Neural Correlates of Inhibition in Episodic Memory

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Preface

Our ability to act in a complex environment depends critically on the ability to orchestrate our thoughts and actions in a goal-directed manner. The term *cognitive control* refers to all processes that help us to select between relevant and irrelevant stimuli (input), and between relevant and irrelevant behavior (output). As a simple illustration, imagine you lost a friend at a concert, and are trying to spot him in the crowd. Knowing that he is wearing a blue t-shirt allows you to focus on blue colors only, and ignore any potentially distracting colors in the scene. This situation certainly requires some degree of attentional control over the many sources of potentially interfering information, and it is still unclear how a cognitive control mechanism operates to selectively activate the relevant information. At the heart of the debate in cognitive psychology is the question whether interference resolution happens via a mechanism that amplifies the relevant features, or via a mechanism that deactivates the irrelevant features, or both. In the concert situation, for example, an efficient control mechanism could either amplify all blue visual input from the environment, or inhibit all non-blue input, or both. Whereas the amplificatory function of attention for stimulus processing is well known (e.g., Aron, 2007; Miller & D'Esposito, 2005), it is still a matter of debate to what extent *inhibitory processes* help to reduce cognitive interference by deactivating irrelevant stimuli or response tendencies (see Anderson & Spellman, 1995; MacLeod, Dodd, Sheard, Wilson, & Bibi, 2003).

The brain – the hardware of cognition – is known to function properly only through its subtle balance between excitation and inhibition, and both mechanisms are directly observable on a neural level (Smith, 1992). On the level of cognitive processes, however, the impact of inhibition is still a matter of debate (e.g., Aron, 2007; MacLeod et al., 2003). The assumption that irrelevant stimuli are actively inhibited is based largely on the observation that people are typically slower or less accurate in responding to a stimulus that had been ignored on a previous occasion (e.g., Neill, 1977; Lowe, 1979; Tipper, 1985). This finding referred to as *negative priming* has been taken as evidence that ignoring a stimulus at least temporarily

deactivates the mental representation of that stimulus (e.g., Tipper, 2001; but see MacLeod et al., 2003).

The need for cognitive control over interfering information is clearly not restricted to stimuli in our environment, but applies to human *memory* in a similar way. Consider the incredibly vast amount of information about the past that accumulates over a lifetime. In turn, every attempt to retrieve a particular memory is almost inevitably fraught with interference from irrelevant, distracting memories. For example, trying to remember on which occasion we last met an old school friend, many different evenings spent together with this friend might come to mind, only one of which is the sought-after occasion. Very similar to the domain of visual attention described above, the key question is again how we manage to selectively activate this particular past memory among all the distracting memories. Is memory control achieved via the amplification of the relevant memory traces, or via deactivation of all the irrelevant memories, or both? Paralleling the finding of negative priming, research on human memory has revealed that people typically show poorer memory for events that had to be ignored on previous occasions. Not surprisingly, it has been argued that ignoring interfering or unwanted past events involves the action of an inhibitory control mechanism that deactivates the memory representations of these events (Anderson, 2003; Anderson, Bjork, & Bjork, 1994). Counter-intuitively, this finding therefore suggests that *forgetting* can be a consequence of cognitive control processes that help us to focus on relevant memory contents by attenuating interference from distracting memories.

Cognitive control, be it in the area of selective attention, long-term memory or motor inhibition, is seen as a function implemented by the prefrontal cortex, and exerted over posterior areas that process the sensory, mnemonic or motor information (Curtis & D'Esposito, 2003; Miller & Cohen, 2001). For example, patients with frontal lobe damage are substantially impaired in ignoring task-irrelevant information (e.g., Incisa della Rocchetta & Milner, 1993). Evidence from animal studies suggests that the prefrontal cortex can directly modify activity in posterior sensory areas, according to the current demands of a task (Fuster, Bauer, & Jervey, 1985; Moore & Armstrong, 2003; Tomita, Ohbayashi, Nakahara, Hasegawa, & Miyashita, 1999). Moreover, functional imaging studies provide strong evidence for a critical role of the prefrontal cortex in exerting top-down

control over cognitive processes (e.g., Duncan & Owen, 2000; Fuster, 1989; Luria, 1969; Petrides, 1996, 2005; Postle & D'Esposito, 2000; Shallice & Burgess, 1996), although it is still debated if its function is purely amplificatory (e.g., Egner & Hirsch, 2005) or both amplificatory and inhibitory (e.g., Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005) in nature. Functional imaging research to date has tended to focus on cognitive control in the area of visual attention and motor behavior (e.g., Aron & Poldrack, 2006; Egner & Hirsch, 2005; Garavan, Ross, Murphy, Roche, & Stein, 2002; Gazzaley et al., 2005). Only little attention has been paid to the memory domain, and so far, many of the conclusions drawn about control processes in memory rest largely on behavioral findings.

This thesis is about the neural correlates of memory control, and about the possible neural mechanisms that resolve interference and make it possible to memorize and retrieve relevant information in the face of competition. A central question in this context concerns the involvement of inhibitory mechanisms in mnemonic processing and interference resolution. As described above, it has been hypothesized that forgetting can be induced by inhibitory control, and forgetting thus provides a useful tool for studying inhibitory processes in long-term memory. The aim of the present work was to combine two tools – forgetting research and functional imaging – to investigate the neural substrates of memory control and the involvement of inhibition in controlling mnemonic interference.

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Abstract

Behavioral studies on long-term memory over the past decades suggest that forgetting can be the consequence of inhibitory control processes that act to keep unwanted or interfering memories from coming to mind. However, it is still debated to what extent inhibition is involved in causing different forms of forgetting in episodic memory. Moreover, although the prefrontal cortex has traditionally been implicated in subserving cognitive control processes, the nature of the neural mechanisms underlying memory control is still unresolved. The present thesis reports four functional magnetic resonance imaging (fMRI) experiments aimed at shedding light on the neural substrates of inhibition and forgetting in episodic memory. Using the retrieval practice paradigm, Experiments 1 and 2 revealed that left dorsolateral prefrontal areas are critically involved in causing *retrieval-induced forgetting*, and that left ventrolateral prefrontal areas support the retrieval of previously inhibited memories. The results of Experiment 3 suggest that retrieval-induced forgetting and *part-list cuing impairment* might share a common neural mechanism. Finally, Experiment 4 investigated list-method *directed forgetting*, indicating that such intentional forgetting may rely mainly on right lateralized dorsolateral prefrontal processes. Together, the findings provide first evidence that unintentional and intentional forgetting may depend on distinct neural processes, challenging unifying views of memory inhibition.

Part I:

Literature Background

Forgetting, Interference and Inhibition

Our memory is constantly challenged by interfering, out-of-date and distracting information. A vast body of behavioral literature documents how substantially memory performance can drop when related, interfering memories disturb our current cognitive processing. For example, remembering new information can be disturbed by older information (proactive interference), and the retrieval of older memories can be impaired because similar new information has been encoded in the meantime (retroactive interference, see Crowder, 1976, for a review). As a general rule, the more similar information is available from memory, and the stronger the competing memories are activated, the more difficult it is to remember a target memory (Rundus, 1973; Tulving & Hastie, 1972; Watkins & Watkins, 1975). This simple observation is known as interference or retrieval competition (Anderson & Neely, 1996), and has long been thought of as the primary reason why we forget. However, given the vast amount of information available from memory, an attempt to retrieve a particular past information is almost inevitably fraught with competition. The simple fact that we are nevertheless able to remember information from this large pool of interfering memories makes it appear plausible that mechanisms have evolved that control or reduce competition. Research over the last decades has provided firm evidence that inhibitory control mechanisms support mnemonic processing by reducing interference (for a recent review, see Bäuml, 2008).

The four experiments reported in this thesis used three different paradigms to behaviorally induce forgetting, and to investigate the underlying functional neuroanatomy. These three different forms of forgetting – *retrieval-induced forgetting*, *part-list cuing impairment* and *directed forgetting* – have in common that they have all been linked to inhibitory control mechanisms. Inhibitory control is thought to support memory processing by keeping irrelevant, interfering

memories from coming to mind, making the inhibited memories more susceptible to later forgetting. The next sections give a summary over the paradigms and main findings on which the present functional imaging experiments were based.

Retrieval-Induced Forgetting

Anderson, Bjork and Bjork (1994) designed a series of experiments to specifically test the assumption that, during controlled retrieval, there are mechanisms involved that both strengthen relevant and weaken the irrelevant memories. In the so called *retrieval practice paradigm* (see Fig. 1.1), participants study lists of category-exemplar pairs (e.g. SPORT-Tennis, FRUIT – Banana, SPORT – Volleyball), with more than one exemplar associated with each category. In the following retrieval practice phase, participants actively retrieve a subset of the previously studied exemplars (e.g. SPORT – Vol_____), only from a subset of the previously studied categories. After retrieval practice, and following a short distracter phase, recall performance for all of the initially studied items is assessed in a category plus first letter (e.g. SPORT – T_____, SPORT – V_____, FRUIT – O_____) cued recall test. This procedure allowed the authors to examine how partial retrieval practice affects the recall of practiced items themselves, of nonpracticed items from the same categories as practiced items, which are assumed to compete during retrieval practice, and of nonpracticed items that are unrelated to practiced items, and should therefore not compete during retrieval practice. The following picture emerged: First, retrieval practiced items (e.g. SPORT – Volleyball) were recalled at a higher level than neutral items that are unrelated to the practiced items (e.g., FRUIT – Banana). Second, nonpracticed exemplars from practiced categories (e.g. SPORT – Tennis) were recalled at a lower level than neutral exemplars from nonpracticed categories (e.g. FRUIT – Banana).

The finding of enhanced memory for retrieval practiced items (retrieval-induced enhancement) supports the view that retrieval indeed strengthens the relevant, to-be-retrieved memories. This result is in line with prior evidence that retrieval is a powerful means to enhance memory performance (e.g., Roediger & Karpicke, 2006). More interesting is the finding that retrieval practice negatively

affects memory performance for nonpracticed, but related items. At least three interpretations might account for this basic pattern of impairment called *retrieval-induced forgetting*. First, in the light of findings from interference research, the impairment of related items could be explained most parsimoniously in terms of a *blocking* account. The strengthening of some items during retrieval practice might introduce a competition bias within a category, such that during the final recall, practiced items come to mind more easily, are recalled first and block access to the weaker nonpracticed items (e.g., McGeoch, 1942; Mensink & Raaijmakers, 1988). Blocking theories thus assume that the impairment observed for nonpracticed items is the indirect consequence of strengthening related memory items. Second, retrieval practice of some category exemplars may strengthen the connections of practiced items to the category cue, and simultaneously deactivate the connections between the category cue and the nonpracticed items. Such *associative unlearning* theories (e.g., Melton & Irwin, 1940) assign the impairment to deactivation of the retrieval route from a cue to the nonpracticed item, but not to a change of the memory representation of the nonpracticed item itself. Third, retrieval-induced forgetting may be caused by an active *inhibitory mechanism* that 'punishes' competing items during retrieval practice by deactivating the memory representations of related, competing items themselves (Anderson et al., 1994).

Subsequent investigations have shown that retrieval-induced forgetting has some characteristic features that speak in favor of the inhibitory account. An important finding is that the impairment found in the retrieval practice paradigm is retrieval specific. *Retrieval specificity* means that retrieval competition is a necessary condition for retrieval-induced forgetting to occur. Other ways of strengthening some members of a category, like rehearsal or longer study exposure to some items, do not cause the same impairment of the remaining category exemplars (Anderson et al., 2000; Bäuml & Aslan, 2004; Ciranni & Shimamura, 1999). Retrieval specificity is not compatible with blocking accounts, because blocking attributes the impairment of nonpracticed category members solely to the strengthening of practiced items. In contrast, the inhibitory account predicts retrieval specificity, because other forms of strengthening do not involve competition, and should therefore not trigger inhibitory competition resolution.

Related to retrieval specificity, and inconsistent with a blocking view, retrieval-induced forgetting has been found to primarily affect strong category members. According to blocking accounts, weak items within a category should particularly suffer from the strengthening of related memories (list strength effect), and forgetting should therefore be most pronounced when the nonpracticed exemplars are low frequency members of a category (Anderson et al, 1994, Appendix). In contrast, inhibition theory assumes that during retrieval practice, inhibition mainly affects strong nonpracticed category members, because they have the highest potential to interfere during retrieval. Indeed, it was found that retrieval-induced forgetting is restricted to high frequency members of a category (Anderson et al., 1994), supporting the inhibitory explanation of retrieval-induced forgetting.

Recent findings have provided firm evidence for the view that the detrimental and facilitatory effects of retrieval practice are dissociable. In sharp contrast to the predictions of blocking accounts, the degree of retrieval-induced forgetting has been shown to be independent of the degree to which practiced items show retrieval-induced facilitation (see Anderson, 2003). For example, retrieving some category exemplars one versus five times causes a substantial increase in memory performance for the practiced items, whereas the impairment observed for nonpracticed category exemplars remains constant (Shivde & Anderson, 2001). In a study that manipulated participants' mood during retrieval practice (Bäuml & Kuhbandner, 2007), the same degree of retrieval-induced enhancement was found in neutral, positive and negative mood, but retrieval-induced forgetting was eliminated by negative mood, presumably because negative mood prevents associative item processing. Together with the finding of retrieval specificity, this apparent independence of retrieval-induced enhancement and forgetting challenges blocking accounts, favoring an inhibitory view.

The possibly strongest support for the inhibitory account has been obtained from studies demonstrating that forgetting in the retrieval practice paradigm, unlike interference-induced forgetting, occurs independently of the testing situation. Retrieval-induced impairment has been found not only in free and cued recall tests, but also in recognition tests (Hicks & Starns, 2004; Spitzer & Bäuml, 2007; Verde, 2004), and even with implicit measures of memory performance (Veling & van

Knippenberg, 2004). Retrieval-induced forgetting has also been found with independent extralist cues that were not presented during study and retrieval practice (Anderson, Green, & McCulloch, 2000; Anderson & Spellman, 1995; Aslan, Bäuml, & Pastötter, 2007; Saunders & MacLeod, 2006; but see Perfect et al., 2004; Williams & Zacks, 2001). These findings point to an item specific impairment that occurs independently of how participants try to access the impaired memory trace. This picture cannot easily be accounted for by blocking or associative unlearning theories, but suggests that the item specific impairment is caused by a mechanism that weakens the representations of competing memories themselves.

On the basis of the above findings, it is now widely agreed that retrieval-induced forgetting is the consequence of an inhibitory mechanism that operates during retrieval practice, and deactivates memory traces that have the potential to disturb the retrieval process. Retrieval-induced forgetting is therefore a core finding in support of the involvement of both amplificatory and inhibitory mechanisms in human memory.

Part-List Cuing Impairment

Another unintentional form of forgetting that has been related to the action of inhibitory processes is *part-list cuing* impairment. Part-list cuing may be the most counterintuitive way in which forgetting can be induced. On the one hand, theories of memory retrieval highlight the importance of retrieval cues for guiding memory search and facilitating the access to stored memory representations (e.g., Tulving, 1974). Therefore, the first demonstration that cuing can have detrimental effects on memory performance was more than unexpected, and was initially even seen as an artifact (Slamecka, 1968). In a typical part-list cuing setting, several categorized item lists are studied and, in the baseline condition, tested by means of a standard free or cued recall test. In the cuing condition, part of the study list is provided as retrieval cue. Ironically, instead of facilitating memory performance for the remaining items, these part-list cues often impair recall of the remaining items (Roediger, 1973; Rundus, 1973; Slamecka, 1968). This effect was first explained in

terms of blocking theory, assuming that cuing strengthens the cue items, which are in turn *covertly retrieved* when participants try to recall the relatively weaker, non-cued items (Roediger, 1973; Rundus, 1973). However, later investigations were able to demonstrate that the detrimental effects of part-list cuing are distinct from the effects of merely strengthening some items.

For example, Bäuml and Aslan (2004) provided participants with a subset of previously studied category exemplars, and instructed them to either rehearse these items (part-list relearning), or to use them as retrieval cues for the recall of the remaining items (part-list cuing). Interestingly, this slight change in the instruction substantially changed memory for the remaining items, with part-list cuing, but not part-list relearning, impairing recall of the target items. This pattern is unlikely to be caused by blocking, because both cuing and relearning strengthened some category exemplars, which should have led to comparable blocking in both conditions. The authors argue that part-list cuing mimics the effects of retrieval practice, because the cuing instruction leads participants to covertly retrieve (as opposed to rehearse) the part-list cues, causing an unintentional case of retrieval-induced forgetting. As opposed to older accounts (see Roediger, 1973; Rundus, 1973), part-list cues may then not cause the impairment via blocking, but via the inhibition of the remaining category members during covert retrieval.

This view is supported by several studies that noted parallels in the nature of forgetting induced by part-list cuing and forgetting induced by retrieval practice. For example, in contrast to the effects of strength manipulations (e.g., rehearsal), both part-list cuing impairment and retrieval-induced forgetting are found in recognition tests (Todres & Watkins, 1981). Both part-list cuing impairment and retrieval-induced impairment have been argued to be based on a reduction in familiarity or general memory strength (Neely, Schmidt, & Roediger, 1983; Oswald, Serra, & Krishna, 2006; Spitzer & Bäuml, 2007). Moreover, both forms of forgetting have been found in tests using independent cues, suggesting that forgetting is not due to changes in associative unlearning, but due to changes in the representational strength of an episode itself (Aslan, Bäuml, & Grundgeiger, 2007). Finally, both part-list cuing and retrieval practice induce forgetting of false memories, that is, of items that were not studied, but presumably compete during

recall because they are highly associated with practiced items (Bäuml & Kuhbandner, 2003).

However, there are some reports that part-list cuing impairment is not persistent, and disappears if, at a later point, the same items are again tested without the distracting part-list cues (Basden, Basden & Galloway, 1977). Based on these observations, a *strategy disruption* view on part-list cuing emerged, with the impairment attributed to the fact that providing some items as cues disturbs participants' subjective retrieval strategies (Basden & Basden, 1995). Although strategy disruption cannot fully account for all the findings reported in the above studies, it is still one of the main alternatives to an inhibitory view. Recently, it has been postulated that part-list cuing impairment might be caused by inhibition whenever the items that constitute a memory set are encoded under conditions that do not favor a serial representation of the set, and by strategy disruption if participants use serial encoding strategies (Aslan & Bäuml, 2007; Bäuml & Aslan, 2006). Based on these behavioral findings, it might thus be assumed that encoding strategy determines if part-list cuing and retrieval-induced forgetting are caused by a single mechanism.

Directed Forgetting

Forgetting may be intended and desired when there is the need to memorize new, relevant against out-of-date, irrelevant information. For example, when asking someone the way, the initial answer might be followed by a sentence like "Sorry, forget what I just said. It's easier if you take the following route…" In this case, we have already heard (encoded) a particular piece of information, but have to replace it with new, more up-to-date information. In laboratory settings, this kind of memory control has been investigated with the *directed forgetting* (DF) method (Bjork, 1970, 1989), by simply asking participants to forget previously studied material (for a review, see MacLeod, 1998).

Two different procedures have been established for instructing subjects which material to forget, and which to remember: In an *item-method* DF experiment,

participants are given a remember or a forget instruction directly after each presentation of a study item. By contrast, in a *list-method* DF experiment, participants are instructed to forget a first list of items before studying a second list, or to remember both lists. On a final test, memory performance is assessed for all initially studied items, including the to-be-forgotten items. Under free recall conditions, both item and list-method settings typically produce reduced memory for to-be-forgotten information (see Bäuml, 2008; MacLeod, 1998). In item-method DF, this reduced memory performance is calculated as the difference between items cued to remember and items cued to forget. In list-method DF, the remember condition, in which both the first and the second list have to be remembered, serves as a baseline for memory performance in the forget condition, in which participants are instructed to forget the first list, but remember the second list. Using the list method, one typically observes not only reduced memory for first list items, but also enhanced memory for second list items (MacLeod, 1998).

There are several traditional explanations for the effects of forget instructions, the most prominent ones being *selective rehearsal* and *inhibition* (see MacLeod, 1998). According to the selective rehearsal account (Bjork, 1970), forgetting arises because participants stop rehearsing to-be-forgotten items, and continue to selectively rehearse to-be-remembered items. According to the inhibitory account of directed forgetting (Bjork, 1989; Geiselman, Bjork, & Fishman, 1983), participants actively inhibit the supposedly irrelevant items after an instruction to forget. With respect to list-method DF, second list enhancement after an instruction to forget has traditionally been attributed to reduced proactive interference on second list retrieval, both by advocates of selective rehearsal and inhibition (MacLeod, 1998).

Importantly, item-method and list-method paradigms produce qualitatively different results, suggesting that different mechanisms might underlie directed forgetting induced by the two procedures (Basden, Basden, & Gargano, 1993). It is now widely agreed that item-method directed forgetting is caused by selective rehearsal (see MacLeod, 1998), because forgetting with this procedure occurs both in free recall and cued recall tests, and in item recognition (Basden et al., 1993), consistent with the idea that to-be-forgotten items are less thoroughly encoded, and

thus more weakly represented. By contrast, inhibition is the most prominent explanation for list-method directed forgetting, although alternative views are still being debated (see Bäuml, 2008). The inhibitory account is mainly based on the crucial observation that the list method typically produces forgetting in free recall tests, but neither in item recognition (e.g., Basden et al., 1993; Geiselman et al., 1983a; Golding & Gottlob, 2006; but see Benjamin, 2006), nor in implicit memory tests (Basden & Basden, 1996; Basden et al., 1993). It has therefore been theorized that list-method DF is induced by an inhibitory process that renders the to-be-forgotten information temporarily less accessible, and that inhibition might be released when item specific probes are presented (Basden et al., 1993). Although list-method directed forgetting is typically not observed in item recognition, source memory for forget items appears to be impaired (Geiselman et al., 1983b; Gottlob & Golding, 2007), suggesting that forget instructions impair recollection-based remembering.

Provided directed forgetting is caused by an inhibitory mechanism, the dependency on the retrieval cues might suggest that inhibition in directed forgetting is mediated by a different mechanism than inhibition in retrieval-induced forgetting. For example, inhibition in directed forgetting may operate on the level of retrieval cues (e.g., the list context, see Anderson, 2005), potentially deactivating the retrieval routes to single items, unbinding the items from their encoding context (Bjork, 1989; see Bäuml, 2008). Moreover, the selective rehearsal account of list-method DF has been challenged by the findings of Geiselman and colleagues (1983a), who used a variation of list-method directed forgetting, in which participants intentionally studied only part of a word list, and did pleasantness judgments on the remaining items. Interestingly, the typical pattern of first list forgetting and second list enhancement was found for both types of study items, judged and intentionally encoded items. This finding is incompatible with a selective rehearsal account, because the judge items should not be subject to any differential rehearsal.

An alternative explanation of directed forgetting that has recently been proposed is the *context change* account (Sahakyan & Kelley, 2002). According to this view, the forget instruction prompts participants to change their internal

encoding context, such that second list items are stored in a different mental context than first list items. Forgetting may then arise due to a lack of overlap between cues present during first list encoding and retrieval (Tulving & Thomson, 1973). Changing the context during encoding can also reduce proactive and retroactive interference between lists (Dallet & Wilcox, 1968; Eckert, Kanak, & Stevens, 1984), a finding that might explain second list enhancement. Further parallels between directed forgetting and context dependent forgetting have been observed in an experiment demonstrating that forgetting in both settings requires the encoding of a second list (Pastötter & Bäuml, 2007). It is not yet clear if the context change explanation can account for the lack of directed forgetting impairment in recognition tests. Whereas early studies have found that context manipulations typically do not affect recognition performance (Godden & Baddeley, 1980; Jacoby, 1983), many recent investigations report robust context effects on recognition memory (e.g., Dalton, 1993; McKenzie & Tiberghien, 2004; Smith & Vela, 1992). Therefore, the behavioral literature does currently now allow a clear distinction between directed forgetting and context dependent forgetting. However, two recent electrophysiological studies, using a directed forgetting manipulation (Bäuml, Hanslmayr, Pastötter, & Klimesch, 2008) and a context change manipulation (Pastötter, Bäuml, & Hanslmayr, in press), report distinct neural correlates of directed forgetting and context dependent forgetting. Interestingly, these studies also suggest separable mechanisms underlying first list forgetting and second list enhancement in directed forgetting (see section "A Neural Perspective on Memory Inhibition" below).

