented side by side at the bottom of the screen. Participants indicated by a *forced-choice judgment* which of the two faces at the bottom of the screen was paired with the single test face presented above them by pressing the left or right key (cf. Bastin & Van der Linden, 2006). The three faces stayed on the screen until a response was made or for maximally 3500 ms for younger and 4200 ms for older adults. Before the next test trial started, a blank screen was presented for 1000 ms.

There were 6 test trials in the intra-item condition and 4 test trials in the inter-item condition (i.e., half of the trial numbers of the study phase). In the intra-item condition, the target (i.e., correct) photograph of the forced-choice task was the 0% morphed face, while the non-target (i.e., incorrect) photograph was the 70% morphed face of the same morph-continuum. Hence, both faces differed by a morph-degree of 35% along the morph-continuum from the single test face (i.e., the 35% morphed face). By this, decisions could not be made solely on the basis of differences in face similarity.

The sequence of *study trials* was pseudorandomly intermixed for every novel participant with the constraints that the same gender did not appear more than twice consecutively, that the face-pairs belonging to the same morph-continua were separated by at least 3 intervening study trials, and that the study trials that included the faces used to form recombined pairs for the subsequent test phase were separated by at least 3 intervening study trials. The *test trials* were pseudorandomly intermixed for every novel participant with the constraints that the same gender and the assignment of the target faces of the forced-choice judgments to the left or right side of the screen did not appear more than twice consecutively.

Within all intra- and inter-item condition blocks, half of the face-pairs were female and half were male. The random assignment of the face-pairs to the 15 blocks was kept constant across participants, but the sequence of blocks was pseudorandomly intermixed for every novel participant with the constraints that there were no more than two consecutive blocks from the same condition and that every half of participants of each group started with an intra- or an inter-item block, respectively.

Procedure

Participants were tested individually in sessions lasting ca. 90 min for younger and ca. 120 min for older adults. Participants provided informed consent and sociodemographic information, instructions for the associative recognition memory task were given, and four practice blocks of the task were performed. Then the associative recognition memory task was carried out, with a short break after the first eight blocks. At the end, the neuropsychological tests were administered and participants were debriefed and thanked for their participation.

2.3.4 Results

Figure 10 shows the proportion of correct forced-choice judgments in the associative recognition memory task. Performance was significantly above chance in both conditions and both age groups, t-values (19) $\geq$ 3.32, p-values $\leq$ .01. Since we specifically aimed at investigating age differences in intra- versus inter-item associations, planned comparisons were applied to examine age effects in the two conditions, separately. Performance was significantly higher for younger than for older adults in the inter-item condition, $t(38) = 2.14$, $p < .05$. However, there was an even greater age deficit in the intra-item condition, $t(38) = 4.23$, $p < .001$. The age effect turned out to be nearly three times larger in the intra- compared with the inter-item condition, as revealed by effect sizes eta squared: intra-item condition: $\eta^2 = .32$, inter-item condition: $\eta^2 = .11$. The observation of a greater age effect in the intra-item

condition was also confirmed by an Age Group × Condition analysis of variance (ANOVA). There was a significant main effect of Age Group, $F(1,38) = 12.15$, $p < .01$, revealing better performance for younger adults, a significant main effect of Condition, $F(1,38) = 26.26$, $p < .001$, showing higher performance in the intra- than in the inter-item condition, and a significant Age Group × Condition interaction, $F(1,38) = 4.03$, $p = .05$.

Figure 10

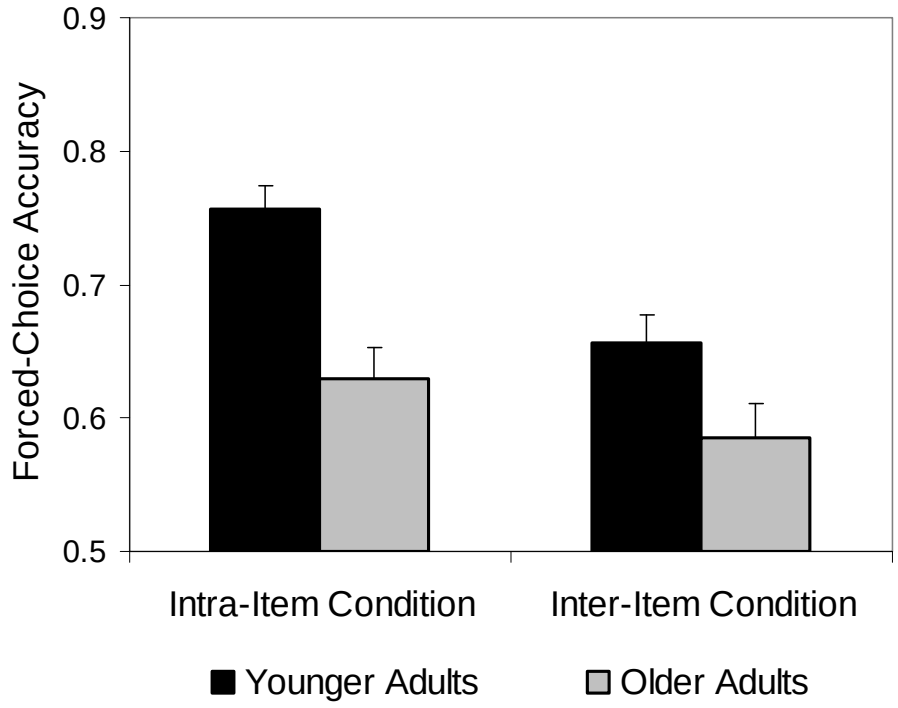


Figure 10: Effects of aging on intra- and inter-item associations.

Notes. Error bars represent standard errors of the means.

Reaction times for correct forced-choice judgments were analyzed by an Age Group × Condition ANOVA. Reaction times in ms were [$M \pm SE$] 1641 ± 80 and 2420 ± 98 for younger and older adults in the intra-item condition; and 1797 ± 106

and 2560 ± 112 for younger and older adults in the inter-item condition. There were significant main effects of Age Group, $F(1,38) = 32.91$, $p < .001$, reflecting faster reaction times for younger adults, and of Condition, $F(1,38) = 12.63$, $p < .01$, revealing faster reaction times for the intra- relative to the inter-item condition. There was no Age Group × Condition interaction, $F(1,38) < 1$.

2.3.5 Discussion of Study 2

In the present study, we compared adult age differences in two types of associative recognition memory situations: Participants either memorized face-pairs depicting two different, arbitrarily paired persons (inter-item condition) or pairs of physically different photographs that were perceived as representing the same person and thus can be unitized (intra-item condition; cf. Jäger et al., 2006). Consistent with previous findings that old age is associated with substantial impairments in memory for unrelated item-pairings (e.g., Bastin & Van der Linden, 2006; Castel & Craik, 2003; Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2003, 2004, 2007), a first finding of our study was a reliable deficit of older adults in the retrieval of inter-item associations between arbitrarily paired face stimuli. In line with previous suggestions and findings, this impairment can be accounted for by an age-related reduction in recollection, as is proposed by dual-process theories of recognition memory (see Prull, Dawes, Martin, Rosenberg, & Light, 2006).

A novel issue addressed in the present study was whether older adults show more or less of a deficit in associative recognition memory when the to-be-associated items *can potentially be unitized into a single representation*. Recent studies found that associative retrieval of items that are unitized during encoding benefits from familiarity-based recognition at the time of retrieval (Giovanello et al., 2006; Jäger et al., 2006; Quamme, 2004; Quamme et al., 2007; Rhodes & Donaldson, 2007; Yonelinas et al., 1999). As some studies revealed that older adults show smaller deficits in familiarity than in recollection (e.g., Bastin & Van der Linden, 2003; Daselaar et al., 2006; Howard et al., 2006), it could have been expected that older

adults exhibit only mild impairments in the retrieval of (intra-item) associations between unitizable face stimuli. However, it should be stressed that the data on age effects on familiarity and recollection are controversial, with some studies reporting even stronger age effects on familiarity than on recollection (e.g., Duarte et al., 2006; Li et al., 2004).

In the present study we revealed that – contrary to the possible expectation as described above – older adults were disproportionately impaired in their memory for associations between unitizable face-pairs compared to memory for pairings of arbitrary faces. In fact, the effect size for the age difference was nearly three times larger in the intra- than the inter-item condition. In terms of the dual-process account, one interpretation of these findings would be that familiarity may *not* necessarily be spared by cognitive aging and – in certain situations – can even be more strongly affected than recollection (cf. Duarte et al., 2006; Li et al., 2004). However, our data are not able to resolve the abovementioned inconsistencies in the literature of age effects on familiarity and recollection.

On the other hand, alternatively to this retrieval-related interpretation in the dual-process framework, it has to be emphasized that unitization during encoding and familiarity-based recognition *are no isomorphic cognitive processes* and by this may be differentially affected by old age. It is thus conceivable that older adults are specifically impaired in *forming* (i.e., encoding) intra-item associations between highly similar face-pairs while familiarity-based recognition during retrieval is relatively unaffected by cognitive aging, as is suggested by the majority of studies on age differences in familiarity and recollection.

Before elaborating this view in more detail, potential objections against the present findings should be considered. A first objection could be that the results reflect age-related differences in general performance levels across conditions rather than differential memory impairments in old age. We believe that several points argue against this possibility. First, for both age groups and both conditions, performance was well and significantly above chance, but also far from perfect. By this, neither floor nor ceiling effects can account for the pattern of results. Second,

there was nearly identical variability of performance within each age group across conditions, indicating that both conditions had a similar discriminating power to detect age differences in performance (cf. Naveh-Benjamin et al., 2004). Third, our findings cannot be explained in terms of an age × complexity effect, which is typically raised to explain greater age differences in more difficult compared with easier conditions. In fact, in our study the greater age impairment actually occurred in the *easier* (i.e., intra-item) condition, as indicated by performance of younger adults, which reflected a typical advantage for unitized compared to non-unitized associations (Quamme et al., 2007; Rhodes & Donaldson, 2007). Fourth, as will be described below, we found that even when high-performing older adults were matched to their younger counterparts with respect to performance levels in the inter-item condition, they nevertheless showed a *selective* deficit in the intra-item condition.

Another objection to be addressed is whether the differences in the timing of trial events across the two age groups, which was aimed at adapting the task to the needs of older adults, could potentially account for the effects found in the present study. However, the slight differences in the timing of events can unlikely account for the pattern of results, because in a previous study with young adults (Jäger, Mecklinger, & Kliegel, in preparation), we found that memory performance for intra- and inter-item associations is not influenced by manipulations of the retention interval (20 s vs. 40 s) or of the time available between the presentation of faces of each face-pair during encoding (700 ms vs. 1200 ms). In conclusion, the results of our study could be interpreted as evidence that aging has deleterious effects on memory for unitizable associations.

Turning to a more detailed interpretation of the present findings, our study revealed an empirical phenomenon that deserves further studies to examine the potential neurocognitive mechanisms responsible for the disproportionate problems of older adults in the formation of associations between unitizable face-pairs. As indicated above, the age-deficit can probably be traced back to processes occurring during the *encoding* of face-pairs. As face stimuli are highly overlapping in the intra-

item condition, they can engage unitization processes, by this resulting in the establishment of a single memory representation for each face-pair (Jäger et al., 2006). Unitization may be a neurocomputational mechanism that presumably involves enhanced activation of the two images' overlapping features within the medial temporal lobe cortex and reduced activation of nonoverlapping ones (a process termed "sharpening"), and may be supported by processes such as Hebbian learning and competitory inhibition (Norman & O'Reilly, 2003). Given the fine-grained nature of such neuronal changes, unitization processes at encoding may be very sensitive for the subtle changes in functional and biochemical attributes of neural networks in old age. We could speculate that pathological changes within the medial temporal lobe such as the accumulation of senile plaques and neurofibrillary tangles that are also present in healthy older adults may be neuronal mechanisms responsible for the age deficit in unitization (see Yang et al., 2005).

An implication of this latter view may be that in the inter-item condition older adults successfully recruit prefrontally mediated, strategic cognitive processes in order to enhance the encoding and retrieval of arbitrary face-pairs, while such compensation processes may be less efficient for the encoding and retrieval of unitized associations in the *intra*-item condition. This suggestion dovetails with the finding that bilateral prefrontal cortex activity seems to reflect compensatory mechanisms helping older adults to increase source memory performance (which critically depends on recollection) to a level equivalent to that of younger adults (Cabeza et al., 2002; cf. Naveh-Benjamin et al., 2007; see Buckner, 2004, for a review) and with findings that older adults are able to apply effective encoding strategies to form associations between unrelated items to a similar degree as younger adults do, which may specifically enhance older adults' performance in the inter-item condition (see Hertzog & Dunlosky, 2004, for a review). Examples for such strategic compensatory mechanisms in the inter-item condition may be the assignment of verbal labels to the arbitrary faces and the formation of associations between these labels, or the application of interactive imagery in order to associate the face-pairs (Hertzog & Dunlosky, 2004). By contrast, as indicated above, such strategic

cognitive processes may be less helpful for the formation of *intra*-item associations between highly similar photographs of the same person, resulting in a more pronounced impairment of older adults in this type of associations due to a lack of possibilities for compensation. This latter view is indirectly supported by the outcome of another study (Jäger et al., in preparation), which showed that memory for inter-item associations strongly benefits from the availability of attention that can be allocated to the encoding of arbitrary face pairs, whereas the encoding of unitizable intra-item associations benefits to a lower extent from the availability of attentional resources. This may indicate that such unitizable associations can be established relatively automatically.

Importantly, the selective compensation view described above receives more direct support by a post-hoc analysis in which we found that high-performing older adults reached equivalent levels of performance in the inter-item condition as their younger counterparts and still showed a *selective* deficit in the intra-item condition (cf. Duarte et al., 2006; Li et al., 2004). Specifically, in this additional explorative analysis, older adults were median split into high- (n = 12) versus low-performing (n = 8) participants on the basis of performance collapsed across conditions. Forced-choice accuracy of younger adults was .66 and .76 in the inter- and the intra-item condition, respectively. Importantly, although high-performing older adults reached equivalent levels as the younger adults in the inter-item condition (i.e., accuracy of .65), $t(30) = .07$, $p = .946$, they nevertheless showed a significant deficit in the intra-item condition (i.e., accuracy of .68), $t(30) = 2.63$, $p < .05$. By contrast, low-performing older adults showed an impairment in both conditions (i.e., accuracy of .48 and .55 in the inter- and the intra-item condition, respectively), t-values > 4.99, p-values < .001[3].

[3] Note that virtually the same pattern of results emerged when older adults were split into high- versus low-performing participants (1) either by using another measure of long-term memory abilities, namely the subtest of the DemTect in which delayed recall of a word list was required (2) or by using scores on a single latent factor derived by factor analysis on the scores of processing speed, inhibitory control, working memory, and four subtests of the DemTect (immediate recall, word fluency, digit span backwards, delayed recall; omitting the number transcoding task because this measure produced strong ceiling effects).

To conclude, a possible, though preliminary, explanation for the present findings is that (especially high-performing) older adults may at least partly compensate their age-related deficits in memory tasks that benefit from the engagement of strategic encoding operations such as the formation of inter-item associations between arbitrary face-pairs. By contrast, older adults may not be able to compensate their reduced ability to encode associations between highly similar and thus unitizable item-pairings (i.e., intra-item associations), because in such tasks the processing components are more automatized and may not strongly benefit from the application of strategic encoding processes to overcome the age-related diminutions in the underlying neurocognitive processes. Little research has so far investigated whether older adults may show more or less of a deficit in memory for item-pairings if the to-be-associated stimuli can be unitized into a single representation. The findings of the present study indicate that older adults demonstrate a disproportionate impairment in the formation of associations between highly overlapping face stimuli that presumably relies on unitization processes. Further studies are warranted to examine this empirical phenomenon and to understand its potential neurocognitive mechanisms.

2.3.6 Conclusions of Study 2

Study 2 replicated the finding of a dissociability of intra- and inter-item associative recognition memory for face-pairs (Study 1; Jäger et al., 2006), since normal cognitive aging turned out to have differential effects on memory for intra- versus inter-item associations. This result further supports the view that different (associative recognition) memory tasks may engage at least partly dissociable memory processes rather than a single memory process alone. However, the age effects on intra- and inter-item associations did not mirror the initial hypothesis that due to reduced recollection but intact familiarity older adults should be disproportionately impaired in the inter-item condition. Several possibilities exist

how to explain this unexpected finding. Among others, it may be that in some situations familiarity is actually more strongly diminished in older adults than recollection (cf. Duarte et al., 2006; Li et al., 2004). Alternatively, it could be the case that (at least some) older adults successfully engage strategic compensatory cognitive processes during encoding or retrieval which may be suited to enhance performance only in the inter- but not in the intra-item condition.

Taken together, Studies 1 and 2 have shown that despite their superficial similarity, the tasks applied in the intra- and the inter-item condition produce a dissociation of performance patterns that strongly indicate the involvement of (at least partly) different underlying memory subprocesses. Hence, the two studies provide support for a fractionation of episodic memory into different memory subprocesses.

2.4 Study 3: The Transience and Nature of Cognitive Impairments in Transient Global Amnesia: A Meta-Analysis[4]

2.4.1 Rationale for Study 3

While Studies 1 and 2 investigated the memory processes that are involved in a circumscribed and specific experimental paradigm of episodic (associative recognition) memory, Study 3 broadened the examined range of memory systems and subprocesses to a systemic or 'macro' level. It was the aim to demonstrate that a particular brain dysfunction may have differential effects on tasks thought to tap different memory systems, by this providing further evidence for the view that human memory is not a unitary but rather a multi-faceted construct (e.g., Moscovitch et al., 2005; Squire et al., 1993; Squire & Zola, 1996).

To this end, Study 3 capitalized on the characteristics of a specific patient group (see below for diagnostic criteria) that typically shows small and circumscribed transient lesions and dysfunctions within one of the most important brain structures relevant for memory, i.e., in the medial temporal lobe (with a particular locus within the hippocampus; see Study 4, for discussion and illustration), whereas the rest of the brain remains largely unaffected. This patient group refers to individuals who experience an episode of transient global amnesia (TGA), which is a sudden and transient but nearly complete loss of the ability to encode novel information and to recall certain kinds of stored information (Fisher & Adams, 1964; for reviews see Brown, 1998; Frederiks, 1993; Hodges, 1991; Kritchevsky, 1989; Markowitsch, 1990; Mazzucchi & Parma, 1990; Szabo & Bäzner, 2007; for overviews on neuroimaging findings see Baron et al., 1994; Bartsch et al., 2006, 2007; Eustache et

[4]The data reported in this study are also reported in the following article: Jäger, T., Bäzner, H., Kliegel, M., Szabo, K., & Hennerici, M. G. (2009). The transience and nature of cognitive impairments in transient global amnesia: A meta-analysis. *Journal of Clinical and Experimental Neuropsychology, 31,* 8-19.

al., 1997; Frederiks, 1993; Guillery et al., 2002; Pantoni et al., 2000; Sedlaczek et al., 2004). Importantly, patients suffering an episode of TGA recover quickly and seemingly completely, such that no long-term effects are assumed to result from this transient amnestic state that may be so surprising for the patients and their relatives. Nevertheless, recent studies have shown that during the very post-acute phase, TGA patients show subtle performance reductions specific memory tasks (see below).

The specific aim of Study 3 was to demonstrate that the transient medial temporal lobe dysfunction in patients with TGA affects some but spares other memory tasks, by this providing evidence for the view that human memory is not a single entity. It was hypothesized that a TGA episode should be marked by a disproportionate disruption of episodic long-term memory but a complete sparing of short-term and semantic memory, which could be expected on the basis of the assumed neural basis of the memory systems under investigation.

In order to provide a powerful and reliable analysis of whether TGA affects some but spares other memory systems, Study 3 did not collect new behavioural data from a small sample of encountered TGA patients in different memory tasks; rather, a meta-analytic approach was undertaken that examined the outlined research question by analyzing the body of existing literature on the cognitive sequelae of TGA. This approach of integrating the results of studies overcomes the limitation that most previous studies on patients with TGA included relatively small sample sizes, thereby resulting in low statistical power to detect small effects.

In addition to the examination of the potentially differential effects of transient amnestic attacks on different memory systems, the time course of the cognitive changes induced by TGA was investigated to test the hypothesis that TGA-induced cognitive disruptions recover completely within a few days or weeks after the attack along with the resolution of the transient changes visible in the brains of these patients. In other words, it is expected that the meta-analysis confirms that TGA has no cognitive long-term effects as is typically assumed by neurologists and clinical neuropsychologists treating such patients.

Study 3 was also conducted in anticipation of Study 4, because the former aimed to demonstrate a selective impairment of episodic memory in patients with TGA, whereas the latter followed-up on this hypothesis to more specifically disentangle the episodic memory subprocesses that are affected or spared by the changes of brain function as found in TGA, respectively.

2.4.2 Introduction of Study 3

The extraordinary experience of an episode of *transient global amnesia* (TGA) is often frightening for patients and their relatives, even though TGA is traditionally viewed as a rather benign syndrome (Fisher & Adams, 1964; for reviews see Brown, 1998; Hodges, 1991; Kritchevsky, 1989; Markowitsch, 1990). The diagnostic criteria of TGA (Hodges & Warlow, 1990a) imply that (1) there is an abrupt onset of severe anterograde amnesia, usually accompanied by variable retrograde amnesia and repetitive questioning (2) but without the presence of concomitant focal neurological symptoms, epileptic features, or head injuries. (3) Attacks have to be witnessed. (4) Clouding of consciousness and loss of personal identity must be absent and the cognitive changes limited to amnesia. (5) Attacks must resolve within 24 hours, leaving the patient with no disability except for a permanent (partial or full) amnesia for the events that took place during the attack.

The exact aetiology of TGA is still a matter of debate. It is assumed that transient medial-temporal dysfunction (Borroni et al., 2004) or a dysfunction of other brain regions such as the thalamus (Goldenberg et al., 1991) or the prefrontal cortex (Eustache et al., 1997) is responsible for the inability to learn and recall novel information. Previous authors have suggested that the pathophysiological mechanisms leading to such dysfunction may carry aspects of transient ischaemia, seizure, or migraine (Eustache et al., 1997; Frederiks, 1993; Hodges &Warlow, 1990b). However, none of these hypotheses is fully convincing (Brown, 1998; Pantoni et al., 2000) and current clinical criteria of TGA (see above) explicitly prevent the diagnosis of TGA when epileptic features or other focal neurological

symptoms are observed. Also physical or psychological stressors have been proposed to be concomitant causal factors (Brown, 1998; Frederiks, 1993; Le Pira et al., 2005; Pantoni et al., 2000), such as unique emotions, reactive stress, anxiety, physical exertion, sexual intercourse, or immersion into cold water, although it should be noted that a large proportion of episodes do not have any clear precipitating factors (Kritchevsky et al., 1997). In line with the hypothesis of transient neuronal dysfunctions, some neuroimaging studies using PET or SPECT revealed changes during the acute or post-acute phase of TGA (for overviews, see Baron et al., 1994; Eustache et al., 1997; Frederiks, 1993; Guillery et al., 2002; Pantoni et al., 2000), such as alterations of the cerebral perfusion or metabolism in the thalamus, the amygdala, the medial temporal lobes, particularly the hippocampus, or the right or left prefrontal cortex.

This selective review of the potential pathophysiological mechanisms of TGA that have been proposed by previous authors clearly shows that the exact etiology of TGA is still unresolved and a matter of debate. The literature did not yet identify a single causal factor of TGA. This raises the possibility that TGA could be caused by *multiple* factors that may induce transient dysfunctions of memory-related networks in the human brain. However, recent studies have revealed that small lesions within the hippocampus seem to be the most consistent neuroimaging finding in patients with TGA (Bartsch et al., 2006; Sedlaczek et al., 2004). Thus, in our personal opinion, transient disruptions of a memory network including the hippocampus seem to reflect the most important pathophysiological mechanism for the emergence of episodes of TGA (cf. Hodges, 1998). In addition to these ‘core’ lesions within the hippocampus, other brain regions such as the thalamus or the prefrontal cortex may be additionally disturbed during episodes of TGA, as well. Further studies are clearly necessary to gain more insight into the exact etiology of TGA.

