Cross-Functional Brain Imaging of Attention, Memory, and Executive Functions: Unity and Diversity of Neurocognitive Component Processes
ABSTRACT


The central theme of the present thesis revolves around the exploration of similarities and differences in brain activity patterns invoked by the component processes underlying mnemonic, executive and attentional functions. The primary aim was to identify and functionally characterize commonly recruited brain regions in terms of shared component processes, which has been a largely neglected area of research in cognitive neuroscience. The vast majority of functional brain imaging investigations of cognition has focused on delineating differences between cognitive functions or processes, with the purpose of isolating the unique functional neuroanatomy that underlies specific cognitive domains. By contrast, the present thesis builds on the results from three imaging studies that focused primarily on detecting commonalities in functional brain activity across different forms of memory processes. In study I, the imaging data from two positron emission tomography (PET) experiments were re-analyzed to identify common activation patterns associated with nine different memory tasks incorporated across the experiments, three each separately indexing working memory, episodic memory, and semantic memory. A generic prefrontal cortex (PFC) network involving discrete subregions of the left hemisphere located in ventrolateral (BA 45/47), dorsolateral (BA 9/44/46), and frontopolar (BA 10) sectors of PFC, as well as a midline portion of the frontal lobes, encompassing the dorsal part of the anterior cingulate cortex (ACC) (BA 24/32), was conjointly recruited across all tasks. In study II, we used a novel mixed blocked/event-related functional magnetic resonance imaging (fMRI) design, which enables separation of brain responses associated with different temporal dynamics to further investigate commonalities of neural activation across working memory, episodic memory, semantic memory, and attention/vigilance. A similar set of common PFC regions, as that discovered in Study I, was found to elicit overlapping brain activity across all memory tasks, with a subset of regions also activated in the attention/vigilance task. Furthermore, the task-induced brain activity was dissociated in terms of the temporal profiles of the evoked neural responses. A common pattern of sustained activity seen across all memory tasks and the attention task involved bilateral (predominantly right-lateralized) ventrolateral PFC (BA 45/47), and the dorsal ACC (BA 24/32), which was assumed to reflect general processes of attention/vigilance. A pattern of sustained activity elicited in all memory tasks, in the absence of attention-related activity, involved the right frontopolar cortex (BA 10), which was assumed to reflect control processes underlying task set maintenance. In addition, common transient activation evoked in the memory tasks relative to the attention task was
found in the dorsolateral (BA 9/44) and ventrolateral (BA 47) PFC, the superior parietal cortex (BA 7), and cerebellum. In study III, a mixed fMRI design was used to assess the degree of common brain activity associated with increased executive demand, which was independently manipulated within episodic and working memory. Unitary control modulations involved a shared tonic executive component subserved by fronto-striatal-cerebellar circuitry, assumed to govern top-down context processing throughout task periods, and a stimulus-synchronous phasic component mediated by the intraparietal sulcus (BA 7), assumed to support dynamic shifting of the ‘focus of attention’ among internal representations. Collectively, the theoretical implications of shared neural mechanisms are discussed, with a special focus on human memory and its multifaceted relationships with attention and executive control functions. Finally, the presented imaging data are used to outline a tentative hierarchical neurocognitive model that attempts to give an account of how different unitary component processes might work together during cognitive task performance.

**Key words:** Human memory, executive functions, prefrontal cortex, sustained and transient neural activity, declarative long-term memory, attention, working memory, functional neuroimaging, cognitive control.
ACKNOWLEDGEMENTS

First and foremost I wish to express my gratitude toward my outstanding supervisor Lars Nyberg, for inviting me to become part of a first class research team of cognitive neuroscientists, and for being a source of astute knowledge and continuing inspiration. From the eminent group of collaborators I have had the opportunity to work with, I would especially like to thank Peter Fransson for his invaluable advice on miscellaneous issues.

I would also like to thank Johan Eriksson, Anna-Stigsdotter-Neely, and Håkan Fischer for reading and providing helpful comments on an earlier draft of the present thesis. Much appreciation is also dedicated to the inventor of DataZ, Micael Andersson, for making imaging data analyses a dozen clicks faster. Ann-Louise Söderlund deserves an honorary salute for helping out with various practical matters during the last days of finalization of this thesis.

Also, my fellow doctoral students, the doctors, professors and all the other staff at the Department of Psychology, deserve many thanks for providing a creative atmosphere, within which no topic appeared too sophisticated (or obscure) to plunge into.

During the two years prior to becoming a Ph.D. student, I had a most memorable time working as a psychometrician (i.e. memory inquisitor) in the Betula study thanks to an incredible staff.

Thanks also to my dear friends outside of work.

And finally, a great many thanks, of course, to my marvellous family!