Think/No-Think Forgetting

Recent studies suggest that people are capable of targeting inhibitory control directly at unwanted memories. Direct memory suppression has been investigated with the so called think/no-think paradigm (Anderson & Green, 2001), a memory variant of the Go/NoGo task used to study motor inhibition. In the think/no-think paradigm, participants study weakly associated word pairs (e.g. ordeal - roach) until they are able to reproduce the target word (e.g., roach) upon presentation of

its cue word (e.g., ordeal). This study phase is followed by the critical think/no-think phase. If a cue word is presented in the think condition (as typically indicated by green font color), participants are instructed to recall the appropriate target word. If a cue word is presented in the no-think condition (as typically indicated by red font color), participants are instructed to suppress the recall of the target word. The think or no-think procedure is repeated up to 16 times for a given cue-target pair. Moreover, some initially studied baseline word pairs occur neither in the think, nor in the no-think condition. The consequences of suppression are assessed in a final recall, in which all initially studied word pairs are to be recalled again.

Several studies using this paradigm have demonstrated that suppressing the recall of a target word 16 times impairs its later retrievability on the final recall test, compared to control words (Anderson & Green, 2001; Anderson et al., 2004; Depue, Banich, & Curran, 2006; Hertel & Calcaterra, 2005). Forgetting of suppressed words was also found when participants were given independent test cues to access the forgotten information (Anderson & Green, 2001; Anderson et al., 2004), favoring an inhibitory explanation. However, forgetting in this paradigm may not be very robust, as it is only found after a large number of suppression trials, and even then affects only a small number of items. A recent study failed to replicate forgetting in the think/no-think paradigm in three experiments (Bulevich, Roediger, Balota, & Butler, 2006), and the authors suggested that think/no-think forgetting may not be the consequence of memory inhibition. Alternatively, is has been postulated that participants may distract themselves from thinking about the target during no-think trials by thinking about alternative associates to the cue word. New associations might in turn cause increased interference during the final recall, reducing the accessibility of the original associate via the cue item (Bulevich et al., 2006; Hertel & Calcaterra, 2005). Although this interpretation is inconsistent with the finding of cue independent forgetting in the think/no-think paradigm (Anderson & Green, 2001; Anderson et al., 2004), there is yet no published evidence that the effects of direct suppression can be observed on recognition tests or implicit memory tests. Such demonstrations would be necessary to conclusively reject alternative non-inhibitory explanations of forgetting in the think/no-think paradigm.

A Neural Perspective on Memory Inhibition

Executive control processes in human memory and in other cognitive domains have traditionally been linked to prefrontal functioning (for a review, see Miller & Cohen, 2001). In terms of its connectivity and plasticity, the rodent PFC meets all demands that predispose it for exerting top-down control over multiple processing pathways, and to bias processing in simultaneously active (e.g., visual) pathways towards goal-relevant features and actions (Petrides, 2005). The prefrontal cortex is assumed to store abstract representations of our current goals, and representations of knowledge about how to achieve these goals ("the rules of the game", see Miller & Cohen, 2001). Without such control, behavior would become inappropriate, perseverating or disorganized, and indeed, the behavior of patients with prefrontal lobe damage is characterized by these exact symptoms (Luria, 1969; Shallice & Burgess, 1996).

Regarding long-term memory functions, patients with frontal lobe lesions do not show the typical amnesic syndrome like patients with damage to their medial temporal lobes (including the hippocampus), but are instead unable to use efficient encoding and retrieval strategies. Provided externally with the appropriate strategies and retrieval cues, the deficits can be attenuated or even disappear (Incisa della Rocchetta & Milner, 1993). Providing item specific probes in recognition tests, patients with prefrontal lesions show memory performance comparable to healthy subjects (Janowsky, Shimamura, Kritchevsky, & Squire, 1989c). Moreover, prefrontal brain lesions appear to make patients more vulnerable to interference from irrelevant, distracting memories (Moscovich, 1992; Petrides & Milner, 1982; Shimamura, Jurica, Mangels, Gershberg, & Knight, 1995). For example, patients with frontal lobe damage are more susceptible to proactive interference from previously established memory associations in paired-associative learning paradigms, like the AB-AC paradigm (Shimamura et al., 1995). This

increased interference susceptibility may be the result of dysfunctional prefrontal filtering of irrelevant information (Shimamura, 2000), or dysfunctions in biasing processing towards the relevant information (Miller & Cohen, 2001).

The neural mechanisms underlying different forms of forgetting in episodic memory, and the possible involvement of inhibitory mechanisms, have not extensively been investigated. First evidence for the involvement of the prefrontal cortex in causing forgetting came from a number of clinical studies employing episodic forgetting paradigms. Two studies using list-method *directed forgetting* in neuropsychological samples found that patients with left frontal lesions are no longer capable of intentionally forgetting episodic information (Conway & Fthenaki, 2003; MacDonald, Bauer, Filoteo, Grande, Roper, & Gilmore, 2006). In one of these studies, frontal lobe patients showed reduced directed forgetting, but intact retrieval-induced forgetting. In contrast, patients with damage to their temporal lobes showed intact directed forgetting, but attenuated *retrieval-induced forgetting* (Conway & Fthenaki, 2003). The dissociation between lesion site and intentionality of forgetting has been taken as support for the assumption that intentional, but not unintentional forgetting relies on intact prefrontal processing (Conway & Fthenaki, 2003). Intact retrieval-induced forgetting has also been demonstrated in psychiatric patients suffering from schizophrenia (Nestor et al., 2005) and Alzheimer's disease (Moulin et al., 2002). However, it should be noted that none of these clinical studies did control the output order at test, which leaves it open if forgetting in the patient samples was the result of inhibition, or rather caused by strengthening. Strengthening and competition might play a more crucial role in clinical samples that are highly susceptible to interference, which may be particularly the case in patients with prefrontal dysfunctions. Finally, *part-list cuing* appears to be intact or even increased in patients with frontally mediated deficits (Christensen, Girard, Benjamin, & Vidailhet, 2006; Kissler & Bäuml, 2005; Incisa della Rocchetta & Milner, 1993). Hitherto, clinical investigations in neuropsychological and psychiatric populations have not provided unique evidence for frontal lobe specific impairment in unintentional forgetting.

More direct evidence for the neural correlates of forgetting could be obtained from electrophysiological and hemodynamic imaging studies, but there is as yet

little imaging evidence regarding the neural substrates underlying different forms of forgetting in episodic memory. To date, two studies have investigated the neural correlates of *retrieval-induced forgetting*. In an EEG experiment (Johansson et al., 2007), it could be shown that a late frontal slow-shift in event-related potentials is related to retrieval-induced forgetting. This ERP component was most pronounced in the subsample showing the greatest retrieval-induced impairment. A second used fMRI to investigate whether hemodynamic response decreases across repeated retrieval practice trials are related to retrieval-induced forgetting (Kuhl, Dudukovic, Kahn, & Wagner, 2007). They found that decreasing recruitment of the anterior cingulate and right ventrolateral prefrontal cortex predicted later retrieval-induced forgetting. The authors of both studies interpreted their findings as reflecting frontally mediated inhibitory control processes operating during selective retrieval practice.

The first fMRI investigation of think/no-think impairment also suggests that the brain regions implicated in memory inhibition are located in the prefrontal cortex (Anderson et al., 2004). Regions found to interact with the hippocampus, and to predict later think/no-think forgetting, were located in the left and right dorsolateral prefrontal cortex (DLPFC, mainly areas 9/46). The authors conclude that executive control can be exerted over mnemonic processing in the hippocampus, producing forgetting of intrusive information while participants make an effort not to remember. This conclusion was supported by a recent fMRI investigation showing emotion specific effects on memory suppression, suggesting that prefrontal suppression mechanisms can target material specific brain regions. These regions were – depending on the emotional valence of the to-be-suppressed memories – located in either the hippocampus or the amygdala (Depue, Curran, & Banich, 2007). Further, there is electrophysiological evidence that the intention not to think about previously studied memories is associated with an attenuated ERP component typically associated with conscious recollection (Bergström, Velmans, de Fockert, & Richardson-Klavehn, 2007).

List-method directed forgetting has so far only been examined with electrophysiological measures (Bäuml et al., 2008). In this study, distinct oscillatory correlates were found for first list forgetting and second list

enhancement after an instruction to forget. Reduced phase coupling (a measure of synchrony between distant brain areas) in the alpha frequency band (8-12 Hz) was related to first list forgetting, whereas increased alpha band power (a measure of synchrony in local neural assemblies) was related to second list enhancement. The authors suggest that two distinct cognitive processes cause enhancement and forgetting in memory updating paradigms, and attribute forgetting to inhibition, and enhancement to a change in encoding strategy after a forget instruction. Interestingly, the results of a second study using a similar design, but replacing the forget instruction with a context change instruction (Pastötter et al., in press) revealed that the neural mechanisms underlying second list enhancement after a context change are similar to those underlying directed forgetting, reflected by a change in alpha power. By contrast, first list forgetting in directed forgetting appears to rely on neural processes distinct from those underlying context dependent forgetting. Whereas directed forgetting is associated with reduced alpha phase coupling (Bäuml et al., 2008), context dependent forgetting is reflected by differential theta and alpha power increases between lists, depending on the presence or absence of a context change between lists. These finings strengthen the inhibitory account of directed forgetting, suggesting that distinct neural processes are initiated after a forget instruction and a mental context change instruction.

There is yet no published electrophysiological or hemodynamic evidence concerning the neural mechanisms underlying part-list cuing impairment.

In summary, conflicting evidence exists to date concerning the involvement of prefrontal control mechanisms in different forms of episodic forgetting. Whereas clinical studies support the view that intentional, but not unintentional forgetting relies on prefrontal resources, imaging and electrophysiological investigations suggest a central involvement of prefrontal areas in both intentional and unintentional forgetting.

Scope of the Present Work

Prior behavioral work on forgetting in episodic memory indicates that forgetting can be caused by inhibitory control processes that deactivate interfering, out-of-date, or unwanted memories. However, it is still an unresolved issue to what extent different forms of forgetting are based on common or distinct mechanisms. This might partly be due to different concepts of inhibition that have been expressed in the literature (see MacLeod, 2003). Whereas some authors speak of inhibition if, empirically, task performance is pushed below a baseline by an experimental manipulation, other authors regard inhibition as the cognitive mechanism behind these effects. For example, Bäuml (2008) conceptualizes memory inhibition as a summation of inhibitory processes that can lead to a reduced accessibility or availability of target memories. Notably, he makes the point that inhibition in different forms of episodic forgetting (including strength-dependent forgetting) relies on distinct mechanisms, causing distinct patterns of memory impairment that can be disentangled using different testing procedures. In contrast, other authors (Anderson, 2005; Levy & Anderson, 2002) conceptualize inhibition as a single executive *mechanism* that can be flexibly recruited to actively suppress the activation of irrelevant or unwanted memories. Importantly, this unifying view implicates that one and the same inhibitory mechanism is recruited for intentional and unintentional forms of episodic forgetting (excluding strength-induced forgetting), and that inhibition in memory relies on the same prefrontal circuits as inhibition in other cognitive domains.

The focus of the present work is on neural mechanisms underlying inhibition in retrieval-induced forgetting, because there is broad consensus that inhibition plays a central role in causing forgetting in the retrieval practice paradigm. A recently published fMRI study indicates that prefrontal areas might be critically involved in causing retrieval-induced forgetting (Kuhl et al., 2007). In this study, participants repeatedly retrieval practiced part of the study material, which was associated with a decrease in brain activation from the first to the third practice

trial. This decrease predicted forgetting in medial and right prefrontal regions, which was interpreted as reflecting decreased demands on inhibitory control. However, activation decreases with this experimental setting may also reflect strengthening of the practiced material across repetitions, and such strengthening might substantially influence forgetting as assessed in the Kuhl et al. (2008) study. *Experiment 1* of the present thesis examined the retrieval specific neural effects of retrieval practice on later forgetting, by introducing a baseline condition that controlled for strength-induced effects on memory performance, ensuring that both behavioral and neural measures of forgetting were free from contamination by retrieval-induced enhancement.

Second, the neural mechanism causing retrieval-induced forgetting has so far been investigated exclusively during retrieval practice, that is, at the time inhibition is supposed to operate. *Experiment 2* was designed to study the neural substrates of retrieval-induced forgetting and enhancement during the final recall. The central question in this experiment was whether impairment and enhancement found after retrieval practice are neurally observable at the time participants access this information again. If so, the effects of inhibition on a single memory trace should be found in areas that have previously been implicated in the controlled retrieval of weakly represented memories. Moreover, the inhibitory account predicts that the effects of enhancement and forgetting are neurally separable, and characterized by qualitatively different neural activation patterns.

A third goal of the present work was to examine if retrieval-induced forgetting and part-list cuing share a common neural substrate. To this end, *Experiment 3* directly compared retrieval-induced forgetting, part-list cuing and strength-induced forgetting in a within-subjects design. As no prior study has addressed the neural mechanisms associated with part-list cuing, the analysis was guided by the hypothesis, derived from behavioral studies, that retrieval-induced forgetting and part-list cuing are caused by a common cognitive mechanism, and should therefore share a common neural correlate.

Forth, functional imaging methods have so far not been applied to the study of directed forgetting using the list-method. List-method directed forgetting has

traditionally been explained by inhibition, although alternative accounts are also compatible with the currently available behavioral literature. *Experiment 4* investigated directed forgetting with fMRI, focusing on the question if intentional forgetting in the directed forgetting paradigm is neurally related to direct suppression in the think/no-think paradigm, which has recently been investigated with functional imaging methods (Anderson et al., 2004).

Finally, these four experiments in combination can also address the key issue whether inhibition represents a single executive function that can be recruited to overcome memory interference (Levy & Anderson, 2002). Support for a unifying view of inhibition would be obtained if a similar pattern of brain activations relates to forgetting in different experimental paradigms. One focus throughout this thesis will be on the question whether intentional (directed forgetting) and unintentional (retrieval-induced forgetting, part-list cuing) forgetting share a common neural substrate, because neuropsychological evidence suggests that the prefrontal cortex is differentially involved in intentional and unintentional forgetting (Conway & Fthenaki, 2003).

Part II
Retrieval-Induced Forgetting

Experiment 1

Experiment 1 sought to determine the functional neuroanatomy of the mechanism underlying *retrieval-induced forgetting*, using a variant of the classical retrieval practice paradigm optimized for use with fMRI. Functional images were acquired during retrieval practice, that is, at the time inhibition is thought to weaken interfering items (e.g., Anderson, 2003; Bäuml & Aslan, 2004). In this respect, Experiment 1 resembled one foregoing functional imaging investigation of retrieval-induced forgetting (Kuhl et al., 2007). Kuhl and colleagues (2007) used event-related fMRI to test the hypothesis that brain mechanisms initially engaged during retrieval practice become less engaged over repeated practice trials, due to decreasing control demands. They found repetition related activation decreases in a variety of frontal and posterior brain regions. In the anterior cingulate and the right ventrolateral prefrontal cortex, these activation decreases predicted later retrieval-induced forgetting, and a dorsolateral prefrontal region functionally coupled with the anterior cingulate cortex (ACC). Kuhl and colleagues thus conclude that these areas reflect the action of an inhibitory mechanism during retrieval practice, with the ACC indicating conflict between concurrently activated memory representations, and the right ventrolateral prefrontal cortex resolving this mnemonic conflict. One major problem with this interpretation, however, is that repetition related neural decreases are typically thought to generally indicate the more efficient processing of a repeated stimulus (Henson & Rugg, 2003), and do not necessarily reflect successful competition resolution. The brain-behavior correlations in the Kuhl et al. (2007) study might thus be caused by the strengthening and more efficient processing of the to-be-practiced items over time, and such strengthening may have contributed to forgetting found in the final recall test.

The present experiment ruled out strength related effects by implementing a behavioral and neural rehearsal baseline that equally involved strengthening of some category members, but should not involve retrieval competition (Bäuml &

Aslan, 2004). Prior behavioral research has shown that retrieval-induced forgetting is retrieval specific: Having participants rehearse a subset of previously studied items strengthens the rehearsed items to the same degree as selective retrieval practice. However, mere rehearsal without the need to actively select an item does not induce forgetting of related material if output order is controlled during the final recall (Anderson et al., 2000; Bäuml, 2002; Bäuml & Aslan, 2004; Ciranni & Shimamura, 1999; Johansson et al., 2007). This finding is plausible given that rehearsal should not involve retrieval competition, and should therefore not trigger inhibitory mechanisms. From a neural perspective, rehearsal can control for potential effects of repeated stimulus processing without involving the critical mechanisms implicated in retrieval practice. Thus, extra rehearsal of some category members provides an ideal behavioral and neural baseline for isolating the inhibitory components of the retrieval process.

It was hypothesized that, replicating prior behavioral work (e.g. Bäuml & Aslan, 2004; Ciranni & Shimamura, 1999), selective retrieval and rehearsal would strengthen the practiced items to a comparable degree. However, selective retrieval, but not rehearsal, should impair the recall of nonpracticed items. With respect to the underlying neural processes, it was expected that selective retrieval is associated with activation increases in brain regions implicated in controlled retrieval from episodic memory (Buckner, Koustaal, Schacter, Wagner, & Rosen, 1998; Rugg, Otten, & Henson, 2002). Impairment of competing items should be predicted by retrieval specific activation in some of the regions that have been implicated in competition resolution, that is, in one or more of the candidate regions (ACC, VLPFC, DLPFC) suggested by the previous fMRI study on retrieval-induced forgetting (Kuhl et al., 2007).

Methods

Participants

Twenty-four healthy right-handed volunteers (11 males, 13 females; age 20-29, mean age 23.6) were recruited at Regensburg University. All participants gave their written informed consent approved by the Regensburg University Ethics Committee and received 12 € payment for participation. Two participants had to be excluded from the sample due to poor memory performance (zero remembered items in three or more runs), leaving twenty-two participants for further analyses.

Task Procedures

Scanning data were collected on a Siemens Sonata 1.5 T scanner (Siemens, Erlangen, Germany), equipped with an 8-channel phased array head coil (MRI Devices). Stimuli were back projected centrally onto a screen at the rear of the magnet bore and viewed via a mirror attached to the head coil. Stimuli were 216 German nouns from 18 semantic categories, drawn from published norms (Battig & Montague, 1969; Scheithe & Bäuml, 1995). The experimental material was divided into three lists with six categories each. For each individual participant, six lists were assigned to the *selective retrieval* condition, six lists to the *rehearsal* condition, and six further lists to the *cuing* condition (the data of which are reported in Experiment 3). Lists were matched according to mean word length and mean rank of an item in a category (see Battig & Montague, 1969; Scheithe & Bäuml, 1995). Assignment of list to condition was counterbalanced across participants, such that each category occurred equally often in the selective retrieval, the rehearsal and the cuing condition. Within one list, presentation order of the six categories was counterbalanced across participants such that the mean position of each category was equal.

Each category consisted of 12 items with unique first letters with respect to their category. Within a category, the 5 items with the lowest rank order (mean rank 31.8, SD = 8.2) had to be practiced, whereas the 7 items most strongly associated with the category (mean rank 11.8, SD = 5.0) served as competitors.

Strong items were chosen as competitors because prior behavioral work has shown that strong, but not weak items have the potential to interfere during retrieval practice, and consequently need to be inhibited (Anderson et al., 1994; Bäuml, 1998).

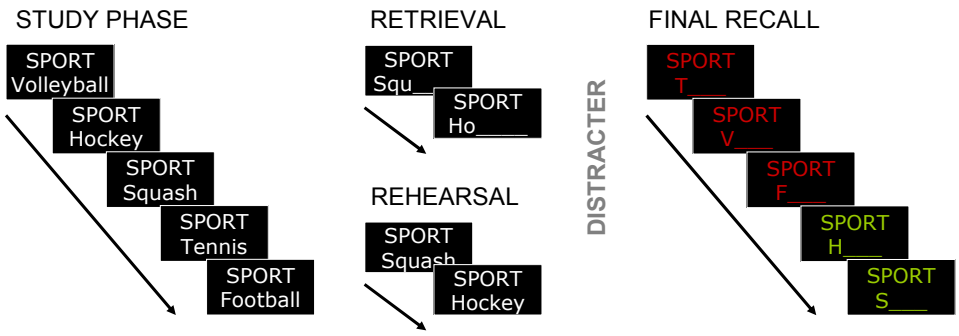

Figure 1.1 Schematic illustration of the design of Experiment 1. Participants first studied lists of category-exemplar pairs, and then practiced part of a list through either retrieval or rehearsal. On a final cued recall test, all previously studied items were tested with category plus first letter cues., with non-practiced items always being recalled first. Green color indicates practiced items that are supposed to show enhancement during final recall, red color indicates items that are assumed to be impaired in the retrieval, but not the rehearsal condition.

The experiment consisted of 12 separate runs, each comprising the same serial arrangement of a study phase, followed by a practice phase, a short distracter phase, and a cued recall test (see Figure 1.1). During study, 12 items from a single semantic category were displayed sequentially and in random order for 2 sec each, with a 1-sec fixation interval between items. The critical experimental manipulation took place in the subsequent practice phase, in which participants reprocessed a subset of 5 of the previously studied 12 items in random order. In the *retrieval condition*, participants were given word stems (first 2-3 letters) as retrieval cues, and were asked to covertly complete the stems with the appropriate items from the study list. In the baseline condition, referred to as *rehearsal condition*, participants were re-presented five complete list items with the instruction to rehearse them for the final recall test (for a similar procedure, see Johansson et al., 2007). In both conditions, practice stimuli were shown for

3 sec each, with an inter-stimulus interval of 1 sec. To exclude short-term memory effects, the practice phase was followed by a 30 sec distracter task in which participants ordered digits in an ascending manner. During the final memory test, scanning was interrupted to allow subject's answers to be recorded via the local intercom system. Participants were provided with the category name and a unique first letter cue and were asked to respond with the corresponding item from the study list. Nonpracticed items were always tested before practiced items to control for output order effects (e.g. Anderson et al., 1994). After each run, participants were allowed a few seconds break, and were given a warning directly before the beginning of a new run.

FMRI Data Acquisition and Statistical Analyses

A blocked design was used to ensure that all items experienced the same degree of strengthening by keeping the inter-trial interval constant. Blocked designs have the advantage of leaving enough power for BOLD signal estimation even with few events and fixed inter-trial intervals in the critical practice phases. However, BOLD responses to events of different types, e.g. correct and incorrect items, could not be estimated within this design.

Functional images were acquired using a T2*-weighted EPI sequence sensitive to blood oxygenation level dependent (BOLD) contrast, with a TR of 3000 ms, a TE of 40 ms and a flip angle of 90°. Each of the twelve runs lasted for about 180 sec, which resulted in 720 whole-brain acquisitions from one subject over the whole experiment. Each volume comprised 32 contiguous axial slices with an in-plane resolution of 3.0 x 3.0 mm. The first three volumes of each session were discarded to allow tissue magnetization to reach a steady state. High-resolution T1-weighted (MP-RAGE) anatomical images were collected from each participant for visualization at the end of the experiment. Head motion was restricted by using a pillow and foam inserts, and participants were asked to move as little as possible during scanning, and especially during the breaks that included overt speech.

Data preprocessing and statistical analyses were performed with the SPM2 software (Wellcome Department of Cognitive Neurology, London, UK: http://www.fil.ion.ucl.ac.uk/spm/spm2.html) under the assumption of the General Linear Model (Friston et al., 1995). EPI images were unwarped and spatially realigned to the first image acquired in the first session. Structural and functional images were spatially normalized to a T1-weighted MNI template (Cocosco, Kollokian, Kwan, & Evans, 1997). Functional images were then resampled into 2 x 2 x 2 mm voxels and smoothed with an 8 mm FWHM isotropic Gaussian kernel.
For first level analyses, blocked regressors were formed by convolving box-car functions over periods of interest with a canonical hemodynamic response function (HRF). Four regressors per run were modeled, each of the 12 runs starting with 'fixation' (20 sec), 'study' (24 sec), 'distracter' (28 sec), followed by either 'selective retrieval', rehearsal' or 'cuing' (20 sec), according to condition. The main contrast of interest in the present experiment was the differential activation between blocks of retrieval (six blocks) and blocks of rehearsal (six blocks). Differences between these conditions (selective retrieval – rehearsal) were estimated using linear contrasts within a subject specific fixed-effects model, with session specific effects and low-frequency signal components (> 128 s) treated as confounds.