The present study addresses the cognitive changes that are evoked by an episode of TGA. The first of two main issues concerns the particular cognitive domains that are affected by TGA, as described in our selective review above. The most salient cognitive dysfunction during TGA is a substantial reduction of

anterograde episodic long-term memory, i.e., patients have difficulty in learning and subsequently recalling novel episodic information after a variable delay during which no active rehearsal of the to-be-remembered information is possible (Mazzucchi & Parma, 1990). Most, but not all patients also exhibit a partial loss of *retrograde episodic long-term memory*, i.e., patients have difficulty recalling episodic information that was learned (hours, days or months, etc.) before the onset of the amnestic episode (Kazui et al., 1996; Kritchevsky et al., 1997; Simons & Hodges, 2000). By contrast, there seems to be a complete sparing of other cognitive functions such as *short-term memory* (i.e., the immediate reproduction of information without a delay or after a short delay during which the information can actively be rehearsed; Hodges, 1994; Pantoni et al., 2000; see Mazzucchi & Parma, 1990, for an overview), *semantic memory* (i.e., general and acontextual knowledge about the world; Hodges, 1994), or *implicit and procedural memory* (i.e., non-declarative memory contents such as skills and perceptual or motor abilities; Beauregard et al., 1997; Eustache et al., 1997; Kapur et al., 1996; Kazui et al., 1995) during episodes of TGA. The analysis of potential reductions of *executive functions* (including the executive component of working memory) is underrepresented in the literature (e.g., Hodges, 1994). Executive functions (and the executive component of working memory, also termed *central executive*; e.g., Baddeley, 1996) refer to cognitive control processes that control and coordinate both cognition and behavior. While some studies found preserved executive functions during the acute phase of TGA (Quinette et al., 2003), other studies indicate subtle executive dysfunction during TGA (Baron et al., 1994; Stillhard et al., 1990; cf. Mazzucchi & Parma, 1990).

In the present study, we carried out a meta-analysis in order to find cumulative evidence for the assumption that TGA episodes affect some but spare other cognitive functions. We hypothesized severe reductions of anterograde and retrograde episodic long-term memory during the acute phase of TGA. By contrast, we expected no significant changes of short-term memory and semantic memory. Because of the relative lack of studies addressing executive functions during TGA episodes, we had

no clear prediction with regard to potential signs of executive dysfunction during episodes of TGA.

The second main issue addressed in the present study refers to the *recovery* of cognitive functions after episodes of TGA. One of the critical diagnostic criteria is that the transient amnesia resolves quickly and must not have a duration of more than 24 hours (Hodges & Warlow, 1990a). In line with this criterion, many studies found complete recovery of cognitive (including memory) functioning post-TGA (e.g., Bartsch et al., 2006; Faglioni et al., 1992; Kritchevsky & Squire, 1989; Kritchevsky et al., 1988; Quinette et al., 2003). However, there is a continuing debate about the assumed total absence or potential persistence of amnestic sequelae following TGA (Frederiks, 1993), as some authors proposed that contrary to the diagnostic criteria of TGA the memory reductions may persist in the longer term after the occurrence of a TGA episode (e.g., Hodges & Oxbury, 1990; Hodges & Ward, 1989; Le Pira et al., 2005; see Brown, 1998; Mazzucchi & Parma, 1990). In line with this suggestion, some studies have found long-term performance reductions of TGA patients mainly in the domain of anterograde episodic long-term memory (e.g., Beauregard et al., 1997; Borroni et al., 2004; Caffarra et al., 1981; Cattaino et al., 1984; Guillery-Gilard et al., 2006; Mazzucchi et al., 1980; Zinelli et al., 1988), suggesting that there is only an incomplete recovery of memory function. This long-term memory reduction is found even in patients who suffered a single episode of TGA, did not report any memory deficits in follow-up examinations, and showed no signs of mental deterioration (Mazzucchi et al., 1980). Moreover, some other studies also revealed long-term retrograde memory reductions in TGA patients (e.g., Hodges & Oxbury, 1990; Kapur et al., 1986). These observations have led to the suggestion that TGA patients show a “partially transient” rather than a transient amnesia (Mazzucchi et al., 1980). A somewhat weaker version of the hypothesis that TGA-induced memory alterations also persist in the longer term is reflected by the alternative view that performance reductions in cognitive tasks due to episodes of TGA may recover slower than within the assumed short time period of 24 hours (Hodges & Oxbury, 1990; see Bartsch et al., 2006; Hodges & Ward, 1989; Kessler et al., 2001; see

Kritchevsky et al., 1997; Mazzucchi & Parma, 1990, for overviews). In consequence, cognitive changes may be present in TGA patients also some days or weeks after the amnestic episode, but not necessarily in the longer term (i.e., weeks or months) post-TGA.

In the present study, we further investigated whether there is partial persistence or total absence of neuropsychological sequelae following the occurrence of TGA. We hypothesized that the reductions in cognitive functions show a significant recovery after an episode of TGA. By examining the magnitude of cognitive alterations in the post-acute phase and in the long-term phase after TGA, we examined whether significant cognitive reductions of TGA patients persist after an episode of TGA. We applied specific inclusion criteria to find studies that examined cognitive changes of TGA patients relative to groups of healthy comparison subjects and analyzed the magnitude and recovery of TGA-associated performance reductions in five cognitive domains: anterograde episodic long-term memory, retrograde episodic long-term memory, short-term memory, semantic memory, and executive function. Through the application of the meta-analytic method, it was possible to combine the results of a moderately large number of individual studies, by this allowing an integrative view on and comparison of performance reductions of TGA patients in different cognitive domains and their recovery rates. The analysis was also aimed at obtaining a clearer picture on some inconsistent findings in the literature, particularly on the diverging results of the cognitive long-term effects of TGA. Integrating the results of studies also overcomes the limitation that most previous studies included relatively small sample sizes, thereby resulting in low statistical power to detect small effects.

2.4.3 Methods

Selection of studies

A computer-based search involving *PubMed* and *PsycInfo* was conducted to find to-be-included studies that were published since the year of 1980 (note that until

the early 1980s, only few TGA cases had been formally tested using neuropsychological tests; Mazzucchi & Parma, 1990). In addition, a backward citation search was also undertaken (i.e., references in each of the articles retrieved were checked). The literature search was completed in June 2007. Studies to be included in the meta-analysis had to fulfill the following criteria: (1) The study applied neuropsychological tests referring to at least one of the following domains: anterograde episodic long-term memory, retrograde episodic long-term memory, short-term memory, semantic memory, or executive function. (2) Neuropsychological test performance of TGA patients was compared to performance of one or more comparison groups consisting of healthy individuals. (3) The paper provided sufficient information to allow the calculation of effect sizes (see below). (4) The study was published in a peer-reviewed journal (this criterion avoids the potential problem of the same or highly related data being reported in journals and book chapters). (5) The paper was written in English.

Classification of tasks

The tasks or neuropsychological tests applied in the studies were classified into the following five categories (the cognitive domains were already defined in the Introduction): (1) *anterograde episodic long-term memory* (irrespective of type of material, e.g., verbal vs. nonverbal; examples: free recall or recognition memory tasks), (2) *retrograde episodic long-term memory* (examples: recall of autobiographical or episodic information occurring before the onset of TGA), (3) *short-term memory* (including tasks primarily tapping the phonological loop and the visuo-spatial sketchpad of the working memory system; cf. Quinette et al., 2003; examples: digit or spatial span forwards), (4) *semantic memory* (examples: production of personal semantic memory, naming), or (5) *executive function* (including working memory tasks primarily tapping the central executive subcomponent; cf. Eustache et al., 1997; Le Pira et al., 2005; Quinette et al., 2003; examples: category or letter fluency, digit or spatial span backwards; note that in case of verbal fluency tasks, we excluded measures of perseverative errors because it is

unclear whether word repetitions result from perseverative tendencies or whether they are a simple consequence of the amnestic syndrome; Schnider, 2004). The reason for why the executive component of working memory – also termed the *central executive* (e.g., Baddeley, 1996) – was considered part of executive functions was that the central executive is thought to have controlling and coordinating functions similar to how 'executive functions' are traditionally conceptualized.

Note that many tasks that were used in the studies included in the meta-analysis were established and well-know neuropsychological tests (e.g., Rey's 15 Words test, Rey-Osterrieth Complex Figure test, Famous Faces test, digit or spatial span forwards and backwards, category or letter fluency, etc.). By contrast, a few studies applied experimental tasks to assess a particular cognitive domain (e.g., Eustache et al., 1999; Guillery-Girard et al., 2004; Quinette et al., 2003, 2006). In any case, in the present meta-analysis, patients' performance was quantified in relation to performance of a sample of comparison subjects and not in relation to normative data that may be available for standardized neuropsychological tests.

Calculation of effect sizes

Meta-analysis is a rigorous, quantitative alternative to the traditional review process, as it involves statistical integration of results (Henry et al., 2004). The basis of this methodology is the effect size, a standardized statistic that quantifies the magnitude of an effect. In the present study, effect sizes for performance differences between TGA patients and comparison subjects were calculated in terms of Hedges' *g* and then transformed to unbiased estimates Hedges' *d*, because the former measure is an overestimation of effect sizes, particularly in small samples (DeCoster, 2004; Hedges & Olkin, 1985; Rustenbach, 2003). Accurate calculation of effect sizes depends on the availability of key information, including number of participants, means for cognitive performance of each group, and their accompanying standard deviations or standard errors. If these data were not reported, we computed Hedges' *g* from *z* statistics, which quantified patients' performance in relation to comparison

subjects; or in a few cases from *F* statistics with one degree of freedom in the numerator. For five studies (i.e., Kapur et al., 1998; Kazui et al., 1996; Kessler et al., 2001; Kritchevsky & Squire, 1989; Kritchevsky et al., 1988), descriptive statistics were derived from published figures using the program *DataThief*, which recovers *x* and *y* coordinates for selected points from graphs (see Kliegel et al., 2008; Light et al., 2000, for applications). In a few studies, it was reported that there were no performance differences between TGA patients and comparison subjects, but no exact descriptive or inferential statistics were provided in order to calculate effect sizes. Therefore, effect sizes were estimated as zero for the respective results in these studies (i.e., for the studies of Faglioni et al., 1992; Hodges & Oxbury, 1990; Laine et al., 1984). Some studies had to be excluded from the meta-analysis because insufficient data were reported to calculate or estimate effect sizes (Kapur et al., 1986, 1996; Stillhard et al., 1990; Wilson et al., 1980; Zinelli et al., 1988).

We avoided including dependent effect sizes on the same cognitive domain in order to meet the assumption of statistical independence between effects. Therefore, multiple effect sizes on a particular cognitive domain were permitted from the same study only in cases when more than one experiment was carried out or when subgroups were created within a particular experiment so long as the groups differed from another in terms of participants sampled. Moreover, if a study included more than one performance measure for the *same* cognitive domain (e.g., if multiple measures of anterograde episodic long-term memory were applied) without reporting mean performance across the multiple measures, we calculated the arithmetic mean of multiple dependent effect sizes Hedges' *g*s before deriving a single effect size Hedges' *d*. However, similarly as in many previous meta-analyses, statistical independence between effect sizes could not be achieved completely because of the following reasons: Many studies used longitudinal designs including multiple measurements on the same patients; many studies assessed several of the five cognitive domains in the same samples; and a few studies used data from comparison groups that were collected in previously published studies (e.g., Guillery et al., 2000).

Statistical analyses

Initial analyses included evaluating the assumption of homogeneity of effect sizes Hedges' *d*s within a particular cognitive domain in order to determine whether the studies can reasonably be described as sharing a common effect size. Homegeneity was evaluated by computing Q_{Wi} statistics. If Q_{Wi} statistics are nonsignificant, homogeneity of effect sizes can be assumed (Hedges & Olkin, 1985; Rustenbach, 2003). If Q_{Wi} statistics are significant, outliers can be removed to create a homogeneous sample of effect sizes (see Light et al., 2000). After excluding potential outliers, individual effect sizes Hedges' *d*s were then pooled to derive the weighted average effect sizes *d*• for each cognitive domain (Hedges & Olkin, 1985; Rustenbach, 2003), for three time intervals after the TGA episode, separately (see below). Importantly, the weighted average effect sizes take into account the precision of each single effect when deriving the estimate of the population effect size, by this reducing the influence of studies that used very small sample sizes (Rustenbach, 2003).

2.4.4 Results

Twenty-five studies fulfilled the criteria to be included in the meta-analysis. Table 2 shows the age and number of patients/comparison subjects and the source of calculated effect sizes for all studies included. From these studies, a total of 185 study-level effects were calculated, 67 for anterograde episodic long-term memory, 14 for retrograde episodic long-term memory, 46 for short-term memory, 9 for semantic memory, and 49 for executive function. In total, data from 1134 different (i.e., non-overlapping) participants were incorporated, namely 374 TGA patients and 760 comparison subjects. Averaged mean ages were 61.66 and 61.60 years for TGA patients and comparison subjects, respectively.

Table 2

Study	**Age Patients**	**Age Comparison Subjects**	***N* Patients**	***N* Comparison Subjects**	**Source of Effect Sizes**	**Notes**
Borroni et al. (2004)	67.00	68.50	55	80	*M*s and *SD*s	
Eustache et al. (1997)	59.00	59.40	1	7	*z*-values	
Eustache et al. (1999)	54.00 / 69.50	48.70 / 65.70	3	40	*z*-values	two patient and comparison groups were used
Faglioni et al. (1992)	58.07	59.17	30	30	Effect size estimated as zero	
Gallassi et al. (1986)	48.00	49.60	1	5	*z*-values	
Gallassi et al. (1993)	62.70	62.40	41	41	*M*s and *SD*s	two patient groups were used
Guillery et al. (2000)	67.00	65.70	1	20	*z*-values	
Guillery et al. (2001)	62.33	61.70	3	10	*z*-values	
Guillery et al. (2002)	68.00 / 63.70	65.70 / 63.70	2	20 / 30	*z*-values	two patient and comparison groups were used

Guillery-Girard et al. (2004)	63.75	59.20	4	20	*z*-values	
Guillery-Girard et al. (2006a)	66.25	64.50 / 68.45	32	36 / 53	*F*-values with 1 df in the numerator	two comparison groups were used
Hodges (1994)	65.50	65.50	2	25	*z*-values	age of comparison group estimated as equal to the patient group
Hodges and Oxbury (1990)	64.30	65.50	41	41	*M*s and *SD*s, *F*-values with 1 df in the numerator	
Hodges and Ward (1989)	61.60	64.50	5	50	*z*-values	
Kapur et al. (1998)	39.00	41.00	1	5	*z*-values	
Kazui et al. (1996)	63.00	63.00	1	15	*z*-values	age of comparison group estimated as equal to the patient group
Kessler et al. (2001)	63.50	60.48	14	21	*M*s and *SD*s	
Kritchevsky and Squire (1989)	65.17	69.00	6	10	*M*s and *SE*s (recovered from figures)	

Kritchevsky et al. (1988)	65.80	69.00	5	10	*M*s and *SE*s (recovered from figures)	
Laine et al. (1984)	61.70	61.70	69	61	Effect size estimated as zero	age of comparison group estimated as equal to the patient group
Le Pira et al. (2005)	57.40	55.80	14	13	*M*s and *SD*s	
Mazzucchi et al. (1980)	56.86	54.00	16	16	*M*s and *SD*s	
Quinette et al. (2003)	67.67 / 63.43	64.50 / 66.80 / 60.50	3 / 7	10 / 17 / 20	*z*-values	two patient and three comparison groups were used across two experiments
Quinette et al. (2006)	63.00	60.50 / 66.30	16	20 / 20	*M*s and *SD*s	two comparison groups were used
Stracciari et al. (1987)	59.00	59.20	1	14	*z*-values	

Table 2: Studies included in the meta-analysis.

Classification of effect sizes into three time intervals

To examine the dynamic recovery of cognitive functions after an episode of TGA, we recorded the time interval between the onset of the TGA episode and the time of neuropsychological testing (note that examinations during the *acute* phase of TGA without mention of exact time intervals after the onset of TGA were coded as 0 hours after onset of TGA; examinations described as occurring the next day after the TGA episode were coded as 24 hours after onset of TGA). As 82.2% of all study-level effects referred to neuropsychological tests that were carried out 30 days or less after the onset of the TGA (while longer follow-up intervals were only rarely examined), we excluded the remaining 17.7% of study-level effects that were obtained more than 30 days after the onset of TGA, resulting in a total of 152 study-level effects that were analyzed. There were 54 effects for anterograde episodic long-term memory, 12 effects for retrograde episodic long-term memory, 38 effects for short-term memory, 7 effects for semantic memory, and 41 effects for executive function. To evaluate the magnitude of potential performance reductions of TGA patients in different time intervals after an episode of TGA, we subdivided these 152 effects into three (arbitrary) time-intervals: (1) *acute phase* [0 to 24 hours after TGA onset], (2) *post-acute phase* [24 hours to 5 days after TGA onset], and (3) *long-term phase* [5 to 30 days after TGA onset].

Homogeneity of effect sizes

Within each time interval (i.e., acute, post-acute, and long-term phase), there was homogeneity of effect sizes for the domains of retrograde episodic long-term memory, short-term memory, semantic memory, and executive function (ps > .05). For the long-term phase, there was also homogeneity of effect sizes for anterograde episodic long-term memory ($p > .05$), but for the acute and the post-acute phase there was no homogeneity of effect sizes for anterograde episodic long-term memory (acute phase: $Q_W(20) = 103.61$, $p < .001$; post-acute phase: $Q_W(16) = 35.53$, $p < .01$). Therefore, five effect sizes were excluded for the acute phase (i.e., Eustache et al.,

1999, patients A and B; Guillery et al., 2000; Guillery et al., 2002, patient MLP; Quinette et al., 2003, Experiment 1) and one effect size was excluded for the post-acute phase (i.e., Guillery et al., 2001) in order to create homogeneous sets of effect sizes. Indeed, excluding these outliers resulted in homogeneous sets of effect sizes for anterograde episodic long-term memory in all time intervals (*p*s > .05). Figure 11 shows scatterplots for the obtained study-level effects as a function of time after TGA onset for the cognitive domains of anterograde episodic long-term memory, short-term memory, and executive function after excluding effect sizes that contributed to significant heterogeneity. No scatterplots are shown for the domains of retrograde episodic long-term memory and semantic memory because only few effect sizes could be calculated for these two domains during the post-acute and long-term phase.

Figure 11

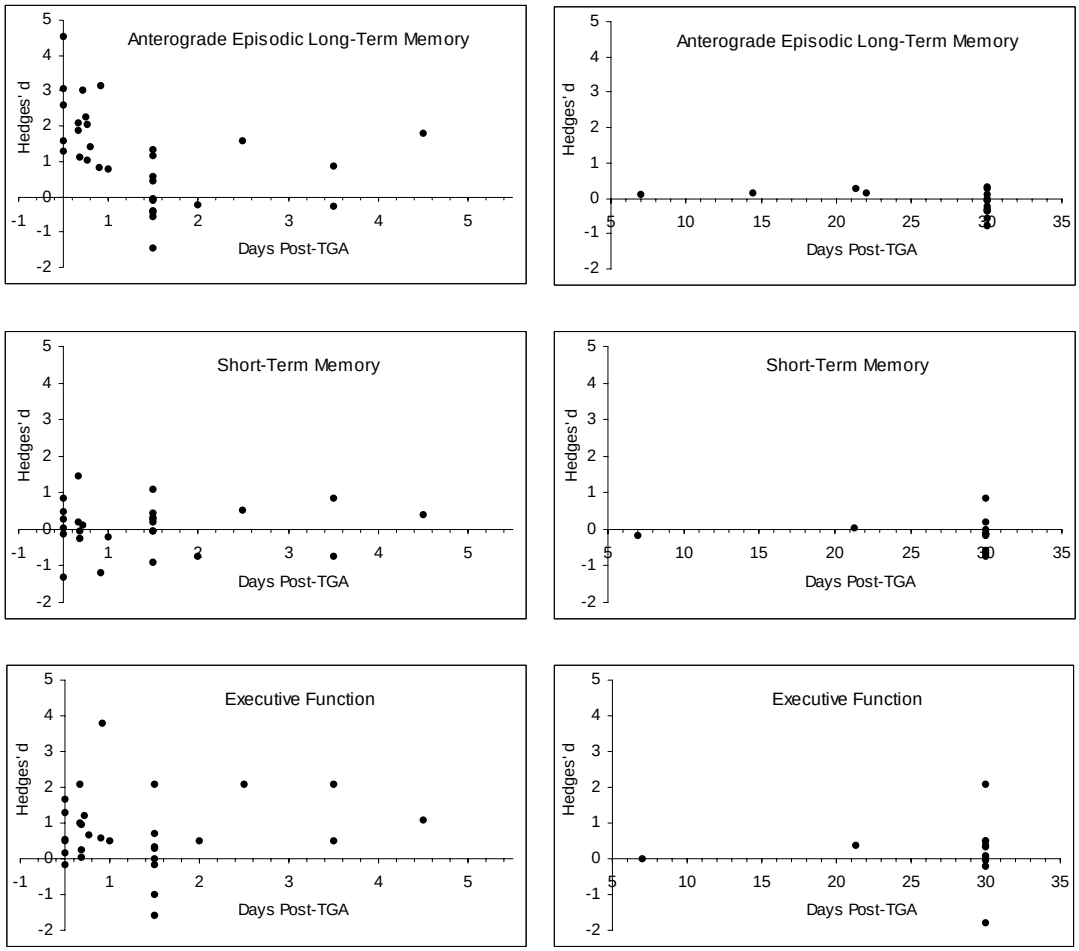


Figure 11: Study-level effects for the cognitive domains of anterograde episodic long-term memory, short-term memory, and executive function, separately shown for the acute-/post-acute phase (left column) and for the long-term phase (right column).

Weighted average effect sizes

Weighted average effect sizes *d*• were calculated after excluding effect sizes that contributed to significant heterogeneity. The weighted average effect sizes *d*• (plus their standard deviations) are shown in Figure 12, for each cognitive domain and each time interval, separately. Positive values of *d*• indicate higher performance

of comparison subjects, whereas negative values of *d*• indicate higher performance of TGA patients. Figure 12 shows that during the acute phase, the effect sizes of anteregrade episodic long-term memory, retrograde episodic long-term memory, and executive function were significantly greater than zero (*p*s < .001). By contrast, during the acute phase no significant difference emerged between performance of TGA patients and comparison subjects for short-term memory and semantic memory. From the acute phase to the post-acute phase, the effect size dropped from 1.89 to .32 for anterograde episodic long-term memory; the latter effect was still numerically (but not significantly) greater than zero. All other effects during the post-acute or long-term phase were not significantly different from zero, except a medium-sized effect (.44) for executive function during the post-acute phase that approached significance ($p < .10$).

For the acute phase, selected single comparisons between effect sizes were conducted to compare the TGA-associated cognitive changes across domains. As shown in Figure 12, the effect size reflecting the performance reductions of TGA patients relative to comparison subjects was significantly greater for anterograde episodic long-term memory than for retrograde episodic long-term memory, $Z = 2.04$, $p < .05$ (two-tailed), or executive function, $Z = 3.10$, $p < .01$ (two-tailed), as was revealed by *Z*-tests (cf. Henry et al., 2004; Kliegel et al., 2008). The difference between the effect sizes for retrograde episodic long-term memory and executive function was not significant, $Z = 1.25$, $p = .212$ (two-tailed).