Umeå, May, 2006

Petter Marklund
LIST OF PAPERS

This doctoral dissertation is based on the following studies, which will be referred to in the text by their Roman numerals:


# TABLE OF CONTENTS

**INTRODUCTION** ................................................................................................................................................ 1

**BACKGROUND** .................................................................................................................................................. 2

- Theoretical models of the relationship between attention, working memory and long-term memory .......................................................... 2
- Exploring the points of intersection: Human brain mapping ................................................................. 5
- The mixed fMRI design ................................................................................................................................. 6
- A brief review of previous findings ......................................................................................................... 8
  - Functional neuroimaging of sustained attention ................................................................................. 8
  - Functional neuroimaging of working memory .................................................................................. 9
  - Functional neuroimaging of episodic memory ............................................................................... 10
- Brain activation similarities across domains ......................................................................................... 11

**RESEARCH OBJECTIVES** .............................................................................................................................. 14

**SUMMARY OF EMPIRICAL STUDIES** .............................................................................................................. 14

- Study I: Common prefrontal activations during working memory, episodic memory, and semantic memory .......................................................................................................................... 14
- Study II: Sustained and transient neural modulations in prefrontal cortex related to declarative long-term memory, working memory, and attention ......................................................... 16
- Study III: Unity and diversity of tonic and phasic executive control in episodic and working memory .......................................................................................................................................................... 19

**GENERAL DISCUSSION** ................................................................................................................................... 21

- Overlapping sustained neural activity: Common control processes related to maintenance of an attentive state and task set representation .............................................................................................. 22
- Selective sustained neural activity: Distinct processes related to active maintenance and monitoring within working memory ......................................................................................................................... 26
- Overlapping transient neural activity: Shared control processes related to response selection or context-integrative item coding .......................................................................................................................... 28
- Selective transient neural activity: Updating and temporal coding of working memory items and active long-term memory probing for episodic traces .................................................................................. 36
- Control-modulation of overlapping regions by increased executive demands ................................................. 38
- Domain-selective control modulations by increased executive demands ......................................................... 39
- A hierarchical neurocognitive model .............................................................................................................. 41

**CONCLUSIONS** ................................................................................................................................................... 50

- Caveats and directives for future research ................................................................................................... 50

**REFERENCES** .................................................................................................................................................... 53
INTRODUCTION

“Metaphorically, memory, attention, and executive functions may be interrelated as past, present, and future are interrelated”

(Paul J. Eslinger, 1996, p. 392)

Since the early division of human memory into primary (short-term or active) and secondary (long-term) memory, postulated by William James (James, 1890), the idea of fractionating different mnemonic and cognitive abilities into separate, ‘independent’, and functionally distinct systems has dominated the scientific exploration of mental faculties in both experimental psychology and cognitive neuroscience. Because of this situation, empirical investigation and theoretical discussion of specific cognitive functions have principally been conducted in isolation, which for long discouraged any attempt to discover shared elements (e.g. common neural substrates and/or processing resources) among separate cognitive domains.

There is broad agreement that human memory is not a unitary function of monolithic nature, but rather a composite of different capacities that have been defined and classified within the framework of multiple memory systems, where each system is labelled by the form of memory it contains, and the operations being subsumed (e.g. Squire, 1992a; Tulving, 1995; Nyberg and Tulving, 1996; Schacter et al., 2000). This, however, does not preclude the existence of across-systems similarities (Jones and Anderson, 1987; Cabeza and Nyberg, 2000).

Inasmuch as purported memory systems can be assumed to be composed of multiple component processes (Moscovitch, 1992), which at the neural level are implemented in widely distributed neurocognitive networks (e.g. Smith et al., 1998; Nyberg et al., 2000; Martin and Chao, 2001), it has been reasoned that the underlying neural and cognitive mechanisms of different memory systems involve both shared and distinct elements (e.g. Roediger et al., 1999).

According to the components-of-processing view, the sum of component processes that subserve different memory systems comprise some components that are domain-specific and characterized by a high degree of functional specialization, and other components that are posited to perform more general computations, which are therefore believed to be shared between memory systems (and tentatively other cognitive functions as well) (Moscovitch, 1992; Roediger et al., 1999). For example, the majority of current models of working memory assume some kind of domain-general executive control mechanism that (at least implicitly) is posited to generalize to any cognitive challenge that impose a sufficient load on mental operations that selectively pertain to that control mechanism (e.g. Baddeley, 1986; Norman and Shallice, 1986; Engle et al., 1999; Miyake and Shah, 1999). On the
basis of neuropsychological studies, such executive control functions have for long been ascribed to the prefrontal cortex (PFC) (Luria, 1966; Fuster, 1980; Goldman-Rakic, 1995). More recently, functional neuroimaging studies have revealed that various long-term memory processes also engage PFC (for review, see Cabeza and Nyberg, 2000), including subregions that previously were thought to be rather specific for working memory and executive control functions (Wagner, 1999, 2002).

It has been argued that functional neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), can inform psychological theories by providing exceptional tools for the identification and disambiguation of the component processes involved in cognitive functions (Roediger et al., 1999; Henson, 2005). Still, the notion of shared or unitary component processes has, until recently, been almost completely ignored in functional brain imaging research.