Resulting estimates were then entered into a second-level analysis with participant as a random factor. Mean differences were tested with one-sample t-tests against the hypothesis of a zero contrast value. For brain-behavior correlations, a simple regression model was used to test for voxels where estimates for the selective retrieval versus rehearsal contrast were significantly correlated with individual forgetting indices across participants. That is, retrieval-induced forgetting was used to predict the difference between the retrieval and the rehearsal condition. Functional regions of interest (ROI) with a radius of 6 mm were created around voxels that showed the highest correlation with forgetting. For description purposes, regression statistics (correlation coefficients) were then calculated for each ROI with retrieval-induced forgetting as a regressor for mean ROI activation. No statistical tests were performed on these coefficients, as they were derived from post-hoc tests.

A possible problem with the contrast between retrieval and rehearsal is that the two conditions were realized in different scanning runs with scanning breaks between runs. As the general linear model applied here takes into account between-sessions variance, some effects between conditions might have been missed due to a lack of statistical power in the main contrast of interest. Therefore, an additional, explorative analyses was conducted which separately contrasted blocks of retrieval and rehearsal with a non-memory, within-session baseline (distracter blocks). To further investigate activations related to the detrimental effects of retrieval practice on later remembering, the whole sample was median split into participants with high and participants with low levels of retrieval-induced forgetting (high forgetters and low forgetters), and the activation difference between retrieval and the distracter baseline was calculated separately for each group (n = 11).

Unless otherwise specified, only effects surviving a statistical threshold of $p < .001$, uncorrected for multiple comparisons and comprising at least 10 adjacent voxels, are reported. For visualization of cortical activations, SPM contrast images were mapped onto the surface-based human PALS-B12 atlas in SPM2 space, using the Caret 5.51 software (Van Essen, Dickson, Harwell, Hanlon, Anderson, & Drury, 2001, http://brainmap.wustl.edu/caret). Anatomical labeling and the assignment of Brodmann areas to peak locations were done using the WFU Pickatlas (Wake Forest University, School of Medicine, Winston-Salem, USA: http://www.fmri.wfubmc.edu/cms/software) and its Talairach Daemon.

As for analyses of the behavioral data, retrieval-induced forgetting (RIF in %) was calculated as percent difference in recall performance between nonpracticed items in the rehearsal condition and nonpracticed items in the retrieval condition. The resulting RIF index has a positive value if – in line with the inhibitory account – nonpracticed items are recalled worse in the retrieval than in the rehearsal condition. Two-tailed t-tests ($\alpha = .05$) were performed to test forgetting against the null hypothesis of zero difference.

Results

Behavioral Results

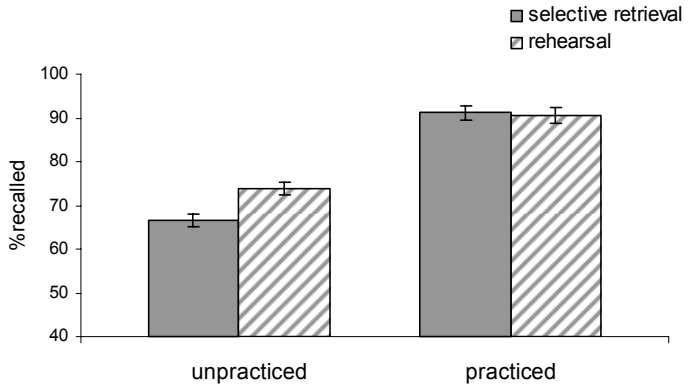

Figure 1.2 *Behavioral results from Experiment 1, showing mean recall performance (error bars correspond to standard errors) for different item types in the two conditions. Participants showed comparable recall performance for practiced items irrespective of condition. Recall of nonpracticed items was impaired in the retrieval compared to the rehearsal condition.*

Behavioral data revealed that practice through both retrieval and rehearsal led to a comparable mean recall performance for practiced items. 90.5% (SE = 1.7%) of the previously practiced items were recalled in the rehearsal condition, and 91.1% (SE = 1.6%) in the retrieval condition, with no significant difference between the two conditions, $t_{22} = -0.54$, $p = .60$. In contrast, correct recall of nonpracticed items was significantly worse in the retrieval condition (M = 66.6 %, SE = 1.6%) than in the rehearsal baseline condition (M = 73.8%, SE = 1.8%), resulting in an average retrieval-induced forgetting effect of 7.2% (SE = 1.4%), $t_{22} = 5.15$, $p < .0001$ (Figure 1.2).

Imaging Results

Retrieval related brain activation. Modeling blocks of selective retrieval, both frontal and posterior regions showed an increase in BOLD signal relative to blocks of rehearsal (see Figure 1.3 and Appendix, Table A). Posterior activations included areas in bilateral posterior temporal association cortices extending over the inferior

and middle temporal gyri (both BA 37), in left superior parietal cortex (BA 7), precuneus (BA 19), posterior cingulate cortex (BA 31), and the middle occipital gyrus (BA 19). Prefrontal response increases during selective retrieval were found in the left medial frontal (BA 8) and inferior frontal (BA 9) cortex. In contrast, there were only two small clusters that were significantly more active during rehearsal than during retrieval, located in the left lingual gyrus (BA 18) and putamen (see Figure 1.3, and Appendix, Table A).

When testing the same contrast with a more liberal threshold ($p < .005$, uncorrected for multiple comparisons), the bilateral hippocampi (see Figure 1.3), right fusiform gyrus (BA 37), and another right middle temporal (BA 37) and left posterior cingulate (BA 23) region were found to be more active during retrieval compared to rehearsal. Additional frontal activations with this threshold were found in the left middle (BA 46, BA 6, BA 8/9 and BA 8) and inferior (BA 10/46) frontal gyrus (see Appendix, Table A). With the same liberal threshold, the reverse contrast, i.e., rehearsal > retrieval, yielded additional activation peaks in the left lingual gyrus (BA 18), right putamen, right cingulate gyrus (BA 31), left insula (BA 13), and right cuneus (BA 17).

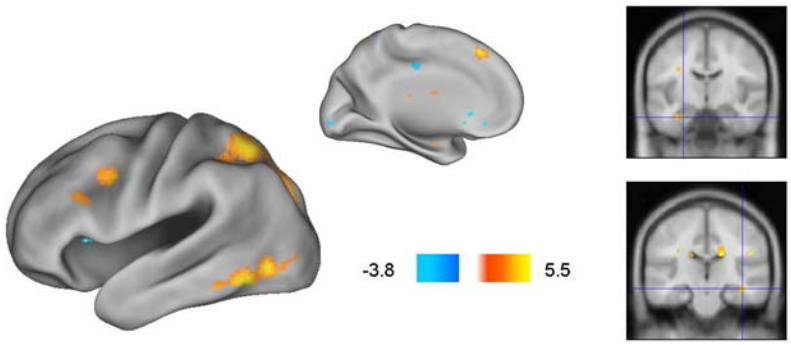

Figure 1.3 *Contrasting memory retrieval against rehearsal of some previously studied episodes. For visualization purposes, the statistical comparison is thresholded at $p < .005$ (uncorrected for multiple comparisons), and overlaid onto a standard cortical surface in MNI space. The right panel shows left and right hippocampus activation peaks, showing significantly more activation in the retrieval condition on a statistical threshold of $p < .005$.*

In addition to the contrast between retrieval and rehearsal, both conditions were compared separately against a non-memory baseline (digit ordering during distracter blocks). The results of these contrasts are shown in Figure 1.4, where red regions were activated by the selective retrieval condition, green regions by the rehearsal condition, and yellow regions by both conditions. As can be seen from the surface overlay, the two memory conditions activated largely overlapping brain regions in the lateral prefrontal, parietal and temporal cortices, with more extensive activation in the retrieval condition in all of these areas, but most pronounced in the ventrolateral prefrontal cortex (BA 45 and BA 47). However, it is important to consider that differences in inferior prefrontal areas were not found in the direct statistical comparison between retrieval and rehearsal.

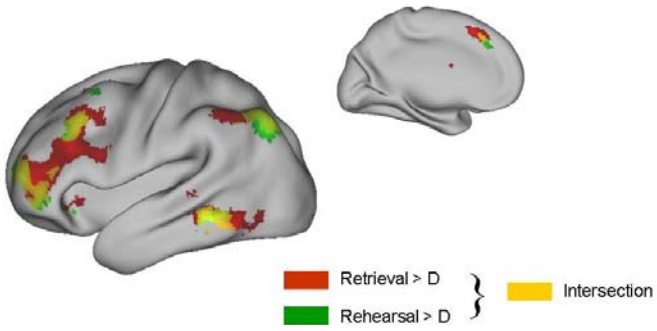

Figure 1.4 *T-maps of areas showing significant (p < .001, uncorrected) activation in the retrieval and the rehearsal condition, contrasted separately against a non-memory baseline (digit ordering = D), overlaid onto a single flattened cortical surface (PALS B12 in SPM2 space).*

Brain-Behavior Correlations. As the main purpose of the present study was to isolate inhibitory components of the retrieval process that cause subsequent forgetting, Experiment 1 focused on the correlation analysis between activation patterns during selective retrieval and later forgetting. A regression analysis revealed that activation in some regions varied systematically with the degree of retrieval-induced forgetting (see Table 1.1). The two largest clusters showing this pattern were localized in the left middle frontal cortex (BA 8/9), r = -.82, and in the anterior cingulate cortex (BA 32), r = -.76, and a smaller cluster in a left medial

frontal region (BA 6/8), r = -.84. All three areas showed a significant inverse relationship to individual forgetting indices (see Figure 1.5).

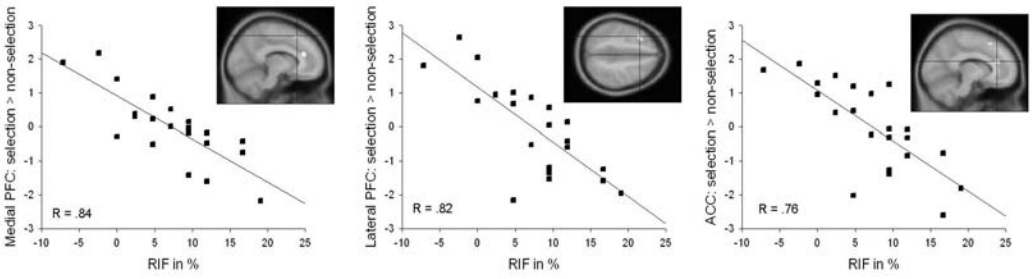

Figure 1.5 *Regions that showed a significant correlation between participants' retrieval specific brain activation and retrieval-induced forgetting (RIF in %). The highest correlations were found in the left medial prefrontal cortex (top, BA 6/8), left posterior prefrontal cortex (middle, BA 8/9), and anterior cingulate cortex (bottom, BA 32). Scatter plots show activation differences (beta weights) between the retrieval and the rehearsal condition on the y axis, with corresponding forgetting indices (RIF in %) for each individual participant plotted on the x axis.*

Two of the regions predicting retrieval-induced forgetting, namely the left middle frontal cortex (BA 8/9) and the left medial frontal cortex (BA 6/8), seemed to be located close to areas that were found in the retrieval versus rehearsal contrast (BA 8/9 and BA 8, respectively) with a threshold of $p < .005$, whereas no region in the retrieval versus rehearsal contrast corresponded to the anterior cingulate (BA 32) peak that predicted forgetting. To test the degree of functional overlap between the two analyses, ROIs with a radius of 6 mm were built around voxels showing a significant ($p < .005$, uncorrected) effect of retrieval (compared with rehearsal), and being the maxima closest to the maxima found in the correlation analysis. This procedure yielded two ROIs, one in the left middle frontal cortex (centered around coordinates -38 12 32, BA 8/9), and one in the left medial frontal cortex (centered around coordinates -12 24 44, BA 8). Mean activity in these ROIs was then tested for a significant correlation with later forgetting. Activity in the left middle frontal ROI (BA 8/9) correlated with RIF with $r = -.55$ ($p < .001$), and so did activity in the medial frontal ROI (BA 8, $r = -.55$, $p < .001$). The results suggest that there is substantial functional overlap between regions that show retrieval specific activation, and regions predicting retrieval-induced forgetting.

Table 1.1 Peak locations showing a significant ($p < .001$, uncorrected) correlation with subsequent retrieval-induced forgetting

	Anatomical Label	x	y	z	BA	T	size
Frontal Lobe:							
L	Medial Frontal G.	-10	22	54	6/8	6.87	29
L	Middle Frontal G.	-34	16	48	8/9	6.50	102
		-44	12	40		4.31	
L	Anterior Cingulate	-10	34	20	32	5.22	103
R	Anterior Cingulate	12	36	18	32	3.50	26
R	Medial Frontal G.	10	-8	58	6	5.07	37
Others:							
L	Superior Temporal G.	58	-52	-26	41	5.13	58
		71	-44	-24		4.53	71
R	Fusiform G.	30	38	-48	37	4.40	30
L	Lingual G.	22	-22	86	17	4.83	22

BA = approximate Brodmann Area; L = left hemisphere, R = right hemisphere, B = bilateral; size = number of voxels in a cluster

For a complete overview over forgetting relevant activations during practice, the whole sample was median split into participants with high, and participants with low retrieval-induced forgetting, and retrieval related activation was then contrasted against a low-level, within-session baseline (blocks of distracter task) separately for each group (see Figure 1.6). In the high forgetting group, the strongest retrieval related activations were located in the left posterior temporal cortex (-64 -44 -4, area 21), the left inferior frontal gyrus (-52 32 4, BA 45; -50 10 22, BA 44), and in the left medial frontal gyrus (-6 26 44, BA 8). The same comparison in the low forgetting group resulted in a similar activation peak in the left posterior temporal cortex (-60 -36 -4, BA 21), but different frontal activation peaks, the latter being located in the left middle frontal gyrus (-46 18 46, BA 8/9) and the bilateral superior frontal gyri (30 54 -2 and -30 60 10, both BA 10).

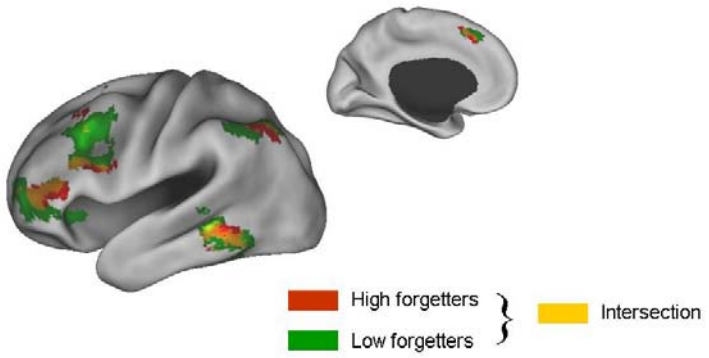

Figure 1.6 *T-maps (p < .001, uncorrected) of retrieval related activations compared against a non-memory baseline (digit ordering), separately for the high and low forgetting participants. It can be seen that middle/superior prefrontal areas were more extensively recruited by low forgetting subjects.*

Discussion

Replicating prior behavioral work (Anderson et al., 2002; Bäuml & Aslan, 2004), the behavioral results of Experiment 1 suggest that retrieval-induced forgetting is indeed retrieval specific. Practicing some members of a memory set improved later recall of the practiced items, regardless of whether practice occurred through selective retrieval or rehearsal. In contrast, later recall of related, but nonpracticed items proved to be worse in the retrieval condition than in the rehearsal condition. The latter finding is consistent with the assumption that retrieval, but not rehearsal, involves competition, and that inhibitory processes operate to resolve mnemonic competition during retrieval (e.g., Anderson, 2003).

Selection specific activations

The imaging findings of Experiment 1 showed that posterior and prefrontal association cortices increased BOLD responses during memory retrieval compared to rehearsal. Retrieval specific activations in posterior cortices were found in the left and right lateral temporal cortex, the left inferior parietal cortex, and in the left and right hippocampus. Prefrontal activations were located in medial premotor and anterior cingulate cortex, and in the left dorsolateral prefrontal cortex. Similar activation patterns have been reported in prior fMRI studies of long-term memory retrieval. Involvement of posterior temporal association areas is commonly thought

to reflect the automatic activation of semantic knowledge (Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005; Thompson-Schill, D'Esposito, & Kan, 1999). As semantic material was employed in both conditions, a posterior temporal activation increase in the retrieval condition may indicate the spreading activation of semantic associations upon cue presentation, constituting the basis for retrieval competition. It is not yet clear to what extent the inferior parietal cortex serves memory specific functions (Wagner, Shannon, Kahn, & Buckner, 2007), and involvement of these areas has been found in such distinct cognitive processes as attention, working memory, episodic memory, and visual perception. In episodic memory, it has been suggested that the typical fronto-posterior activation pattern might reflect the reactivation of an integrated memory trace at the time of retrieval (Naghavi & Nyberg, 2005; Sakai, 2003).

The hippocampus has been linked to binding processes and the conscious recollection of recent events (Bunge, Burrows, & Wagner, 2004; Rugg & Yonelinas, 2003; Squire, Stark, & Clark, 2004). However, hippocampal activation has also been associated with memory intrusions, that is, with the unintentional retrieval of unwanted information (Anderson et al., 2004). Involvement of the hippocampus in the retrieval condition could thus indicate the coactivation of currently irrelevant episodes that are linked to the same retrieval cue, whereas no such activation emerged in the rehearsal condition.

The prefrontal cortex and memory retrieval

The major focus of the present analysis was on prefrontal contributions to selective retrieval, and their possible function in competition resolution. Contrasting retrieval and rehearsal, the left supplementary-motor cortex (BA 8) and the dorsolateral prefrontal cortex (BA 9) showed selection specific response increases. It is a well established view that the medial prefrontal cortex is essential for processing and monitoring conflict related information (Botvinick, Braver, Barch, Carter, & Cohen, 2001), and medial area 8 might particularly contribute to semantic conflict processing and resolution (van Veen & Carter, 2005). The dorsolateral activation peak was located very posterior, close to the inferior frontal junction. This region has been found to be exclusively engaged during memory tasks that require some degree of memory for source information. For example, the posterior DLPFC activates when episodic details about the encoding context are to

be recollected, but not during simple item recognition (Dobbins, Foley, Schacter, & Wagner, 2002). Apart from the memory domain, this region is held essential for maintaining an attentional set and selecting appropriate responses in the light of conflicting information (Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002; Derfuss, Brass, & von Cramon, 2004; Zysset, Müller, Lohnamm, & von Cramon, 2001). Thus, the present finding of increased activation in both medial and lateral prefrontal cortex is likely to reflect increased demands on conflict monitoring and resolution mechanisms.

This interpretation is supported by the brain-behavior correlations, using retrieval-induced forgetting as a predictor for retrieval specific activation. Left medial prefrontal cortex (BA 6/8), left middle lateral PFC (BA 8/9) and the left anterior cingulate (BA 32) showed the strongest relation to retrieval-induced forgetting. Maxima in the medial and lateral PFC were located close to the prefrontal areas found in the retrieval versus rehearsal contrast, whereas the ACC showed no significant activation in this comparison. This functional overlap was confirmed by an additional ROI analysis, strengthening the assumption that medial (BA 8) and lateral (BA 8/9) prefrontal regions are not only sensitive to the retrieval of relevant memories, but also functionally linked to the inhibition of momentarily irrelevant memories.

A finding that was not expected a priori was that all brain-behavior correlations were negative in direction. If the prefrontal cortex plays a crucial role for competition resolution, retrieval-relevant prefrontal regions might be expected to show a positive relation to retrieval-induced forgetting. At least two possible explanations for the negative correlations, and the lack of a positive correlation, have to be considered. First, if competition within the current memory set is being resolved early during retrieval practice, less inhibitory control might be needed on subsequent practice trials. As a consequence, participants who are highly successful in suppressing competing items early during retrieval practice might exhibit an overall decrease of inhibition related activation. Provided this assumption is correct, the present findings would basically replicate the results of Kuhl et al. (2007), who showed that decreasing prefrontal activation over repeated retrieval attempts predicts later forgetting.

Second, participants who are successful in inhibiting irrelevant memories might more selectively recruit the relevant brain regions, whereas less successful

inhibitors recruit a broader network of frontal regions. Such fine-tuning of cortical responses has, for example, been demonstrated in working memory studies, which have shown that frontal regions respond more and more precisely as participants become practiced in performing working memory tasks (e.g., Garavan, Kelley, Rosen, Rao, & Stein, 2000). Across participants, good working memory performance has previously been associated with a general decrease of prefrontal involvement (Jaeggi, Buschkuehl, Etienne, Ozdoba, Perrig, & Nirrko, 2007). In long-term memory, it has been shown that poorer recognition performance is associated with broader recruitment of ventrolateral prefrontal areas at both encoding and retrieval (Bertolino et al., 2006). With respect to the present task, these findings might implicate that the areas showing a negative correlation with forgetting are not relevant for inhibitory control per se, and are – quite the reverse – the more recruited the less participants manage to inhibit irrelevant and competing memories. The finding from an additional sample split (see Figure 1.6) supports the latter explanation, showing less focal recruitment of prefrontal regions in low compared with high forgetting participants. Whereas high forgetters demonstrated focal activations in anterior and mid-VLPFC cortex during retrieval practice, low forgetters appear to additionally recruit middle and superior frontal regions.

Taken together, the findings of Experiment 1 speak in favor of the inhibitory account of retrieval-induced forgetting, and against strength-dependent blocking accounts. First, the behavioral pattern is inconsistent with the view that forgetting in the retrieval practice paradigm is caused purely by strengthening of a subset of category members. Both conditions involved the same degree of strengthening, but only selective retrieval induced forgetting of competitors. Second, the imaging data suggest that neural activity during selective retrieval is functionally linked to the forgetting of items that compete during practice. Again, this finding is incompatible with blocking explanations of retrieval-induced forgetting, because blocking implies that the critical mechanism operates during the final recall test. However, it should be noted that no scanning took place during the final recall in Experiment 1, and the conclusion that the critical mechanism acts *only* during retrieval practice can thus not be inferred from the present data. Notably, forgetting was predicted by retrieval specific activation in left-lateralized brain regions that have previously been associated with interference monitoring and resolution, pointing to inter-individual differences in successful competition resolution.

However, no positive correlation with forgetting was found, and therefore, no direct evidence could be obtained from Experiment 1 as to the causal involvement of prefrontal cortex in memory inhibition. Rather, posterior dorsolateral prefrontal areas were recruited more extensively by low forgetters, consistent with the hypothesis that low inhibiting participants experience more interference during retrieval practice.

Experiment 2

In Experiment 1, it could be demonstrated that selective retrieval induces retrieval specific impairment, and that retrieval specific prefrontal processes are predictive of the degree to which participants show forgetting on a later recall test. Although these findings speak in favor of an inhibitory account of retrieval-induced forgetting, brain activity measures were only obtained during selective retrieval practice, at the time inhibitory processes are assumed to operate. Experiment 1, and the fMRI study by Kuhl et al. (2008), can only provide clues as to the substrates of retrieval-induced forgetting as it is created. Moreover, Experiment 1 used a behavioral and neural baseline that was specifically designed to test the detrimental effects of retrieval practice independently of strengthening processes, such that the neural basis of enhancement and forgetting could not be investigated separately.

Experiment 2 examined the neural markers of both retrieval-induced enhancement and forgetting at the time the impairment is observed, that is, during the final recall. The main goal was to test the inhibitory account of retrieval-induced forgetting (Anderson & Spellman, 1995) against alternative accounts that ascribe the impairment to blocking mechanisms during the final memory test (Williams & Zacks, 2001). A recent model of controlled memory retrieval postulates that left anterior ventrolateral prefrontal cortex (VLPFC) subserves the controlled retrieval of weakly represented memories, whereas mid-VLPFC subserves the selection of a memory among competing memories (Badre & Wagner, 2007). Based on this model, if the impaired retrieval of nonpracticed information reflects reduced memory availability via *inhibition*, this reduction should increase control demands, thus activating left anterior VLPFC. By contrast, if the impairment reflects *blocking* via increased competition by practiced information, retrieval of impaired memories should be most strongly associated with activation increases in mid-VLPFC.