Figure 12

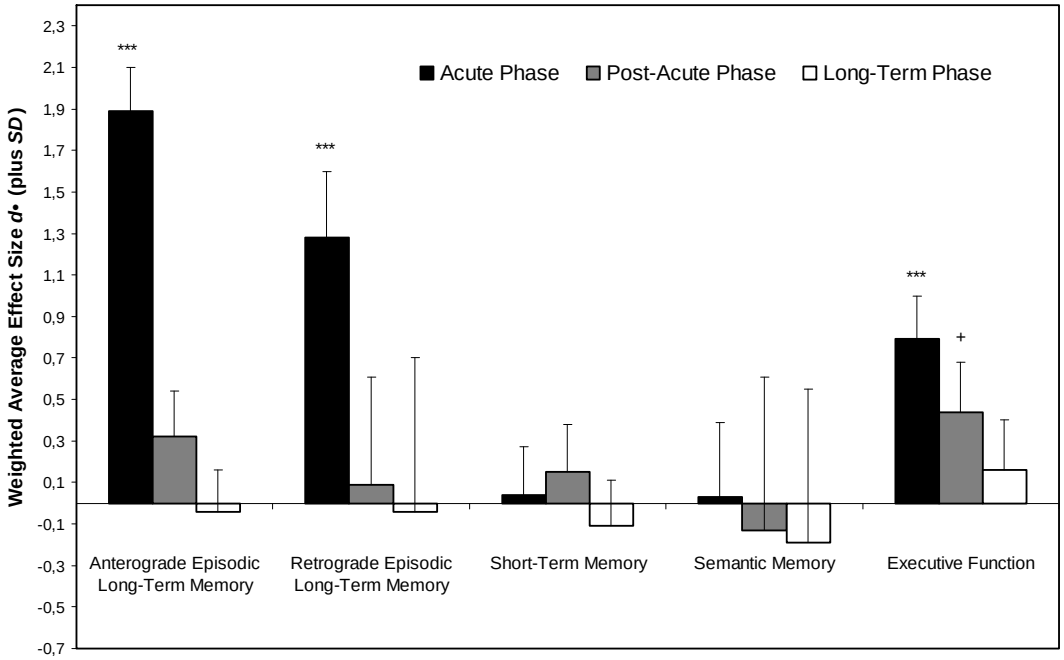


Figure 12: Weighted average effect sizes (plus standard deviations) for each cognitive domain and each time interval.

Notes. Weighted average effect sizes *d*• were calculated after excluding study-level effects that contributed to significant heterogeneity between effects in the domain of anterograde episodic long-term memory. Positive values of *d*• indicate higher performance of comparison subjects, whereas negative values of *d*• indicate higher performance of TGA patients.Number of studies contributing to each weighted average effect size for acute/post-acute/long-term phase: anterograde episodic long-term memory: 16/16/16; retrograde episodic long-term memory: 8/3/1; short-term memory: 13/13/12; semantic memory: 5/1/1; executive function: 16/13/12. ***greater than zero with $p < .001$; +greater than zero with $p < .10$.

2.4.5 Discussion of Study 3

The present meta-analysis investigated the cognitive sequelae of transient global amnesia (TGA). We aimed at addressing two issues that are currently debated

in the literature. By integrating the results of previous studies on the neuropsychological aspects of TGA, we analyzed the magnitude, extent, and recovery of TGA-associated performance reductions in five cognitive domains: anterograde episodic long-term memory, retrograde episodic long-term memory, short-term memory, semantic memory, and executive function (including the central executive subcomponent of working memory).

The first issue that we addressed concerned the particular cognitive domains that are affected during the acute phase of TGA. In line with the classical view on TGA and its diagnostic criteria, we revealed that, compared to healthy comparison subjects, TGA patients show a substantial reduction of anterograde episodic long-term memory. The weighted average effect size (which takes into account the precision of each study-level effect) was 1.89 and thus extraordinarily large (according to Cohen, 1988, an effect size of d = .80 can be regarded as 'large'). The weighted average effect size was 1.28 for retrograde episodic memory and by this significantly smaller than the performance reduction of TGA patients in anterograde episodic long-term memory. This finding is consistent with previous results (Kazui et al., 1996; Kritchevsky et al., 1997; Simons & Hodges, 2000), however, the retrograde amnesia seems to be more patchy and less consistent than the anterograde amnesia during TGA (Kritchevsky et al., 1988). In sum, the performance diminution seems to be somewhat milder in retrograde than in anterograde episodic long-term memory during an episode of TGA.

By contrast, during the acute phase of TGA the weighted average effect sizes for short-term memory and semantic memory were very close to zero and far from significant. In conclusion, these findings clearly support the proposal that short-term memory and semantic memory are completely spared during the dense amnesia that is experienced in the course of episodes of TGA (Hodges, 1994; Mazzucchi & Parma, 1990).

The weighted average effect size was .79 for executive function, reflecting a 'large' reduction of executive function of TGA patients in relation to comparison subjects (Cohen, 1988). Importantly, as we excluded measures of perseverative

behavior that could be explained by amnestic symptoms (i.e., perseverative responses during verbal fluency tasks), the executive dysfunction of TGA patients seems to be an additional cognitive change. The finding of significant reductions of executive function including working memory processes during episodes of TGA was not expected, because executive dysfunction is not explicitly included in the diagnostic criteria of TGA and is obviously masked by the significantly greater and clearly more impressive changes in anterograde episodic long-term memory.

Although only few studies have directly addressed executive functions during episodes of TGA, our findings are consistent with previous studies proposing subtle executive dysfunctions or reduced working memory processes in TGA (e.g., Baron et al., 1994; Stillhard et al., 1990; cf. Mazzucchi & Parma, 1990). For instance, in combination with a possible frontal hypoperfusion, Stillhard et al. (1990) found poorer performance of TGA patients in tests of prefrontal function as long as 22 days after the TGA episode. Eustache et al. (1997) noted hypometabolism in the left prefrontal cortex in a patient during the acute phase of TGA and suggested that this may be associated with reductions in episodic memory retrieval and verbal fluency, functions in which the left prefrontal cortex is thought to be involved (Eustache et al., 1997). Similarly, Baron et al. (1994) suggested that TGA may be associated with dysfunctions in lateral prefrontal cortex that could lead to both diminished episodic memory retrieval and executive (including working memory) dysfunction. Le Pira et al. (2005) suggested that TGA patients show poorer planning skills thought to be subserved by the frontal lobes. Finally, our findings also dovetail with the summary of Mazzucchi and Parma (1990) revealing that some TGA patients show substantially reduced backward digit span (i.e., working memory) combined with fully intact forward digit span (i.e., short-term memory). While this finding was not sufficiently explained previously (Mazzucchi & Parma, 1990), the present findings suggest that the diminished backward digit spans may result from reductions of executive functions during episodes of TGA, while forward digit span is intact due to completely preserved short-term memory abilities.

However, in light of the finding of Quinette et al. (2003), who explicitly focused on executive functions and found preserved working memory processes during TGA, it is clear that further studies are warranted to examine the neglected issue about the nature of executive dysfunctions in TGA. The findings of the present study suggest significant reductions of executive functions during episodes of TGA that may be overlooked in clinical examinations or may be masked by the impressive presentation with dense amnesia. We suggest that a reduction of executive control processes may be partially responsible for the acute states of confusion, disorientiation, desorganized and perseverative behaviors during TGA (cf. Frederiks, 1993). Transient neurophysiological changes in the function of the prefrontal cortex that may be due to phenomena of diaschisis or disturbances of complex frontal-subcortical neuronal networks may be the cause of the alterations of executive functions (Baron et al., 1994; Eustache et al., 1997). Moreover, as briefly mentioned above, there may exist a link between these prefrontal abnormalities, the reductions of executive functions, and the strong diminution of episodic long-term memory abilities in patients with TGA. This is because the prefrontal cortex is assumed to play a significant role in the executive control of successful memory encoding and retrieval processes that take place in the medial temporal lobes (e.g., Simons & Spiers, 2003).

Indeed, an additional analysis provided evidence for the view that the memory reductions in TGA may partly be due to reductions of executive function. Specifically, we calculated the correlation between the effect sizes (which express patients' performance in relation to comparison subjects) for anterograde episodic long-term memory and executive function for the effects of the three examined time intervals. This could be done for studies that investigated both anterograde episodic long-term memory and executive function within the same samples of patients and comparison subjects at the same points in time. Importantly, this resulted in a positive correlation of moderate size between the effect sizes for performance in anterograde episodic long-term memory and executive function that approached statistical significance [$r(40) = .30$, $p = .063$; note, however, that calculating this correlation

was not possible using independent data points because some of the studies repeatedly tested the same samples across several time-points]. Hence, this result provides some evidence for the view that there is a relationship between performance reductions in anterograde episodic long-term memory and performance reductions in executive functions in patients with TGA. In conclusion, it could be that the amnesic symptoms of TGA patients are due to abnormalities in both the medial temporal lobes and the prefrontal cortex.

The second issue addressed in the present meta-analysis refers to the recovery of cognitive functions after an episode of TGA. While many previous studies suggested complete recovery of cognitive (including memory) functioning after an episode of TGA (e.g., Bartsch et al., 2006; Faglioni et al., 1992; Kritchevsky & Squire, 1989; Kritchevsky et al., 1988; Quinette et al., 2003), some other findings indicate that subtle memory reductions may persist in the long-term phase (e.g., Beauregard et al., 1997; Borroni et al., 2004; Hodges & Oxbury, 1990; Hodges & Ward, 1989; Le Pira et al., 2005; Mazzucchi et al., 1980), proposing that there is only an incomplete recovery of memory function. The present cumulative analysis revealed that between 5 to 30 days after the onset of a TGA episode there is no significant performance difference between patients and comparison subjects in any cognitive domain under investigation, as effect sizes for all types of memory tasks and executive functions were close to (and not statistically different from) zero. For instance, the weighted average from 16 effect sizes was $d_{\bullet}$ = -.04 for anterograde episodic long-term memory and by this far from significantly different from zero (z = -.20, p = .421). Given that already within a month the TGA-associated memory reductions disappeared completely, it seems unlikely that TGA leads to permanent memory changes in the long-term phase post-TGA. The present study is thus consistent with the generally held view that TGA is benign and transient disorder without significant long-term sequelae (Frederiks, 1993) and thus challenges the results of previous studies, which indicated significant long-term effects of TGA episodes.

It could be speculated that previous results of significantly poorer performance of TGA patients in relation to comparison subjects in the longer term may reflect nothing more than pre-existent, premorbid differences in cognitive ability levels, as was suggested by several authors (Hodges & Oxbury, 1990; Kritchevsky et al., 1997). Another possibility is that findings from research on *long*-term effects of TGA are biased by the file-drawer problem, i.e., there could be a tendency to publish "positive" results showing significant memory reductions of TGA patients in the longer term, whereas "negative" results (i.e., no differences in cognitive function between TGA patients and comparison subjects) may less likely be submitted or considered for publication. Another, though debatable possibility is that TGA-induced cognitive changes show a complete recovery throughout the first few weeks post-attack but that TGA patients might be more susceptible for the development of mild cognitive impairments (e.g., in the domain of episodic long-term memory) months or years after the experience of the amnestic attack (see Borroni et al., 2004).

With regard to the post-acute phase, we found that anterograde episodic long-term memory seems to be subtly diminished and not fully recovered in the time interval between 1 and 5 days after TGA onset ($d_{\bullet}$ = .32), although the effect size was only small in Cohen's (1988) terms and failed to be statistically different from zero, presumably as a result of the relatively low statistical power. This finding is consistent with the proposal that TGA patients show a "partially transient" rather than a purely transient amnesia (Mazzucchi et al., 1980), because memory reductions seem to recover slower than within only a few hours after the attack (Hodges & Oxbury, 1990; see Bartsch et al., 2006; Hodges & Ward, 1989; Kessler et al., 2001; see Kritchevsky et al., 1997; Mazzucchi & Parma, 1990, for overviews). For instance, Kessler et al. (2001) found significant reductions of anterograde episodic long-term memory (and executive function) 3 to 4 days after the end of TGA episodes. Kessler et al. proposed that although TGA patients may not show amnesia or disorientation in the post-acute phase of TGA, they still seem to show slightly diminished memory performance. Similarly, Hodges and Ward (1989) revealed that although memory was subjectively normal 24 hours after an episode of TGA, patients had reduced learning

abilities for at least a week post-TGA. Thus, the present results are consistent with Brown's (1998) observation that "cognitive function usually takes several days to weeks to fully recover" after an episode of TGA, although patients, their relatives, and physicians/neuropsychologists often state a complete recovery of cognitive function immediately after the episode (Brown, 1998). The result of subtle memory reductions in the post-acute phase of TGA also mirrors the time-course of small (ca. 1-5 mm) and punctuate, uni- or bilateral MR-signal diffusion-weighted imaging (DWI) lesions that can be found within a few days after the TGA episode and are located within the CA-1 subfield of the hippocampus (Bartsch et al., 2006; Gass et al., 2004; Sedlaczek et al., 2004).

In addition to the finding of a reduction of executive functions during the acute phase as discussed above, the present meta-analysis also revealed subtle executive dysfunction during the post-acute phase which approached statistical significance, indicating that the changes in executive function also show a somewhat slow (rather than very fast) recovery after an episode of TGA (see also Le Pira et al., 2005). It could be speculated that a somewhat slow recovery of prefrontal cortex function may be the underlying mechanism of the delayed recovery of executive control processes after an episode of TGA.

Before summarizing the conclusions that may arise from the present data, we should note several limitations that are limiting the inferences drawn from our study. First, the studies included in the meta-analysis differed in the tests that were used to assess the particular cognitive functions. Second, patients and comparison subjects may not have been exactly matched in a number of dimensions (e.g., health, personality traits, age, gender, education, general cognitive performance levels, etc.). Third, there is wide variation in the number of patients and comparison subjects tested in the studies (see Table 2). Finally, the studies included in the meta-analysis could not provide information on the patients' cognitive performance prior to TGA. Thus, any inferences on post-TGA performance remain somewhat speculative.

In conclusion, the present meta-analysis confirmed that the most important feature of TGA episodes is a severe reduction of anterograde episodic long-term

memory. There is also a smaller but significant degree of retrograde episodic long-term memory diminution during TGA, while short-term memory and semantic memory are completely spared. However, our results also indicate the existence of additional, nonamnestic cognitive sequelae of TGA, namely subtle performance reductions in the domain of executive function. In addition, we revealed that the recovery of TGA-induced diminution of anterograde episodic long-term memory and executive function is somewhat delayed, as slightly poorer performance in these cognitive domains seem to be present also in the post-acute phase of TGA. On the basis of our findings, we suggest to extend the current criteria for the diagnosis of TGA (Caplan, 1986; Hodges & Warlow, 1990a) by (1) the possible presence of mild reductions of anterograde episodic long-term memory in the post-acute phase and by (2) the possible presence of subtle dysexecutive symptoms during the acute and post-acute phase of TGA.

2.4.6 Conclusions of Study 3

Using the powerful and reliable approach of meta-analysis (DeCoster, 2004; Hedges & Olkin, 1985; Rustenbach, 2003), Study 3 confirmed the expectation derived from a considerable number of previous studies and innumerable individual clinical observations that the transient amnestic attacks observed during TGA result in a selective impairment of episodic memory but seemingly spare short-term and semantic memory (Caplan, 1986; Hodges & Warlow, 1990a). In addition, however, also non-mnestic cognitive functions mainly mediated by the prefrontal cortex, so-called ‘executive functions’ seem to operate less efficiently during and for some time after an episode of TGA (cf. Baron et al., 1994; Eustache et al.; 1997; Le Pira et al., 2005; Stillhard et al., 1990).

Taken together, Study 3 provided further evidence for a dissociation of different memory systems. In line with the assumed strong link between episodic memory and the medial temporal lobe, Study 3 revealed that the transient dysfunction of the medial temporal lobe in patients with TGA – as was found in previous studies

– selectively impairs the episodic memory system, with an even more pronounced effect on anterograde compared to retrograde episodic memories (Kritchevsky et al., 1988).

This latter result may be consistent with the consolidation view of retrograde memories, which proposes that through a graded process of reorganization, connections among neocortical regions (which have initially been linked by the hippocampus) are progressively strengthened until the memory content can be accessed directly from the neocortex and independently from the hippocampus (Squire et al., 2004). Thus, while hippocampal dysfunction may severely disrupt anterograde episodic memory, i.e., the ability to acquire novel memory entries, it does not seem to reduce retrograde episodic memory to an equivalent degree because some (and presumably *only* some) of the retrograde memory entries seem to be recalled independently from the hippocampus even though the recollection of the majority of retrograde memory entries may still be dependent on the functional integrity of the hippocampus.

By contrast, Study 3 confirmed that TGA typically spares short-term and semantic memory, a finding which is consistent with the assumption that both of these memory abilities are mainly subserved by brain structures outside the medial temporal lobe, that is, by the prefrontal cortex and other (neocortical) brain regions outside the medial temporal lobe in the case of short-term memory or by more anterior and lateral temporal brain regions in the case of semantic memories. To conclude, Study 3 provided evidence for the assumption that the medial temporal lobe specifically supports our ability to retrieve episodic information, whereas there seem to co-exist other, dissociable memory systems or abilities that are mainly subserved by brain regions outside the medial temporal lobe.

2.5 Study 4: Selective Disruption of Hippocampus-Mediated Recognition Memory Processes After Episodes of Transient Global Amnesia[5]

2.5.1 Rationale for Study 4

Study 4 followed-up on the result that disturbances of medial temporal lobe function seem to selectively disrupt episodic memory processes but spare other mnemonic abilities such as short-term or semantic memory (Study 3). Again capitalizing on the interesting and circumscribed transient brain abnormality found in patients with TGA, the aim of Study 4 was to further elaborate on the episodic memory disturbance induced by TGA by examining whether the circumscribed lesions within the medial temporal lobe could lead to a fractionation of episodic memory by disrupting some but preserving other subprocesses of episodic memory. This is in contrast to Study 3, which treated episodic memory as a unitary construct and more generally investigated different memory systems on a macro- rather than on a micro-level.

Study 4 was again based on dual-process models of recognition memory (cf. Studies 1 and 2) and examined whether the two putative subprocesses underlying recognition memory – and by this also underlying episodic memory – namely familiarity and recollection are differentially affected by the medial temporal lobe dysfunction induced by TGA. If the specific brain dysfunction found in TGA disrupts episodic memory generally, then both familiarity and recollection should be affected to a similar degree. If, however, TGA affects familiarity and recollection differentially, then specific episodic memory subprocesses have been identified that

[5]The data reported in this study are also reported in the following article: Jäger, T., Szabo, K., Griebe, M., Bäzner, H., Möller, J., & Hennerici, M. G. (2009). Selective disruption of hippocampus-mediated recognition memory processes after episodes of transient global amnesia. *Neuropsychologia, 47*, 70-76.

are affected or spared by the amnestic attacks, respectively. The latter expectation may be given preference in the light of recent findings that the main locus of the medial temporal lobe dysfunction arising during an experience of TGA lies within the hippocampus (Bartsch et al., 2006, 2007; Sedlaczek et al., 2004) and in the light of the proposed strong link between the hippocampus and recollection but not familiarity (e.g., Eichenbaum et al., 2007; Norman & O'Reilly, 2003).

To investigate this potential dissociation of memory processes underlying episodic (recognition) memory, a sample of healthy older adults and TGA patients during the post-acute phase was recruited and examined using a standard item recognition memory task. On the basis of previous findings (e.g., Beauregard et al., 1997; Borroni et al., 2004; Hodges & Oxbury, 1990; Hodges & Ward, 1989; Le Pira et al., 2005; Mazzucchi et al., 1980) and the findings of Study 3, it could be expected that TGA patients still exhibit subtle reductions of memory performance also for some days after the resolution of the dense amnestic state, i.e., during the post-acute phase. This expectation is also consistent with the finding of a delayed disappearance of the hippocampal lesions that accompany the transient amnestic states (Bartsch et al., 2006; Sedlaczek et al., 2004). More specifically, we expected these subtle memory reductions during the post-acute phase to consist of disrupted hippocampus-mediated recollection during the recognition of previously encountered items, whereas familiarity is expected to be intact in patients with TGA and may thus underlie their above-chance-levels memory performance during the post-acute phase. To summarize, Study 4 expected to reveal a disproportionate reduction of recollection- compared to familiarity-based recognition memory in patients with TGA, reflecting a selective deficit of specific episodic memory subprocesses.

2.5.2 Introduction of Study 4

Transient global amnesia (TGA) is an intriguing clinical syndrome. It is characterized by the abrupt onset of severe anterograde and retrograde amnesia that typically resolves within 24 hours (Fisher & Adams, 1964; for reviews see e.g.,

Brown, 1998; Frederiks, 1993; Markowitsch, 1990). Patients usually present with an acute state of confusion, show disorganized behaviors, and repetitively ask the same questions. The syndrome arises without any concomitant focal neurological symptoms, epileptic features, or head injuries (Hodges & Warlow, 1990). After the amnesic state has resolved, patients are left with no disability except for a permanent amnesia for the events that took place during the attack.

The most prominent cognitive dysfunction during the acute phase of TGA is a substantial reduction of *anterograde episodic long-term memory*, i.e., patients have difficulty in learning and subsequently recalling novel episodic information (see e.g., Jäger, Bäzner, Kliegel, Szabo, & Hennerici, 2008; Mazzucchi & Parma, 1990, for overviews). Most, but not all patients also exhibit a partial loss of *retrograde episodic long-term memory*, i.e., patients have difficulty recalling episodic information that was learned (hours, days or months, etc.) before the onset of the amnestic attack. By contrast, there seems to be a complete sparing of other cognitive functions such as *short-term memory* (i.e., the immediate reproduction of information without a delay or after a short delay during which the information can actively be rehearsed), *semantic memory* (i.e., general and acontextual knowledge about the world), or *implicit and procedural memory* (i.e., non-declarative memory contents such as skills and perceptual or motor abilities) during episodes of TGA. Even though the dense amnestic state of TGA patients resolves quickly, i.e., typically within 24 hours, there seems to be a persistence of subtle cognitive changes also during the post-acute phase of TGA. Specifically, the anterograde episodic long-term memory reductions of TGA patients seem to recover somewhat slowly, as subtle memory reductions can still be observed for some days after the attack, but not in the longer-term (see Jäger et al., 2008; Kritchevsky, Zouzounis, & Squire, 1997; Mazzucchi & Parma, 1990, for overviews).

The exact etiology of the symptoms during episodes of TGA is still a matter of debate. Previous authors have suggested that the pathophysiological mechanisms leading to the amnestic attacks may carry aspects of transient ischaemia, seizure, or migraine (Frederiks, 1993; Hodges &Warlow, 1990b). However, none of these

hypotheses is fully convincing (Brown, 1998). Also physical or psychological stressors have been proposed to be concomitant causal factors (Brown, 1998; Frederiks, 1993), such as unique emotions, reactive stress, anxiety, physical exertion, sexual intercourse, or immersion into cold water, although it should be noted that a large proportion of episodes do not have any clear precipitating factors (Kritchevsky et al., 1997).

With regard to the underlying neurophysiological mechanisms of TGA, it is assumed that mainly a transient dysfunction of the medial temporal lobes is responsible for the complete inability to learn and recall novel information (Borroni et al., 2004), but also dysfunctions of other brain regions such as the thalamus (Goldenberg, Podreka, Pfaffelmeyer, Wessely, & Deecke, 1991) or the prefrontal cortex (Eustache et al., 1997) have been suspected as potential mechanisms of TGA. Indeed, some neuroimaging studies using PET or SPECT revealed neurophysiological changes during the acute or post-acute phase of TGA (for overviews, see Baron et al., 1994; Eustache et al., 1997; Frederiks, 1993), such as alterations of the cerebral perfusion or metabolism in the thalamus, the amygdala, the medial temporal lobes, or the right or left prefrontal cortex.

More recently, imaging findings in a large number of patients have linked TGA to the hippocampus. Specifically, recent studies revealed that most TGA patients show small (ca. 1-5 mm), punctate, uni- or bilateral MR-signal diffusion-weighted imaging (DWI) lesions that are located within the CA-1 subfield of the hippocampus (Bartsch et al., 2006; Sedlaczek et al., 2004) and can be observed during the post-acute phase, i.e., during some days after the amnestic attack. The pathophysiology of these punctate hippocampal DWI lesions is not well understood, but they can reasonably be considered as a sign of hippocampal dysfunction in TGA patients. In summary, it seems that transient disruptions of a memory network including the hippocampus reflect the most important pathophysiological mechanism for the emergence of episodes of TGA (cf. Hodges, 1998). This assumption is supported by the consistent finding of small hippocampal DWI lesions in most patients with TGA (Bartsch et al., 2006; Sedlaczek et al., 2004). Importantly, these

DWI lesions show a delayed resolution, as they can still be observed for some days during the post-acute phase of TGA. This delayed resolution of the hippocampal lesions thus represents a likely explanation for the subtle memory reductions that TGA patients show for some days during the post acute phase (see Jäger et al., 2008).