Moreover, it was examined if retrieval-induced enhancement and forgetting have distinct neural correlates. The latter question is of high theoretical impact, because blocking accounts of retrieval-induced forgetting are based on the assumption that the impairment caused by selective retrieval practice is dependent on the degree to which practice strengthens related memories (Williams & Zacks, 2001). In contrast, the inhibitory account assumes that inhibition affects the representations of competing memories themselves, independently of how much strengthening the retrieval practiced items experience (Anderson, 2003). Consistent with this idea, it has been demonstrated that some items of a memory set can be substantially strengthened without inducing forgetting of the remaining items. For example, memory for the practiced items can be reliably enhanced having participants practice one versus five times, with no reliable effect on nonpracticed category exemplars (Shivde & Anderson, 2001). Moreover, as shown in Experiment 1 and in numerous prior experiments (Anderson et al., 2000; Bäuml, 2002; Bäuml & Aslan, 2004; Ciranni & Shimamura, 1999; Johansson et al., 2007), practice without retrieval competition does not induce the typical pattern of forgetting found after retrieval practice. Provided the impairment os caused by an inhibitory mechanism, enhancement- and forgetting related effects should thus be found in distinct brain networks.

Methods

Participants

Twenty-three right-handed native German speakers (10 male, mean age 23.5 years, SD = 2.4) were recruited at the University of Magdeburg for paid participation. They had no known history of neurological or psychiatric disease, normal or corrected to normal vision, and gave their written informed consent. The experiment was conducted in accordance with the guidelines of the Ethics Commission of the University of Magdeburg Faculty of Medicine.

Behavioral Procedure

The experiment consisted of six separate runs, each comprising a study phase, an intermediate practice phase, a distracter phase, and a final recall test (see Figure 2.1). Materials were 288 German nouns from 36 semantic categories, drawn from published norms (Battig & Montague, 1969; Scheithe & Bäuml, 1995). Within each category, all items had unique first letters. Word lists were counterbalanced across conditions to control for effects of material.

In the study phase, participants were presented 48 items out of 6 categories (e.g. SPORT – Volleyball) in pseudo-random order. Each study trial began with the presentation of a word for 1200 ms, followed by 1300 ms of fixation, a question mark for 1200 ms, and fixation for 800 ms. Upon presentation on the question mark, participants were instructed to respond with a yes/no button press whether the item was personally familiar to them or not. Half of the participants responded with the right, half of them with the left hand. To exclude short-term memory effects, the study phase was followed by a short distracter task, in which 5 digits on the screen had to be ordered in an ascending manner for 30 sec.

In the retrieval practice phase, participants were asked to covertly complete unique word stems that corresponded to a subset of the previously studied material (e.g. SPORT – Voll_____). A retrieval practice trial consisted of 1000 ms presentation of the word stem, 1300 ms fixation, 1200 ms presentation of a question mark, and 1000 ms fixation. Participants were instructed to covertly complete the word stems only with items from the prior study list, and, upon presentation of the question mark, to indicate by a button press if they could correctly remember the corresponding word. Importantly, retrieval practice occurred for half of the items out of two thirds of the studied categories in each run. With this procedure, the 48 study items could – after retrieval practice – be divided into three classes of items: 16 retrieval **p**racticed items (called P^+ items, e.g. SPORT - Volleyball), 16 nonpracticed items out of practiced categories (called P^- items, e.g. SPORT – Tennis), and 16 nonpracticed items out of completely nonpracticed categories (called control or C items, e.g. VEGETABLE – Zucchini).

During the final cued recall, all of the previously studied words had to be recalled. Participants were provided with categories along with the first letter of a study item (e.g. SPORT – T_____), and were asked to overtly respond with the corresponding word, or to answer "next" (German: "weiter") whenever they didn't know the correct answer. Each test trial began with the presentation of the category plus first letter cue for 1000 ms, followed by a fixation cross for 1000 ms, three exclamation marks for 1500 ms, and another fixation cross for 1000 ms. Oral responses were not to be given before presentation of the exclamation marks. Answers were recorded via a microphone fixed to the head coil, and were digitalized for later sorting into correctly remembered and forgotten items.

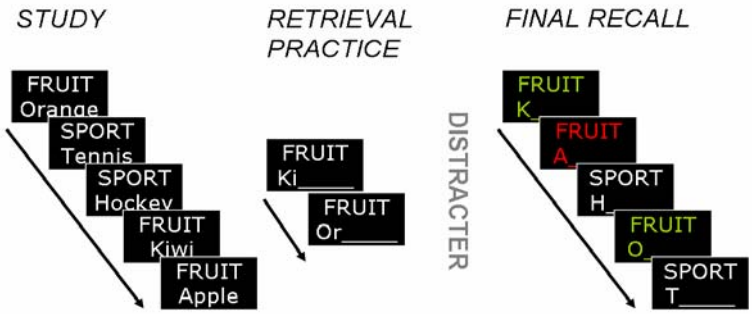

Figure 2.1 *Schematic figure showing the behavioral procedure used in Experiment 2. Each of the six scanning sessions consisted of a study phase, where exemplars from several categories were to be studied; a retrieval practice phase, during which half of the exemplars from two thirds of the categories were to be retrieved; a digit ordering distracter task; and a final recall phase, in which all initially studied exemplars were to be recalled. In the final recall, this procedure produced three different types of items: P^+ (retrieval practiced, shown in green), P^- (nonpracticed exemplars from practiced categories, shown in red), and C (nonpracticed control items, shown in white).*

The scanner was run continuously during each session consisting of study phase, retrieval practice phase, distracter phase, and final recall test. After the final recall test, scanning was interrupted for one or two minutes to allow participants a short break before the beginning of a new run. In the study phase, the retrieval practice phase and the final recall test, trials were interspersed with null events in pseudorandom order, to allow better modeling of the event-related hemodynamic response functions. Null events were set up similar to "real" trials, except that in

the beginning of a null event, a fixation cross was presented instead of an item. In these trials, participants always pressed the left response button (practice phase), or responded with "next" (final recall phase), upon presentation of the question mark or exclamation marks, respectively.

FMRI data acquisition and analysis

Scanning took place on a GE Medical Systems Signa 1.5 T MRI scanner, located at the University of Magdeburg's Medical Faculty. Functional images were acquired using an interleaved (bottom to top) echo-planar imaging sequence (repetition time = 2000 ms, echo time = 35 ms) sensitive to blood oxygenation level dependent (BOLD) contrast. In each run, 342 whole-brain volumes were acquired, with the first 3 volumes being discarded to guarantee steady state tissue magnetization. Images consisted of 23 axial slices, with a slice thickness of 5 mm plus 1 mm gap, and an in-plane resolution of 3.15 x 3.15 mm. High resolution, T1 weighted anatomical images for visualization purposes were available from each participant. Head movement was restricted using pillows and foam inserts.

Data preprocessing and statistical analysis were performed using statistical parametrical mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, UK: www.fil.ion.ucl.ac.uk/spm/). Functional images were temporally and spatially realigned, co-registered to anatomical images, normalized to an average T1 template in standard stereotactic MNI space (Montreal Neurological Institute, Montreal, Canada: www.bic.mni.mcgill.ca), and finally smoothed with a Gaussian kernel of 8 mm at FWHM.

For first level (single subject) statistical analyses, event-related hemodynamic responses were modeled with delta stick functions at the onset of each event of interest, convolved with a canonical hemodynamic response function (HRF) (Friston et al., 1995). The resulting time series of single voxels were then used to form covariates in a fixed effects general linear model. Practice trials were modeled as two separate events, one for the word stem presentation, and one for the motor response. During the study and final recall phases of the experiment, remembered and forgotten items were modeled separately, as were items of the

type P^+ (practiced), P^- (inhibited) and C (baseline). Learning and retrieval practice phases additionally included one regressor to capture the manual responses, while final recall phases included one regressor for each speech event. Session specific effects, as well as the six rigid-body movement parameters determined from realignment, were included as separate covariates. Statistical parametric maps of linear contrasts were estimated, with low-frequency signal components (cut-off 128 s) treated as confounds. Planned comparisons at the first level included the contrasts between P^- and C items, P^+ and C items, and P^- and P^+ items. These contrasts could only be estimated for remembered items, because the high recall performance for P^+ items did not leave enough statistical power for a comparison between forgotten items.

The first level contrast estimates were entered into a second level analysis, with subject treated as a random factor. Individual parameter estimates (beta weights) for event-related responses during retrieval practice trials were tested with one-sample t-tests against the hypothesis of a zero beta value. With respect to the final recall test, mean differences between estimates were tested with one-sample t-tests against the hypothesis of a zero difference. This was done for differences between P^- and C items, P^+ and C items, and P^- and P^+ items. A simple regression model was used to assess linear relationships between behavioral indices and brain activation. For brain-behavior correlations, individual indices of retrieval-induced forgetting (RIF in %) and retrieval-induced enhancement (Enhancement in %) were used to predict differences in neural activity during the final recall of P- compared to P^+ items. Unless otherwise mentioned, all differences and correlations were considered significant if they exceeded a threshold of $p < .001$, uncorrected for multiple comparisons.

For the analyses of the behavioral data, two-tailed t-tests with a statistical threshold of $p < .05$ were performed. Retrieval induced forgetting was calculated as the difference between P^- items and the matched C^- baseline items. Likewise, strengthening through practice was calculated as the difference between P^+ items and the matched C^+ baseline items.

Results

Behavioral Results

During retrieval practice, participants indicated via button presses that they were successful in completing a given word stem with an item from the study list in 64.1 % of the cases. Although this practice success rate is based purely on a subjective measure, it was positively correlated, across participants, with later P^+ performance (r = .69), and with general memory performance (r = .49).

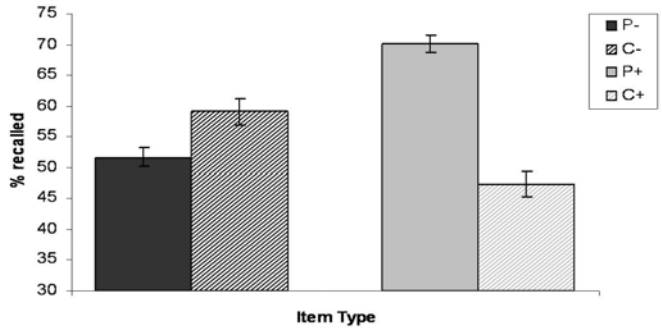

Figure 2.2 *Costs and benefits of selective retrieval practice. Bars with error indicators correspond to mean percent final cued recall performance (with standard errors of the mean) for the different item types: P^+ (retrieval practiced items), P^- (non-practiced items out of practiced categories), C^+ (control items matched to P^+ items), C^- (control items matched to P^- items). Compared to baseline, P^- items showed 7.4% retrieval-induced forgetting, whereas P^+ items showed 22.8% retrieval-induced enhancement.*

Statistical analyses of the behavioral data during the final cued recall (see Fig. 2.2) revealed that practicing some members of a category led to significant strengthening of practiced P^+ items (M = 70.1%) compared to the matching nonpracticed C^+ items (47.3%), yielding retrieval-induced enhancement of 22.8% (SE = 1.9%, $p < .05$). More importantly, significant retrieval-induced forgetting was found, with nonpracticed P^- items out of practiced categories (M = 51.6%) being significantly worse recalled than the matching nonpracticed C^- baseline items (M = 59.0%), resulting in an average of 7.4% retrieval-induced forgetting (SE = 2.7%, $p < .05$).

Imaging Results

Although fMRI measures were collected during all phases of the experiment, only data collected during retrieval practice and the final recall are reported here.

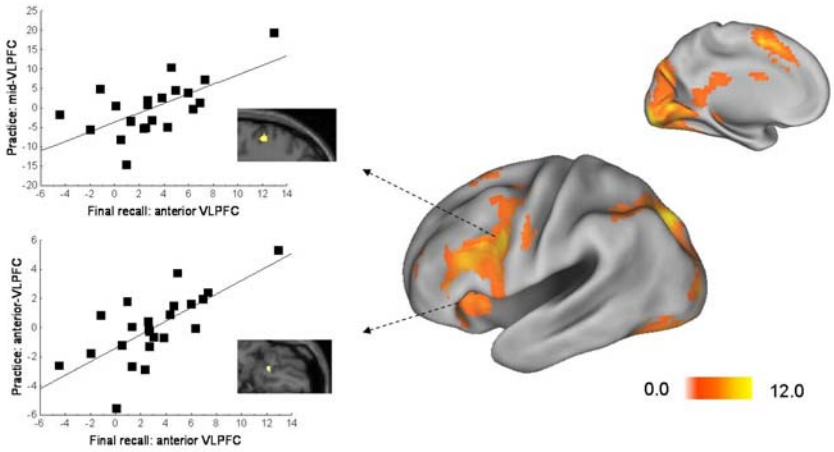

Figure 2.3 *Event-related hemodynamic activity during retrieval practice trials. Surface overlays show t-maps of voxels showing significant (p < .001, uncorrected for multiple comparisons) hemodynamic increases during retrieval practice trials against fixation, overlaid onto a flattened standard cortical surface (PALS-B12) in SPM2 space. Scatter plots refer to areas where retrieval practice activation significantly (p < .001, uncorrected) correlated with final recall activation in anterior VLPFC (BA 47). Peaks were located in the mid-VLPFC (-24 26 -16, r = .64) and anterior VLPFC (-52 9 24, r = .71).*

Selective retrieval practice. Event-related activity during retrieval practice trials yielded significant (p < .001, uncorrected) hemodynamic response increases in prefrontal, occipital, and medial temporal lobes (Fig 2.3 and Appendix, Table B). Prefrontal activations included one cluster extending over left premotor and ventrolateral prefrontal areas (BA 6/44/45), and one in the medial pre-supplementary motor area (preSMA, BA 6). Posterior activation extended bilaterally from late visual areas (BA 18/19) to the superior parietal cortex (BA 7). Moreover, both the left and right hippocampus increased signal relative to baseline during the selective retrieval of prior episodes. Areas showing negative BOLD amplitudes included the medial (BA 32 and BA 6) and lateral (BA 8) prefrontal

cortices, the right supramarginal gyrus (BA 40), and some right lateral temporal areas (BA 20/21).

Final recall test. The most obvious comparison of interest during the final recall test appears to be the contrast between the impaired P^- and the unimpaired control (C) items, because this comparison parallels the behavioral contrast for calculating retrieval-induced forgetting. However, note that from an imaging point of view, the contrast between P^- and C items may be contaminated by the effects of differential category familiarity. More specifically, P^- items, although not explicitly practiced, come from categories that are presented several times during retrieval practice. Therefore, differences between P^- and C items are likely not genuinely related to inhibition, but simply related to increased familiarity to practice categories. Accordingly, activations related to category priming should also be reflected in the contrast between P^+ and C items.

Significant hemodynamic increases for P^- items were found bilaterally in the supramarginal gyrus (BA 40), bilaterally in the anterior cingulate (BA 32), and in the right superior frontal gyrus (BA 8). As shown in detail in Figure 2.4A and Table C (Appendix), these activations mostly overlapped with the results of the comparison between P^+ and C items, which also yielded hemodynamic increases in the left and right supramarginal gyrus (BA 40), the anterior cingulate (BA 32), the right superior frontal gyrus (BA 8), but with one additional activation in the precuneus (BA 31) (see Fig. 2.4A). Hemodynamic response decreases during the final recall of both P^- and P^+ compared to control items were more widespread, but also found mainly in overlapping regions (see Appendix, Table D, for a complete list of peak activations), with both comparisons including one large bilateral posterior cluster extending over late visual areas (BA 17/18) and the precuneus (BA 19), and two left prefrontal clusters, one extending medially from the supplementary motor area (BA 6) to the cingulate gyrus (BA 32), and the second one covering the area from the left lateral precentral gyrus (BA 6) to the inferior frontal gyrus (BA 45). Moreover, the bilateral inferior frontal area 47 emerged in both of the above contrasts, being more left lateralized in P^- compared with C items, and more right lateralized in P^+ compared with C items (see Fig. 2.4B).

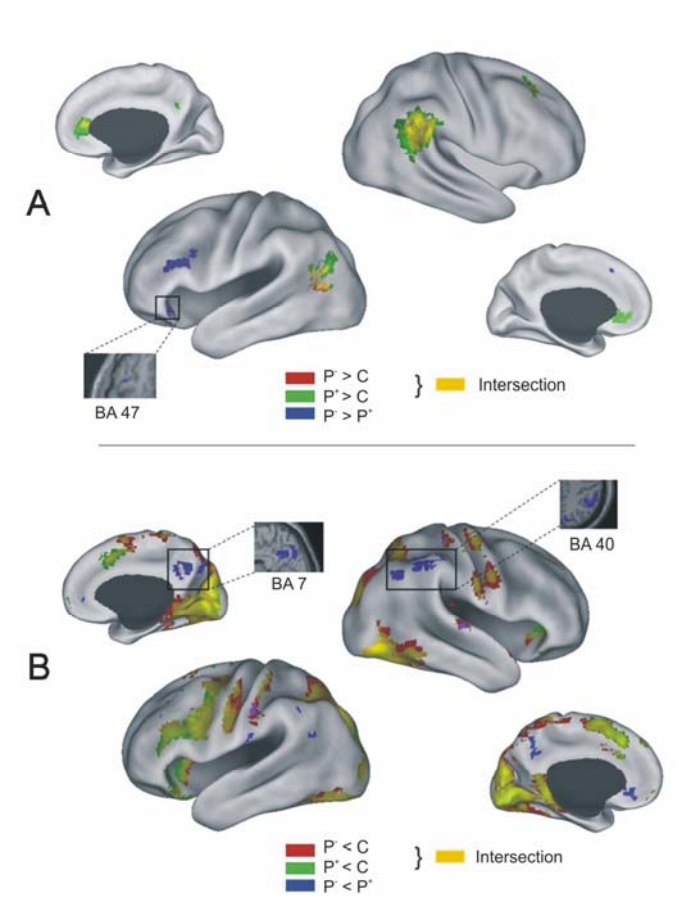

Figure 2.4 *Hemodynamic increases (A) and decreases (B) associated with the retrieval of different item types during the final cued recall test. Areas where P^- (red) and P^+ (green) items both significantly differed from control items are shown in yellow, whereas areas showing a significant difference between P^- and P^+ items are colored in blue. Highlighted are regions where the contrast between P^- and P^+ items significantly correlated with retrieval-induced forgetting or enhancement (see also Fig. 2.5).*

Impairment and enhancement during final recall. The planned comparisons described above revealed the predicted finding that P^- and P^+ items, compared with control items, elicited overall very similar hemodynamic responses during final recall, which are likely related to increases in category familiarity through prior practice. Therefore, neural differences between P^- and P^+ items were directly examined (see Figure 2.4, blue regions). Importantly, the contrast between P^- and P^+ items is not contaminated by differential category familiarity, and may therefore be best suited to isolate activations specifically related to inhibition and

enhancement. With this direct comparison, P^- recall elicited more activation in two ventrolateral prefrontal regions, one in posterior ventrolateral BA 45 (-48 26 20), and one in anterior ventrolateral BA 47 (-38 30 -12), both left lateralized. The reverse comparison yielded the strongest signal increases during P^+ recall compared with P^- recall in the precuneus (BA 7), the supramarginal gyrus (BA 40), and in the orbital part of the medial frontal wall (area 11).

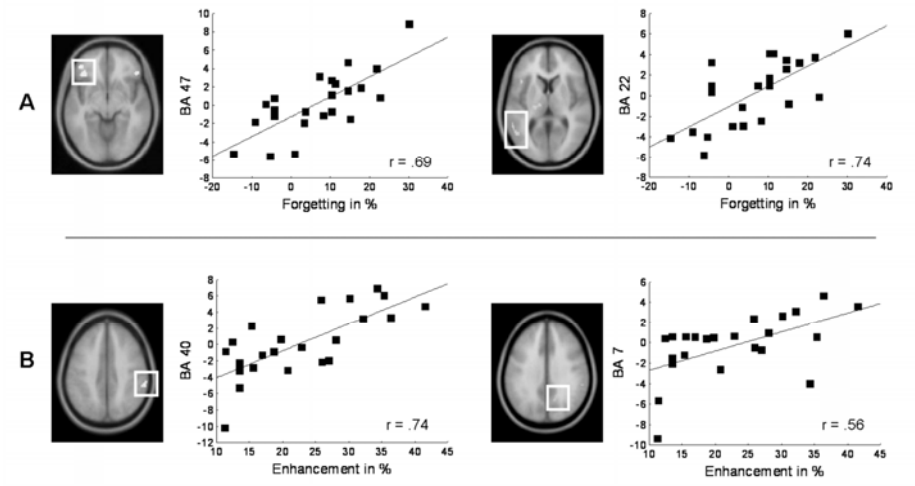

Figure 2.5 *Brain-behavior correlations. The upper row shows regions where retrieval-induced forgetting (Forgetting in %) was significantly correlated with differences in hemodynamic activity during the final cued recall test between P^- and P^+ items. The highest correlations were found in the left inferior frontal gyrus (area 47), and in the left superior temporal gyrus (area 22). The lower row shows regions where retrieval-induced enhancement (Enhancement in %) was significantly ($p < .001$, uncorrected) correlated with differences in final recall hemodynamic activity between P^- and P^+ items. The highest correlations were found in the right precuneus (area 7) and inferior parietal lobule (area 40). Maps are thresholded with $p < .001$ (uncorrected), and overlaid onto a standard anatomical T1 volume in SPM2 space.*

Note that these neural differences between P^- and P^+ items cannot be attributed solely to the effects of inhibition acting on P^- items, but can occur due to other influences, like differences in strength due to the practice of P^+ items. To assess which areas show inhibition specific effects during the final recall, the next analysis step was aimed at searching for activation differences between P^- and P^+ items that vary with the degree to which participants show retrieval-induced forgetting (see Table 2.1 and Figure 2.5). The two areas showing the strongest correlation with forgetting were located in the left superior temporal gyrus (STS,

area 22, R = .74), and in the left inferior frontal gyrus (LIFG, area 47, r = .69). Importantly, activation in these areas was not predicted by overall memory performance, nor by retrieval-induced enhancement of the P^+ items. Regions that correlated with the individual level of enhancement through retrieval practice were located in right medial and lateral parietal areas (see Table 2.1 and figure 2.4B). Here, the strongest correlations were found in the right precuneus (area 7, r = .74), and in the right lateral inferior parietal lobe (IPL, area 40, r = .56).

Table 2.1 *Peak locations showing a significant (p < .001, uncorrected) positive correlation with retrieval-induced forgetting and enhancement (see also Figure 2.5).*

	Anatomical Label	x	y	z	BA	T	size
	Correlation with forgetting						
L	Superior/Middle Temporal G.	-50	-58	12	22	5,81	51
		-58	-50	8	22	4,2	
		-52	-44	4	22	3,74	
L	Inferior Frontal G.	-42	26	-4	47	4,79	129
		-44	18	4	45	4,49	
		-42	26	-4	47	3,98	
L	Thalamus	-22	-20	8	NA	4,62	26
	(Ventral Posterior Lateral Nucleus)	-14	-16	8	NA	4,05	
R	Inferior Frontal G.	48	32	-8	47	4,5	14
	Correlation with enhancement						
R	Precuneus	22	-72	36	7	5,66	23
R	Inferior Parietal Lobule	62	-36	40	40	5,3	46
R	Posterior Cingulate G.	16	48	28	31	4,5	15
R	Precuneus	12	56	36	7	4,07	12

BA = approximate Brodmann Area, L = left hemisphere, R = right hemisphere, B = bilateral; size = number of voxels in a cluster

Figure 2.5 shows the beta estimates extracted from BA 45 and BA 47, separately for P^+, P^-, C^+ and C^- items. In left anterior VLPFC (BA 47), a significant interaction between practice status (P or C) and a priori item strength (weak + or strong -) was found $F_{1,22} = 22.82$, $p < .001$, but no main effect of practice status ($F_{1,22} = 2.48$, p =

.13) or a priori strength ($F_{1,22}$ = 0.23, p = .64). By contrast, left mid-VLPFC showed no significant practice by strength interaction ($F_{1,22}$ = 3.05, p = .09) and no significant main effect of practice ($F_{1,22}$ = 1.02, p = .32), but a significant main effect of a priori strength ($F_{1,22}$ = 7.20, p < .05). These findings support the view that BA 47 responds to semantic item strength, activating during the retrieval of weak control items (C^+) more than during the retrieval of strong control items (C^-). However, this effect reverses after retrieval practice, with BA 47 now showing more activation during the retrieval of initially strong, but now impaired items (P^-) than to the retrieval of initially weak, but now facilitated (P^+) items.

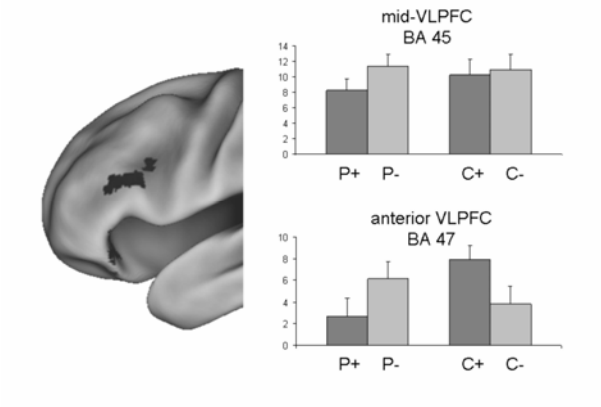

Figure 2.5. *Mid- and anterior VLPFC responses during the final recall of different item types. Mid-VLPFC showed no significantly different response to a priori strong and weak control items (C^- and C^+, respectively), but significantly more activation during P^- compared to P^+ recall. In contrast, anterior VLPFC showed activation increases during both the recall of weak control items, and impaired P^- items, suggesting that (a priori strong) P^- items are weakened after retrieval practice.*

To test for functional coupling between posterior temporal and prefrontal regions, contrast estimates were extracted from the BA 22 cluster that predicted forgetting, and from the BA 45 and BA 47 clusters that showed a significant difference between P^- and P^+ recall. Across subjects, activation in BA 22 was significantly correlated with activation in BA 47 (r = .73, p < .0001), but not in BA 45 (r = .36, p = .10).

Relation between retrieval practice and final recall. Finally, an additional post-hoc analysis regarding the relationship between prefrontal involvement during retrieval

practice and the final recall was carried out. Based on the above results of the comparison between P^- and P^+ items, the brain-behavior correlations, and prior imaging work (Badre & Wagner, 2007), it could be hypothesized that if activation in left anterior VLPFC (BA 47) does indeed reflect the impaired state of P^- items, selection related activations during retrieval practice should predict later BA 47 activation during final recall. This hypothesis was tested by extracting mean BA 47 activation during the final recall (ROI defined as the cluster activated during $P^- > P^+$ retrieval), and using the resulting estimates as a regressor for event-related activation during retrieval practice, restricting the analysis to bilateral inferior prefrontal cortices. The results of this ROI analysis are shown in Figure 2.3. The two regions that showed a significant ($p < .005$, uncorrected) correlation with later left anterior VLPFC (BA 47) activation were located in left BA 47 (-24 26 -16, $t = 4.71$, 42 voxels; $r = .57$, $p < .005$), and in left BA 45 (-52 9 24, $t = 3.75$, 38 voxels; $r = .50$, $p < .05$).

Discussion

Behaviorally, the results of Experiment 2 replicated the typical pattern of retrieval-induced enhancement and forgetting. Practice led to enhanced recall performance for practiced relative to nonpracticed items. More importantly, practice of only some items out of a category led to impaired recall performance for related, competing items, as compared to unrelated, non-competing items. The behavioral results are therefore in accordance with the concept of retrieval inhibition (Anderson, 2003).

From a neural perspective, whereas Experiment 1 investigated the neural substrates of retrieval-induced forgetting during retrieval practice, the primary goal of Experiment 2 was to identify the neural markers during final recall that might indicate the inhibited state of P^- items. The comparison of P^- and P^+ with control items suggests that there was strong repetition priming (e.g., Henson & Rugg, 2003) during the final recall of both item types, most likely due to repeated presentation of the practiced categories. In order to search for specific neural correlates of the behavioral enhancement and impairment, a direct comparison

between P^- and P^+ items revealed that there were indeed reliable activation differences. Final recall of P^- items, compared with P^+ items, was associated with more activation in two left ventrolateral frontal areas (45 and 47), and with less activation in medial and lateral parietal areas. Moreover, activation in the anterior portion of the VLPFC (BA 47) and in the posterior lateral temporal cortex was highly predictive of the degree to which participants showed retrieval-induced forgetting. In contrast, activation in the right medial and lateral parietal cortex (BA 7) was highly predictive of the degree to which participants showed retrieval-induced enhancement. Thus, the brain-behavior correlations suggest dissociable brain substrates of impairment and enhancement during final recall, with prefrontal differences reflecting the impairment of the nonpracticed P^- items, whereas parietal differences reflect the enhancement of the practiced P^+ items.

Previous evidence indicates that different subregions of the VLPFC subserve different processes during long-term memory retrieval. The anterior VLPFC (BA 47) is assumed to support *controlled retrieval* by activating semantic knowledge in the lateral temporal cortex, whereas the mid-VLPFC has been linked to *post-retrieval selection* processes, which are more generally required whenever relevant information has to be discriminated from irrelevant, competing information (Badre et al., 2005; Badre & Wagner, 2007). For example, anterior VLPFC shows a selective response increase when weak associates to a given cue word are to be retrieved (Badre et al., 2005), when conceptual knowledge about items is required (Dobbins & Wagner, 2005), and when the inter-stimulus interval is long enough to allow controlled retrieval (Gold et al., 2006). By contrast, mid-VLPFC activates when irrelevant, competing primes for a target word are presented (Gold et al., 2006), when the number of competing targets is increased (Badre et al., 2005), and responds to interference from negative recent memory trials (Badre & Wagner, 2005). Moreover, anterior, but not mid-VLPFC functionally couples with lateral temporal regions thought to store semantic representations (Badre et al., 2005; Gold et al., 2006). Together, these findings have been taken as evidence for a two-process account of left VLPFC function (Badre & Wagner, 2007), with the anterior portion (BA 47) supporting controlled retrieval, and the dorsocaudal portion (BA 45) mediating retrieval competition and selection.

Provided the two-process account is correct, the present finding that activity in area 47 and the lateral temporal cortex predicts retrieval-induced forgetting might be especially relevant with respect to the two alternative views of how retrieval practice leads to retrieval-induced forgetting. According to the inhibitory account, inhibitory processes act on the nonpracticed P^- items during retrieval practice of the P^+ items, weakening the memory representations of the P^- items (e.g., Anderson & Spellman, 1995; Spitzer & Bäuml, 2007). According to the blocking theory, P^+ items are strengthened during retrieval practice and subsequently block access to the nonpracticed P^- items during final recall, without affecting the nonpracticed items' memory representations themselves (e.g., Williams & Zacks, 2001; Rundus, 1973). Regarding VLPFC involvement, the inhibitory account predicts that the final recall of P^- items requires more controlled retrieval, presumably supported by anterior VLPFC (BA 47) and lateral temporal areas (Badre & Wagner, 2007), because their weakened representations are temporarily less available. Moreover, anterior VLPFC activation during P^- retrieval should be associated with more activation in lateral temporal areas, because the controlled retrieval of a weak representation requires the activation of additional semantic information in more posterior storage areas (Badre & Wagner, 2007). In contrast, blocking predicts that the final recall of P^- items makes higher demands on selection processes, presumably supported by mid-VLPFC (BA 45), because practiced P^+ items block access to related P^- items.

The data from Experiment 2 demonstrate that both anterior and mid-VLFPC showed stronger activation during P^- compared with P^+ recall, but this activation difference was related to the degree of retrieval-induced forgetting almost exclusively in the anterior VLPFC. Moreover, a strong positive correlation with retrieval-induced forgetting was found in the lateral temporal cortex, and in line with the two-process view (Badre & Wagner, 2007), this area functionally coupled with the anterior VLFPC, but not with mid-VLPFC. These findings most likely reflect increased demands on controlled retrieval during the final recall of P^- items, caused by an inhibitory process that reduces their memory availability during retrieval practice. Strengthening this conclusion, both anterior VLFPC and temporal BA 22 did not show any correlation with the degree of enhancement of

the P^+ items. Anterior VLPFC, but not mid-VLFPC, appears to activate specifically when weakly represented memories have to be retrieved. In line with this interpretation, the highest activation in BA 47 was found during the final recall of impaired P^-, but also a priori weakly associated C^+ items. This pattern (see Fig. 2.5) suggests that BA 47 is primarily sensitive to the momentary *availability* of a memory trace. Finally, anterior VLPFC activation during P^- recall was predicted by both anterior and mid-VLPFC activation during retrieval practice (see Fig. 2.3), suggesting that controlled retrieval and selection processes play a crucial role for determining the later availability of memories that competed during retrieval practice.

Based on prior research, these findings most likely reflect increased demands on controlled retrieval during the final recall of P^- items, caused by an inhibitory process during retrieval practice that reduces their later memory availability. Strengthening this conclusion, activity in both anterior VLPFC and lateral temporal cortex did not correlate with the degree of enhancement of the P^+ items, instead showing a trend in the opposite direction. Regions correlated with the degree of retrieval-induced enhancement were located more posteriorly, in the medial and lateral parietal cortex, possibly reflecting the increased accessibility of practiced items (Wagner et al., 2005). A similar dissociation between the neural substrates of retrieval-induced forgetting and enhancement has recently been reported in an electrophysiological study (Spitzer, Hanslmayr, Opitz, Mecklinger, & Bäuml, in press). In this study, impaired recognition of P^- items was associated with early frontal ERP and theta power effects, whereas enhanced recognition of P^+ items was associated with late parietal ERP and alpha power effects, providing further evidence for the inhibitory view, according to which forgetting and enhancement are mediated by distinct processes.

The hypothesis that retrieval-induced forgetting results from an inhibition process that renders interfering items less available has previously been based on behavioral modeling work (e.g., Spitzer & Bäuml, 2007), and on behavioral results indicating that retrieval-induced forgetting occurs independently of the way participants try to access the impaired items, including in incidental tests (Veling & Van Knippenberg, 2004), and tests providing novel retrieval cues (Anderson &

Spellman, 1995; Aslan et al., 2007). All these findings argue against an interpretation of retrieval-induced forgetting in terms of blocking, because they suggest that the memory representation of the impaired information has itself been rendered less available. Experiment 2 provided first neural evidence for such inhibitory effects.

Summarizing Experiment 2, selective retrieval practice induced both enhancement and forgetting. Inhibition specific effects were found in anterior VLPFC and lateral temporal cortex, areas that are implicated in the controlled retrieval of weak representations from semantic and episodic memory. These were distinct from enhancement related effects, which were found in medial and lateral parietal regions. The findings of Experiment 2 therefore strengthen the view that retrieval-induced forgetting operates via an inhibitory mechanism that lowers the availability of competing memory representations.

Part III:
Part-List Cuing
Impairment

Experiment 3

Experiment 3 examined the neural processes involved in *part-list cuing* impairment. Part-list cuing impairment shows many similarities to retrieval-induced forgetting, in that it occurs, for example, not only in free recall tests, but also in recognition tests (Todres & Watkins, 1981), in implicit memory tests (Peynircioglu & Moro, 1995), and in tests using independent cues (Aslan et al., 2007). In the light of these behavioral parallels, it has been postulated that the two forms of episodic forgetting might be attributable to the same underlying cognitive process (Bäuml & Aslan, 2004). Recent behavioral studies suggest that part-list cuing mimics the effects of retrieval practice when participants adopt encoding strategies that prevent a serial representation of the study material. If, by contrast, such serial representations are favored by the encoding strategy, part-list cuing impairment is more likely produced by strategy disruption, and not by inhibition (Bäuml & Aslan, 2006; Aslan & Bäuml, 2007).

Bäuml and Aslan (2004) used an experimental setting that enabled them to directly compare the effects of retrieval practice, part-list cuing and part-list rehearsal. Participants studied lists of category-exemplar pairs, and then reprocessed a subset of category exemplars under three different instructions. In the retrieval practice condition, participants selectively retrieved a subset of category exemplars guided by category plus word stem cues. In the cuing condition, participants were presented a subset of category exemplars with the instruction to use these items as retrieval cues for the final cued recall test. In the relearning condition, participants were instructed to simply rehearse a subset of previously studied items. Finally, a baseline condition without any reprocessing of the study material was included. The behavioral data from the retrieval practice and the cuing condition showed a very similar pattern, with significantly worse cued recall performance for non-reprocessed words in both conditions, compared to relearning and to baseline. The authors explain this pattern in terms of a covert retrieval account of part-list cuing. In their view, the cuing instruction prompts participants

to covertly retrieve the category exemplars provided as cues. Such covert retrieval might trigger the inhibition of the remaining items, causing a behavioral pattern of impairment similar to overt retrieval practice. Note that traditional explanations of part-list cuing also attribute the impairment to covert retrieval of the cue items (e.g., Rundus, 1973), but assume that covert retrieval leads to blocking effects during the recall of the remaining items.

Experiment 3 tested the hypothesis that the impairment induced by part-list cuing and retrieval practice is caused by a common neural mechanism. Data were collected in the same scanning sessions as the data for Experiment 1, using the same basic experimental setting as Bäuml and Aslan (2004). This setting allows a direct comparison of neural processes involved in part-list cuing and selective retrieval practice, and to contrast both conditions with a relearning manipulation that is assumed to not involve inhibitory processes. The covert retrieval hypothesis predicts that neural activations in the part-list cuing condition resemble retrieval related activations, and that activation in the same brain regions predicts both part-list cuing and retrieval-induced forgetting. It was therefore hypothesized that a cuing instruction (compared to mere rehearsal) would induce neural changes in a similar fronto-posterior network that showed retrieval specific activations in Experiment 1.

Methods

Participants

Participants in Experiment 3 were the same that participated in Experiment 1. Data were acquired in the same scanning session, using the same basic experimental procedure and scanning parameters as in Experiment 1. The following section therefore describes only the experimental manipulations that differed from those reported in the Method section of Experiment 1.

Behavioral Procedure

Stimuli used for the cuing condition were drawn from the same normed word pool as in Experiment 1 (Battig & Montague, 1969; Scheithe & Bäuml, 1995), with word list being rotated such that each category occurred equally often in the retrieval, cuing and rehearsal condition across participants. As in the retrieval and the rehearsal condition, a category consisted of 12 items with unique first letters within a category. The five items with the lowest rank order (mean rank 31.8, SD = 8.2) served as retrieval cues, and the seven items with the highest association to the category cue (mean rank 11.8, SD = 5.0) had to be recalled in the test phases of the experiment. The rehearsal condition served as a baseline for behavioral and neural comparisons.

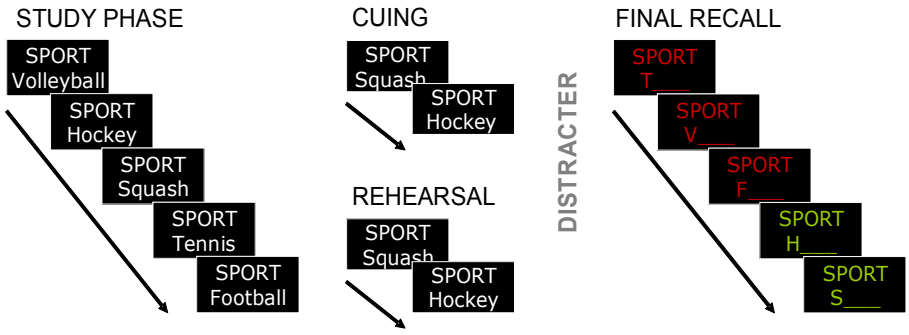

Figure 3.1 *Schematic illustration of the design of Experiment 3. Paralleling Experiment 1, participants first studied lists of category-exemplar pairs, and were then reexposed to part of a list. Participants were asked to use these words as retrieval cues in the cuing condition, and to rehearse them for the final recall in the rehearsal condition. On the final cued recall test, all previously studied items were tested with category plus first letter cues., with non-practiced items always being recalled first. The only difference between the cuing*

Paralleling the retrieval and rehearsal conditions, a scanning run in the *cuing* condition consisted of a study phase, followed by a cuing phase, a short distracter phase (digit ordering), and a cued recall test. Trials were arranged using the same timing parameters as in Experiment 1. In the cuing phase, participants were presented five of the previously studied 12 items in random order, with the instruction to use these words as retrieval cues for the remaining items of a category. Note that the only difference between the cuing and the rehearsal

condition was the instruction about how to treat these words. In the rehearsal condition, the five items had to be rehearsed for the final recall, whereas in the cuing condition, participants were asked to actively use these items as retrieval cues. A second difference between cuing and rehearsal was the final recall test, where only the seven remaining items had to be recalled in the cuing condition. In contrast, all initially studied 12 items were tested again on the final recall test in the rehearsal (and retrieval) condition.

FMRI Statistical Analyses

In line with Experiment 1, four first level blocked regressors were modeled per run, including 'fixation' (20 sec), 'study' (24 sec), 'distracter' (28 sec), and 'cuing' (20 sec). Two contrasts were of main interest. First, mean activation in cuing blocks was compared with mean activation in rehearsal blocks. In a second comparison, cuing blocks were directly compared with blocks of selective retrieval. Differences between these conditions (cuing – rehearsal, and cuing – retrieval) were estimated using linear contrasts, and the resulting estimates were entered into a second-level analysis with participant as a random factor. Mean differences were tested with one-sample t-tests against the hypothesis of a zero contrast value.

Brain-behavior correlations were calculated using the same basic ROI procedure as in Experiment 1, but using part-list cuing – the behavioral difference between the cuing and the rehearsal condition – as a regressor to predict the differential BOLD estimates between the cuing and the rehearsal condition. Finally, a sample split was done to reveal cuing related activations separately in high and low forgetting participants. For reasons of statistical power, this split (n = 11 in each group) was done using the images contrasting cuing with a non-memory, within-session baseline (digit ordering during distracter phases).

Results

Behavioral Results

Participants recalled a mean of 71.0% of the target items in the cuing condition, whereas recall performance for the same items in the rehearsal baseline condition was 73.8%. The statistical comparison yielded a non-significant difference of 2.8% (SE = 2.3%) between conditions, t(22) = 1.22, p = .23 (Figure 3.2).

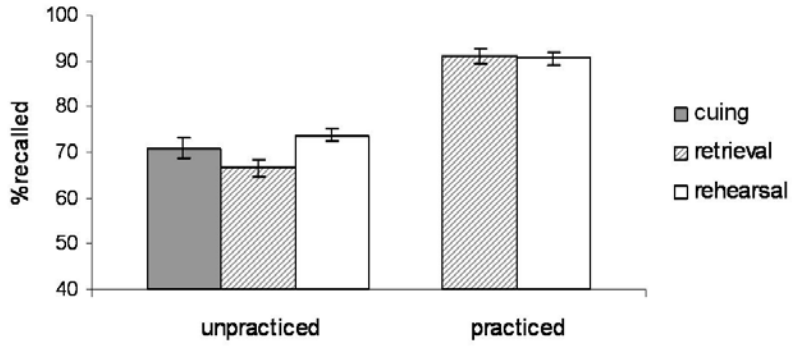

Figure 3.2 *Behavioral results from Experiment 3, showing mean recall performance (error bars correspond to standard errors) for different item types in the three conditions, including the retrieval and rehearsal conditions of Experiment 1. Recall of nonpracticed items was impaired in the retrieval compared to the rehearsal condition, but no significant impairment was found in the cuing condition.*

Imaging Results

The statistical comparison between cuing and rehearsal (see Figure 3.3 and Table 3.1) yielded significantly more cortical activation in the cuing condition in the left middle frontal gyrus (BA 9 and BA 10), left inferior temporal gyrus (BA 21), and left medial frontal gyrus (BA 6). Subcortical differences were found in the left (pulvinar) and right (ventral lateral nucleus) thalamus, and left basal ganglia (globus pallidus). No area showed increased activation during rehearsal.

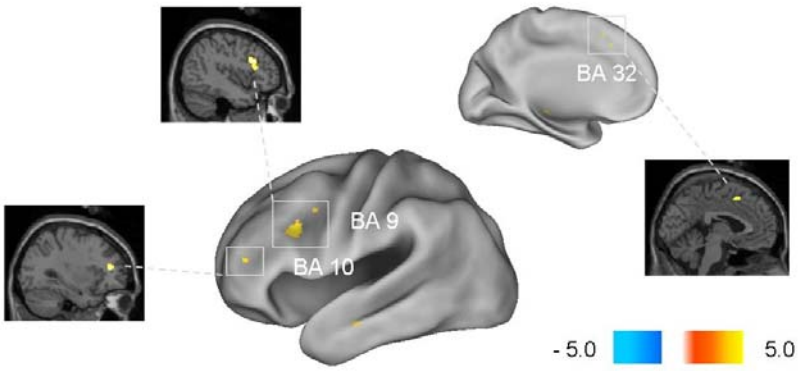

Figure 3.3 *T-maps (p < .001, uncorrected) of the statistical comparison between cuing and rehearsal. Note that this difference is purely based on an instructional effect: Participants were told to use the re-presented words as retrieval cues in the cuing condition, and relearn them in the rehearsal condition.*

Table 3.1 *Peak locations of cuing related activations, statistically contrasted with activation during rehearsal (p < .001, uncorrected).*

	Anatomical Label	x	y	z	BA	T	size
L	Middle Frontal G.	-42	18	28	9	4.82	179
		-42	22	16	9	4.48	
L	Middle Frontal G.	-30	40	14	10	4.55	53
L	Inferior Temporal G.	-58	-12	-20	21	3.97	11
L	Medial Frontal G.	-2	14	50	6	3.81	29
L	Thalamus	-18	-24	8	-	3.98	28
R	Thalamus	16	-18	18	-	4.21	18
R	Globus Pallidus	-24	-14	-4	-	3.98	28

BA = approximate Brodmann Area, L = left hemisphere, R = right hemisphere, B = bilateral; size = number of voxels in a cluster

Sample split. A statistical comparison of cuing related activation in the high forgetting (n = 11) compared to the low forgetting (n = 11) group showed no significant differences in either direction, even with a more liberal threshold of p < .005 (uncorrected).

Figure 3.4 (see also Table 3.2) shows the results of an additional descriptive analysis, in which the sample was median split into participants with high and participants with low part-list cuing impairment. Comparing the cuing condition against a low-level baseline (distracter task) separately for high and low forgetting participants, the high forgetting group showed cuing related activation in the left middle temporal gyrus (BA 21), left middle frontal gyrus (BA 9, BA 10 and 6), right middle frontal gyrus (BA 10 and BA 46), left medial frontal gyrus (BA 8), and in the left inferior parietal lobule (BA 40). The same contrast in the low forgetting group showed only small activation clusters in the left inferior parietal lobe (BA 40), left and right middle frontal gyrus (BA 10 and BA 10), and left middle temporal gyrus (BA 21).

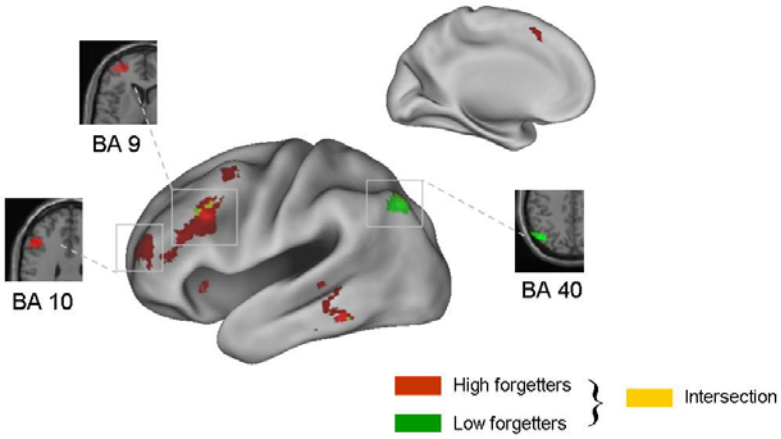

Figure 3.4 *Statistical t-maps (p < .001, uncorrected), showing cuing related activations against a non-memory baseline, displayed separately for participants with high (red) and low (green) levels of part-list cuing impairment. Yellow regions show areas that were significantly activated in both groups.*

Table 3.2 *Peak locations of cuing related activations, compared with a non-memory baseline separately for high and low forgetting subjects (p < .001, uncorrected).*

	Anatomical Label	x	y	z	BA	T	size
	High forgetting (cuing > non-memory)						
L	Middle Temporal G.	-62	-42	-14	21	10.69	127
L	Middle Frontal G.	-44	-20	30	9	9.82	576
L	Middle Frontal G.	-30	56	12	10	9.20	568
L	Middle Frontal G.	-40	10	56	6	5.47	48
R	Middle Frontal G.	28	62	14	10	7.32	24
R	Middle Frontal G.	38	50	18	10	5.47	67
R	Middle Frontal G.	48	30	28	46	5.25	120
L	Medial Frontal G.	-4	18	52	8	5.91	78
L	Inferior Parietal Lobule	-38	-68	48	40	4.48	49
	Low forgetting (cuing > non-memory)						
L	Inferior Parietal Lobule	-46	-68	44	40	7.18	255
L	Middle Frontal G.	-34	62	10	10	5.41	27
R	Middle Frontal G.	32	54	0	10	4.80	22
L	Middle Temporal G.	-52	-36	-14	21	5.41	49

BA = approximate Brodmann Area, L = left hemisphere, R = right hemisphere, B = bilateral; size = number of voxels in a cluster

Discussion

Behaviorally, the part-list cuing manipulation induced a tendency, but no reliable forgetting of the remaining items in a category across all participants. This result is in contrast with a prior study using the same experimental design as employed in the present experiment (Bäuml & Aslan, 2004). One potential cause for this lack of a behavioral difference might be some procedural restrictions associated with the fMRI setting of the present study. For example, participants were given the instructions to either rehearse the items or use them as retrieval cues before they entered the scanner. Although a reminder of the task instruction was presented during scanning prior to each run, some participants may not have been aware of the exact task instructions after the delay.