In the present study, we aimed (1) to investigate the effects of hippocampal dysfunction on specific recognition memory processes in patients with TGA and (2) to further evaluate the neurocognitive functions of the hippocampus. The theoretical framework motivating our study is provided by so-called *dual-process models* of recognition memory (Aggleton & Brown, 2006; Jäger, Mecklinger, & Kipp, 2006; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Montaldi, Spencer, Roberts, & Mayes, 2006; Norman & O'Reilly, 2003; Yonelinas, 2002). These models propose that the hippocampus generates a recognition memory process termed *recollection*, which refers to the conscious remembering of a prior episode including the retrieval of contextual details, such as the episode's spatio-temporal context or other related information. By contrast, the surrounding neocortices of the medial temporal lobes (i.e., perirhinal, entorhinal, and parahippocampal cortices) are assumed to support another, qualitatively distinct recognition memory subprocess, which is termed *familiarity*. Familiarity is conceptualized as an acontextual form of remembering, referring to the experience that a particular item "reminds one of something" without retrieving further contextual information.

On the basis of this theoretical framework, we tested the hypothesis that hippocampal dysfunction as suggested by the presence of punctate hippocampal DWI lesions in patients with TGA disrupts the ability to consciously retrieve previously encountered information via hippocampal recollection during the post-acute phase. By contrast, familiarity-based recognition memory, which is assumed to be supported by extra-hippocampal brain regions, should be unaffected. To examine this hypothesis, we administered a recognition memory task for faces and words to TGA patients in the post-acute phase and healthy controls.

2.5.3 Methods

Participants

Eleven TGA patients (7 females) and 11 matched controls (9 females) provided informed consent to take part in this study, which was approved by the local ethical committee. The two groups did not differ in age (*M* ± *SD*: patients = 70.0 ± 5.7, controls = 68.1 ± 8.8), $t(20) = -.61$, $p = .552$, education expressed as years of formal schooling (patients = 8.5 ± .9, controls = 9.8 ± 2.6), $t(20) = 1.55$, $p = .146$, and gender distribution, $\chi^2(1) = .92$, $p = .338$, Fisher's exact test: $p = .635$. All patients fulfilled standard clinical criteria for the diagnosis of TGA (Hodges & Warlow, 1990a). The mean duration of the amnestic episodes was 8.1 hours (*SD* = 7.6). The cognitive tasks were administered during the post-acute phase, i.e., when the dense amnesic state had resolved and the patients did not experience any memory problems anymore. Neuropsychological testing partly occurred within the same session as the recognition memory task and in a second session some hours or one day thereafter. On average, the recognition memory task and the neuropsychological tests were administered 52.5 hours (*SD* = 35.7) and 57.4 hours (*SD* = 26.0) after the onset of the TGA episode, respectively. Expressed as delays between the *offset* of the amnestic attacks and testing, the recognition memory task and the neuropsychological tests were administered 44.4 hours (*SD* = 32.1) and 49.3 hours (*SD* = 24.9) after the TGA episode had resolved, respectively.

Materials and Procedure

Neuropsychological testing. All TGA patients underwent detailed neuropsychological testing. The tests were mainly taken from the authorized German version of the CERAD neuropsychological assessment battery (Thalmann et al., 2000) and the German version of the Wechsler Memory Scale – Revised (WMS-R; Härting et al., 2000). The following domains were assessed with the specific tests indicated in parentheses: global cognitive function (Mini Mental State Examination

[MMSE] of the CERAD), attention (subscore of the WMS-R), visuoconstruction (subtest of the CERAD), speed of information processing (Trail Making Test Part A from the CERAD; Stroop Test Part II taken from a German test battery – Oswald & Fleischmann, 1997), executive function (phonemic fluency and Trail Making Test Part B divided by Part A of the CERAD; Stroop Test Part III minus Part II), semantic memory (object naming test of the CERAD; categorical fluency test of the CERAD), verbal and nonverbal short-term memory (digit and block span forwards of the WMS-R), verbal and nonverbal working memory (digit and block span backwards of the WMS-R), and verbal and nonverbal long-term memory (subscores of the WMS-R).

Recognition memory task. We administered a recognition memory task that included learning and recognizing faces and words. To measure the contributions of familiarity and recollection to memory performance, we obtained *receiver operating characteristics* (ROCs; see Yonelinas & Parks, 2007). ROCs plot the proportion of hits and false alarms across a number of response criteria. The left-most point on the ROC function is created by relating hits and false alarms for the most strict response criterion, including only the most confident responses. The remaining points on the ROC reflect continuously more relaxed response criteria. Importantly, the shape of an ROC provides information about the underlying memory subprocesses. If performance relies exclusively on familiarity, then the dual-process model predicts a curvilinear ROC that is symmetrical along the diagonal. By contrast, if performance is marked by an additional contribution of recollection, the lower left part of the ROC is shifted upward on the *y* axis because recollection is associated with high-confidence responses, resulting in an ROC that is asymmetrical along the diagonal. Capitalizing on these characteristics, ROC curves were used to estimate the contribution of familiarity and recollection to recognition memory performance.

Patients and controls performed four blocks of a recognition memory task, each consisting of a study phase, a distractor task, and a test phase. In the first and third block, participants memorized and recognized photographs of faces (‘faces condition’). In the second and fourth block, participants memorized and recognized

words (‘words condition’). The face stimuli were 120 gray-photographs of unfamiliar and emotionally neutral faces taken from a picture database (Jäger, Seiler, & Mecklinger, 2005). The words were 120 concrete, two-syllable German nouns collected from the CELEX data base (Baayen, Piepenbrock, & vanRijn, 1993). All stimuli were presented on white background on the computer screen using the software E-Prime.

In each study phase, participants were presented with a total of 30 faces or words, respectively. Stimuli were presented sequentially in the centre of the screen, each for 2500 ms with an inter-stimulus interval of 1000 ms. Participants were instructed to memorize the stimuli for a subsequent recognition memory test. Within each block, the sequence of study trials was randomly intermixed for every novel participant. After the study phase, a distractor task was performed for 60 s during which participants had to count aloud backwards from a randomly presented number between 150 and 250.

In each test phase, 30 studied and 30 unstudied stimuli were presented that had to be judged as ‘old’ (i.e., studied) or ‘new’ (i.e., unstudied). Stimuli stayed on the screen until an old/new judgment was made or for maximally 3000 ms. If participants did not respond within 3000 ms, the screen remained blank until a response was made. After a 500 ms blank screen, participants had to give a confidence judgment about their old/new decision from ‘1’ (lowest confidence) to ‘3’ (highest confidence) in order to derive ROC curves. After the confidence judgment was made, the next test trial was presented after an inter-stimulus interval of 1000 ms. Within each block, the sequence of test trials was randomly intermixed for every novel participant. To reduce the cognitive load of the task, participants gave their responses verbally and the experimenter entered their responses on the computer keyboard.

ROC analyses

To test our specific predictions regarding the contributions of familiarity and recollection to memory performance, a formal dual-process model put forth by Yonelinas and colleagues was fitted to the empirical ROC points in order to obtain behavioral estimates of familiarity and recollection (Yonelinas, Dobbins, Szymanski, Dhaliwal, & King, 1996; Yonelinas & Parks, 2007). This model conceptualizes familiarity as a Gaussian equal-variance signal-detection process whereby the probability of accepting an item depends upon sensitivity (*d'*, the distance between the means of the old and new distributions, which provides a measure of familiarity) and response criterion (c_i). If performance exclusively relies on familiarity, the probability that an old item's familiarity exceeds the response criterion is $P(\text{'yes'}|\text{old})_i = \Phi(d'/2 - c_i)$ and the probability that a new item is sufficiently familiar to be incorrectly accepted as ‚old' is $P(\text{'yes'}|\text{new})_i = \Phi(-d'/2 - c_i)$.

By also taking into account the potential contributions of recollection, the model assumes that the probability of a hit is $P(\text{'yes'}|\text{old})_i = R_o + (1 - R_o) * \Phi(d'/2 - c_i)$. This equation reflects the assumption that a hit occurs when an old item is either recollected [i.e., R_o] or accepted on the basis of familiarity given that the item is not recollected [i.e., $(1 - R_o)*\Phi(d'/2 - c_i)$]. Importantly, findings show that participants can also sometimes recollect new items as 'new' (R_n; e.g., "I would have remembered this face if I had seen it during the study phase"; Yonelinas & Parks, 2007). Thus, in the formal dual-process model we also allowed the possibility that participants can recollect new items as 'new'. In consequence, false alarms only occur when a new item is sufficiently familiar to be judged as 'old' in the absence of recollection that the item is new. Hence, the probability of a false alarm is $P(\text{'yes'}|\text{new})_i = (1 - R_n)*\Phi(-d'/2 - c_i)$.

To summarize, the final equations of the dual-process model are: $P(\text{'yes'}|\text{old})_i = R_o + (1 - R_o) * \Phi(d'/2 - c_i)$ and $P(\text{'yes'}|\text{new})_i = (1 - R_n)*\Phi(-d'/2 - c_i)$. Each point on the ROC is described by these equations. Assuming that memory (i.e., R_o, R_n, & *d'*) remains constant across the ROC and only response criterion c_i varies, the equations can be used to derive estimates for the parameters of the model using the five empirically obtained data points of each ROC. This derivation was done using

Microsoft Excel's Solver (Dodson et al., 1998) to find the best fitting parameters for the equations by minimizing the sum of squared errors between observed and predicted values (Yonelinas et al., 1996). The derived memory parameters (i.e., R_o, R_n, & *d'*) can finally be used to plot the entire theoretical ROC curves by choosing any desired response criterion c_i and calculating its respective hit and false alarm rates using the equations provided above.

Magnetic resonance imaging (MRI)

MRI was performed with a 1.5 T scanner (Magnetom Sonata; Siemens Medical Systems, Erlangen, Germany) with echo planar hardware. All patients were examined with a dedicated protocol including proton density- and T2-weighted images, T1-weighted images, as well as diffusion-weighted (DW) sequences (echo planar, SE, 240-mm FOV, 5-mm slice thickness, 128 x 128 matrix, three *b* values = 0 to 1,000 s/mm^2, diffusion gradients in three orthogonal planes) in the transverse oblique plane. Further DW sequences aligned with the hippocampus and coronal sequences positioned perpendicular to the hippocampus were performed. DW images were analyzed visually by two experienced readers (M.G., K.S.) unaware of clinical patient data. In 8 of the 11 TGA patients, punctate hippocampal lesions were detected on diffusion-weighted MRI (2 patients showed bilateral lesions; 2 patients showed lesions in the left and 4 patients in the right hippocampus; Figure 13; cf. Bartsch et al., 2006; Bartsch, Alfke, Deuschl, & Jansen, 2007; Sedlaczek et al., 2004).

Figure 13

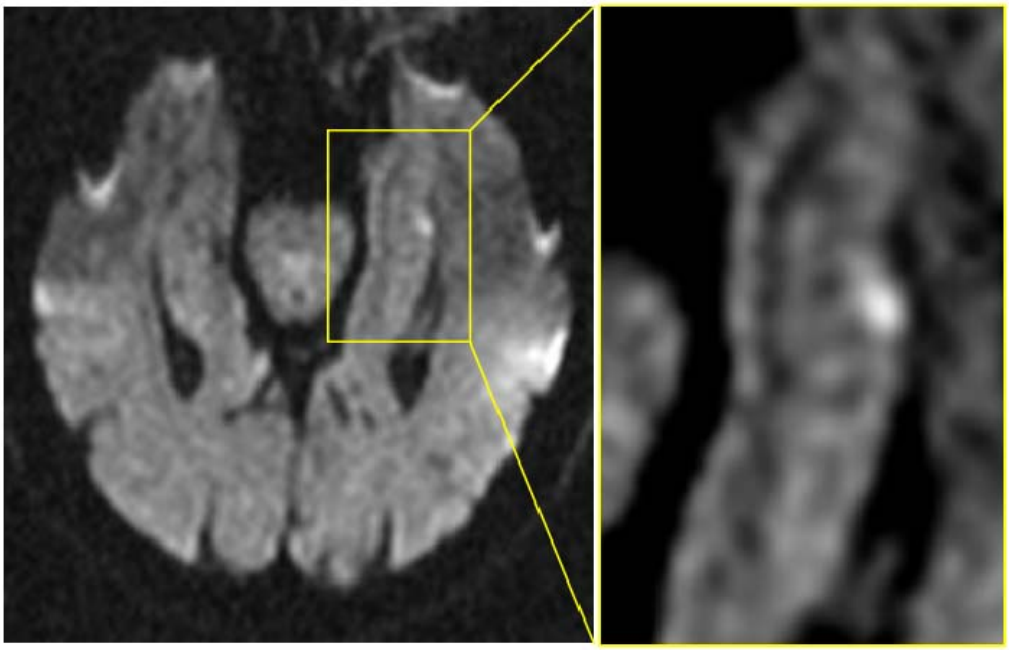


Figure 13: Images from 1.5-Tesla diffusion-weighted magnetic resonance imaging (MRI) showing a small, punctate hyperintense lesion in the body of the left hippocampus in patient G.Z. 21 hours after the onset of the amnestic attack.

2.5.4 Results

Neuropsychological testing

The TGA patients scored within the normal range in the MMSE, which provides a measure of global cognitive function; all scores were equal or greater than 26 ($M \pm SD$: 28.00 ± 1.23) and none of the patients evidenced an MMSE score that fell below the fifth percentile of age- and education-matched normative samples (Grigoletto, Zappala, Anderson, & Lebowitz, 1999). Performance of the patients in further neuropsychological tests is shown in Table 3, which tabulates performance of each test in terms of *z*-scores; *z*-scores below -1.65 are typically considered as evidence of an impairment. As can be seen in Table 3, the patients performed normally in tests of attention, visuoconstruction, speed of information processing,

executive function, semantic memory, short-term memory, and working memory. However, as evident in the long-term memory subscores of the WMS-R, the patients showed mild performance reductions in long-term memory, which, however, did not reflect clinically relevant memory impairments. Note that two patients did not complete all neuropsychological tests because they were discharged from the clinic before the neuropsychological tests could be completed (cf. Table 3).

Table 3

	N	*M* ± *SD*
Attention		
Attention Subscore of the WMS-R	10	-.13 ± ,51
Visuoconstruction		
Subtest of the CERAD	10	.23 ± 1.09
Speed of Information Processing		
Trail Making Test Part A of the CERAD	10	.87 ± .95
Stroop Test Part II	9	.17 ± .72
Executive Function		
Phonemic Fluency of the CERAD	10	.25 ± 1.18
Trail Making Test Part B/Part A of the CERAD	10	-.59 ± .81
Stroop Test Part III-Part II	9	.12 ± .70
Semantic Memory		
Object Naming Naming Test of the CERAD	10	.21 ± 1.10
Categorical Fluency of the CERAD	10	.35 ± .95

Short-Term Memory		
Digit Span Forwards of the WMS-R	10	-.23 ± .88
Block Span Forwards of the WMS-R	10	-.03 ± .68
Working Memory		
Digit Span Backwards of the WMS-R	10	.03 ± .95
Block Span Backwards of the WMS-R	10	-.11 ± .64
Long-Term Memory		
Verbal Memory Subscore of the WMS-R	10	-.55 ± 1.24
Visual Memory Subscore of the WMS-R	10	-1.00 ± .94
General Memory Subscore of the WMS-R	10	-.79 ± .97
Delayed Recall Subscore of the WMS-R	10	-.66 ± .76

Table 3: Results of TGA patients in neuropsychological tests (expressed as *z*-scores).

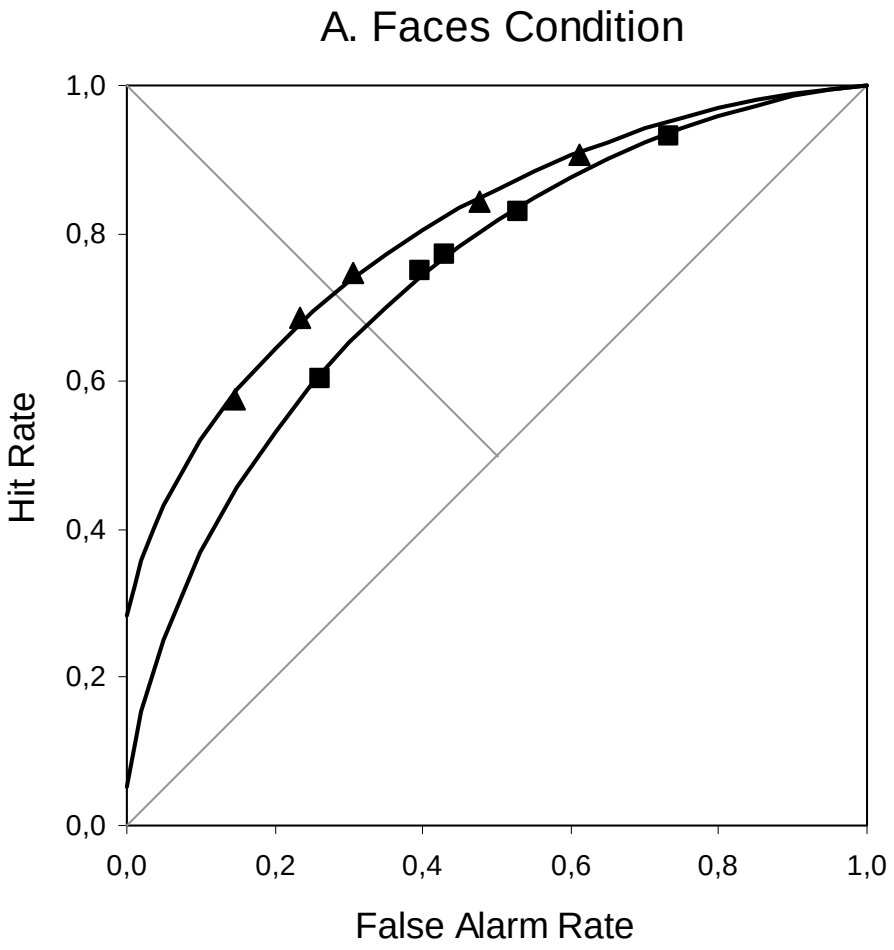
Recognition memory task: Old/new discrimination accuracy

The accuracy of old/new discrimination was measured by Pr, a corrected recognition memory score that is calculated by subtracting the false alarm rate (i.e., the proportion of 'old' responses to unstudied stimuli) from the hit rate (i.e., the proportion of 'old' responses to studied stimuli). In the 'faces condition', there was a nonsignificant trend towards lower performance by patients ($M \pm SD$: .34 ± .12) than by controls (.44 ± .17), $t(20) = 1.61$, $p = .123$, as was revealed by an independent-samples *t*-test. In the 'words condition', patients (.58 ± .19) performed significantly poorer than controls (.77 ± .13), $t(20) = 2.70$, $p < .05$.

Recognition memory task: ROC analyses

First, we calculated the empirical ROC points for cumulated responses across participants of each group. Observed proportions of hits and false alarms across response criteria are shown as triangles (controls) and squares (patients) in Figure 14A ('faces condition') and Figure 14B ('words condition'). Next, we fitted the formal dual-process model to the empirical ROC points. The model was used to derive estimates for familiarity (*d*'), recollection for studied stimuli (R_o), and recollection for unstudied stimuli (R_n) from both cumulated and individual ROC curves. Estimates of recollection for studied (R_o) and unstudied (R_n) stimuli were summed to obtain an estimate of total recollection (R_{tot}). Model-generated curves for cumulated ROC points are shown as lines in Figures 14A and 14B. As can be seen from the figures, there was an accurate fit of the model to the empirical ROC points.

Figure 14



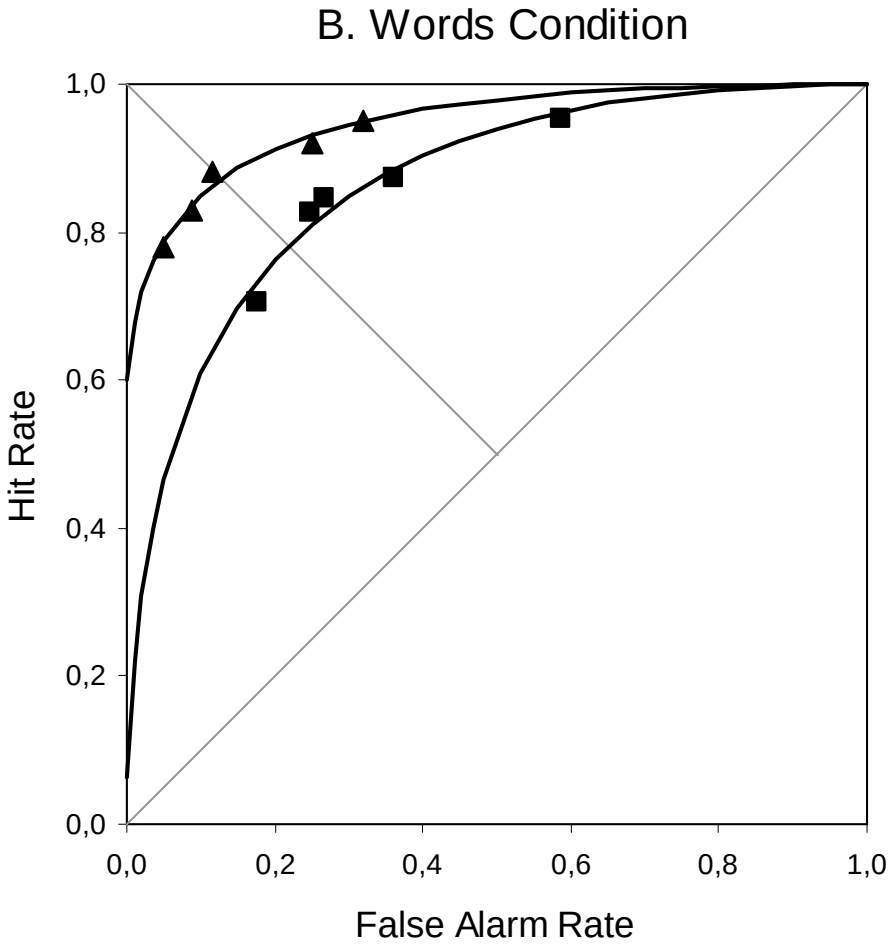


Figure 14: Observed ROC points and fitted theoretical ROC curves.

Figure 14A shows ROCs of the 'faces condition', Figure 14B shows ROCs of the 'words condition'. Triangles represent observed ROC points from controls, squares are ROC points from TGA patients. Lines represent the fitted theoretical ROC curves derived from the formal dual-process model.

With regard to their shape, the ROC curves were curvilinear for both patients and controls. However, the ROCs of the patients appeared to be relatively symmetrical along the diagonal, whereas the ROCs of the controls appeared to be asymmetrical along the diagonal and shifted upward on the *y* axis on their lower left parts. This pattern indicates that familiarity contributed to memory performance in both patients and controls, but recollection seemed to be only evident (or at least

stronger) in controls compared with TGA patients. Minimizing the sum of squared error terms for the difference between observed and expected values on the cumulated ROCs revealed the parameter estimates shown in Figure 15: Patients and controls indeed demonstrated very similar levels of familiarity (*d*') in both conditions. By contrast, the patients showed substantially lower estimates of total recollection (R_{tot}) than controls. In fact, the patients' estimates of recollection were close to zero.

Figure 15

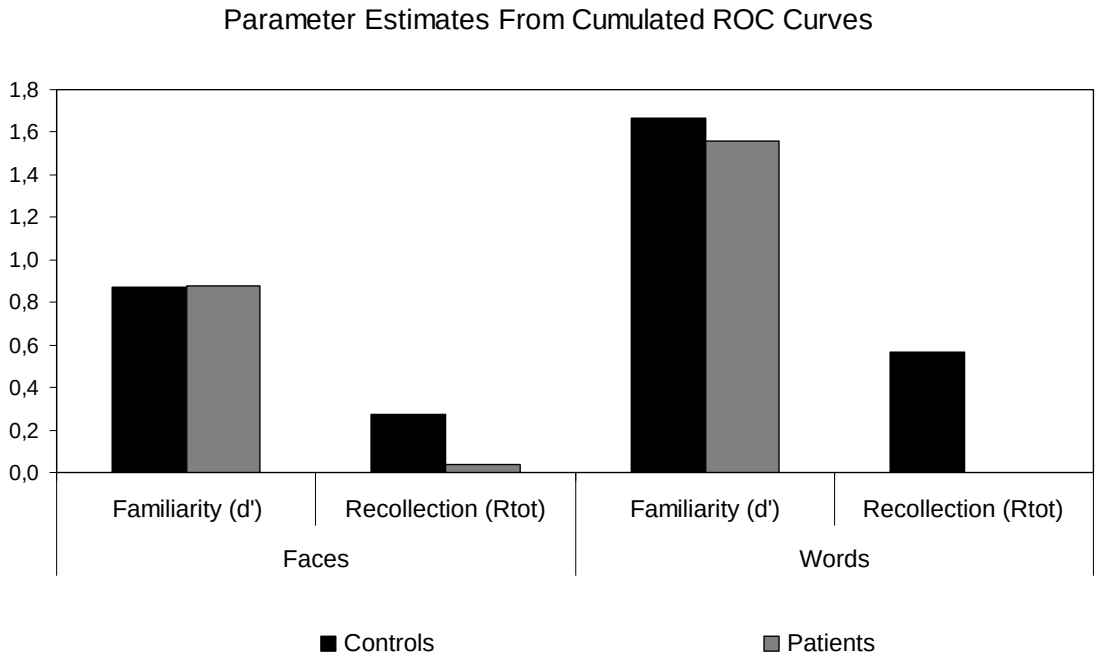


Figure 15: Parameter estimates derived from cumulated ROC points using the formal dual-process model.