Despite this lack of a behavioral difference, average activation revealed an instructional effect on the neural correlates of item reprocessing (see Figure 3.3). Cortical differences between cuing and rehearsal were located in lateral (BA 9 and 10) and medial (BA 6) prefrontal cortices, and in the inferior temporal lobe (area 21). The largest cluster showing cuing specific activation was located in left dorsolateral BA 9, and overlapped with retrieval specific activation found in Experiment 1. Figure 3.5 shows the two main contrasts of interest in Experiment 1 and Experiment 3 overlaid onto the same cortical surface.

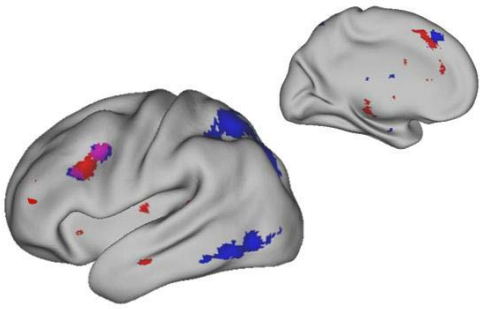

Figure 3.5 *FMRI activations associated with part-list cuing (red) and selective retrieval (blue), both contrasted against the rehearsal baseline. Violet regions show regions where the two contrasts overlapped. For visualization purpose, the contrasts are thresholded on a statistical level of p < .005 (uncorrected).*

Cuing specific frontal activation, like retrieval specific activation, was found in the left posterior DLPFC, a region that has previously been found to specifically activate when past episodes have to be actively reconstructed, as opposed to recognized (Dobbins et al., 2002). Moreover, the posterior DLPFC area close to the left inferior frontal junction has been implicated in the active maintenance of abstract goal-relevant task representations, and in the selection of appropriate responses in the light of conflicting alternatives (Bunge et al., 2002; Derfuss et al., 2004; Zysset et al., 2001). The left medial prefrontal peak found in the contrast between cuing and rehearsal (in pre-supplementary motor area 6) was located more posterior than the one found in the contrast between retrieval and rehearsal (which was located in medial superior area 8). However, there is yet no evidence for

distinctive roles of the two pre-supplementary motor areas 6 and 8 (Ridderinkof, Ullsperger, Crone, & Nieuwenhuis, 2004). Both areas have been implicated in performance monitoring and conflict detection (Ridderinkof et al., 2004), and in the suppression of irrelevant task sets (Crone et al., 2006). It is therefore most likely that the two medial prefrontal activation peaks related to cuing and retrieval are linked to similar conflict related processes.

However, cuing did not cause increased posterior activations to the same extent as they were observed in the contrast between retrieval and rehearsal in Experiment 1. Indeed, no parietal differences between cuing and rehearsal were found, and only a small cluster on the middle temporal gyrus showed more activation in the cuing than the rehearsal condition. Based on findings that link the posterior temporal cortex to semantic retrieval (Badre et al., 2005; Thompson-Schill et al., 1999), and the parietal cortex to episodic retrieval (Wagner et al., 2007), this lack of activation of temporal and parietal activations potentially indicates that cuing did not involve the same degree of spreading activation in areas assumed to store long-term memory representations.

Interestingly, the results of the sample split suggest that strong cuing related activation in the frontal cortex was not present in the complete sample, but only in participants showing later part-list cuing impairment. The mid-dorsolateral, medial and fronto-polar cortices were almost exclusively activated in participants showing a behavioral part-list cuing effect, and frontal engagement was widely absent in participants showing no part-list cuing. Although there was no significant overall part-list cuing effect, the sample split suggests that participants adopted different strategies of processing the items provided as part-list cues. Participants with significant behavioral part-list cuing impairment recruited the left and right prefrontal cortices more extensively than did participants who showed no significant part-list cuing impairment. The pattern of cuing related activations in the high forgetting group resembled the typical pattern of frontal activations associated with controlled retrieval (Buckner, 2003), but not item recognition (Dobbins et al., 2002), and basically mirrored the frontal activation pattern found in the retrieval condition in Experiment 1. The functional similarity between cuing and retrieval in the high forgetting group might indicate that participants who used

the part-list cues as retrieval cues for the subsequent memory test showed not only the strongest behavioral impairment, but also a neural activity pattern similar to the retrieval condition.

Two possible interpretations of this pattern might be considered. First, part-list cuing impairment has traditionally been explained in terms of covert retrieval of the cue items, causing blocking during the recall of the remaining items (Rundus, 1973). Provided covert retrieval caused the impairment in the high forgetting group, the present findings suggest that participants covertly retrieved the cue items not at the time the remaining items had to be recalled (at which no measures of brain activation were obtained), but at the time the cues were presented, causing inhibition of the remaining category exemplars (see Bäuml & Aslan, 2004). Second, the cuing instruction might prompt high forgetting subjects to adopt an active retrieval mode (e.g., Sakai, 2003), as possibly reflected by the prefrontal brain activations found in this group (see Buckner, 2003; Dobbins et al., 2002). Strengthening part of a memory set in a retrieval mode might in turn release the spreading activation of associated memories, triggering their inhibition. Both the modified covert retrieval explanation and the retrieval mode explanation can equally account for the neural parallels found between the high forgetting group in the part-list cuing condition and the retrieval practice condition.

In summary, the imaging findings of Experiment 3 suggest an instructional effect on brain activations related to item reprocessing. The high forgetting group, in which the cuing instruction induced significant forgetting of related items, showed increased neural activity mainly in the left prefrontal cortex, mimicking the retrieval related pattern observed in Experiment 1. Participants that use the items as memory cues might therefore either covertly retrieve the cue items during their presentation, or adopt a retrieval mode as opposed to a learning mode during cue processing.

Part IV:
Directed Forgetting

Experiment 4

Experiment 4 examined the neural correlates of listwise *directed forgetting*. In contrast to retrieval-induced forgetting and part-list cuing, directed forgetting is intentional, that is, participants are given an explicit instruction to forget previously encoded information (e.g., Bjork, 1970, 1989). In list-method directed forgetting, the forget instruction is given after a first list of items has already been encoded, and before a second list of items is being studied. In the control (remember) condition, participants are instructed to remember the first list, and subsequently proceed to encoding the second list. This procedure typically leads to impaired memory performance for the to-be-forgotten items, compared to the remember condition. However, forgetting also entails beneficial effects, because participants tend to show enhanced memory for second list items after an instruction to forget the first list.

One difference between directed forgetting and retrieval-induced forgetting (and possibly part-list cuing) is that directed forgetting occurs in free or cued recall test, but not in recognition tests (e.g., Geiselman & Bagheri, 1985). In other words, the impairment is observed only if participants try to actively access first list items, but not when item specific probes are provided. Advocates of an inhibitory view of directed forgetting have taken this finding as evidence that inhibition in directed forgetting reduces the accessibility of memory traces by deactivating the retrieval route from the cue to an item (Bjork, 1989). Providing participants with the item itself will accordingly cause an immediate release from inhibition (MacLeod, 1998). In contrast, if participants would simply stop rehearsing first list items after an instruction to forget, then the impairment should be observed with any memory test, including recognition tests.

Experiment 4 used a within-subjects design, with functional images acquired from each participant during the encoding of a first and second list of items in the forget *and* the remember condition (for a similar procedure, see Bäuml et al., 2008;

Bäuml & Kuhbahnder, in press; Zellner & Bäuml, 2006). Behavioral evidence suggests that the critical mechanism causing forgetting operates during second list encoding after the instruction to forget, because second list encoding is a necessary condition for directed forgetting to occur (Pastötter & Bäuml, 2007). A prior electrophysiological study employing the same experimental setting as the present experiment found that distinct oscillatory correlates during second list encoding predict directed forgetting and enhancement (Bäuml et al., 2008). Therefore, one hypothesis in the present investigation was that the detrimental and beneficial effects of forget instructions have distinct functional neuroanatomical correlates. Moreover, directed forgetting is similar to think/no-think forgetting in that both forms of episodic forgetting require participants to intentionally suppress some previously encoded memory information. A second hypothesis for Experiment 4 was that directed forgetting is predicted by prefrontal activations similar to those that have been found to predict intentional forgetting in the think/no-think paradigm (Anderson et al., 2004; Depue et al., 2007). Drawing on these fMRI studies, it can be hypothesized that intentional memory inhibition in the directed forgetting paradigm should be associated with hemodynamic responses mainly in right lateralized prefrontal regions, including the anterior cingulate and the dorsolateral prefrontal cortex.

Methods

Participants

Twenty-four right-handed native German speakers took part in the experiment, all being recruited at the University of Regensburg, and paid 10 € for participation. No participant had any known history of neurological or psychiatric disorders. Written informed consent had to be given prior to participation, in accordance with the guidelines of the ethics committee of the University of Regensburg. Two participants were excluded from all further analyses due to strong within-session movement in the functional imaging time series.

Materials

Verbal stimuli were drawn from the CELEX database (www.ru.nl/celex/, MPI for Psycholinguistics, Nijmegen, NL), using the Wordgen software (Duyck, Desmet, Verbeke & Brysbaert, 2004). A total of 96 medium-frequency, concrete German nouns were selected, with word length ranging from four to seven characters. For counterbalancing across participants and conditions, items were grouped into four different sets with 24 items each, matched according to mean frequency and word length. These sets were rotated across participants and conditions, such that each set served equally often as first or second list, and equally often in the forget and remember condition. Order of conditions was counterbalanced across participants.

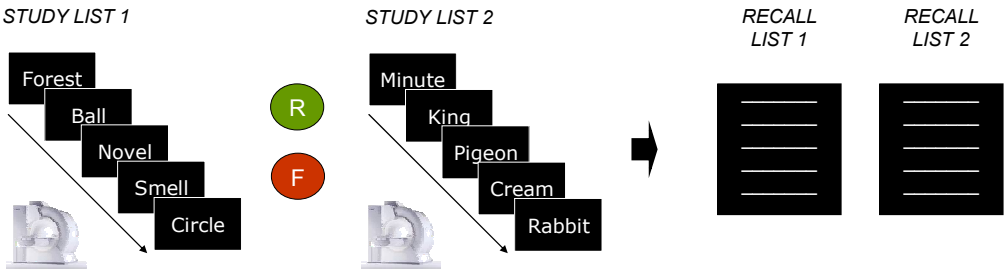

Figure 4.1 *Schematic figure showing the behavioral paradigm of Experiment 4. In the remember condition (R), a cue to remember the first list of items was given before participants studied the second list. In the forget condition (F), participants were asked to forget all previously studied items before they studied the second list. After second list encoding and a short distracter, participants were asked to recall as many items as they were able to remember, with the first list always tested before the second list. Scanning took place during encoding only.*

Behavioral Procedure

The experiment consisted of two within-subjects conditions (Remember and Forget), each condition comprising the encoding of two 24-item lists (List 1 and List 2). Traditionally, the different instructions in list-method DF are realized between subjects, with one group being instructed to forget the first list, and a second group being instructed to remember both lists. However, it has repeatedly been demonstrated that using a within-subjects design produces the usual pattern of first list forgetting and second list enhancement (Bäuml et al., 2008; Bäuml & Kuhbandner, in press; Zellner, & Bäuml, 2006). For imaging purposes, it is

therefore reasonable to rely on within-subjects comparisons to reduce noise that might be introduced by inter-individual variability in functional neuroanatomy.

Before scanning started, participants were informed that their task would be to memorize four word lists overall, but that after each list, a cue would tell them if the just studied words were to remember for the final recall test, or were no longer relevant and could be forgotten. Moreover, they were instructed that a test would occur after the first (condition 1) and the second (condition 2) two word lists. The only difference between the two conditions was the instruction given between the encoding of the first and second list. In the remember condition, participants were asked to remember List 1 before continuing with the encoding of List 2. In the forget condition, participants were asked to forget List 1, and instead encode a second list. The second list was always followed by a 30 sec distracter task (ordering digits in an ascending manner), followed by a free recall test. During encoding, the 24 items of one list were displayed individually and in random order for 2500 msec each, followed by a 1000 msec fixation interval. In addition, 16 fixation trials of 3000 msec length were interspersed to allow better modeling of the hemodynamic response. In the test phase, participants were instructed to reproduce as much of the learned material as they could, and were given 90 sec for the recall of each list. List 1 always had to be recalled before List 2 to control for output interference effects (for similar procedures, see Sahakyan & Delaney, 2003; Zellner & Bäuml, 2006). No scanning took place during the recall phases of the experiment, and oral answers were recorded via the local intercom system.

FMRI Data Acquisition and Statistical Analyses

Data were collected on a Siemens Magenta 1.5 T scanner (Siemens, Erlangen, Germany). Stimuli were back projected centrally onto a screen at the rear of the magnet bore and viewed via a mirror attached to the head coil. Whole-brain functional images were acquired using a T2*-weighted EPI sequence of 32 contiguous axial slices (TR = 3000 msec, TE = 40 msec, flip angle = 90°) sensitive to blood oxygenation level dependent (BOLD) contrast. Images were collected in two scanning runs, each comprising 135 whole-brain acquisitions (32 axial slices

with an in-plane resolution of 3.0 x 3.0 mm). The first three volumes of each session were discarded to allow tissue magnetization to reach a steady state. High-resolution T1-weighted (MP-RAGE) anatomical images were collected from each subject at the end of the experiment. Head motion was restricted by using a pillow and foam inserts, and participants were instructed not to move through the whole scanning session, including the test phases when the scanner was offset and verbal responses had to be given.

Data preprocessing and statistical analyses were performed with the SPM2 software (Wellcome Department of Cognitive Neurology, London, UK: www.fil.ion.ucl.ac.uk/spm/spm2.html; Friston et al., 1995). EPI volumes were slice time corrected, unwarped and spatially realigned to the first image acquired in the first session. Structural and functional images were spatially normalized to the MNI template (Cocosco et al., 1997). Functional images were resampled into 2 x 2 x 2 mm voxels, and smoothed with an 8 mm FWHM isotropic Gaussian kernel. For first level analyses, event-related regressors were formed to model each event of interest by convolving a delta stick function at the onset of an event with the canonical hemodynamic response function. Events of interest were defined at the onset of the presentation of a study item, separately for the conditions 'List 1 forget (F1)', 'List 2 forget (F2)', 'List 1 remember (R1)', 'List 2 remember (R2)'. Events in the 'Distracter task (D)' were modeled as an additional regressor. The only planned comparison was differential BOLD responses to item encoding after a forget instruction compared with item encoding after a remember instruction, that is, the contrast between F2 and R2 events. A statistical parametric t-map of the linear contrast was estimated, with low-frequency signal components (cut-off 128 s) treated as confound.

For second level analyses, first level parameter estimates of the F2 > R2 contrast were tested with a one-sample t-test against the hypothesis of a zero mean difference. For the calculation of brain-behavior correlations, mean activation differences between F2 and R2 (two-tailed) for each subject were entered into a correlation analysis, with first list forgetting and second list enhancement as a regressor, respectively. First list forgetting was calculated as percent difference between first list performance in the remember minus forget condition; second list

enhancement was calculated as percent difference between second list performance in the forget minus remember condition. To calculate correlation coefficients, regions of interest (ROIs) with a radius of 6 mm were built around the voxels showing significant brain-behavior correlations. Mean Eigenvariates of single participants across all voxels enclosed in a ROI were extracted, and correlation coefficients calculated between Eigenvariate values and individual forgetting and enhancement indices, respectively. For the calculation of brain-brain correlations, Eigenvariates of ROIs were extracted using the same basic procedure, and correlation coefficients were calculated between mean activation of two ROIs. Unless otherwise specified, all effects survived a threshold of $p < .001$, uncorrected for multiple comparisons and comprising at least 10 adjacent voxels.

Behaviorally, directed forgetting was calculated as percent difference between free recall performance for first list items in the remember condition minus the forget condition. Likewise, second list enhancement was calculated as percent difference between free recall performance for second list items in the forget condition minus the remember condition. These differences were tested with one-sample, two-tailed t-tests against the hypothesis of zero difference.

Results

Behavioral Results

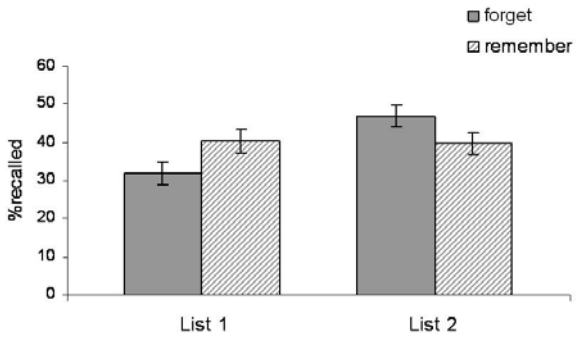

Figure 4.2 *Mean recall performance (with standard deviations of the mean) for fist and second list items after an instruction to forget or to remember the first list.*

Figure 4.2 shows the mean proportions of correct recall across lists and conditions. Significantly less first list items were recalled after an instruction to forget (M = 31.8 %) than to remember (M = 40.2 %), t_{21} = -2.78, $p < .05$. The difference between first list recall in the remember and the forget condition was 8.3 % (SE = 3.0%), demonstrating the typical detrimental effect of a forget instruction. In contrast, more second list items were correctly recalled after an instruction to forget (M = 46.8 %) than to remember (M = 39.8 %), t_{21} = 2.49, $p < .05$, resulting in the typical beneficial effect of forget instructions of 7.0 % (SE = 2.8 %).

Imaging Results

Instruction related activity differences. When contrasting event-related activations associated with item encoding after an instruction to forget (F2) and after an instruction to remember (R2), clusters showing an increased response to item encoding in F2 were located in the right superior frontal gyrus (BA 9), in the right supramarginal gyrus (BA 40), and in the right anterior cingulate gyrus (BA 32). No area showed significantly more activation during R2 than during F2 encoding, even when tested on a lower statistical threshold of $p < .005$ (uncorrected).

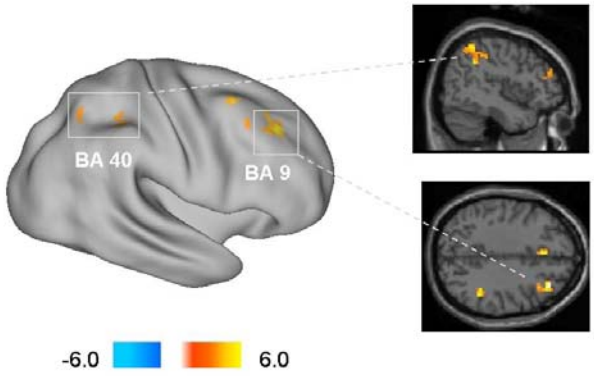

Figure 4.3 *Two-tailed t-maps (p < .001, uncorrected) of brain regions that showed significant activation differences between item encoding after an instruction to remember or to forget a first list of items. Red/yellow areas indicate areas that were significantly more active after a forget compared to a remember instruction. No regions showed significantly more activation after an instruction to remember than to forget the first list. T-maps are overlaid onto a normalized single subject anatomical image (top row), and on a standard flattened cortical surface (PALS-B12 in SPM2 space, bottom).*

Table 4.1 Peak locations showing a significant (p < .001, uncorrected) event-related hemodynamic increase during encoding of second list items in the forget condition compared with the remember condition.

	Anatomical Label	x	y	z	BA	T	size
R	Middle Frontal G.	36	33	36	9	5.43	38
		30	27	33	9	4.67	
R	Supramarginal G.	46	-42	36	40	4.84	18
		45	-48	36	40	3.81	
R	Supramarginal G.	42	-51	54	40	3.79	19
L	Cingulate G.	-2	24	39	32	3.58	12

BA = approximate Brodmann Area; L = left hemisphere, R = right hemisphere, B = bilateral; size = number of voxels in a cluster

Brain-Behavior Correlations. Using individual directed forgetting indices as a predictor of differential activation during second list encoding (F2 versus R2), two regions exhibited a significant positive correlation with forgetting, one located in the right superior prefrontal gyrus (24 28 36, BA 9), the other one in the anterior cingulate (8 46 4, BA 32) (see Figure 4.4). Correlations between ROI activation and forgetting were r = .73 (p = .0001) for the right superior prefrontal peak, and r = .68 (p = .0006) for the anterior cingulate peak. Mean activation in the right superior PFC region and in the ACC correlated with r = .48 (p < .05). No region showed a significant negative correlation with forgetting.

Using the individual degree of List 2 enhancement in the forget condition (versus remember condition) as a regressor for differential activation during second list encoding, no region showed either a positive or a negative correlation with second list enhancement. Moreover, activation in the ROIs predicting first list forgetting (see Fig. 4.4) was uncorrelated with second list enhancement, with r = .004 (p = .86) in the dorsolateral ROI, and r = -.22 (p = .32) in the anterior cingulate ROI.

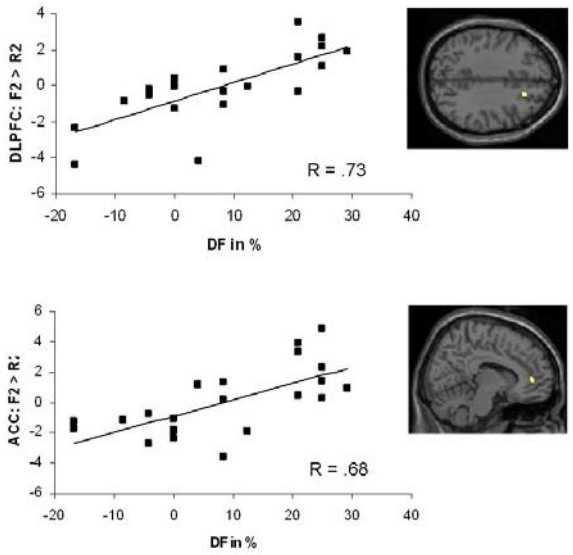

Figure 4.4 *Regions showing a significant (p < .001, uncorrected) correlation with directed forgetting, defined as the difference between first list memory performance in the forget and remember condition, were found in the right superior dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate (ACC).*

Discussion

Experiment 4 replicated the typical behavioral pattern of first list forgetting and second list enhancement, induced by an instruction to forget first list mnemonic information. Participants were showed significant directed forgetting, with reduced memory for first list items in the forget condition compared to the remember condition. At the same time, significant second list enhancement was found, with participants being more successful in recalling information studied after a forget instruction than after a remember instruction.

The imaging data revealed that item encoding in the forget and in the remember condition were associated with differential neural activity during encoding of a second list of items. Activation changes were found in the right superior dorsolateral prefrontal cortex (BA 9), in the anterior cingulate (ACC, BA 32), in the right temporal-parietal junction (BA 39/40), and more superior in the inferior parietal lobe (BA 40). All these areas were more active after a forget than

after a remember instruction, whereas no region was more active after an instruction to remember than to forget.

Posterior activations during second list encoding

Posterior activation differences between second list encoding in the remember and forget condition were located in two circumscribed regions of the right parietal and the temporal-parietal cortex. These regions have previously been linked to attentional, rather than memory specific, processes. Both the right inferior parietal lobe and supramarginal gyrus appear to be critically involved in attentional orienting and cuing tasks (Lepsien & Pollmann, 2002; Mayer, Harrington, Stephen, Adair, & Lee, 2007). Increased activation in these areas could thus indicate enhanced attention to second list items after a cue to forget, with participants narrowing their focus of attention to up-to-date information only. On the other hand, *deactivation* of the temporal-parietal junction has been functionally linked to dynamic filtering of irrelevant information, for example in visual search paradigms (Shulman, Astafeiv, McAvoy, d'Avossa, & Corbetta, 2007). Differential encoding activity in the two conditions might thus be based on a more pronounced posterior decrease during second list processing in the remember condition, rather than an increase of activation in the forget condition. In line with the behavioral finding of second list enhancement, stronger encoding related deactivation might therefore reflect increased proactive interference by currently irrelevant first list items in the remember condition, or reduced proactive interference in the forget condition.

The finding of enhanced attentional processing after an instruction to forget is consistent with the results of two recent EEG studies on directed forgetting (Bäuml et al., 2008) and context-dependent forgetting (Pastötter et al., in press). The findings of both studies demonstrated that second list enhancement is related to power changes in the alpha frequency band, suggesting that attentional resources during second list encoding might determine better subsequent memory for second list items.

Higher prefrontal involvement after an instruction to forget

Two prefrontal regions – the anterior cingulate and the right dorsolateral prefrontal cortex – showed increased activation during second list encoding after an instruction to forget. The finding that the anterior cingulate is more active after a forget cue is consistent with the well established hypothesis that the ACC responds to the occurrence of conflict (Botvinick et al., 2004; Mac Donald, Cohen, Stenger, & Carter, 2004). This assumption is based on a large body of evidence showing that the ACC plays a critical evaluative role in overriding prepotent responses, like in Stroop, Eriksen flanker, and Go/NoGo tasks (Botvinick et al., 2004). Moreover, the ACC is active in tasks that require the active generation of a verbal response in the context of conflicting verbal information (Palmer, Rosen, Ojemann, Buckner, Kelley, & Petersen, 2001; Thompson-Schill et al., 1997). In the present directed forgetting task, the ACC might thus serve the detection of no longer goal-relevant, to-be-forgotten information in memory, and signal the need for additional control to right dorsolateral prefrontal regions, as suggested by the correlation between ACC and right DLPFC activity in the present experiment. The right DLPFC has been assigned a major role in implementing conflict resolution. For example, the right DLPFC has been found to predict participants' ability to efficiently resolve interference in a Sternberg working memory paradigm (Bunge et al., 2001). In long-term associative retrieval, it has been linked to the retrieval of weak target memories (Bunge, Burrows, & Wagner, 2004). Moreover, right superior prefrontal areas have been found to support both visual and memory search in a single experiment (Makino, Yokosawa, Takeda, & Kumada, 2004), suggesting a central role in cognitive control over interfering environmental and mental representations.

Closely related to the present task, the right DLPFC has been implicated in the suppression of interfering memories in the think/no-think paradigm (Anderson et al., 2004), and in retrieval-induced forgetting (Kuhl et al., 2007). With respect to the present findings, the ACC might be central for detecting conflict by interfering, no longer relevant first list memories. Right DLPFC activation might in turn be recruited to actively resolve this conflict by suppressing the out-of-date information, favoring efficient processing of the relevant information. Importantly,

differential activity in both the anterior cingulate and the dorsolateral prefrontal cortex during second list encoding was significantly correlated, and predicted first list forgetting across participants. This finding strengthens the assumption that an interaction of these prefrontal regions is central for the mechanism causing directed forgetting.

Implications for a potential inhibitory mechanism

As pointed out above, the inhibitory account of directed forgetting puts forward that forgetting, in this paradigm, is the result of an inhibitory mechanism operating during second list encoding, suppressing interfering information from no longer relevant first list items (Bjork, 1989). The two main alternative accounts that exist to date explain the behavioral pattern by participants either stopping rehearsal of first list items after the forget cue (MacLeod et al., 2003), or by participants initiating a mental context change after presentation of the forget cue (Sahakyan & Kelley, 2002). The results of Experiment 4 are well in line with the inhibitory account of directed forgetting. First, the forget instruction caused an increase in neural activation in areas that have previously been related to the detection, filtering and suppression of irrelevant information (Anderson et al., 2004; Bunge et al., 2001; Shulman et al., 2007). Stopping rehearsal, by contrast, should lead to decreased demands on prefrontal conflict monitoring and resolution mechanisms, which is incompatible with the present results. On the other hand, if the behavioral pattern of directed forgetting would be attributable to an internal context change, forgetting should be due to a lack of overlap between the study and the retrieval context. Consequently, the critical mechanism causing forgetting is not likely to be found during second list encoding, but during the final recall of the now out-of context information. This assumption is strengthened by a recent EEG study (Pastötter et al., in press), demonstrating that first list forgetting cannot be predicted by neural changes during second list encoding in a context change paradigm. Therefore, although no scanning took place during final recall in the present study, the finding that neural responses during second list encoding predict first list forgetting is compatible with an inhibitory account of directed forgetting.

In line with this interpretation, prior behavioral work shows that encoding a second list is necessary for directed forgetting to occur (Pastötter & Bäuml, 2007).

The present fMRI findings suggest that inhibition in directed forgetting is mediated by an interaction of right dorsolateral prefrontal and anterior cingulate cortex. Inhibition might cause an unbinding of first list items from the second list context, as postulated by advocates of the inhibitory view (Bäuml, 2008; Bäuml et al, 2008; see also Anderson, 2004; Bjork, 1989). A prior EEG study found evidence for such unbinding, showing that reduced alpha phase coupling during second list encoding predicted later first list forgetting. In contrast to this electrophysiological investigation (Bäuml et al., 2008), no evidence for a neural correlate of second list enhancement could be obtained in the present experiment. However, activation in the prefrontal regions predicting directed forgetting was uncorrelated with second list enhancement, supporting the conclusion, drawn from the above EEG findings (Bäuml et al., 2008), that first list forgetting and second list enhancement are mediated by separate cognitive and neural processes. Taken together, the results of Experiment 4 support an inhibitory account of directed forgetting, suggesting that increased demands on neural interference resolution processes reflect the mechanisms involved in the inhibition of out-of-date mnemonic information.

Part V:
General Discussion

Neural Correlates of Memory Inhibition

Facilitation and inhibition are seen as central components in the efficient use of memory, but there is as yet little agreement about the involvement and nature of inhibitory processes in causing forgetting. Based on the behavioral literature, it is still a matter of debate if and to what extent particular types of forgetting depend on common cognitive processes (Bäuml, 2008). The experiments reported here were aimed at shedding light on the neural substrates of retrieval-induced forgetting, part-list cuing impairment, and directed forgetting. Except in Experiment 2, functional imaging data in all experiments were acquired at the time inhibitory mechanisms are assumed to operate, aimed at providing direct evidence for inhibitory involvement on a neural level.

The inhibitory account of *retrieval-induced forgetting* assumes that selective retrieval involves retrieval competition between simultaneously active memory representations, and therefore triggers inhibitory processes that deactivate related, competing items (Anderson, 2003). By contrast, mere rehearsal of some items should not lead to a coactivation of competing items, and should therefore not trigger inhibitory processes. Retrieval specific forgetting is predicted by the inhibitory account, but not by strength dependent accounts (Williams & Zacks, 2001). In *Experiment 1*, retrieval and rehearsal were directly compared, and scanning took place during the critical retrieval practice phases, at the time inhibition is assumed to weaken competing memories. Consistent with prior behavioral findings (Anderson et al., 2002; Bäuml & Aslan, 2004), retrieval specific impairment was observed, with more forgetting occurring for related items in the retrieval than in the rehearsal condition. This pattern emerged despite the fact that both conditions involved a substantial degree of selective strengthening of some category members. The behavioral findings from Experiment 1 are thus incompatible with strength-dependent accounts (e.g., Mensink & Raaijmakers,

1988; Williams & Zacks, 2001), and speak in favor of an inhibitory account of retrieval-induced forgetting.

Retrieval specific brain activations in Experiment 1 were found in prefrontal, posterior temporal, inferior parietal and hippocampal areas, suggesting a central role of these regions in the active reconstruction of long-term memories (Badre et al., 2005; Eichenbaum et al., 1999; Squire, 1992; Thompson-Schill et al., 1999; Wagner et al., 2007; Zola-Morgan & Squire, 1993). However, a correlation with retrieval-induced forgetting was found predominantly in the prefrontal cortex, more particularly in the anterior cingulate, supplementary motor cortex and left inferior frontal junction, regions implicated in the monitoring of conflict related information (Botvinick et al., 2004; Mac Donald et al., 2004), and in the maintenance of goal-relevant representations in the light of conflict (Bunge et al., 2002; Derfuss et al., 2004; Zysset et al., 2001). The most puzzling finding from Experiment 1 was the negative direction of the brain-behavior correlations between forgetting and prefrontal activation. This finding speaks in favor of the supposed role of these prefrontal regions in monitoring and resolving competition, but does not necessarily implicate these areas in inhibitory functioning itself. Possible interpretations of the role of medial and left lateral prefrontal cortex in conflict processing and resolution are discussed in more detail below (see section on "Neural Mechanism of Retrieval-Induced Forgetting").

Whereas Experiment 1 investigated neural processes during retrieval practice, *Experiment 2* examined the neural correlates of retrieval-induced forgetting and enhancement during the final recall test. The imaging results showed that forgetting and enhancement have distinct neural substrates. This finding cannot easily be accounted for by strength-dependent theories of retrieval-induced forgetting (Williams & Zacks, 2001), because these theories assume that forgetting is merely a consequence of the enhanced memory performance for retrieval practiced items. The results of Experiment 2 demonstrated that retrieval-induced enhancement is correlated with activity in medial and lateral parietal regions, areas that have been linked to the subjective experience of recollecting prior episodes (Wagner et al., 2007). This finding might indicate facilitated conscious access to previously practiced items. Forgetting, by contrast, was associated with increased activation of

the left anterior ventrolateral prefrontal cortex and the left posterior temporal cortex, regions that are implicated in the strategic retrieval of weak semantic memory representations (Badre & Wagner, 2007; Gold et al., 2006). In line with prior behavioral evidence (Bäuml, Zellner, & Vilimek, 2005; Spitzer & Bäuml, 2007), these findings suggest that inhibition in retrieval-induced forgetting deactivates the memory representations of competing items themselves. Therefore, the results of Experiment 2 support the hypothesis that retrieval-induced forgetting is caused by an inhibitory process that weakens the (semantic) memory representations of competitors on an item level, lowering their availability on later retrieval attempts.

Experiment 3 was based on the hypothesis that, at least in certain encoding situation, *part-list cuing* is caused by the same mechanism as retrieval-induced forgetting (Bäuml & Aslan, 2004; Bäuml & Aslan, 2006; Aslan & Bäuml, 2007). The part-list cuing manipulation was realized in the same experimental session as the retrieval and rehearsal conditions reported in Experiment 1, allowing a direct comparison between the three experimental conditions. Part-list cuing differed from mere rehearsal in prefrontal regions that overlapped with retrieval related activations (Experiment 1), suggesting parallels between retrieval and cuing scenarios. In contrast to prefrontal regions, the hippocampus and several posterior association areas, which showed retrieval related responses in Experiment 1, did not significantly differ between item processing in the cuing and the rehearsal condition. This lack of a difference may be explained by the fact that item specific cues were provided in both the cuing and the rehearsal condition, and that both conditions did thus not require participants to actively reconstruct past episodes. Importantly, a sample split suggested that participants with a high level of part-list cuing impairment engaged retrieval related left prefrontal regions, whereas participants with a low level of part-list cuing impairment did not engage these regions, or to a much lesser extent. This pattern, although based on a qualitative observation, is in line with the assumption that part-list cuing impairment, dependent on how participants process the items provided as cues, is caused by covert retrieval of the part-list cues (Bäuml & Aslan, 2004). Alternatively, depending on instruction, participants may adopt a retrieval mode (Sakai, 2003), as

opposed to a learning mode, during the presentation of the cue items. Supported by prefrontal gating processes (e.g., Buckner, 2003; Miller & Cohen, 2001), cue presentation in a retrieval mode might lead to the weakening of related memories.

Experiment 4 examined the neural correlates of intentional forgetting, using a list-method *directed forgetting* paradigm. Functional images were acquired during second list encoding after an instruction to either forget or remember a first study list. Prior behavioral work shows that the encoding of a second list is critical for causing directed forgetting (Pastötter & Bäuml, 2007), suggesting that the mechanism implicated in directed forgetting operates during second list encoding. This assumption has been strengthened by recent EEG work (Bäuml et al., 2008), demonstrating that neural processes during second list encoding determine the degree to which participants forget first list items. Behaviorally, Experiment 4 revealed the typical pattern of first list impairment and second list enhancement after an instruction to forget. Neurally, second list encoding in the forget condition, compared to the remember condition, was associated with increased activation of the right temporal-parietal junction, right superior dorsolateral prefrontal cortex, and left anterior cingulate cortex. Deactivation of the right temporal-parietal junction has been associated with attentional filtering of distracting information (Shulman et al., 2007), and might thus indicate reduced demands on attentional filtering in the forget condition, possibly due to decreased proactive interference by first list item intrusions. Both the right DLPFC and the ACC showed a strong positive correlation with first list forgetting, but not with second list enhancement. The right DLPFC has previously been implicated in the control of unwanted memory intrusions (Anderson et al., 2004), and seems to play a crucial role in motor inhibition tasks (Garavan et al., 2002). The finding that this area predicts intentional forgetting in a list-method directed forgetting paradigm supports the view that intentional forgetting engages unique prefrontal areas, and suggests functional parallels between intentional memory control and the control of dominant motor responses (see Levy & Anderson, 2002). As the right DLPFC showed no relation to retrieval-induced forgetting and part-list cuing, it might be suspected that intentional forgetting is based on neural circuits that are distinct from the ones involved in unintentional forgetting, as discussed in the next section.

Neural Mechanism of Retrieval-Induced Forgetting

As outlined in the introduction, retrieval-induced forgetting is a very robust finding, and it is broadly agreed that it is caused by an inhibitory mechanism (Anderson, 2003; Bäuml, 2008; but see Williams & Zacks, 2001). Forgetting is observed independently of the way participants try to access the impaired items, suggesting that these memories are not only temporarily inaccessible, but intrinsically weakened. Consistent with this view, retrieval-induced forgetting has been observed in tests using item recognition (Spitzer & Bäuml, 2007; Verde, 2002), independent cues (Anderson & Spellman, 2005; Bäuml et al., 2007), and in implicit memory tests (Levy et al., 2007; Veling & Van Knippenberg, 2004). Evidence that retrieval-induced forgetting is associated with reduced item familiarity, not recollection, supports the hypothesis that inhibition reduces the representational strength of competing memories (Spitzer & Bäuml, 2007). The findings of Experiment 2 underpin this assumption, showing that retrieval-induced forgetting during final recall is predicted by activation in areas implicated in the retrieval of weakly represented memories (Badre & Wagner, 2007; Gold et al., 2006). This finding is also in line with a recent investigation of retrieval-induced forgetting using response latency modeling (Bäuml, Zellner & Vilimek, 2005). In this study, it could be shown that retrieval-induced impairment is due to a specific reduction in memory strength, a finding that mirrors the results from studies manipulating item strength by either exposure duration during study, or repeated study trials (Rohrer, 1996; Wixted et al., 1997). The final recall data from Experiment 2 provide first evidence that the neural process underlying retrieval-induced forgetting is distinct from enhancement related processes, and might affect the semantic strength of an item. This data pattern is highly consistent with a recent EEG study on retrieval-induced forgetting (Spitzer et al., in press), in which an early frontal effect was associated with retrieval-induced forgetting, and a late

parietal effect with retrieval-induced enhancement. Consistent with this finding, the present results support the view that retrieval-induced forgetting is caused by an inhibitory mechanism that affects the intrinsic state of a memory representation, rendering it – at least temporarily – less available.

Levy and Anderson (2002) discuss two different theoretical mechanisms – direct suppression and lateral inhibition – that might cause retrieval-induced forgetting. Both models have previously been used to describe the mechanisms underlying inhibitory attentional control and motor control, but can theoretically be extended to memory inhibition. *Direct suppression* models conceptualize inhibition as an executive control function that can be flexibly directed towards unwanted or interfering memories. According to these models, conflicting information in memory is monitored during acts of selective retrieval. If retrieval competition is detected, inhibitory executive functions are recruited to overcome this competition, directly suppressing irrelevant items in working memory. Although Levy and Anderson (2002) favor the view that both retrieval-induced forgetting and think/no-think impairment are caused by direct suppression, the data of Experiment 1 did not provide evidence for (presumably right DLPFC or VLPFC, see Anderson et al., 2004) executive prefrontal mechanisms that are positively related to forgetting.

The present findings might thus be more compatible with a *lateral inhibition* view of retrieval-induced forgetting, regarding the inhibition of related items as an automatic process that is the consequence of retrieving related information within a mnemonic network. However, as explained in more detail below, a pure lateral inhibition view is challenged by evidence for distinct mechanisms underlying retrieval-induced forgetting and enhancement, as found in Experiment 2 and prior studies (e.g., Shivde & Anderson, Bäuml & Aslan, 2004; Spitzer et al., in press). According to the lateral inhibition view, competition during retrieval can be resolved automatically by inhibitory connections between interfering memory representations in posterior networks (Miller & Cohen, 2001). For example, Desimone and Duncan (1995) propose a model of how the prefrontal cortex might implement competition resolution in visual selective attention. They suggest that different neural pathways originating in the visual sensory cortex represent separate streams of information, e.g. different aspects of a visual scene. Competition

between pathways occurs through the existence of mutually inhibitory interneurons, and the neurons with the highest activation level generally win the competition over interconnected neurons.

Top-down influence on such a network can be exerted by prefrontal neurons that code abstract representations of the relevant features of the current attentional set. Recent computational simulations (e.g., Braver & Cohen, 2000) demonstrated that such representations can theoretically be acquired in a self-organizing manner via reinforcement learning, without having to assume a "homunculus" that decides between relevant and irrelevant input and output. The prefrontal cortex can modulate the sensitivity of neurons processing the goal-relevant information, improving the quality of information that enters working memory (Miller & Cohen, 2001; Miller & D'Esposito, 2005). Attention to certain stimulus features increases the sensitivity of neurons processing those features, and often decreases the sensitivity of neurons processing irrelevant features simultaneously (Reynolds & Desimone, 2003). Interestingly, attention related increases in neural responsiveness occur primarily if the target information is highly similar to the distracting information, and is less pronounced if target and distracting information are very distinct (Boudreau et al., 2006).

Similar models for the modulatory role of the PFC can theoretically be applied to memory retrieval, where attention is not directed towards external stimuli, like in visual search, but towards internal memory representations (see Makino et al., 2004). Acts of selective retrieval might activate competing information streams in a semantic or an episodic representational network, presumably stored in posterior association areas. Attention to the cued features of a memory trace, by top-down influence of prefrontal regions, may then bias retrieval by strengthening streams that carry relevant mnemonic information, which in turn deactivates interrelated, irrelevant information streams. Attentional biasing of information processing may be most pronounced if competing memories are highly similar to the target memory (see Boudreau et al., 2006), that is, for memories that potentially compete during retrieval (Anderson et al., 1994).

Norman and colleagues (Norman, Newman, & Detre, 2007) developed and tested a neural network model that can explain many of the behavioral findings related to retrieval-induced forgetting, including retrieval specificity, cue independency and competition dependency. The algorithm they use is based on theta oscillations, suggesting a potential brain correlate of retrieval-induced forgetting that has indeed been associated with human learning mechanisms in the hippocampus and the cortex (Sederberg, Kahana, Howard, Donnald, & Madsen, 2003). Inhibition, in their model, is implemented as a k-winner-take-all rule, which might mimic the action of inhibitory interneurons in posterior brain regions. The prefrontal cortex, albeit being critically involved during retrieval practice, does not directly inhibit irrelevant items, but biases competition in favor of the to-be-retrieved items. Weakening of competitors, according to Norman and colleagues (2007), is mediated via inhibitory interneurons in representational networks, and is therefore only indirectly caused by PFC intervention, assuming no direct inhibitory connections between the prefrontal cortex and posterior storage networks.

A major challenge for the lateral inhibition account and the Norman et al. (2006) model is the finding that enhancement and forgetting appear to be behaviorally and neurally independent, as supported by the results of both Experiment 1 and 2. Lateral inhibition implicates that enhancement and forgetting are "two sides of the same coin", that is, that successful inhibition is regarded as the result of strengthening the relevant memories. To fully account for the independence of retrieval-induced forgetting and enhancement, one would have to modify the pure lateral inhibition view, considering that more than one process may be involved in causing the typical outcome of retrieval practice. For example, in line with prior theorization (Miller & Cohen, 2001; Norman et al., 2006), the prefrontal cortex may indeed represent the current task set, as defined by the retrieval cue. In an early processing step, the category cue might release the spreading activation within the cued memory set that is represented in posterior association areas. More specific cues (e.g., word stems) might limit spreading activation, guiding the amplification of relevant features, and inhibition of irrelevant features within the network. Early lateral inhibition may cause item specific impairment during retrieval practice, with inhibition acting on the level of

single item representations in posterior memory networks. As a consequence of this early processing, only information exceeding a certain threshold might enter working memory (Miller & Cohen, 2001; Miller & D'Esposito, 2005). In a later processing step, as implemented in many neural models of controlled retrieval (e.g., Buckner, 2003; Badre & Wagner, 2007), post-retrieval mechanisms in the medial and lateral PFC might then be engaged to evaluate the retrieved contents within working memory. Provided there is still competition within working memory, additional post-retrieval selection mechanisms, presumably subserved by left posterior PFC (Badre & Wagner, 2007), may be recruited to strengthen the target memory. Information that is amplified to a degree that it enters working memory might experience an increase in contextual strength, as possibly reflected by increased recollection-related activation in parietal cortex (see Experiment 2, and Spitzer et al., in press).

This extended lateral inhibition view is compatible with the results of Experiment 1, suggesting that "high inhibitors" show a more fine-tuned cortical response, whereas "low inhibitors" recruit additional left posterior PFC areas. Early inhibition in posterior networks can explain the decrease in general memory strength found for inhibited items (Spitzer & Bäuml, 2007), consistent with an item specific impairment that is retrieval specific, cue independent and competition dependent (see Norman et al., 2007). Moreover, the assumption that automatic inhibition acts on the level of single item representations is strongly supported by the results of Experiment 2, showing that inhibited items during the final memory test neurally "behave" like weakly represented semantic memories that are less available (Badre & Wagner, 2007; Gold et al., 2006). The behavioral and neural effects of retrieval-induced enhancement, by contrast, may be best explained in terms of prefrontal processes that lead to the conscious recall of practiced items, causing a subsequent increase in item accessibility. Empirical evidence for this modified lateral inhibition account could be obtained from studies using electrophysiological measures with high temporal resolution, which might be able to differentiate between early and late neural processes during retrieval practice.

In summary, neither the executive inhibition view, nor the lateral inhibition view can fully account for the results of Experiments 1 and 2. The prefrontal cortex

appears to play a central role for controlled retrieval and retrieval-induced forgetting, and is anatomically predisposed to represent the current task set, bias activation in posterior association areas, and support controlled retrieval and post-retrieval selection processes (Badre & Wagner, 2007; Miller & Cohen, 2001). In line with an executive inhibitory view, the findings of Experiment 1 might reflect reduced demands on executive control in participants who are capable of resolving interference early during retrieval practice. Alternatively, a modified lateral inhibition view, taking into account the role of prefrontal areas in post-retrieval selection, could explain the current findings from Experiments 1 and 2, including the distinct neural correlates of retrieval-induced forgetting and enhancement.

Single or Multiple Inhibitory Mechanism(s)?