In an additional analysis, we examined ROCs plotted in *z*-space (i.e., *z*-ROCs), because if the slope of the z-ROC approaches 1.0, then recognition memory performance can be regarded as mainly relying on familiarity, whereas an additional contribution of recollection can be assumed if the slope of the z-ROC is less than 1.0 (Yonelinas, 1994, 1997). Consistent with a major involvement of familiarity-based

responding, the z-ROCs of the TGA patients had slopes that approached 1.0 (i.e., slopes of .96 and .92 for the 'faces' and the 'words' condition, respectively). By contrast, consistent with an additional contribution of recollection, the z-ROCs of the controls had slopes well below 1.0 (i.e., slopes of .83 and .71 for the 'faces' and the 'words' condition, respectively).

To test the statistical significance of the observations derived from the cumulated ROCs, the model was next fit to *individual* ROCs in order to obtain parameter estimates of familiarity and recollection for every participant (Figure 16). In the 'faces condition', independent-samples *t*-tests revealed no significant difference between patients and controls neither in the estimates of familiarity (i.e., *d*'), $t(20) = 1.14$, $p = .269$, nor in the estimates of recollection (i.e., R_{tot}), $t(20) = .07$, $p = .941$ (Figure 16), even though the cumulated ROC curves indicated that familiarity did not differ across groups while recollection appeared to be stronger in controls than in patients (Figure 14). In the 'words condition', consistent with the results from the cumulated ROC curves, there was no difference in the estimates of familiarity (*d*') between patients and controls, $t(20) = -1.10$, $p = .284$, but estimates of recollection (R_{tot}) were significantly smaller for patients than for controls, $t(20) = 2.70$, $p < .05$ (Figure 16)[6,7]

[6] Pilot testing, observation of participants' behaviour, and the shapes of the empirical ROC curves strongly indicated that the dual-process model that also includes the possibility for recollection of new items (R_n) provides a better fit to the data than the model that only includes recollection for old items (R_o). In a corresponding analysis we found that the goodness of fit (expressed as the sum of squared errors between observed and predicted values) turned out to be better for the model that also includes the R_n parameter compared with the model that only applies the R_o parameter (faces condition: $t(21) = 1.74$, $p = .097$; words condition: $t(21) = 3.37$, $p = .003$). On the basis of these results, we believe that the application of the model including the R_n parameter is further justified because this model shows a (marginally) significantly better fit to the empirical data than the model which only includes the R_o parameter.

Nevertheless, we also investigated the data on the estimates of familiarity and recollection when a dual-process model is applied that only includes estimates for familiarity (*d*') and recollection for studied stimuli (R_o) [excluding the parameter for recollection for novel stimuli (R_n)]. Results from the analysis of individual ROCs in the 'faces condition' revealed no significant difference between patients and controls in the estimates of familiarity (i.e., *d*') (*M* ± *SD*: patients = .82 ± .45, controls = .82 ± .63), $t(20) = .03$, $p = .979$, but a strong trend towards lower estimates of recollection for the patients compared with the controls (i.e., R_o) (patients = .14 ± .16, controls = .30 ± .23), $t(20) = 1.93$, $p = .068$. In the 'words condition', there was also no difference in the estimates of familiarity (*d*') (patients = 1.46 ± .69, controls = 1.85 ± .55), $t(20) = .62$, $p = .439$, but a strong trend towards lower estimates of recollection (R_o) for the patients compared with the controls (patients = .22 ± .30, controls = .48 ± .40), $t(20) = 1.74$, $p = .097$.

Figure 16

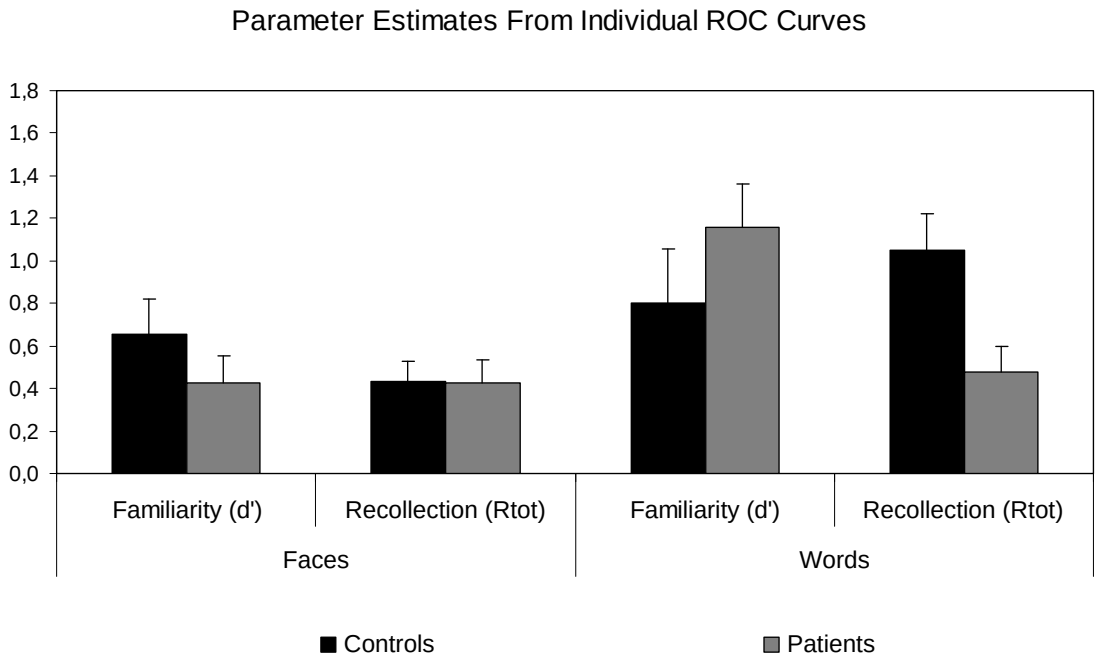


Figure 16: Parameter estimates derived from individual ROC points using the formal dual-process model.

Recognition memory task: Analyses of differences between patients with and patients without MR confirmed hippocampal DWI lesions

The previous analyses were based on the entire sample of TGA patients, that is, patients with (N = 8) and patients without (N = 3) visible hippocampal DWI lesions were treated as one group of TGA patients given that the presence of hippocampal DWI lesions is not included in the diagnostic criteria of TGA (Hodges

[7]Because this may be of interest to some readers, we additionally fitted the unequal variance signal detection model (see Yonelinas & Parks, 2007) to our data. Results indicated that the patients showed reduced familiarity for both faces (patients = .99 ± .22, controls = 1.44 ± .62), $t(20) = 2.30$, $p = .033$, and words (patients = 1.94 ± 1.07, controls = 3.93 ± 2.11), $t(20) = 2.79$, $p = .011$. With regard to the variance ratio component (i.e., the ratio of the variance of the old item distribution to the variance of the new item distribution), patients showed a trend towards a reduced variance ratio component for faces (patients = 1.05 ± .34, controls = 1.33 ± .33), $t(20) = 1.96$, $p = .064$, but no difference in the variance ratio component for words (patients = 1.20 ± .67, controls = 1.68 ± 1.67), $t(20) = .88$, $p = .388$.

& Warlow, 1990a). Nevertheless, in a post-hoc analysis, we aimed to explore whether the presence of visible hippocampal DWI lesions is significantly related to the extent to which familiarity and recollection contributed to recognition memory performance. It could be hypothesized that particularly those patients show deficits in recollection who also demonstrate visible hippocampal lesions on diffusion-weighted MR imaging. It should be noted, however, that the analysis of TGA patients with visible DWI lesions versus those patients without visible DWI lesions should be considered as exploratory, particularly because the group of TGA patients without DWI lesions represents an unacceptably small sample (i.e., $N = 3$).

Results from one-way analyses of variance (ANOVAs) on parameter estimates derived from individual ROCs in the 'faces condition' revealed no significant difference between patients and controls neither in the estimates of familiarity (i.e., *d*'), $F(2,19) = .71$, $p = .504$, nor in the estimates of recollection (i.e., R_{tot}), $F(2,19) = .003$, $p = .997$ (Figure 17). By contrast, in the 'words condition', there was no significant difference between patients and controls in the estimates of familiarity (i.e., *d*'), $F(2,19) = 1.32$, $p = .290$ (although there was a trend of TGA patients with visible DWI lesions to rely more strongly on familiarity than the other two groups), but there were group differences in the estimates of recollection (i.e., R_{tot}), $F(2,19) = 4.72$, $p < .05$, which – compared to the controls – reflected significantly diminished recollection in the eight TGA patients with visible hippocampal DWI lesions, $t(17) = 3.73$, $p < .01$, but not in the three TGA patients without lesions, $t(12) = -.64$, $p = .537$ (Figure 17).

Figure 17

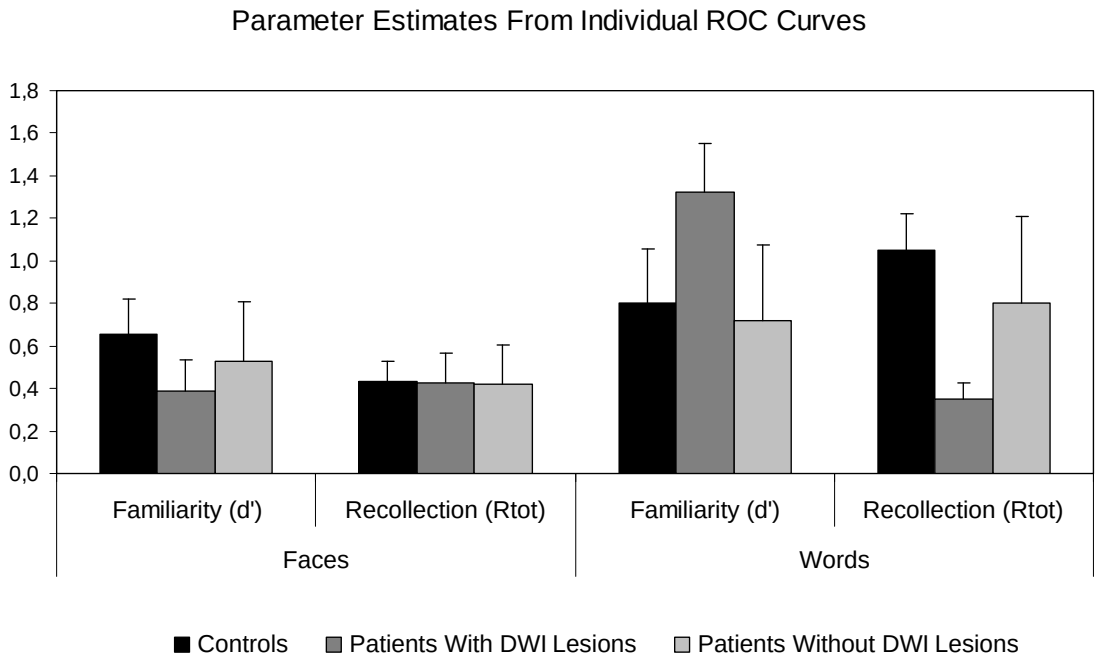


Figure 17: Parameter estimates derived from individual ROC points using the formal dual-process model, separately shown for controls, patients with and patients without visible DWI lesions.

2.5.5 Discussion of Study 4

The present study investigated the specific subprocesses of recognition memory that are affected by transient hippocampal dysfunction as suggested by the transient presence of small, punctate hippocampal DWI lesions in individuals who suffered an episode of TGA (Bartsch et al., 2006, 2007; Sedlaczek et al., 2004). On the basis of dual-process models of recognition memory (e.g., Aggleton & Brown, 2006; Jäger et al., 2006; Mayes et al., 2002; Montaldi et al., 2006; Norman & O'Reilly, 2003; Yonelinas, 2002), we tested the hypothesis that hippocampal dysfunction in TGA patients disrupts the ability to consciously retrieve previously encountered information via hippocampal recollection, whereas familiarity-based recognition memory that is supported by extra-hippocampal brain regions was expected to be unaffected.

Consistent with previous reports of subtle memory reductions of TGA patients during the post-acute phase (Brown, 1998; Hodges & Ward, 1989; Jäger et al., 2008; Kessler et al., 2001), which we propose to be related to the sustained hippocampal lesions, we found that the TGA patients showed poorer old/new decisions than controls in both conditions of the recognition memory task, although this effect did not reach statistical significance in the 'faces condition'. More importantly, however, we revealed that the memory impairment of TGA patients was selective rather than general. Specifically, the cumulated ROC curves of the 'words condition' revealed significantly lower estimates of (hippocampus-mediated) recollection in TGA patients than in controls (Figures 14 & 15). By contrast, the patients showed entirely intact levels of familiarity-based recognition memory of single words compared with matched controls. Importantly, this pattern was confirmed in the analyses of estimates of familiarity and recollection derived from individual ROC curves and in a post-hoc analysis it could be shown that particularly those patients seem to show a disruption of hippocampus-mediated recollection who also evidence visible hippocampal DWI lesions, whereas recollection estimates of patients without detectable hippocampal DWI lesions approached those of the matched controls (Figure 17). This pattern of findings is consistent with the theoretical assumption that the functional integrity of the hippocampus is crucial for successful recollection (note, however, that the post-hoc analysis is restricted especially by the small size [i.e., $N = 3$] of the patient group without visible hippocampal lesions).

In the 'faces condition', the cumulated ROC curves indicated a diminution of recollection and a preservation of familiarity in TGA patients as was the case in the 'words condition' (Figures 14 & 15), but the analyses of the estimates of familiarity and recollection derived from individual ROC curves failed to confirm this pattern of results (Figurees 16 & 17). The reason for this discrepancy remains largely unclear. It is possible that the more difficult task (i.e., the task of the 'faces condition') was not sensitive enough to consistently reveal a selective deficit of TGA patients in recollection, perhaps due to a floor effect in this condition or other variables such as high variability among the patients with regard to the presence/absence or the

location of hippocampal DWI lesions. By the same token, the easier task (i.e., the task of the 'words condition') may have had a higher sensitivity in separating patients from controls in terms of recollection, while there may have been a generally low chance for recollection to occur in the more difficult 'faces condition'.

The implications of our study are twofold. First, our findings indicate that the subtle memory reductions that TGA patients still demonstrate after their dense amnesic state has resolved (Brown, 1998; Hodges & Ward, 1989; Jäger et al., 2008; Kessler et al., 2001) are due to a disruption of hippocampus-dependent memory processes (i.e., recollection). This impairment can most probably be linked to the transient hippocampal dysfunction that is reflected by the presence of small, punctate hippocampal lesions. By contrast, our findings indicate that familiarity-based recognition memory, which seems to be mediated by extra-hippocampal brain regions, remains unaffected in TGA and mainly underlies patients' recognition memory performance during the post-acute phase. Second, the present findings also have theoretical implications. Specifically, our study revealed that the presence of hippocampal abnormalities disrupts recollection but leaves familiarity unaffected. Thus, our results provide strong support for the (still highly debated) neuroanatomical dual-process models, which posit that the hippocampus subserves recollection, whereas familiarity is generated by extra-hippocampal structures, namely by the surrounding neocortices of the medial temporal lobes, indicating that the subprocesses of recognition memory are neurophysiologically dissociable (cf. Aggleton & Brown, 2006; Jäger et al., 2006; Mayes et al., 2002; Montaldi et al., 2006; Norman & O'Reilly, 2003; Yonelinas, 2002).

In conclusion, the present study suggests that transient hippocampal dysfunction as reflected by small, punctate hippocampal lesions found after episodes of TGA produces subtle memory impairments during the post-acute phase. While there seems to be a disruption of hippocampus-mediated recollection, familiarity-based recognition memory processes appear to be unaffected. Future studies should further investigate the neuropsychological sequelae of the hippocampal abnormalities in patients with TGA in order to extend our knowledge on the neurocognitive

functions of the hippocampal formation. For instance, an interesting question for future studies would be to examine whether or not the selective deficit of TGA patients in recollection during the post-acute phase resolves in the longer-term after the amnestic attack, especially as the hippocampal DWI lesions are not visible anymore weeks or months after the attack (Bartsch et al., 2006). Another avenue for future studies – especially in the light of the small size of the present group of TGA patients without visible DWI lesions – would be to collect larger samples of TGA patients to more directly compare those patients with versus those patients without visible hippocampal DWI lesions to further determine the effects of visible hippocampal lesions on the sub-processes of recognition memory.

2.5.6 Conclusions of Study 4

Study 4 revealed that a selective disruption/preservation of specific episodic memory subprocesses can arise from a localized brain dysfunction as shown by TGA patients during the post-acute phase after their dense amnestic state. Specifically, the visible hippocampal DWI lesions in TGA patients reduced recollection- but not familiarity-based recognition memory for single word or face stimuli (although it should be noted that the findings of cumulated and individual ROCs and from different dual-process models [cf. Footnote 6] were somewhat inconsistent for the faces condition).

In conclusion, Study 4 provided further evidence for the prediction derived from dual-process models of recognition memory that lesions or dysfunctions restricted to the hippocampus disrupt recollection but do not reduce or hinder familiarity to allow well-above-chance levels of memory performance.

3. General Discussion

3. General Discussion

The global aim of the four studies reported in the present thesis was to find conditions or situations which produce or strongly indicate a dissociation of different memory systems and subprocesses by applying different methods and approaches of cognitive psychology. By this, the thesis targeted at contributing further evidence for the view that human memory is not a unitary construct but consists of multiple memory systems that are mediated by (at least partly) different neural networks (see e.g., Moscovitch et al., 2005; Squire et al., 1993; Squire & Zola, 1996, for reviews).

On a 'macro-level' of human memory analysis, Study 3 found meta-analytic evidence that performance in different memory tasks assumed to reflect distinguishable memory systems can be differentially affected by a transient and relatively circumscribed brain dysfunction thought to origin within the medial temporal lobe. Specifically, while performing tasks tapping (anterograde or retrograde) episodic long-term memory is nearly impossible during a state of dense amnesia as known from the experience of patients with transient global amnesia (TGA), these patients are able to achieve equivalent performance levels as control subjects in tasks assumed to assess so-called short-term memory or semantic memory, even during a state of dense amnesia that is so frightening and surprising for persons accompanying someone during an acute episode of TGA. Importantly, through the application of the meta-analytic method, it was possible to combine the results of a moderately large number of individual studies (i.e., $N = 25$), by this allowing an integrative view on the existing literature and a greater statistical power to detect small effects in cognitive performance, which could have been overlooked by previous studies that often included relatively small sample sizes of TGA patients and controls.

With regard to the theoretical implications for the underlying neural substrates of distinguishable memory systems, the findings of Study 3 supported both the proposed strong link between the medial temporal lobe and episodic memory and the suggestion that short-term and semantic memory are mediated by brain structures outside the medial temporal lobe. Short-term memory seems to strongly rely on

processing of the prefrontal cortex (e.g., Fuster & Alexander, 1971) or other neocortical regions outside the medial temporal lobe (see e.g., Baddeley, 2003), whereas semantic memory is assumed to be accessible from neocortical regions outside the medial temporal lobe such as from anterior or lateral temporal lobe regions (e.g., Moscovitch et al., 2005). Although the pathophysiological mechanisms of TGA are still unresolved and a matter of debate, recent studies strongly indicate that small and punctate lesions within the hippocampus seem to be the most consistent (and 'core') neuroimaging finding in patients with TGA (Bartsch et al., 2006; Sedlaczek et al., 2004). This result is of course compatible with the view that the medial temporal lobes – and especially the hippocampus – are important mediators of encoding and retrieval within episodic long-term memory.

While there was a very large disruption of anterograde episodic long-term memory during the acute phase of TGA, the retrograde amnesia turned out to be smaller and thus seemingly more patchy and less consistent (Kritchevsky et al., 1988). This result may be consistent with the consolidation view of retrograde memories, which proposes that through a graded process of reorganization, connections among neocortical regions (which have initially been linked by the hippocampus) are progressively strengthened until the memory content can be accessed directly from the neocortex and independently from the hippocampus (Squire et al., 2004). Thus, while hippocampal dysfunction may severely disrupt anterograde episodic memory, i.e., the ability to acquire novel memory entries, it does not seem to reduce retrograde episodic memory to an equivalent degree because some of the retrograde memory entries may be recalled independently from the hippocampus even though the recollection of the majority of retrograde memory entries may still be dependent on the functional integrity of the hippocampus.

Study 3 also revealed that the memory changes induced by TGA recover completely within a few days or weeks after the amnestic attack (whereas subtle performance reductions seem to exist during the days immediately following the attack; see Kritchevsky et al., 1997; Mazzucchi & Parma, 1990, for overviews). Together with the findings that small and punctuate, uni- or bilateral hippocampal

DWI lesions can be found within a few days after the TGA episode but disappear after some weeks (Bartsch et al., 2006; Sedlaczek et al., 2004), further evidence is provided by Study 3 for the proposed essential role of the hippocampus for episodic remembering.

Unfortunately, the body of existing literature did not allow tasks of nondeclarative memory to be included in the meta-analytic review of Study 3. Given that nondeclarative memory is assumed to depend on brain structures outside the medial temporal lobe, it could reasonably be expected that nondeclarative memory processes remain unaffected during episodes of TGA (see e.g., Beauregard et al., 1997; Eustache et al., 1997; Kapur et al., 1996; Kazui et al., 1995). This dovetails with the fact that during the acute phase TGA patients are often able to carry out complex (but well-learned) activities such as riding a bike or a car despite being in a dense amnestic state (Frederiks, 1993).

Whereas Study 3 examined human memory on a 'macro-level' in terms of memory systems, Studies 1, 2, and 4 targeted 'micro-level' memory processes by focusing on the subprocesses involved in recognition memory tasks that can be situated within the framework of episodic memory. While single-process models posit that the ability to recognize previously encountered information reflects assessments of a unidimensional scalar value of global memory strength (e.g., Donaldson, 1996; Gillund & Shiffrin, 1984), so-called dual-process models posit that two independent memory subprocesses contribute to recognition memory: i.e., familiarity and recollection (Aggleton & Brown, 1999, 2006; Diana et al., 2006, 2007; Eichenbaum et al., 2007; Jacoby, 1991; Mandler, 1980; Norman & O'Reilly, 2003; Yonelinas, 2002). A considerable body of evidence has emerged over the past decades that favours dual- over single-process accounts of recognition memory (Diana et al., 2006), including evidence from behavioral, modeling, patient, and neurophysiological data, but theorists are nevertheless continuing to debate the single- versus dual-process nature of recognition memory. Importantly, neuroimaging and patient studies within the dual-process framework suggest a division of labor within the medial temporal lobe, such that recollection seems to be supported by the

hippocampus, whereas familiarity is generated by neocortical regions of the medial temporal lobe (i.e., entorhinal, perirhinal, and parahippocampal cortices; Aggleton & Brown, 2006; Eichenbaum et al., 2007; Norman & O'Reilly, 2003).

In this context, the findings of Study 4 were especially relevant because behavioral data could be combined with neuroimaging findings from cranial magnetic resonance imaging (MRI). Investigating patients with TGA with a single-item recognition memory task and the application of receiver operating characteristics (ROCs), most of whom showed visible hippocampal lesions on diffusion-weighted MRI, it was possible to demonstrate a selective impairment of recollection but preservation of familiarity in recognition memory for faces and words. Thus, Study 4 provided direct evidence for the assumed strong link between recollection and the hippocampus. By this, the study extended our knowledge on the neurocognitive functions of the hippocampal formation. In addition, Study 4 contributed to the dissociation of different subprocesses within human episodic memory given that the two participant groups (i.e., TGA patients versus healthy controls) differed in the profile of the recognition memory subprocesses underlying their memory performance.

Also the results of neuropsychological testing of the TGA patients in Study 4 converged with the view that the cognitive function most strongly affected by TGA is episodic memory in general and free recall of memory contents in particular, as the patients showed slight (but clinically not relevant) impairments in the episodic long-term memory subscores of the Wechsler Memory Scale-Revised (WMS-R; Härting et al., 2000) while the performance reductions were smaller or even absent in neuropsychological tests tapping other cognitive functions and memory processes such as attention, visuoconstruction, speed of information processing, executive function, semantic memory, short-term memory, or working memory (cf. Study 3).

As in Study 4, in Studies 1 and 2 situations were tried to be identified in which a dissociation of different recognition memory subprocesses is strongly indicated. To this end, Studies 1 and 2 capitalized on the recently formulated 'unitization hypothesis' (e.g., Quamme, 2004), which posits that familiarity and

recollection differentially contribute to recognition memory for associations (i.e., associative recognition memory): While (hippocampus-mediated) recollection is thought to be critically important for the retrieval of associations between *arbitrary* items (e.g., Donaldson & Rugg, 1998, 1999; Hockley & Consoli, 1999; Rotello & Heit, 2000; Rotello, Macmillan, & Van Tassel, 2000; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004; Yonelinas, 1997, 1999), familiarity is proposed to be able to support associative memory given that the to-be-associated items can be 'unitized' into a coherent whole (Jäger et al., 2006; Opitz & Cornell, 2006; Quamme, 2004; Quamme et al., 2007; Rhodes & Donaldson, 2007; Yonelinas et al., 1999).

In consequence, two experimental conditions were created that were superficially similar but should differ from each other in terms of the degree to which they promote relational / recollection-mediated associations between arbitrarily paired items (i.e., inter-item associations between arbitrary face-pairs) and unitized / familiarity-supported associations (i.e., intra-item associations between highly similar face-pairs rated to represent the same person to a high degree; see Jäger et al., 2005). A previous ERP study provided evidence for the expectation that the described intra- and inter-item conditions promote familiarity- and recollection-based recognition memory, respectively, by doubly dissociating the putative electrophysiological correlates of familiarity (early frontal old/new effect), which was present in the intra-item condition, and recollection (late parietal old/new effect), which could be observed in the inter-item condition (Jäger et al., 2006; cf. Mecklinger & Jäger, 2009).

Consistent with this initial ERP evidence, both Studies 1 and 2 of the present thesis supported the view that the two conditions involve at least partly dissociable memory processes. Experiments 1 and 2 of Study 1 consistently revealed ROC curves that differed in their shapes across conditions. Corresponding estimates of familiarity and recollection reflected a higher contribution of familiarity to intra- than to inter-item associations and, conversely, a higher contribution of recollection for recombined pairings for intra- compared to inter-item condition, whereas recollection for studied pairs did not differ across conditions. Study 3 revealed that normal

cognitive aging affected memory for intra- and inter-item associations differentially rather than both to a similar degree. This pattern indicates a different contribution of memory subprocesses to the two conditions (perhaps as a result of differential age effects on cognitive processes involved during the encoding or retrieval of intra- versus inter-item associations), even though the pattern of findings did not fit the initial (albeit debatable) expectation derived from dual-process models of recognition memory but could be alternatively explained by a potential selective compensation of older adults with regard to performance in the inter- but not the intra-item condition.

The findings of the two experiments of Study 1 added further evidence for the highly debated 'unitization hypothesis' which posits that familiarity does not act item-specifically in every situation and can support associative memory given that the to-be-associated item were unitized during encoding. Also in line with this hypothesis, some new studies provided further evidence that familiarity – mediated by the surrounding neocortical region of the hippocampus – is able to support associative memories given that the to-be-associated features are unitizable into a coherent entity (Diana et al., 2008; see Haskins et al., 2008; Staresina & Davachi, 2008, for related neuroimaging findings; see Mayes et al., 2007, for a recent review). For instance, by reporting consistent evidence across different methods to estimate familiarity and recollection (i.e., ROC versus response deadline method), Diana et al. (2008) showed that although source memory is usually subserved by recollection, familiarity is able to support source memory judgments given that source and item information can be unitized. Using functional magnetic resonance imaging, Haskins et al. (2008) found that perirhinal cortex acitivity is increased when pairs of items are processes as a unitized representation and that this activity is correlated with familiarity-based associative recognition memory.

To summarize, there is a growing body of evidence of studies applying different operational definitions of familiarity and recollection to support the view that familiarity mediates associative recognition memory for unitizable items (for behavioral data, see Quamme, 2004; Yonelinas et al., 1999; for patient data, see Giovanello et al., 2006; Quamme et al., 2007; for electrophysiological evidence, see

Jäger et al., 2006; Opitz & Cornell, 2006; Rhodes & Donaldson, 2006). Note also some unpublished data (Jäger et al., in preparation), which showed that memory for inter-item associations strongly benefits from the availability of attention that can be allocated to the encoding of arbitrary face pairs, whereas the encoding of unitizable intra-item associations benefits to a lower extent from the availability of attentional resources. This further supports the view that recollection and familiarity were mainly involved during the retrieval of inter- and intra-item associations, respectively, because recollection is thought to reflect an effortful process that suffers from dividing attention at encoding, whereas familiarity is proposed to be a more automatic process that is unaffected by manipulations of attention during encoding (see Yonelinas, 2002, for a review).

In terms of conclusion of the present thesis, the reported studies add to the considerable body of evidence within memory research, which indicates that human memory is not a unitary construct but consists of different memory systems and dissociable subprocesses. Especially a dissociation of episodic and semantic long-term memory and short-term memory (Studies 3 and 4) and a distinction of familiarity and recollection as independent memory subprocesses of episodic (recognition) memory as proposed by dual-process models of recognition memory (Studies 1, 2, and 4) are supported by the results of the present thesis.

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*References marked with an asterisk indicate studies included in the meta-analysis (i.e., Study 3) of the present thesis.

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German Summary

Allgemeine Einleitung ins menschliche Gedächtnis

Sich an Informationen aus der Vergangenheit zu erinnern ist eine essenzielle kognitive Fähigkeit des Menschen. In seinem Gehirn hat sich ein komplexes Gedächtnissystem entwickelt, das Informationen auf vielfältige Art und Weise enkodiert, speichert und abruft. Das Ziel der modernen Gedächtnisforschung ist es deshalb, die kognitive und neurophysiologische Organisation des Gedächtnisses zu untersuchen.

Eine Grundannahme der Gedächtnisforschung ist diejenige, dass das menschliche Gedächtnis nicht aus einer singulären Entität, sondern aus verschiedenen Komponenten besteht, welche von separierbaren neuralen Systemen unterstützt werden (Moscovitch et al., 2005; Squire et al., 1993; Squire & Zola, 1996). Überzeugende Belege für eine diesbezügliche Unterscheidung stammen aus Untersuchungen von Patienten mit umschriebenen Gedächtnisstörungen, welche häufig deutliche Defizite in manchen, aber vollkommen intakte Leistungen in anderen Gedächtnistests zeigen (Gabrieli, 1998; Squire & Zola, 1996). Modernere Methoden zur Differenzierung verschiedener Gedächtnissysteme sind z.B. die Positron-Emissions-Tomographie, die funktionelle Magnetresonanztomographie oder ereigniskorrelierte Potentiale, welche mittes der Technik der Elektroenzephalographie aufgezeichnet werden können.

Eine der ältesten und weitest verbreiteten Annahmen ist diejenige, dass das sog. Kurzzeitgedächtnis vom sog. Langzeitgedächtnis dissoziiert werden kann (Squire et al., 1993). Ersteres bezeichnet Gedächtnisprozesse, welche Informationen in einer aktiven Form im Bewusstsein aufrechterhalten, letzteres bezieht sich auf das Überdauern von Informationen über längere Zeiträume (Buckner, 2004). Überzeugende Belege für diese Sicht liefert die Tatsache, dass viele amnestische Patienten mit Läsionen im medialen Temporallappen – genauer gesagt im Hippocampus – ein intaktes Kurzzeit- aber ein deutlich gestörtes Langzeitgedächtnis

aufweisen (Gabrieli, 1998; Moscovitch et al., 2005; vgl. Studie 3 dieser Dissertation). Der umgekehrte Fall ist relativ selten, es wurden aber einige Patienten identifiziert, welche ein beeinträchtigtes Kurzzeit- aber ein intaktes Langzeitgedächtnis zeigen (Shallice & Warrington, 1970). Diese doppelte Dissoziation weist auf eine z.T. unterschiedliche neurophysiologische Organisation des Kurzzeit- und Langzeitgedächtnisses hin. Während das erstere v.a. vom präfrontalen Kortex und anderen Gehirnregionen außerhalb des medialen Temporallappens vermittelt wird (Baddeley, 2003; Fuster & Alexander, 1971; Squire et al., 1993), scheint das letztere vom Hippokampus und dem umliegenden Neokortex des medialen Temporallappens abzuhängen.

Über diese grobe Unterscheidung des Kurz- und Langzeitgedächtnisses hinaus wurde das Langzeitgedächtnis wiederum in mehrere Gedächtnissysteme unterschieden (Abbildung 1). Die erste wichtige Unterscheidung ist diejenige zwischen dem deklarativen (d. h. flexible und verbalisierbare, dem Bewusstsein zugängliche Informationen aus dem Gedächtnisspeicher) und dem nicht-deklarativen (d. h. weniger flexible und nicht vollständig ins Bewusstsein eintretende Informationen aus dem Gedächtnisspeicher, welche sich eher in einer bestimmten Performanz-Veränderung als durch einen expliziten Abruf manifestieren) Gedächtnis (Buckner, 2004).

Wiederum liefern amnestische Patienten mit Läsionen im Temporallappen Belege für diese Hypothese, denn diese zeigen häufig gestörte deklarative aber erhaltene nicht-deklarative Gedächtnisleistungen (Gabrieli, 1998; Moscovitch et al., 2005). Somit scheinen die beiden Arten von Gedächtnisleistungen auf (zumindest z.T.) dissoziierbaren neuralen Substraten zu beruhen; während das deklarative Gedächtnis vom medialen und lateralen Anteilen des Temporallappens vermittelt wird, sind Gehirnstrukturen wie z.B. das Striatum, die Amygdala und das Cerebellum für nicht-deklarative Gedächtnisleistungen verantwortlich (Squire et al., 1993, 2004; Squire & Zola, 1996).

Das deklarative Gedächtnis wurde wiederum in zwei wichtige Systeme unterteilt, in das episodische und das semantische Gedächtnis (Abbildung 1; z.B.

Squire et al., 1993; Tulving, 1972, 1983). Das episodische Gedächtnis ermöglicht das Erinnern von autobiographischen Episoden oder bestimmten Ereignissen, welche sich im Leben eines Individuums ereignet haben, inklusive der Erinnerung an spezifische Kontextinformationen wie z.B. der räumliche und zeitliche Zusammenhang des Ereignisses (Moscovitch et al., 2005). Das episodische Gedächtnis scheint von der funktionalen Integrität des medialen Temporallappens abzuhängen. Das semantische Gedächtnis hingegen bezieht sich auf kontextlose Inhalte des Gedächtnisses wie z.B. allgemeines Weltwissen oder die Repräsentation von Konzepten, Kategorien, Tatsachen, Bedeutungen usw. (Moscovitch et al., 2005).

Einige Belege für die Dissoziation des episodischen und semantischen Langzeitgedächtnisses wurden von neuropsychologischen Patienten geliefert, welche zwar semantisches Wissen akkumulieren aber keine episodische Erinnerungen abrufen können (Tulving et al., 1991; Vargha-Khadem et al., 1997). Dies lässt sich dadurch erklären, dass das semantische Gedächtnis eher von lateralen als von medialen Anteilen des Temporallappens abzuhängen scheint (Moscovitch et al., 2005), beispielsweise ist die Größe von Läsionen im lateralen Temporallappen mit dem Schweregrad von semantischen Gedächtnisstörungen korreliert (Squire et al., 2004). Allerdings ist die funktionelle und neurophysiologische Unterscheidung des episodischen und semantischen Langzeitgedächtnisses noch nicht vollkommen überzeugend gelungen, so dass diese eine wichtige Herausforderung für die zukünftige Gedächtnisforschung sein wird (Eysenck & Keane, 2000; Squire et al., 1993).

Wie bereits erwähnt beruht das episodische Erinnern auf dem medialen Temporallappen, nämlich auf dem Hippokampus und den umliegenden entorhinalen, perirhinalen und parahippokampalen Neocortices. Der Hippokampus liegt am Ende einer kortikalen Verarbeitungshierarchie und bezieht den Großteil seines Inputs vom entorhinalen Kortex. Dieser wiederum erhält eine Vielzahl an Afferenzen vom perirhinalen und parahippokampalen Kortex. Letztere werden von weit verteilten, uni- und polymodalen Kortexarealen versorgt (Abbildung 2; Gabrieli, 1998; Moscovitch et al., 2005; Norman & O'Reilly, 2003; Squire et al., 2004; Squire &

Zola, 1996). Vom Hippokampus wird angenommen, dass er eine besondere Rolle in Aufgaben einnimmt, welche das Verknüpfen oder Kombinieren von Informationen aus verschiedenen Quellen beinhaltet (Squire et al., 2004), wie es z.B. in episodischen oder assoziativen Gedächtnisaufgaben der Fall ist.

Diese generelle Einleitung ins menschliche Gedächtnis fasst die grundlegenden Erkenntnisse der aktuellen Forschung bezüglich verschiedener Gedächtnissysteme zusammen. Während das Kurzzeit- vom Langzeitgedächtnis unterschieden werden konnte, beinhaltet das letztere sowohl deklarative als auch nicht-deklarative Gedächtnisinhalte. Das episodische und semantische Gedächtnis scheinen dann die zwei basalen Arten von Gedächtnisleistungen des deklarativen Gedächtnisses auszumachen.

Das Ziel der vorliegenden Studien

Das Globalziel der vorliegenden Studien war es, das menschliche Gedächtnis zu untersuchen, indem weitere Belege für eine Taxonomie des Gedächtnisses in verschiedene Systeme und Subprozesse gesucht wurden. Hierfür wurden verschiedene wissenschaftliche Methoden, experimentelle Paradigmen, Auswertungsmethoden und Stichprobengruppen angewendet. Selbstverständlich können die vorliegenden Studien nicht alle Aspekte des vielfältigen Gedächtnissystems berühren. Neben einer ‚Makro'-Analyse verschiedener Gedächtnissysteme (Studie 3) wurde ein besonderer Fokus auf die kognitiven Prozesse gelegt, welche das sog. Rekognitionsgedächtnis (oder Wiedererkennensgedächtnis) zu unterstützen scheinen (Studien 1, 2 & 4). Letzteres bezieht sich auf die Fähigkeit, darüber zu entscheiden, ob eine angetroffene Information in der Umwelt bereits bekannt ist, also in der Vergangenheit erfahren wurde, oder ob sie neu, also bisher unbekannt ist.

Aktuelle Theorien des Rekognitionsgedächtnisses betonen, dass die Fähigkeit, Informationen als ‚alt' (d.h. bekannt) oder ‚neu' (d.h. unbekannt) einzustufen, auf zwei funktionell und neurophysiologisch dissoziierbaren Gedächtnisprozessen zu

beruhen scheint, welche mit Familiarität bzw. Rekollektion benannt werden (für Überblicke siehe Aggleton & Brown, 1999, 2006; Diana et al., 2006, 2007; Eichenbaum et al., 2007; Jacoby, 1991; Mandler, 1980; Mecklinger & Jäger, 2009; Norman & O'Reilly, 2003; Yonelinas, 2002). Diese sog. ‚Zwei-Prozess-Modelle' stehen im Kontrast zu ‚Ein-Prozess-Modellen' des Rekognitionsgedächtnisses. Letztere nehmen an, dass das Wiedererkennen auf einem eindimensionalen, skalaren Wert der globalen Gedächtnisstärke beruht (z.B. Donaldson, 1996; Gillund & Shiffrin, 1984; siehe Quamme et al., 2004; Yonelinas, 2001, für Diskussionen). Innerhalb des Zwei-Prozess-Modells wird der Prozess der Familiarität als akontextueller, item-spezifischer Gedächtnisprozess konzeptualisiert, welcher ein Individuum dazu bringt, das Gefühl zu haben, dass ihm etwas bekannt vorkommt, aber keine genaueren Details über die Episode abrufen kann, in welcher die Information ursprünglich aufgenommen wurde. Die Familiarität scheint vom Cortex des medialen Temporallappens (d. h. entorhinaler, perirhinaler und parahippocampaler Kortex) generiert zu werden. Im Gegensatz dazu bezieht sich der Prozess der Rekollektion auf den expliziten Abruf von (z.B. räumlichen oder zeitlichen) Kontextinformationen der Episode, in welcher eine Information präsentiert wurde. Die Rekollektion scheint von einer erfolgreichen Verarbeitung der Hippokampus-Formation abzuhängen (z.B. Aggleton & Brown, 1999, 2006; Eichenbaum et al., 2007).

Allerdings wird die Existenz von zwei (unabhängigen) Gedächtnisprozessen als Mediatoren des Rekognitionsgedächtnisses immer noch kontrovers diskutiert. Deshalb war es ein Ziel der vorliegenden Dissertation, weitere experimentelle Bedingungen und Situationen zu identifizieren, welche eine Dissoziation der beiden postulierten Subprozesse des Wiedererkennens nahelegen. Hierfür wurden u.a. zwei verschiedene Arten von assoziativen Rekognitionsgedächtnis-Aufgaben angewendet, von denen angenommen wird, dass sie familiaritäts- bzw. rekollektions-basiertes Wiedererkennen fördern (Studie 1). Des Weiteren wurden zwei verschiedene Stichprobengruppen von jüngeren und älteren Erwachsenen untersucht, welche sich wahrscheinlich in ihrem Profil der Effizienz von Familiarität und Rekollektion

unterscheiden (Studie 2). Schließlich wurden Patienten nach einem kurzzeitigen, aber massiven Gedächtnisverlust (d. h. Patienten mit einer transienten globalen Amnesie – TGA) rekrutiert und mit gesunden Kontrollprobanden verglichen, wobei angenommen wurde, dass die Patienten ein selektives Defizit in einem der beiden postulierten Gedächtnisprozesse des Wiedererkennens aufweisen (Studie 4).

Während die Studien 1 und 2 die Subprozesse des Rekognitionsgedächtnisses auf einer behavioralen Basis untersuchten (d.h. dass nur Verhaltensdaten vorhanden waren), ermöglichte die Studie 4 auch eine explizite Verknüpfung der Subprozesse des Wiedererkennens mit ihrer potenziellen neurophysiologischen Basis, weil die untersuchte Patientengruppe in der Bildgebung eine umschriebene und kleine Störung der Gehirnfunktion aufwies. Genauer gesagt zeigten die Patienten mit TGA während der Erholungsphase nach der amnestischen Attacke sichtbare, kleine Läsionen innerhalb der Hippokampus-Formation. Auf diese Weise war es möglich, zu analysieren, ob die Familiarität und/oder die Rekollektion von der funktionalen Integrität des Hippokampus abhängen.

Die Studie 3 wurde auch als Vorstudie für die Studie 4 durchgeführt und hatte zum Ziel, die Frage zu klären, ob die hippokampalen Läsionen bei Patienten mit TGA in einer selektiven Beeinträchtigung episodischer Langzeitgedächtnisleistungen (nicht aber Kurzzeit- oder semantische Gedächtnisleistungen) führt, was von den meisten Forschern und Klinikern angenommen wird. Dadurch leistete die Studie 3 auch einen generelleren Beitrag zur Untersuchung der Dissoziierbarkeit verschiedener Gedächtnissysteme wie z.B. Kurzzeit- und Langzeitgedächtnis und episodisches und semantisches Gedächtnis. Die Studie 4 fokussierte dann spezifischer auf die Unterteilung des episodischen Gedächtnisses in verschiedene Subprozesse, welche durch eine funktionelle Störung des Hippokampus betroffen sein könnten.

Studie 1: Familiarität unterstützt das assoziative Wiedererkennen für Gesichter-Stimuli, welche unitisiert werden können: Belege aus Receiver Operating Characteristics-Kurven

Fragestellung von Studie 1

Diese erste Studie testete die Dissoziierbarkeit verschiedener Subprozesse des Rekognitionsgedächtnisses bei jungen Erwachsenen. Um eine experimentelle Bedingungen zu finden, welche die Beiträge von Familiarität und Rekollektion zum Wiedererkennen separiert, diente als Grundlage der Befund, dass Familiarität und Rekollektion differenziell zum Erinnern von Assoziationen beizutragen scheint. Es wurde berichtet, dass die (hippokampal-vermittelte) Rekollektion das Erinnern von Assoziationen zwischen arbiträren Items wie z.B. das Wortpaar ‚Kugel-Essen' vermittelt, wohingegen Familiarität das assoziative Wiedererkennen von unitisierbaren (d.h. zu einer Einheit verschmelzbaren) Items wie z.B. das Wortpaar ‚Meer-Wasser' unterstützt, obwohl Familiarität traditionell als item-spezifische, akontextuelle Form des Wiedererkennens konzeptualisiert wird (die sog. ‚Unitisierungs-Hypothese') (z.B. Diana et al., 2008; Giovanello et al., 2006; Jäger et al., 2006; Mayes et al., 2007; Quamme, 2004; Quamme et al., 2007; Rhodes & Donaldson, 2007; Yonelinas et al., 1999). ‚Unitisierung' bezieht sich auf einen Prozess, welcher dazu führt, dass zwei oder mehr ursprünglich getrennte Items zu einer Repräsentation eines singulären Items verschmolzen werden (Graf & Schacter, 1989).

Beispielsweise untersuchte eine kürzliche Studie mit ereigniskorrelierten Gehirnpotentialen (EKP) die Annahme, dass Familiarität das assoziative Erinnern unter besonderen Umständen unterstützen kann (Jäger et al., 2006). In dieser Studie memorierten die Versuchsteilnehmer entweder Paare von Gesichtern von verschiedenen Personen (intra-item Bedingung) oder Paare von sehr ähnlichen Gesichtern, welche als dieselbe Person wahrgenommen wurden (intra-item Bedingung). Konsistent mit der Annahme, dass Rekollektion das Erinnern von

arbiträren Informationen unterstützt, wurde in der inter-item Bedingung hauptsächlich ein später parietaler alt/neu-Effekt entdeckt, welcher als das elektrophysiologische Korrelat der Rekollektion gilt. Umgekehrt wurde in der intra-item Bedingung vorwiegend ein früher frontaler alt/neu-Effekt beobachtet, welcher das neuronale Korrelat der Familiarität entspricht, so dass angenommen werden kann, dass Familiarität das assoziative Wiedererkennen von unitisierbaren Assoziationen unterstützt.

In Anbetracht dieser Befunde wurde in Studie 1 eine Manipulation angewandt, welche das Ausmaß der Unitisierbarkeit von zu assoziierenden Items beeinflusst, um hierdurch die beiden angenommen Subprozesse des Wiedererkennens auf einer behavioralen Basis zu dissoziieren. Hierbei wurde eine modifizierte Version der Aufgabe von Jäger et al. (2006) verwendet, in welcher behaviorale Schätzwerte für Familiarität und Rekollektion abgeleitet werden konnten. Die Versuchspersonen memorierten Gesichterpaare und fällten später in der Testphase Entscheidungen, ob die gezeigten Paare jeweils ‚intakte' (d.h. genau so gelernte) oder ‚rekombinierte' (d.h. zwar jeweils gelernte, aber neu zusammengestellte) Paare darstellten (siehe Abbildung 3).