Assuming that the prefrontal cortex is centrally involved in retrieval-induced forgetting, the critical question arises to what extent similar prefrontal mechanisms are involved in other forms of episodic forgetting that have been associated with inhibition. Experiment 3 yielded first neural evidence that part-list cuing impairment may be based on the same neural processes as retrieval-induced forgetting, a hypothesis that has so far been based purely on behavioral parallels between experimental manipulations (Bäuml, 2008; Bäuml & Aslan, 2004). In Experiment 3, the group of participants that behaviorally showed a detrimental effect of part-list cuing also showed a cuing related pattern of frontal brain activation that was similar to the pattern typically found in controlled retrieval tasks. This finding suggests that the occurrence of part-list cuing impairment depends critically on the way participants process the cue items. Participants might either adopt a (neural) retrieval mode during cue processing (see Sakai, 2003), or covertly retrieve the cue items (Bäuml & Aslan, 2004), causing retrieval-induced forgetting as a "side-effect" in both cases. Although the present results support this interpretation, they provide no final and conclusive evidence, because there was no overall significant behavioral effect of part-list cuing in the present sample. Future investigations may use a more powerful imaging design in which part-list cuing, retrieval and rehearsal are realized in the same scanning session. Further, a larger sample size may give enough power for a statistical comparison between cuing related brain activations in high and low forgetting participants. Alternative accounts of part-list cuing, like strategy disruption (Basden & Basden, 1995; Basden, Basden, & Galloway, 1977), cannot specifically be tested based on the present data, but appear unlikely with the encoding instructions used in Experiment 3, because recent findings suggest that strategy disruption only plays a major role for part-list cuing impairment if participants use encoding strategies that favor

serial representations between items (Bäuml & Aslan, 2006; Aslan & Bäuml, 2007). Therefore, future imaging studies of part-list cuing may include strategy manipulations to test the hypothesis that the impairment is caused by distinct mechanism depending on encoding strategy. Nevertheless, the present findings provide first evidence that part-list cuing and retrieval-induced forgetting might, under certain circumstances, share a common neural mechanism.

Inhibitory processes have also been implicated in causing directed forgetting (e.g., Bjork, 1989). However, there are conflicting views on whether intentional forgetting is caused by the same underlying process as unintentional forgetting. Anderson and colleagues put forward that retrieval-induced forgetting, directed forgetting and think/no-think forgetting are based on a single executive process that is actively recruited to suppress interfering or unwanted information (Anderson, 2005; Levy & Anderson, 2002). According to their view, these different ways to induce forgetting in episodic memory differ only in terms of the level on which the inhibitory control process affects a memory trace. Anderson (2005) argues that inhibition in retrieval-induced forgetting (and think/no-think forgetting) deactivates single competing items, whereas in directed forgetting, the inhibitory process suppresses the whole encoding context of the to-be-forgotten information, which may serve as a superordinate cue during the free recall of single items.

The results of Experiments 1 and 4 challenge this unifying view, suggesting that retrieval-induced forgetting and directed forgetting are based on different neural processes. The regions related to retrieval-induced forgetting were mainly left lateralized, and were negatively correlated with forgetting, suggesting a non-causal involvement in later memory impairment. By contrast, a positive correlation between directed forgetting and right lateralized prefrontal areas was found, suggesting a more direct role of these regions in the conscious control of memory. Differential involvement of prefrontal areas in retrieval-induced forgetting and directed forgetting is supported by clinical evidence. Conway and Fthenaki (2003) investigated neuropsychological patients with brain damage to either their frontal or temporal lobes. They found that frontal lobe patients showed intact retrieval-induced forgetting, but attenuated directed forgetting. By contrast, patients with temporal lobe lesions showed intact directed forgetting, but attenuated retrieval-

induced forgetting. The authors argue that the two forms of forgetting differ in the extent to which executive control processes are involved in producing the impairment, which is in line with the present imaging data on directed forgetting.

Finally, studies investigating episodic forgetting across the lifespan support the view that retrieval-induced forgetting and part-list cuing, but not directed forgetting, share a common neural mechanism. Retrieval-induced forgetting and part-list cuing seem to develop early during childhood (Ford, Keating, & Patel, 2004; Zellner & Bäuml, 2005), and remain stable up to a high age (Aslan, Bäuml, & Pastötter, 2007; Marsh, Dolan, Balota, & Roediger, 2004). In contrast, young children do not show robust directed forgetting (Harnishfeger & Pope, 1996), whereas older adults reliably show the typical directed forgetting pattern (Sego, Golding, & Gottlob, 2006; Zellner & Bäuml, 2006). The failure to find intact directed forgetting in young school children is consistent with the inefficient inhibition hypothesis, putting forward that the ability to intentionally suppress the activation of task-irrelevant information develops across childhood (Harnisfeger & Bjorklund, 1993), and might parallel imaging findings showing that children do not recruit right-lateralized, inhibition-relevant brain regions to the same extent as adults (Bunge & Wright, 2007). Together, these studies support the conclusion, drawn from the present experiments, that intentional and unintentional forgetting engage different prefrontal processes. However, it has to be kept in mind that unlike the part-list cuing manipulation in Experiment 2, directed forgetting was realized in a different experiment than retrieval-induced forgetting, limiting the direct comparability of the imaging findings.

Whereas unintentional and intentional forgetting may not rely on a single critical neural mechanism, the results of Experiment 4 are in line with the assumption that different forms of *intentional* forgetting share a common neural basis. Notably, the critical areas showing a positive correlation with directed forgetting – the anterior cingulate and the right DLPFC – have been associated with the inhibition of unwanted memories in the Think/No-Think paradigm (Anderson et al., 2004). The finding that the same regions showed a strong positive correlation with intentional forgetting in list-method directed forgetting suggests that different forms of intentional forgetting might share common neural substrates,

speaking in favor of a causal involvement of medial and right prefrontal areas in memory inhibition.

It is, however, not possible to determine the exact nature of the mechanism that causes directed forgetting based on the imaging results of Experiment 4. As outlined above, it has recently been suggested that inhibition in directed forgetting deactivates the encoding context of to-be-forgotten items, making it more difficult to access information via the list cue (Anderson, 2004). In the early behavioral literature, somewhat similar, is has been hypothesized that directed forgetting is caused by suppression of the association between cues and associated memory traces (Bjork, 1989). Regarding the list context as an intrinsic feature of a memory trace, both associative unlearning and list context suppression might lead to the same prediction that participants are impaired in accessing first list items because the list context is changed after encoding a second list of items, and the original contextual cues are inhibited. This assumption is in line with the finding that second list encoding is necessary for directed forgetting to occur (Pastötter & Bäuml, 2007). A recent EEG study on list-method directed forgetting revealed a potential neural mechanism for the unbinding of items from their list context, showing that reduced phase coupling in the alpha frequency band predicts first list forgetting (Bäuml et al., 2008). Moreover, decoupling of items from the list context can explain why directed forgetting does typically not occur in tests using item specific probes, like in item recognition (Basden et al., 1993; Geiselman et al., 1983a; Golding & Gottlob, 2006), the assumption being that the list context, which constitutes a retrieval route to first list items, is inhibited after an instruction to forget, but that the items themselves remain available from memory. In line with this view, the results of studies investigating directed forgetting with source memory judgments indicate that directed forgetting is caused by impaired recollection-based remembering (Geiselman et al., 1983b; Gottlob & Golding, 2007). These findings suggest that a forget instruction reduces the accessibility, but not the general availability of first list items.

In summary, the imaging results of Experiment 4 indicate similarities between directed forgetting and other intentional forms of memory suppression (Anderson et al, 2004). Although the present data do not provide further insights into the

nature of the mechanism causing directed forgetting, behavioral and electrophysiological studies suggest that a decoupling of items from contextual cues underlies directed forgetting (see Bäuml, 2008). Provided directed forgetting and think/no-think impairment are indeed caused by a single mechanism, future studies should focus on parallels between different forms of intentional forgetting, investigating whether route deactivation may, for example, underlie the impairment found with think/no-think instructions.

Future Directions

Interference and Memory Inhibition

Inhibition is argued to attenuate interference in cognitive and neural systems, and competition can thus be regarded as the prerequisite for inhibition to occur (see Anderson, 2003). From a neural perspective, it has, however, not yet been investigated how the level of memory interference affects activation in neural systems that are thought to subserve inhibitory functions. For example, interference can be manipulated by varying the number or strength of competing items. Moreover, behavioral studies have isolated some boundary conditions that limit the occurrence of inhibition on a cognitive level. For example, retrieval-induced forgetting is reduced or eliminated if the nonpracticed items in a category are weak associates to the category cue with a reduced potential to interfere during retrieval practice (Anderson et al., 1994). Retrieval-induced forgetting can also be attenuated if practiced and unpracticed items are highly integrated, although a certain degree of similarity between the practiced and the nonpracticed items is necessary to elicit competition (Anderson et al., 2000). This finding has been explained in terms of feature integration, the assumption being that practiced features of items are strengthened, such that competitors that share many features with the practiced items are strengthened rather than inhibited (see Anderson, 2003). As a third example, mood has been shown to differentially affect retrieval-induced forgetting and directed forgetting. Directed forgetting can disappear in positive mood, consistent with the assumption that positive mood favors associative processing, and thus the reactivation of first list items (Bäuml & Kuhbandner, in press). Retrieval-induced forgetting, by contrast, is attenuated in negative mood, consistent with the assumption that non-associative, item-specific processing in negative mood reduces competition, and therefore inhibition (Bäuml & Kuhbandner, 2007). Among others, these manipulations are known to affect the

level of competition during mnemonic processing, and would thus offer ideal starting points to investigate the role of competition in inhibition.

Semantic Influences on Episodic Memory

All experiments reported in the present thesis used semantically meaningful verbal stimuli. Neural effects related to forgetting in the three different experimental manipulations employed here were, as expected using verbal material, mainly left lateralized. In Experiment 2, the strongest inhibition specific effects were found in areas that have previously been implicated in control processes in semantic memory, for example, in accessing semantically weakly represented memories (Badre & Wagner, 2007). However, behavioral work provides strong evidence that retrieval-induced forgetting is not restricted to the use of semantic categories, but also occurs when items are grouped according to episodic categories like perceptual features (Ciranni & Shimamura, 1999). Moreover, there is some neural evidence that similar left prefrontal areas are implicated in episodic memory tasks that involve high competition and selection demands (Dobbins & Wagner, 2005; Henson et al., 2002; Sohn et al., 2003). Future research might investigate whether the neural pattern observed in Experiment 2 generalizes to settings in which interference is purely episodic in nature.

The Role of Repetition Priming in Retrieval-Induced Forgetting

An unexpected finding that emerged from Experiment 2 was the strong neural effect of repetition priming on the final recall of both practiced and inhibited items, likely caused by repetition of the categories during practice. Based on the neuroimaging data, one would expect enhanced recall for both item types, because conceptual priming is typically associated with better memory performance (Henson & Rugg, 2003). Experiment 2 used an explicit free recall test, and therefore, no strong claim about the involvement of priming on the cognitive level can be made based on this study. However, there is behavioral evidence that inhibition in retrieval-induced forgetting affects indirect memory measures (Veling & Van Knippenberg, 2004). In combination with the data from Experiment 2, it

could be concluded that inhibition overcomes or even reverses the effects of priming that might otherwise occur for inhibited items. Investigating the neural correlates of retrieval-induced forgetting using implicit memory measures might add substantially to our understanding of very basic memory processes that may be involved in causing retrieval-induced forgetting.

Inter-Individual Differences in Inhibitory Memory Control

Many of the conclusions drawn from the present experiments rely on the findings from correlations between brain activation and behavioral forgetting indices across participants. Given there appears to be large inter-individual variability in the degree to which participants show forgetting, this approach can provide important additional insights into the functional neuroanatomy underlying the memory processes of interest. However, neuroimaging data alone cannot explain *why* these inter-individual differences exist. A rapidly developing area of neurocognitive research in the last years is dedicated to the investigation of genotypes underlying inter-individual differences in cognitive functioning (e.g., Greene, Braet, Johnson, & Bellgrove, 2008). Particularly interesting findings emerged for some higher cognitive functions that are known to rely on the cortical level of the neurotransmitter dopamine. For example, a polymorphism of the COMT gene, which codes for the production of the dopamine degrading enzyme catechol-O-methyltransferase, has been related to inter-individual variance in attentional control (Blasi et al., 2005). Interestingly, participants with different COMT genotypes also show different levels of anterior cingulate recruitment (Blasi et al., 2005; Heinz & Smolka, 2006), providing direct evidence for a genetic influence on the functional neuroanatomy of attentional control. Parallel findings exist in the working memory domain, where it could be demonstrated that carriers of a certain COMT polymorphism (Val) show poorer working memory performance (Diamond et al., 2004; Goldberg et al., 2003), and less focal responses of the dorsolateral prefrontal cortex during working memory tasks (Egan et al., 2001). In an episodic recognition task, Val carriers showed poorer memory performance, less hippocampal activation, but higher recruitment of the ventrolateral prefrontal

cortex, and less consistent coupling between the hippocampus and the VLPFC, the latter predicting recognition performance (Bertolino et al., 2006).

Taken together, these findings provide unique insights into the genetic modulation of neural processing underlying cognitive functions in healthy subjects and in clinical samples. Using this knowledge and the new evolving techniques for the investigation of memory control processes provides exciting new possibilities towards a direct link between memory functions, functional neuroanatomy and neurophysiology.

Conclusions

The results of four experiments, together with prior findings on memory control, suggest that intentional and unintentional forgetting is based on distinct neural mechanisms. Although prefrontal regions are involved in all forms of episodic forgetting that have been explained in terms of inhibition, direct evidence for a causal involvement of the PFC could only be obtained for intentional forgetting. Intentional forgetting might rely on a right lateralized neural network including the anterior cingulate and the right dorsolateral prefrontal cortex. In contrast, retrieval-induced forgetting (and to some extent also part-list cuing impairment) might be the result of automatic lateral inhibition in pathways processing the mnemonic information, for example, in posterior temporal and parietal association cortices. During selective retrieval, the prefrontal cortex might guide memory retrieval by detecting interference between competing memories, and resolve interference by biasing competition in favor of the target memories.

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Appendix

Tabel A. Peak locations showing a significant ($p < .001$ and $p < .005$, uncorrected) effect of selective retrieval in the contrast retrieval versus rehearsal in Experiment 1.

	Anatomical Label	x	y	z	BA	T	size
	Retrieval > Rehearsal						
	Frontal Lobe:						
L	Medial Frontal G.	-12	24	44	8	4.85	66
L	Middle Frontal G.	-48	22	26	46	3.41*	
		32	8	48	6	3.40*	
		-38	12	32	8/9	3.08*	24
		-52	12	44	8	2.94*	67
L	Inferior Frontal G.	-40	2	32	9	4.17	39
L	Inferior Frontal G.	-36	36	11	10/46		
	Temporal Lobe:						
L	Inferior Temporal G.	-56	-60	-10	37	5.53	89
L	Middle Temporal G.	-42	-62	0	37	5.50	138
		60	-48	-12	37	3.40*	
R	Fusiform G.	48	-54	-18	37	3.11*	
L	Hippocampus	-26	-10	-26	_	3.28*	
R	Hippocampus	40	-22	-14	_	3.55*	
	Parietal Lobe:						
L	Precuneus	-26	-66	38	7/19	5.41	144
L	Superior Parietal L.	-34	-56	62	7	4.92	248
R	Posterior Cingulate	16	26	-68	31	4.50	16
		-4	-66	14	23	3.36*	
L	Precuneus	48	-22	-75	52	4.03	48
	Occipital Lobe:						
R	Middle Occipital G.	44	-70	-12	19	4.61	44
	Rehearsal > Retrieval						
L	Lingual G.	-16	-92	-6	18	4.71	38
L		-28	-78	-8	18	3.80*	
L	Putamen	-18	12	-6	-	4.42	15
R		26	0	-4	-	3.59*	

R	Cingulate G.	10	-30	36	31	3.88*
L	Insula	-36	16	6	13	3.72*
L		-46	6	2	13	3.66*
R	Cuneus	16	-82	10	17	3.54*
		14	-86	18		3.47*

BA = approximate Brodmann Area; * = only found on a more liberal threshold of p < .005 (uncorrected); L = left hemisphere, R = right hemisphere, B = bilateral; size = number of voxels in a cluster

Table B. Peak locations showing significant event-related hemodynamic increases and decreases during retrieval practice trials in Experiment 2, with a statistical threshold of p < .001, uncorrected for multiple comparisons.

	Anatomical Label	x,y,z			BA	T	size
	Increases						
Frontal Lobes:							
L	Precentral/Inferior Frontal G.	-46	-2	36	6	*9,28	2349
		-50	36	4	45	*8,34	
		-50	4	20	44	*7,95	
L	Medial Frontal G.	-8	2	56	6	*8,55	755
		-4	10	52	6	*8,01	
		-14	20	64	6	5,21	
R	Precentral G.	41	0	28	6	4,78	25
L	Superior Frontal G.	-30	48	28	10	3,88	24
Other:							
R	Inferior Occipital G.	28	-92	-16	18	*16,57	14088
		42	-78	20	18	*12,65	
		-18	-92	-12	18	*11,99	
R	Hippocampus	24	-32	-4	-	6,22	87
L	Hippocampus	-24	-30	-8	-	5,83	62
	Decreases						
Frontal Lobes:							
L	Anterior Cingulate	-2	44	0	32	*7,77	456
		-12	44	0	32	5,96	
R	Middle Frontal G.	26	16	48	8	6,14	202
		30	28	40	8	5,64	
L	Medial Frontal/Limbic Lobe	-8	-24	40	NA	6,06	345
		-6	-18	52	6	5,06	
		8	-26	40	31	4,56	
R	Medial/Superior Frontal G.	8	46	36	9	5,24	132
		4	52	28	9	4,37	
		14	50	40	9	4,14	
R	Inferior Frontal G.	58	16	12	44	4,86	77
L	Anterior Cingulate	-4	14	-8	25	4,48	29
L	Middle Frontal G.	-26	26	36	9	4,05	14
Other:							

	Inferior Parietal						
R	Lobule/Supramarginal G.	64	-36	32	40	*7,18	979
		56	-48	36	40	*6,6	
		62	-52	24	40	6,13	
R	Middle/ Temporal G.	60	-22	-16	21	*6,54	339
		54	-10	-24	20	4,97	
		52	0	-32	21	4,8	
L	Superior Temporal G./Insula	-46	0	-8	13	5,94	542
		-42	-22	-4	13	5,76	
		-44	-10	-16	NA	5,5	
R	Insula	40	-12	-4	13	4,78	73
		42	2	-8	13	4,29	
R	Precuneus	10	-56	32	31	4,76	59
L	Precentral G.	-34	-30	56	4	4,48	98
R	Parahippocampal G.	28	-18	-24	-	4,37	19
L	Cingulate G.	-10	-2	40	24	4,25	11
R	Superior Temporal G.	50	-8	4	22	4,19	14
R	Precuneus	18	-54	56	7	4,03	23
L	Precuneus	-10	-52	44	7	3,81	20
R	Superior Parietal Lobule	28	-46	60	40	3,71	11

BA = approximate Brodmann Area; * = survives a statistical threshold of .05 (FWE-corrected); L = left hemisphere, R = right hemisphere, B = bilateral; size = number of voxels in a cluster

Table C. Peak locations showing significant hemodynamic increases ($p < .001$, uncorrected) for nonpracticed P^- compared with baseline C items, and for practiced P^+ compared with baseline C items during the final recall test in Experiment 2.

	Anatomical Label	x	y	z	BA	T	size	x	y	z	BA	T	size
		P- > C						P+ > C					
R	**Supramarginal G.**	**58**	**-54**	**32**	**40**	***7,40**	**296**	**58**	**-54**	**32**	**40**	***7,57**	**442**
		60	-44	32	40	*6,74		54	-56	16	40	4,72	
		48	-56	28	40	5,05							
L	**Superior Temporal/**	**-54**	**-58**	**20**	**39**	**5,01**	**38**	**-54**	**-56**	**28**	**39**	**5,26**	**70**
	Inferior Parietal G.							-50	-66	28	39	5,11	
B	**Medial Frontal G./**	**8**	**38**	**4**	**24**	**5,11**	**79**	**6**	**38**	**4**	**24**	**5,48**	**335**
	Anterior Cingulate							14	42	-4	32	5,05	
								-10	40	0		4,43	
L	**Anterior Cingulate**	**-4**	**42**	**0**	**32**	**3,85**	**11**				**-**		
R	**Superior Frontal G.**	**22**	**24**	**48**	**8**	**3,84**	**16**	**26**	**26**	**40**	**8/9**	**4,3**	**56**
		30	28	44	8	3,83							
R	**Precuneus**				**-**			**12**	**-52**	**28**	**31**	**3,82**	**12**

BA = approximate Brodmann Area; * = survives a statistical threshold of .05 (FWE-corrected); L = left hemisphere, R = right hemisphere, B = bilateral; size = number of voxels in a cluster

Table D. Peak locations showing significant hemodynamic decreases ($p < .001$, uncorrected) for nonpracticed P^- compared with neutral C items, and for practiced P^+ compared with neutral C items, during the final recall test in Experiment 2.

	Anatomical Label	x	y	z	BA	T	size	x	y	z	BA	T	size
		P- < C						P+ < C					
Frontal Lobes:													
L	**Precentral/**	**-48**	**-18**	**52**	**4**	***7,85**	**1373**	**-42**	**12**	**28**	**9**	***7,71**	**1868**
	Inferior Frontal G.	-44	10	28	9	*7,80		-46	2	24	9	*6,65	
		-52	-2	40	6	*7,28		-32	32	-20	47	*6,60	
L	**Medial Frontal/**	**-4**	**22**	**40**	**32**	***7,11**	**958**	**-4**	**22**	**40**	**32**	***7,45**	**1067**
	Cingulate G.	0	4	64	6	*6,61		-2	10	48	6	*6,70	
		-2	8	48	6	*6,55		-6	22	68	6	6,36	
R	**Precentral G.**	**60**	**-6**	**32**	**6**	**6,31**	**390**	**46**	**-14**	**60**	**4/6**	**5,59**	**87**
		64	-12	28	4	6,27		42	-20	64	6	4,18	
		44	-14	60	4	6,13		54	-12	52	4	3,78	
L	**Inferior Frontal G.**	**-32**	**32**	**-20**	**47**	**6,18**	**171**				**-**		
		-32	34	-12	47	5,30							
		-38	22	-8	47	4,95							
R	**Inferior Frontal G.**	**36**	**24**	**-8**	**47**	**4,84**	**23**	**36**	**26**	**-8**	**47**	**5,58**	**140**
								40	20	-28	38	4,45	
								34	30	-20	47	4,30	
R	**Precentral G.**				**-**			**66**	**-12**	**28**	**4/6**	**5,43**	**122**
								60	-6	40	6	4,59	
								66	-6	12	6	3,75	
L	**Inferior Frontal G.**	**-54**	**12**	**-12**	**44**	**4,84**	**17**	**-52**	**16**	**-12**	**44**	**4,49**	**21**
L	**Medial Frontal G.**	**-6**	**50**	**44**	**8**	**4,71**	**17**				**-**		
L	**Paracentral Lobe**				**-**			**-6**	**-44**	**72**	**4**	**4,72**	**103**
								-2	-36	72	4	3,73	
L	**Medial Frontal G.**	**-4**	**58**	**-16**	**11**	**4,47**	**7**	**4**	**64**	**-8**	**10?**	**4,86**	**42**
	(orbital)							-8	62	-12	11	4,07	
								18	62	-12	11	3,79	

Occipital/Parietal/Temporal Lobes:													
B	**Inferior Occipital/**	**30**	**-86**	**-8**	**18**	***13,72**	**17142**	**-2**	**-88**	**0**	**17**	***10,47**	**15035**
	Lingual G.	-6	-90	32	19	*11,85		32	-84	-4	18	*10,36	
		20	-94	-12	18	*11,51		2	-88	8	18/19	*9,86	
R	**Superior Parietal Lobule**						**-**	**28**	**-64**	**44**	**7**	**5,73**	**226**
R	**Superior Temporal G.**	**68**	**-14**	**0**	**22**	**4,99**	**36**				**-**		
		64	-24	4	22	4,55							
	Temporal Pole/												
R	**Superior Temporal G.**	**40**	**20**	**-28**	**38**	**4,78**	**10**						**-**
R	**Superior Parietal/**	**44**	**-36**	**60**	**40**	**4,52**	**34**	**44**	**-36**	**60**	**40**	**4,09**	**13**
	Postcentral G.	42	-46	60	40	3,87							
R	**Insula**	**34**	**-30**	**20**	**13**	**4,32**	**10**				**-**		
R	**Superior Temporal G.**	**62**	**6**	**-8**	**38**	**4,01**	**17**				**-**		
Subcortical:													
R	**Basalganglia (Putamen)**	**26**	**6**	**0**	**NA**	**4,73**	**29**				**-**		
R	**Basalganglia (Caudate)**	**20**	**26**	**4**	**NA**	**4,83**	**22**	**14**	**10**	**4**	**NA**	**3,85**	**17**
								16	18	0		3,66	

BA = approximate Brodmann Area; * = survives a statistical threshold of .05 (FWE-corrected); L = left hemisphere, R = right hemisphere, B = bilateral; size = number of voxels in a cluster