Um die differenziellen Beiträge von Familiarität und Rekollektion zum Wiedererkennen von inter- und intra-item Assoziationen abzuschätzen, wurde die Form von sog. Receiver Operating Characteristics- (ROC-) Kurven untersucht (z.B. Yonelinas, 1994, 1997). ROC-Kurven stellen das Verhältnis von Hits und False Alarms über eine bestimmte Anzahl von Antwortkriterien hinweg dar. Der Punkt ganz links auf der ROC-Funktion wird erzeugt, indem Hits und False Alarms für das strikteste Antwortkriterium zueinander ins Verhältnis gesetzt werden. Die restlichen Punkte der ROC-Kurve widerspiegeln kontinuierlich abgeschwächte Antwortkriterien. In Bezug auf die Form der ROC-Kurven lässt sich sagen, dass eine kurvilineare und entlang der Diagonalen symmetrische Kurve zu erwarten ist, wenn die Gedächtnisleistung ausschließlich auf Familiarität beruht (z.B. Yonelinas et al., 1996). Diese Form wird erzeugt, wenn das Antwortkriterium kontinuierlich abgeschwächt wird und die Familiariäts-Verteilung von ‘alten’ und ‘neuen’ Items

eine Gauß-Form annimmt und eine gleiche Varianz aufweist (z.B. Yonelinas, 1994). Umgekehrt nimmt die ROC-Kurve eine lineare Form an und sollte den Punkt 1,1 des Koordinatensystems erreichen, wenn die Gedächtnisleistung ausschließlich auf Rekollektion basiert. Rekollektion wird als ein Schwellenprozess angesehen, wobei Items, die über eine bestimmte Schwelle fallen, durch Rekollektion abgerufen werden können, während dies für Items, welche unter die Schwelle fallen, nicht der Fall ist. Da Rekollektion mit hoch-konfidenten Antworten in Zusammenhang gebracht wird, sollte ein höherer Beitrag der Rekollektion dazu führen, dass der linke Anteil der ROC-Kurve entlang der *y*-Achse nach oben verschoben wird, was in einer asymmetrischen ROC-Kurve resultiert. Wenn die Gedächtnisleistung allerdings sowohl auf Rekollektion als auch auf Familiarität beruht, so sollte eine ROC-Kurve entstehen, welche kurvilinear und entlang der Diagonalen assymetrisch ist.

Die Hypothese von Studie 1 war diejenige, dass die Schätzwerte für Familiarität, welche aus der Form von ROC-Kurven abgeleitet werden können, in der intra-item Bedingung höher als in der inter-item Bedingung sind. Umgekert wurde erwartet, dass die Rekollektions-Schätzwerte in der inter-item Bedingung größer als in der intra-item Bedingung ausfallen.

Ergebnisse von Studie 1

Studie 1 umfasste zwei Experimente (1 & 2). In beiden wurde eine Stichprobe von gesunden, jungen Erwachsenen untersucht (N = 20 in Experiment 1, N = 32 in Experiment 2). In Experiment 1 wurde für die angewendete assoziative Rekognitionsgedächtnis-Aufgabe (siehe Abbildung 3) gefunden, dass die Anzahl der Hits in der intra-item Bedingung höher ausfiel als in der inter-item Bedingung (p < .001), während die Anzahl der Correct Rejections das gegenteilige Muster aufwies (p = .006). Hingegen unterschieden sich die A_z-Werte, welche einen Index für die generelle Gedächtnisperformanz liefern, nicht signifikant zwischen beiden Bedingungen (p = .119), was auf eine vergleichbare Leistung in den beiden Bedingungen hinweist. Die Reaktionszeiten für die ‚intakt'- versus ‚rekombiniert'-

Entscheidungen waren für die Hits in der intra-item Bedingung schneller als in der inter-item Bedingung (p = .002), dies galt allerdings nicht für die Correct Rejections (p = .149).

Die ROC-Analysen (siehe Abbildungen 4 und 5) ergaben, dass in der intra-item Bedingung ein höherer Anteil an familiaritäts-basiertem Wiedererkennen erfolgte als in der inter-item Bedingung (p = .002), während der Beitrag von Rekollektion für das Zurückweisen von rekombinierten Gesichterpaaren in der inter-item Bedingung höher war als in der intra-item Bedingung (p = .023). Beim Akzeptieren von intakten Gesichterpaaren ergab sich hingegen kein Bedingungsunterschied (p = .472).

Das Experiment 2 wurde durchgeführt, um die Ergebnisse von Experiment 1 zu replizieren, wobei jedoch versucht wurde, eine generell höhere Gedächtnisleistung zu ermöglichen und ein längeres Retentionsintervall (40 anstatt 20 Sekunden) einzuführen. Wie in Experiment 1 ergab sich, dass die Anzahl der Hits in der intra-item Bedingung höher ausfiel als in der inter-item Bedingung (p < .001), während die Anzahl der Correct Rejections das gegenteilige Muster aufwies (p < .001). Hingegen unterschieden sich die A_z-Werte wiederum nicht signifikant zwischen den Bedingungen (p = .091). Die Reaktionszeiten für die ‚intakt'- versus ‚rekombiniert'-Entscheidungen waren für die Hits diesmal vergleichbar über die beiden Bedingungen hinweg (p = .303), wohingegen die Correct Rejections in der inter-item Bedingung schneller ausfielen als in der intra-item Bedingung (p = .007).

Die ROC-Analysen von Experiment 2 (siehe Abbildungen 6 und 7) ergaben, dass wiederum in der intra-item Bedingung ein höherer Anteil an familiaritäts-basiertem Wiedererkennen erfolgte als in der inter-item Bedingung (p = .012), während der Beitrag von Rekollektion für das Zurückweisen von rekombinierten Gesichterpaaren in der inter-item Bedingung höher war als in der intra-item Bedingung (p = .009). Beim Akzeptieren von intakten Gesichterpaaren ergab sich hingegen wiederum kein Bedingungsunterschied (p = .388).

Diskussion von Studie 1

Konsistent mit früheren Befunden, dass Familiarität das assoziative Wiedererkennen unterstützen kann, wenn die zu assoziierenden Items zu einer singulären Repräsentation unitisiert werden können (Jäger et al., 2006; Opitz & Cornell, 2006; Quamme, 2004; Quamme et al., 2007; Rhodes & Donaldson, 2007; Yonelinas et al., 1999; siehe auch Eichenbaum, 1997), wurde in Studie 1 gefunden, dass in der intra-item Bedingung ein höherer Anteil an familiaritäts-basierten Gedächtnisentscheidungen als in der inter-item Bedingung getroffen wurden. Umgekehrt wurde im Einklang mit den Vorhersagen des Zwei-Prozess-Modells beobachtet, dass die Rekollektion für das Zurückweisen von rekombinierten Gesichterpaaren in der inter-item Bedingung eine wichtigere Rolle einnahm als in der intra-item Bedingung. Entgegen den Erwartungen wurde zwar kein höherer Anteil an Rekollektion für das Erinnern intakter Gesichterpaare in der inter-item Bedingung gefunden, dieses Resultat könnte jedoch dadurch zustande gekommen sein, dass die Rekollektionsschätzwerte in beiden Bedingungen relativ niedrig waren, was zu einem Bodeneffekt geführt haben könnte. Zudem war die Gedächtnisleistung in der intra-item Bedingung leicht (aber nicht-signifikant) höher als in der inter-item Bedingung, was zu einer weiteren Verringerung rekollektions-basierter Entscheidungen in der inter-item Bedingung geführt haben könnte.

Um eine mögliche Erklärung für die zugrunde liegenden Prozesse abzugeben, welche das Erinnern von arbiträren (und rekollektions-unterstützten) versus unitisierbaren (und familiaritäts-unterstützten) Assoziationen vermitteln, wurde in Anlehnung an ein Modell von Norman und O'Reilly (2003; siehe auch Aggleton & Brown, 1999) ein Erklärungsmodell aufgestellt (siehe Abbildung 8). Als Schlussfolgerung lässt sich zusammenfassen, dass die Ergebnisse von Studie 1 weitere Belege für die Annahme liefern, dass Familiarität und Rekollektion differenzielle Beiträge zum Erinnern von Assoziationen zu liefern scheinen: Während Rekollektion das Wiedererkennen von arbiträren Verknüpfungen vermittelt, kann das Abrufen von unitisierbaren Assoziationen von Familiarität profitieren. Gleichzeitig trug die Studie 1 dazu bei, eine Unterscheidung von verschiedenen Subprozessen des

Rekognitionsgedächtnisses (und damit auch des episodischen Gedächtnisses) anzunehmen.

Studie 2: Assoziatives Wiedererkennen von Gesichtern: Größere Altersdefizite im Verknüpfen von intra- als inter-item Assoziationen

Fragestellung von Studie 2

Wie die Studie 1 lag auch der Studie 2 der Befund zugrunde, dass intra- und inter-item Assoziationen familiaritäts- bzw. rekollektions-basiertes Wiedererkennen zu fördern scheinen und somit zwei Situationen mit zumindest teilweise verschiedenen involvierten Gedächtnisprozessen darstellen. In der Studie 2 wurde die Fragestellung untersucht, ob das normale kognitive Altern aufgrund einer relativen Beeinträchtigung bzw. Erhaltung von Rekollektion und Familiarität mit einer selektiven Leistungseinbuße in einer der beiden Bedingungen verbunden ist. Frühere Befunde legen es nahe, dass die Rekollektion im höheren Erwachsenenalter vermindert ist, während das familiaritäts-basierte Wiedererkennen altersinvariant zu sein schein (z.B. Bastin et al., 2003; Daselaar et al., 2006; Howard et al., 2006; siehe Light et al., 2000; Prull et al., 2006, für Überblicke). Anhand dieser Befunde konnte die Erwartung aufgestellt werden, dass ältere Erwachsene im Erinnern von arbitäreren inter-item Assoziationen überproportional beeinträchtigt sein müssten.

Diese Erwartung ist z.B. auch im Einklang mit Befunden, dass das kognitive Altern mit einem substanziellen Defizit im Erinnern von Assoziationen zwischen verschiedenen Arten von arbiträren Items verbunden ist (Bastin & Van der Linden, 2006; Castel & Craik, 2003; Naveh-Benjamin, 2000; Naveh-Benjamin, Brav, & Levy, 2007; Naveh-Benjamin, Guez, Kilb, & Reedy, 2004; Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003), was auf eine altersbezogene Reduktion der Rekollektion mit einer gleichzeitigen Volumenminderung des Hippokampus (Raz et al., 2005) zurückgeführt werden könnte.

Allerdings muss bemerkt werden, dass bisher noch keine Studie explizit das Gedächtnis von älteren Erwachsenen für unitisierbare Assoziationen getestet hat und dass die Literatur über die Alterseffekte auf Familiarität und Rekollektion noch inkonsistent ist (z.B. Duarte et al., 2006; Li et al., 2004), was die empirische

Grundlage für die oben formulierte Erwartung abschwächt. Des Weiteren scheinen ältere Erwachsene manchmal in der Lage zu sein, ihr Altersdefizit im Erinnern arbiträrer Assoziationen mithilfe strategischer kognitiver Prozesse zu kompensieren (Cabeza, Anderson, Locantore, & McIntosh, 2002; vgl. Naveh-Benjamin et al., 2007; siehe Buckner, 2004, für einen Überblick), wie z.B. mithilfe von effektiven Enkodierstrategien, die von älteren genau so gut wie von jüngeren Erwachsenen eingesetzt werden können (siehe Hertzog & Dunlosky, 2004, für einen Überblick). Ein weiterer Aspekt, der die oben formulierte Erwartung relativieren könnte ist die Tatsache, dass Unitisierungsprozesse beim Enkodieren und familiaritäts-basiertes Wiedererkennen beim Abruf keine isomorphen kognitiven Prozesse sind, so dass es z.B. denkbar ist, dass Unitisierungsprozesse negativ vom Altern beeinflusst werden, obwohl das familiaritäts-basierte Erinnern in bestimmten Situationen intakt ist.

Zusammenfassend explorierte die Studie 2, ob ältere Erwachsene ein größeres oder kleineres Defizit im Erinnern von Assoziationen aufweisen, wenn die zu assoziierenden Informationen in ein kohärentes Ganzes unitisiert werden können. Auf diesem Wege versuchte die Studie 2 auch, weitere Belege für die Sicht zu liefern, dass das Rekognitionsgedächtnis mehr als nur einen Subprozess beinhaltet, welche in bestimmten Situationen dissoziiert werden können. In Studie 2 wurde wiederum eine ähnliche Aufgabe wie in der EKP-Untersuchung von Jäger et al. (2006) verwendet (siehe Abbildung 9), in welcher die Versuchsteilnehmer jeweils arbiträre (inter-item Bedingung) bzw. unitisierbare (intra-item Bedingung) Gesichterpaare memorieren und sich in der späteren Testphase mittels einer Forced-Choice-Entscheidung an die genauen Paarungen der Lernphase erinnern mussten. Es wurden zwei Stichproben von jüngeren ($N = 20$) und älteren ($N = 20$) Erwachsenen untersucht.

Ergebnisse von Studie 2

Die älteren Erwachsenen zeigten eine höhere verbale Intelligenz als die jüngeren ($p < .001$), während sich die beiden Gruppen jedoch nicht im Bildungsstand, in der Anzahl Schuljahre, in der selbsteingeschätzten Gesundheit und in der Anzahl

eingenommener Medikamente unterschieden. In verschiedenen neuropsychologischen Tests konnten Hinweise gefunden werden, dass keiner der älteren Erwachsenen Anzeichen einer milden kognitiven Beeinträchtigung zeigte, dass die älteren Erwachsenen aber typische Altersdefizite in der Geschwindigkeit der Informationsverarbeitung ($p < .001$), in der inhibitorischen Kontrolle ($p < .01$) und in der Arbeitsgedächtniskapazität ($p < .01$) aufwiesen.

In der Gedächtnisaufgabe zeigte sich, dass beide Altersgruppen in beiden Bedingungen eine Gedächtnisleistung zeigten, welche signifikant über dem Zufallsniveau lag (p-Werte $\leq .01$; siehe Abbildung 10). Die geplanten Kontraste für die Alterseffekte in den beiden Bedingungen ergaben, dass eine signifikant niedrigere Leistung der älteren Erwachsenen in der inter-item Bedingung beobachtet werden konnte ($p < .05$; $\eta^2 = .11$), allerdings war das Altersdefizit in der intra-item Bedingung sogar noch (und fast drei Mal) größer ($p < .001$; $\eta^2 = .32$).

Diskussion von Studie 2

Konsistent mit früheren Befunden, dass das kognitive Altern mit einem substanziellen Defizit im Erinnern unrelatierter, arbiträrer Assoziationen verbunden ist (z.B. Bastin & Van der Linden, 2006; Castel & Craik, 2003; Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2003, 2004, 2007) wurde in Studie 2 gefunden, dass die älteren Erwachsenen ein signifikantes Defizit beim Erinnern von inter-item Assoziationen zwischen arbiträr gepaarten Gesichtern aufwiesen. Dieser Befund kann mit einer altersbezogenen Beeinträchtigung der Rekollektion erklärt werden (siehe Prull et al., 2006).

Eine neue Forschungsfrage, welche in der Studie 2 untersucht wurde, war, ob ältere Erwachsenen ein geringeres oder größeres Altersdefizit zeigen, wenn die zu assoziierenden Items potenziell unitisierbar sind und somit von familiaritäts-basiertem Wiedererkennen profitieren können (Giovanello et al., 2006; Jäger et al., 2006; Quamme, 2004; Quamme et al., 2007; Rhodes & Donaldson, 2007; Yonelinas et al., 1999). Der in der Einleitung formulierten Erwartung widersprechend wurde in

Studie 2 gefunden, dass die älteren Erwachsenen beim Erinnern der unitisierten Gesichterpaare überproportional beeinträchtigt waren. Anhand der Zwei-Prozess-Modelle könnte einerseits spekuliert werden, dass die Familiarität nicht unbedingt in jeder Situation altersinvariant ist und in manchen Fällen sogar eine größere Sensitivität für altersbedingte Veränderungen aufweist als die Rekollektion (vgl. Duarte et al., 2006; Li et al., 2004).

Andererseits muss betont werden, dass Unitisierungs- und Familiaritäts-Prozesse nicht isomorph sind, weshalb ein Altersdefizit beim Unitisieren von Items unabhängig von einer Altersinvarianz familiaritäts-basierter Prozesse existieren kann. Das in Studie 2 gefundene Altersdefizit in der intra-item Bedingung könnte somit auf Prozesse während des Enkodierens der Gesichterpaare zurückgehen. Eine Unitisierung von Items wie z.B. Gesichtern könnte ein äußerst komplexer Prozess sein, welcher vermutlicherweise eine erhöhte Aktivierung der überlappenden Merkmale beider Bilder und eine verminderte Aktivierung von nicht-überlappenden Merkmalen innerhalb des medialen Temporallappens beinhaltet (ein Prozess, welcher auch als „Sharpening“ bezeichnet wird) und von sensiblen Vorgängen wie Hebbsches Lernen und kompetitive Inhibition (Norman & O’Reilly, 2003) abhängen könnte. Diese sensiblen Vorgänge könnten durch subtile Altersveränderungen von funktionellen und biochemischen Attributen neuronaler Netzwerke beeinflusst werden, welche z.B. durch die Ablagerung von Plaques im Gehirn älterer Erwachsener zustande kommen könnten (siehe Yang et al., 2005).

Eine mit dieser Betonung der Prozesse während der Enkodierphase zusammenhängende Möglichkeit ist diejenige, dass ältere Erwachsene möglicherweise erfolgreich strategische kognitive Prozesse einsetzen, welche das assoziative Enkodieren von arbiträren nicht aber von unitisierbaren Items unterstützen. Diese Vermutung stimmt mit Befunden überein, dass ältere Erwachsene bilaterale präfrontale Aktivierungen zeigen können, welche scheinbar kompensatorische Prozesse widerspiegeln, die die Quellengedächtnisleistung (welche stark von einer erfolgreichen Rekollektion abhängt) auf das Niveau der jüngeren Erwachsenen anheben kann (Cabeza et al., 2002; vgl. Naveh-Benjamin et al., 2007;

siehe Buckner, 2004, für einen Überblick) und dass ältere Erwachsene gleich gut wie die jüngeren Versuchsteilnehmer Enkodierstrategien einsetzen können, welche spezifisch dazu geeignet sein könnten, das Verknüpfen von arbiträren (nicht aber unitisierbaren) Items zu erleichtern (siehe Hertzog & Dunlosky, 2004, für einen Überblick). Diese Sichtweise einer selektiven Kompensation in der inter-item Bedingung wird auch durch eine post-hoc Analyse gestützt, welche zeigte, dass die gut abschneidenen älteren Erwachsenen gleich gut wie die jüngeren in der inter-item Bedingung waren (p = .946) und trotzdem ein selektives Defizit in der intra-item Bedingung aufwiesen (p < .05).

Bisher gibt es kaum Untersuchungen, welche das assoziative Erinnern älterer Erwachsener von unitisierbaren Assoziationen untersucht. Die Befunde von Studie 2 legen es nahe, dass das kognitive Altern mit einem substanziellen Defizit in der Bildung von unitisierten Assoziationen zwischen stark überlappenden Items verbunden ist. Der differenzielle Alterseffekt von Studie 2 stützt zudem die Vermutung einer Dissoziierbarkeit von intra- und inter-item Assoziationen, wie es von Studie 1 und einer früheren EKP-Studie (Jäger et al., 2006) nahegelegt wurde. Somit scheint es verschiedene Situationen zu geben, in welchen z.T. voneinander unterscheidbare Subprozesse (und nicht nur ein einziger Prozess) des menschlichen episodischen Gedächtnisses am Werk sind.

Studie 3: Die Transienz und Charakteristiken der kognitiven Beeinträchtigungen bei der Transienten Globalen Amnesie (TGA): Eine Meta-Analyse

Fragestellung von Studie 3

Während die Studien 1 und 2 die Gedächtnisprozesse untersuchten, welche in einem umschriebenen, spezifischen experimentellen Paradigma des episodischen (assoziativen Rekognitions-) Gedächtnisses involviert sind, erweiterte Studie 3 die untersuchte Bandbreite der Gedächtnissysteme und –prozesse zu einem systemischen oder 'Makro'-Ansatz. Das Ziel war es, Belege dafür zu finden, dass eine spezielle Gehirndysfunktion differenzielle Effekte auf Aufgaben ausübt, welche verschiedenen Gedächtnissystemen zugeordnet werden können. Auf diese Weise sollte die Sichtweise, dass das menschliche Gedächtnis kein singuläres sondern ein vielfältiges Konstrukt ist, weiter gestützt werden (z.B. Moscovitch et al., 2005; Squire et al., 1993; Squire & Zola, 1996).

Um dies zu erreichen, wurde eine interessante Patientengruppe untersucht, welche typischerweise kleine und umschriebene Störungen in einer der wichtigsten Strukturen des Gedächtnissystems – im medialen Temporallappen mit einem Fokus im Hippokampus – zeigen. Diese Patienten, welche eine sog. Transiente Globale Amnesie (TGA) erleben, erleben einen plötzlichen und vorübergehenden, aber beinahe kompletten Verlust der Fähigkeit, neue Informationen einzuspeichern und bestimmte Arten von gespeicherten Informationen aus dem Gedächtnis abzurufen (Fisher & Adams, 1964; für Überblicke siehe Brown, 1998; Frederiks, 1993; Hodges, 1991; Kritchevsky, 1989; Markowitsch, 1990; Mazzucchi & Parma, 1990; Szabo & Bäzner, 2007; für Überblicke über Neuroimaging-Befunde siehe Baron et al., 1994; Bartsch et al., 2006, 2007; Eustache et al., 1997; Frederiks, 1993; Guillery et al., 2002; Pantoni et al., 2000; Sedlaczek et al., 2004).

Das Erleben einer TGA-Episode ist für die Patienten und deren Angehörige eine außerordentliche Erfahrung, obwohl die TGA üblicherweise als ein harmloses

Phänomen beurteilt wird. Die diagnostischen Kriterien der TGA beinhalten die Voraussetzungen, dass (1) ein abrupter Beginn einer schweren anterograden Amnesie und einer variablen retrograden Amnesie vorliegt, wobei die Patienten häufig dadurch auffallen, dass sie ständig dieselben Fragen wiederholen und desorganisiert und verwirrt sind, (2) dass allerdings keine gleichzeitigen fokal-neurologischen Symptome (u.a. auch keine epileptischen Anfälle oder Kopfverletzungen) vorhanden sind, (3) dass die Episode fremdbeobachtet wird, (4) dass kein Bewusstseinsverlust und keine Identitätsstörung erfolgen, sondern dass lediglich eine Gedächtnisstörung vorliegt und (5) dass die Attacke sich innerhalb ca. 24 Stunden wieder auflöst und keine langfristigen Folgen hinterlässt, mit Ausnahme einer Gedächtnislücke für die Zeit der Episode (Hodges & Warlow, 1990a).

Obwohl die detaillierte Ätiologie der TGA noch ungeklärt ist, scheint wie oben angesprochen ein relativ konsistenter Befund derjenige zu sein, dass innerhalb des medialen Temporallappens mit einem Fokus im Hippokampus uni- oder bilaterale Störungen der Gehirnfunktionen auftreten (Bartsch et al., 2006; Sedlaczek et al., 2004).

Das spezifische Ziel der Studie 3 war es, zu zeigen, dass transiente Störungen der Funktion des medialen Temporallappens in TGA-Patienten manche Gedächtnisleistungen beeinträchtigen, andere hingegen nicht beeinflussen, was wiederum für ein unterteilbares Gedächtnissystem des Menschen sprechen würde. Die Hypothese wurde getestet, dass eine TGA-Episode zu einer überproportionalen Störung des episodischen Gedächtnisses führt, während das Kurzzeit- und semantische Gedächtnis hingegen erhalten bleiben. Diese Annahme kann u.a. durch die den verschiedenen Gedächtnissystemen unterliegenden neuralen Substrate getroffen und begründet werden. Außerdem liegt eine Vielzahl an Befunden vor, welche folgendes Muster suggerieren: (1) Die salienteste kognitive Dysfunktion während einer TGA-Episode ist eine Störung des anterograden episodischen Langzeitgedächtnisses (Mazzucchi & Parma, 1990). (2) Die meisten, aber nicht alle Patienten zeigen auch einen partiellen Verlust des retrograden episodischen Langzeitgedächtnisses (Kazui et al., 1996; Kritchevsky et al., 1997; Simons &

Hodges, 2000). (3) Das Kurzzeitgedächtnis (Hodges, 1994; Pantoni et al., 2000; siehe Mazzucchi & Parma, 1990, für einen Überblick), das semantische Gedächtnis (Hodges, 1994) und nicht-deklarative Gedächtnisleistungen (Beauregard et al., 1997; Eustache et al., 1997; Kapur et al., 1996; Kazui et al., 1995) scheinen hingegen von der amnestischen Attacke unberührt zu bleiben. Was andere kognitive Funktionen wie z.B. sog. exekutive Funktionen angeht, so liegt hier noch keine ausreichende Datengrundlage für sichere Schlussfolgerungen vor (Baron et al., 1994; Quinette et al., 2003; Stillhard et al., 1990; vgl. Mazzucchi & Parma, 1990).

Um eine teststarke und reliable Untersuchung dieser Hypothese zu ermöglichen, wurden in Studie 3 keine neuen Daten einer (gezwungenermaßen) kleinen Gruppe von TGA-Patienten mittels der Anwendung verschiedener Gedächtnisaufgaben erhoben, sondern es wurde die Methode der Meta-Analyse verwendet (DeCoster, 2004; Hedges & Olkin, 1985; Rustenbach, 2003), welche die genannte Hypothese auf der Grundlage der (möglichst) gesamten bisher existierenden Literatur zum Thema der kognitiven Auswirkungen der TGA zu testen versuchte. U.a. kann mit dieser Methode der Nachteil vieler bisheriger Studien ausgeräumt werden, dass nur kleine Stichproben untersucht wurden und somit eine geringe Wahrscheinlichkeit vorlag, kleine statistische Effekte aufzuspüren.

Über diese erste Hypothese hinaus wurde auch der Zeitverlauf der kognitiven Veränderungen während und nach einer TGA untersucht. Die Annahme war hier, dass sich die TGA-induzierten kognitiven Störungen innerhalb einiger Tage komplett erholen. Als begleitende Grundlage dieser kognitiven Erholung könnte der Befund herangezogen werden, dass die neuralen Störungen im medialen Temporallappen ebenfalls noch einige Tage nach einer TGA-Attacke sichtbar sind, danach aber wieder verschwinden (Bartsch et al., 2006; Gass et al., 2004; Sedlaczek et al., 2004). Während eine TGA-Episode somit scheinbar keine langfristigen kognitiven Beeinträchtigungen nach sich zieht (z.B. Bartsch et al., 2006; Faglioni et al., 1992; Kritchevsky & Squire, 1989; Kritchevsky et al., 1988; Quinette et al., 2003), gibt es allerdings Belege dafür, dass auch nach Ende der amnestischen Attacke zumindest für einige Tage subtile Gedächtnisbeeinträchtigungen bestehen bleiben (z.B. Beauregard

et al., 1997; Borroni et al., 2004; Caffarra et al., 1981; Cattaino et al., 1984; Guillery-Gilard et al., 2006; Mazzucchi et al., 1980; Zinelli et al., 1988).

Die Studie 3 diente auch als Vorstudie zu Studie 4, da die erstere eine selektive Beeinträchtigung des episodischen Gedächtnisses in TGA-Patienten zu belegen suchte, während die letztere dann genauer unterscheiden sollte, welche Subprozesse des episodischen Gedächtnisses durch eine TGA beeinträchtigt bzw. nicht berührt werden.

Ergebnisse von Studie 3

Anhand spezifischer Vorgehensweisen und Kriterien wurden in der Literatur seit 1980 25 einzuschließende Studien gefunden. Tabelle 2 fasst die Charakteristiken der eingeschlossenen Studien zusammen. Die verwendeten Aufgaben wurden in fünf Kategorien eingeteilt: (1) anterogrades episodisches Langzeitgedächtnis, (2) retrogrades episodisches Langzeitgedächtnis, (3) Kurzzeitgedächtnis, (4) semantisches Gedächtnis und (5) exekutive Funktionen. Für jede Aufgabe wurde die Effektstärke berechnet, welche den Leistungsunterschied zwischen einer Gruppe von TGA-Patienten und einer Gruppe von gesunden Kontrollprobanden widerspiegelt. Insgesamt 185 Effektstärken wurden anhand einer Summe von insgesamt 1134 verschiedenen Studienteilnehmern (374 TGA-Patienten und 760 Kontrollprobanden) berechnet.

Nachdem potenzielle Ausreißer unter den berechneten Effektstärken ausgeschlossen wurden, wurde für jede kognitive Domäne eine gewichtete, mittlere Effektstärke berechnet, wobei dies für drei Zeitintervalle während bzw. nach der TGA-Episode getrennt gemacht wurde. In Abbildung 11 sind die berechneten und von Ausreißern bereinigten Effektstärken als Funktion der Zeit nach der Attacke abgetragen (keine Abbildungen für retrogrades episodisches Langzeitgedächtnis und semantisches Gedächtnis aufgrund der geringen Zahl der berechneten Effektstärken).

Die gewichteten, mittleren Effektstärken sind in Abbildung 12 sichtbar. Wie darin zu erkennen ist, ist die akute Phase der TGA durch signifikant größer als Null

($p < .001$) ausgeprägte Defizite der TGA-Patienten in den Bereichen anterogrades episodisches Langzeitgedächtnis, retrogrades episodisches Langzeitgedächtnis (wobei das erstere signifikant stärker betroffen ist als das letztere; $p < .05$) und exekutive Funktionen geprägt, wohingegen die anderen kognitiven Bereiche nicht betroffen sind. Während der Post-Akut-Phase sind die Defizite der TGA-Patienten geringer geworden, dennoch besteht weiterhin eine (nicht-signifikante) subtile Beeinträchtigung anterograder episodischer Langzeitgedächtnisleistungen und ein (nicht-signifkantes) Defizit exekutiver Funktionen.

Diskussion von Studie 3

Konsistent mit der typischen Sichtweise der TGA konnte die Meta-Analyse zeigen, dass TGA-Patienten während der Akutphase eine substanzielle Reduktion der anterograden und eine etwas mildere Beeinträchtigung der retrograden episodischen Langzeitgedächtnisleistungen aufweisen, jedoch keine Veränderungen des Kurzzeit- und semantischen Gedächtnisses zeigen (Hodges, 1994; Mazzucchi & Parma, 1990).

Darüber hinaus wurde auch ein moderates Defizit in den sog. exekutiven Funktionen während der Akutphase gefunden, was einen unerwarteten Befund darstellt. Allerdings ist die diesbezügliche Datengrundlage bisher noch dürftig. Manche Studien haben bereits eine subtile exekutive Dysfunktion bei Patienten mit einer TGA nahegelegt (z.B. Baron et al., 1994; Stillhard et al., 1990; vgl. Mazzucchi & Parma, 1990; siehe aber Quinette et al., 2003), wobei manche Studien gleichzeitig eine Hypofunktion des präfrontalen Kortex als mögliche neurale Ursache fanden (Baron et al., 1994; Eustache et al., 1997; Stillhard et al., 1990). Wahrscheinlich ist die subtile exekutive Dysfunktion deshalb nicht in die diagnostischen Kriterien der TGA eingegangen, da die amnestische Symptomatik viel deutlicher ist und erstere deshalb überdeckt.

Der zweite wichtige Befund der Studie 2 war derjenige, dass nach spätestens ca. 30 Tagen nach der TGA-Episode keine signifikanten kognitiven Veränderungen mehr bestehen. Dieser Befund steht im Einklang mit der Sicht, dass die TGA ein

gutartiges und vorübergehendes Phänomen ohne langfristige Auswirkungen ist (Frederiks, 1993) und widerspricht einigen wenigen Befunden, welche langfristige Reduktionen der Gedächtnisleistung bei TGA-Patienten nahelegten (z.B. Borroni et al., 2004).

In der Post-Akut-Phase zeigte sich jedoch zumindest noch ein subtiles Defizit in den Bereichen anterogrades episodisches Langzeitgedächtnis und exekutive Funktionen. Dies spricht für den Vorschlag, dass die TGA „partiell transient“ anstatt vollkommen transient ist (Mazzucchi et al., 1980), da sich die kognitiven Veränderungen nur langsam und nicht unmittelbar erholen (Hodges & Oxbury, 1990; siehe Bartsch et al., 2006; Hodges & Ward, 1989; Kessler et al., 2001; siehe Kritchevsky et al., 1997; Mazzucchi & Parma, 1990, für Überblicke). Der Befund der subtilen Gedächtnisbeeinträchtigung in der Post-Akut-Phase geht auch mit den Resultaten aus der Gehirnbildgebung einher, welche in der Post-Akut-Phase kleine, punktförmige, uni- oder bilaterale Läsionen im Hippokampus identifizieren konnte (Bartsch et al., 2006; Gass et al., 2004; Sedlaczek et al., 2004). Auch die geringfügige Reduktion der exekutiven Funktionen scheint noch einige Tage nach der Attacke (d.h. in der Post-Akut-Phase) in leichter Form bestehen zu bleiben.

Zusammenfassend kann gesagt werden, dass die Ergebnisse der Studie 3 auch dazu beitragen konnten, eine Dissoziation zwischen verschiedenen Gedächtnissystemen zu belegen, da differenzielle Effekte der TGA auf verschiedene Arten von Gedächtnisaufgaben gefunden wurden. Insbesondere konnte Studie 3 den angenommenen starken Zusammenhang zwischen (Dys-)Funktionen des medialen Temporallappens – speziell des Hippokampus – und (Dys-)Funktionen des episodischen Gedächtnisses und die Erwartung, dass aufgrund einer anderen neuronalen Grundlage keine Auswirkungen einer TGA auf das Kurzzeit- und semantische Gedächtnis vorliegen müssten, unterstützen.

Studie 4: Selektive Beeinträchtigung hippokampal-vermittelter Rekognitionsgedächtnis-Prozesse nach einer Episode einer Transienten Globalen Amnesie (TGA)

Fragestellung von Studie 4

Die Studie 4 verfolgte den Befund, dass Störungen der Funktion des medialen Temporallappens eine selektive Beeinträchtigung des episodischen Langzeitgedächtnisses bewirken, jedoch keinen Effekt auf andere mnestische Leistungen wie das Kurzzeit- oder semantische Gedächtnis ausüben (Studie 3). Wiederum wurde das interessante Muster der umschriebenen und transienten Gehirnabnormalität während und nach einer Episode einer TGA untersucht. Das Ziel der Studie 4 war es, die episodischen Gedächtnisprozesse, welche durch die umschriebenen Läsionen innerhalb des medialen Temporallappens beeinträchtigt werden, genauer zu untersuchen. Es sollte ermittelt werden, ob sich verschiedene episodische Gedächtnisprozesse finden lassen, welche durch die Läsionen von TGA-Patienten beeinträchtigt werden bzw. unbeeinflusst bleiben. Auf diese Weise wurde eine mögliche Dissoziation verschiedener episodischer Gedächtnisleistungen analysiert. Dies steht im Gegensatz zu Studie 3, in welcher das menschliche Gedächtnis auf einer ‚Makro'- als auf einer ‚Mikro'-Ebene untersucht wurde.

Die theoretische Grundlage für Studie 4 bildeten wiederum die sog. Zwei-Prozess-Modelle des Rekognitionsgedächtnisses (vgl. Studien 1 und 2; Aggleton & Brown, 2006; Jäger, Mecklinger, & Kipp, 2006; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Montaldi, Spencer, Roberts, & Mayes, 2006; Norman & O'Reilly, 2003; Yonelinas, 2002). Es sollte getestet werden, ob die zwei vermuteten, dem Wiedererkennen zugrunde liegenden Gedächtnisprozesse, d.h. Familiarität und Rekollektion, unterschiedlich durch die Gehirnabnormalitäten bzw. -läsionen von TGA-Patienten beeinflusst werden. Falls die TGA zu einer generellen Beeinträchtigung des episodischen Gedächtnisses führt, so sollten Familiarität und Rekollektion beide negativ beeinflusst werden. Wenn die neurophysiologische

Abnormalität der TGA aber zu einer differenziellen Beeinflussung von Familiarität und Rekollektion führt, so sind damit zwei unterschiedlich auf (experimentelle) Manipulationen reagierende Subprozesse identifiziert worden. Aufgrund früherer Befunde, dass die Gehirnabnormalitäten während einer TGA (zumindest in der Post-Akut-Phase) hauptsächlich im Hippokampus lokalisiert werden können (Bartsch et al., 2006, 2007; Sedlaczek et al., 2004) und angesichts der vermuteten, starken Abhängigkeit der Rekollektion (nicht aber der Familiarität) vom Hippokampus (z.B. Eichenbaum et al., 2007; Norman & O'Reilly, 2003) dürfte die Hypothese eher in die letztere Richtung gehen.

Um diese potenzielle Dissoziation der Gedächtnisprozesse, welche dem episodischen (Rekognitions-) Gedächtnis zugrunde liegen, zu untersuchen, wurden Stichproben von gesunden, älteren Erwachsenen und TGA-Patienten während der Post-Akut-Phase mittels einer Standard-Item-Rekognitionsgedächtnisaufgabe miteinander verglichen. Auf der Grundlage früherer Befunde (z.B. Beauregard et al., 1997; Borroni et al., 2004; Hodges & Oxbury, 1990; Hodges & Ward, 1989; Le Pira et al., 2005; Mazzucchi et al., 1980) und der Resultate von Studie 3 konnte erwartet werden, dass TGA-Patienten auch einige Tage nach der amnestischen Episode noch subtile Gedächtnisbeeinträchtigungen aufweisen. Diese Erwartung ist mit dem Befund konsistent, dass sich die hippokampalen Läsionen, die eine TGA-Episode begleiten, erst nach einer gewissen Zeit wieder auflösen und somit während der Post-Akut-Phase sichtbar sind (Bartsch et al., 2006; Sedlaczek et al., 2004).

Genauer gesagt wurde die Hypothese aufgestellt, dass diese subtile Verminderung der episodischen Gedächtnisleistung ein selektives Defizit der Rekollektionsprozesse wiederspiegelt, während das familiaritäts-basierte Wiedererkennen als intakt vermutet wird und somit die über dem Zufall liegenden Gedächtnisleistungen von TGA-Patienten in der Post-Akut-Phase zumindest teilweise vermittelt. Die oben formulierte Hypothese wurde bei gesunden Kontrollprobanden (N = 11) und TGA-Patienten (N = 11) getestet, indem eine Standard-Item-Rekognitionsgedächtnisaufgabe für Gesichter und Wörter angewendet und wie in Studie 1 ROC-Kurven abgeleitet wurden. Indem die Auswirkungen von

umschriebenen Läsionen der Hippokampus-Formation auf kognitive Prozesse untersucht wurde, konnte auch eine die Grundlagenforschung betreffende Aussage über die Funktionen des Hippokampus getroffen werden.

Ergebnisse von Studie 4

Die beiden Stichproben dieser Studie unterschieden sich nicht im mittleren Alter (p = .552), in der Anzahl absolvierter Schuljahre (p = .146) und in der Geschlechterverteilung (p = .635). Alle Patienten erfüllten die Standard-Kriterien der TGA (Hodges & Warlow, 1990a) und erlebten eine amnestische Episode, welche im Schnitt 8.1 Stunden andauerte. Die kognitiven Aufgaben wurden jedoch in der Post-Akut-Phase angewendet, im Schnitt 52.5-57.4 Stunden nach der TGA-Episode. In der Untersuchung mittels der strukturellen Magnetresonanztomographie konnten in diffusionsgewichteten Aufnahmen bei 8 TGA-Patienten kleine Läsionen innerhalb des Hippokampus detektiert werden (2 Patienten mit bilateralen, 2 Patienten mit linksseitigen und 4 Patienten mit rechtsseitigen Läsionen des Hippokampus – siehe Abbildung 13; vgl. Bartsch et al., 2006; 2007; Sedlaczek et al., 2004).

In einer detaillierten neuropsychologischen Untersuchung erreichten die Patienten normale, nicht-pathologische Leistungen im Mini-Mental-Status-Test (MMSE), welcher ein Maß für die globale kognitive Funktionsfähigkeit liefert. Wie in Tabelle 3 angegeben, zeigten die Patienten auch normale Leistungen in den Bereichen Aufmerksamkeit, Visuokonstruktion, Geschwindigkeit der Informationsverarbeitung, Exekutivfunktionen, semantisches Gedächtnis und Kurzzeit- und Arbeitsgedächtnis. Hingegen konnten subtile, wenn auch klinisch nicht relevante Leistungsverminderungen in den Langzeitgedächtnismaßen des Wechsler-Gedächtnistests (WMS-R) beobachtet werden.

In der eigentlichen Rekognitionsgedächtnisaufgabe ergab sich in der Gesichter-Bedingung eine marginal signifikante (p = .123) und in der Wörter-Bedingung eine signifikante (p < .05) Leistungsreduzierung der Patienten im Vergleich zu den gesunden Kontrollprobanden im Hinblick auf die sog. Pr-Werte,

welche ein Maß für die Diskriminationsfähigkeit zwischen gelernten und neuen Items liefern. In den ROC-Analysen ergaben sich die Kurven, welche in der Abbildung 14 zu sehen sind. Mittels der Anpassung eines formalen Zwei-Prozess-Modells an die *kumulierten* ROC-Kurven (siehe Studie 1) konnten die in Abbildung 15 abgetragenen Schätzwerte für die Familiarität (*d'*) und die Rekollektion (R_{tot}) gewonnen werden. Tatsächlich schien sich kein Gruppenunterschied in Bezug auf die Familiarität zu ergeben, wohingegen die Rekollektion bei den Patienten deutlich niedriger auszufallen schien.

In der Analyse der Schätzwerte, welche aus den *individuellen* ROC-Kurven abgeleitet wurden, zeigte sich in der Gesichter-Bedingung entgegen den Ergebnissen aus der kumulierten ROC-Kurve (Abbildung 14) kein Gruppenunterschied in der Familiarität ($p = .269$) oder in der Rekollektion ($p = .941$) – siehe Abbildung 16. In der Wörter-Bedingung bestätigte sich jedoch das Muster der kumulierten ROC-Kurve (Abbildung 14), denn hier zeigte sich zwar kein Gruppenunterschied in der Familiarität ($p = .284$), aber eine reduzierte Rekollektion bei TGA-Patienten im Vergleich zu den Kontrollprobanden ($p < .05$) – siehe Abbildung 16, vgl. Fußnoten 1 und 2.

Wenn die Auswertung für die Patienten getrennt nach dem Vorhandensein einer sichtbaren hippokampalen Läsion gemacht wurde, so zeigte sich im Vergleich zur Kontrollgruppe wiederum kein Unterschied zwischen den drei Gruppen in der Gesichter-Bedingung (Familiarität: $p = .504$; Rekollektion: $p = .997$ – siehe Abbildung 17). Hingegen konnte in der Wörter-Bedingung beobachtet werden, dass im Vergleich zur Kontrollgruppe nur diejenige Gruppe von Patienten in der Rekollektion beeinträchtigt war, welche auch sichtbare Hippokampus-Läsionen aufwiesen ($p < .01$ – siehe Abbildung 17), nicht aber die Gruppe von Patienten ohne Läsion ($p = .537$; Unterschied zwischen den drei Gruppen: $p < .05$), wohingegen die Familiarität über die drei Gruppen hinweg invariant war ($p = .290$).

Diskussion von Studie 4

Der Befund von Studie 4, dass die TGA-Patienten eine schlechtere Diskriminationsfähigkeit zwischen gelernten und neuen Items als die Kontrollprobanden aufwiesen, ist im Einklang mit früheren Untersuchungen, welche subtile Gedächtnisbeeinträchtigungen während der Post-Akut-Phase der TGA nahelegten (Brown, 1998; Hodges & Ward, 1989; Kessler et al., 2001; Studie 3), die evtl. von den noch bestehenden Veränderungen der hippokampalen Formation verursacht werden. In einer detaillierteren Auswertung konnte dann aber gezeigt werden, dass dieses Defizit selektiv anstatt global zu sein scheint, denn in der Wörter-Bedingung zeigte sich, dass das Gedächtnisdefizit (besonders bei den Patienten mit sichtbaren Läsionen) alleine auf eine Beeinträchtigung der Rekollektion zurückzuführen ist, während das familiaritäts-basierte Wiedererkennen intakt war. In der Gesichterbedingung konnte in der kumulierten ROC-Kurve ein ähnliches Muster beobachtet werden, die Ergebnisse aus den individuellen ROC-Kurven bestätigten dieses aber nur teilweise. Eine Ursache für diese Diskrepanz könnte sein, dass die Gesichter-Bedingung zu schwierig und/oder nicht genügend sensitiv war, um Gruppenunterschiede in der Rekollektion zu detektieren.

Die Implikationen der Studie 4 nehmen zwei Formen an. Einerseits kann interpretiert werden, dass die subtilen Gedächtnisdefizite von TGA-Patienten in der Post-Akut-Phase auf eine Beeinträchtigung rekollektions-basierter, hippokampal-vermittelter Gedächtnisprozesse zurückgehen, während das familiaritäts-basierte Wiedererkennen intakt zu sein scheint. Andererseits haben die vorliegenden Ergebnisse auch theoretische Implikationen, da sie die Erwartung stützen, dass hippokampale Funktionsstörungen spezifisch die Rekollektion, nicht aber die Familiarität beeinträchtigen, was als weiterer Beleg für die neurophysiologisch formulierten Zwei-Prozess-Modelle der Rekognition gewertet werden kann (vgl. Aggleton & Brown, 2006; Jäger et al., 2006; Mayes et al., 2002; Montaldi et al., 2006; Norman & O'Reilly, 2003; Yonelinas, 2002).

Allgemeine Diskussion

Das Globalziel der vier vorliegenden Studien war es, Situationen zu finden, welche eine Dissoziation verschiedener Gedächtnissysteme oder –prozesse nahelegen, um hiermit weitere Belege dafür zu finden, dass das menschliche Gedächtnis kein singuläres Konstrukt ist (Moscovitch et al., 2005; Squire et al., 1993; Squire & Zola, 1996). Die Studie 3 fand mittels der meta-analytischen Methode entsprechende Belege, dass sich verschiedene Gedächtnissysteme wie z.B. das episodische und semantische Gedächtnis und das Kurzzeitgedächtnis zumindest teilweise voneinander dissoziieren lassen. Des Weiteren war das Befundmuster der Studie 3 im Einklang mit der Annahme, dass das episodische Langzeitgedächtnis vom medialen Temporallappen abhängt, während z.B. das semantische oder Kurzzeitgedächtnis von neuralen Strukturen außerhalb des medialen Temporallappens vermittelt werden.

Im Gegensatz zur Studie 3 untersuchten die Studien 1, 2 und 4 das menschliche Gedächtnis auf einer ‘Mikro’-Ebene, da sie auf Subprozesse anstatt auf Gedächtnissysteme fokussierten. Die Ergebnisse der Studie 4 hatten auch eine Relevanz für die Annahmen über die den verschiedenen Gedächtnisprozessen zugrunde liegenden neuralen Generatoren bzw. Mediatoren. Genauer gesagt fand sich, dass Läsionen der hippokampalen Formation zu einer selektiven Beeinträchtigung rekollektions-basierter Wiedererkennensprozesse führen, während die Familiarität unberührt zu sein scheint, was im Einklang mit den neurophysiologischen Zwei-Prozess-Modellen des Wiedererkennens ist.

Die Studien 1 und 2 untersuchten die sog. ‚Unitisierungs-Hypothese’ (z.B. Quamme, 2004), welche die Behauptung aufstellt, dass Familiarität das assoziative Wiedererkennen unterstützen kann, gegeben dass die zu assoziierenden Items während des Enkodierens ‘unitisiert’ (d.h. zu einem einheitlichen Ganzen verschmolzen) werden können (Jäger et al., 2006; Opitz & Cornell, 2006; Quamme, 2004; Quamme et al., 2007; Rhodes & Donaldson, 2007; Yonelinas et al., 1999). Im Einklang mit früheren EKP-Befunden (Jäger et al., 2006) zeigten die Studien 1 und 2, dass die beiden angewendeten Bedingungen, welche familiaritäts- bzw. rekollektions-

basiertes Wiedererkennen fördern sollten, scheinbar zumindest teilweise unterschiedliche Gedächtnisprozesse zu involvieren scheinen.

Zusammenfassend kann festgestellt werden, dass ein anwachsender Korpus an empirischer Evidenz inklusive der vier vorliegenden Studien dafür spricht, dass das menschliche Gedächtnis nicht aus einer singulären Einheit besteht, sondern ein vielfältiges und von verschiedenen Gehirnregionen unterstütztes System ist. Die vorliegende Dissertation lieferte insbesondere Belege dafür, dass das episodische, semantische und Kurzzeitgedächtnis voneinander unterschieden werden sollten und dass Familiarität und Rekollektion zwei Subprozesse zu sein scheinen, welche essenziell und teilweise unabhängig voneinander zum Wiedererkennen von im Gehirn gespeicherten Informationen beitragen.

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