Toward this end, the topic of the current thesis will revolve around neuroimaging findings of commonalities in the functional brain activation patterns associated primarily with episodic long-term memory and working memory (but also other cognitive functions). The thesis is based on the empirical findings from three cross-functional or cross-domain brain imaging studies that assessed patterns of neural activity across tasks of working memory, episodic and semantic long-term memory, as well as sustained attention/vigilance. A central objective was to relate the current findings to the views of (1) working memory as the activated portion of long-term memory residing in ‘the focus of attention’, and (2) basic attentional and executive control mechanisms as a common denominator of different human memory (and other cognitive) functions. In the final section of this dissertation, the presented imaging data are used as a basis for the outline of a tentative hierarchical neurocognitive model that attempts to give a functional and integrative account of how different unitary component processes might work together in a dynamical fashion within segregated neural circuitry during cognitive task performance.

**BACKGROUND**

**Theoretical models of the relationship between attention, working memory and long-term memory**

Extant findings of overlapping activation patterns for declarative (episodic and semantic) long-term memory and working memory raises the intriguing question as to whether these different functions should be considered to constitute separate systems, or whether working memory may be conceived of as the temporary activation of a subset of long-term memory content currently residing in the focus of attention. There is support from theoretical models and empirical findings for both views. The influential working memory model proposed by Baddeley and
Hitch (1974) postulates a multi-component system which comprises two temporary retention stores (harboring verbal and visuo-spatial representations, respectively) under the supervisory and operational control of a limited-capacity ‘central executive’ processing mechanism. The central executive is intimately linked with the concept of controlled attention (Baddeley, 1986, 1993) and it has been proposed that the supervisory attentional system (SAS) as described by Shallice and colleagues (e.g. Norman and Shallice, 1986; Shallice and Burgess, 1993) represents a fitting model of this overarching control mechanism. According to the working memory model, the processes and stores implicated within the working memory system are considered to be functionally and anatomically separate from declarative (episodic and semantic) long-term memory systems (Baddeley and Logie, 1999). In support of this claim, neuropsychological evidence of double dissociation between short-term and long-term memory ability strongly implicates two distinct and independent systems. First, evidence was provided that amnesic patients show normal short-term memory function despite having severely impaired long-term memory function (Milner, 1966; Baddeley and Warrington, 1970). Second, the converse pattern was demonstrated in some brain-damaged patients who showed pronounced deficits in short-term memory coupled with an intact long-term memory (Shallice and Warrington, 1970; Warrington and Shallice, 1972).

On the other hand, so called processing or ‘proceduralist-activation’ models propose an opposing view as to the structural and functional relationship between working memory and long-term memory. According to this view the temporary retention of information in working memory is ‘simply’ accomplished by the prolonged, selective activation of already existing long-term memory representations reflecting or corresponding to the recently encountered and to-be-retained sensory input(s) (e.g. Cowan, 1999; Engle et al., 1999; Ruchkin et al., 2003). Two basic principles pertaining to this idea have been captured by Fuster and Crowder, respectively, stating that “essentially, working memory is attention focused on an internal representation, that is, on a representation stored in long-term memory that, at a given time, has been activated and updated for the performance of a particular task or sequence of acts” (Fuster, 2003, p. 737), and that “memory storage [i.e., long-term memory representations] for an experience resides in the same neural units that processed that experience when it happened in the first place” (Crowder, 1993, p. 145).

Support for this notion comes from behavioral cognitive studies that have demonstrated better short-term memory span for words than non-words (e.g. Hulme et al., 1991) and for non-words that appeared English as opposed to non-words that deviated from English as to their phonotactic structure (Adams and Gathercole, 1995). Similarly, it has been established that non-word repetition was better for non-words that resembled authentic words than those that did not (Gathercole, 1995). Moreover, the performance on tests of immediate serial recall of word lists was significantly better for lists containing words of the same category as compared to lists comprising words from different categories (Poirier and Saint-
Aubin, 1995). Such findings show that phonological short-term memory is influenced by lexical and semantic long-term knowledge, which clearly indicate that working memory (i.e. the phonological loop) is not independent from long-term memory. Hence, the storage component is claimed to be intrinsically identical between working memory and long-term memory, the shared representational basis of which is hypothesized to be anatomically embedded throughout posterior association cortices.

In these models, the role of a central executive is principally related to the control and selection of the currently relevant portion of activated long-term memory representations (e.g. Cowan, 1999). The selected part of the activated representations denotes the information that is under direct surveillance of the ‘focus of attention’ which represents the capacity-limited part of working memory which may hold only restricted sets of items at any given time (e.g. according to Cowan, this limited capacity is constrained to about four independent representational units) (Cowan, 2001). Recently, it has been argued that the focus of attention as previously defined in the proceduralist literature may need to be further constrained with regard to processing capacity and that it should be divided into two components. First, the limited-capacity subset of working memory that may contain up to four items (i.e. the prior conception of focus of attention) has been referred to as residing in the ‘direct-access region’, meaning that those items are readily available, but not as of yet selected, for ongoing cognitive processing (Oberauer, 2002). Second, the items held in the region of direct access constitute a selection set from which a particular item is to be chosen to enter the focus of attention. Hence, according to this conjecture the focus of attention may hold only the one item that has already been selected for input to currently relevant cognitive processing (McElree, 2001; Oberauer, 2002, 2005). The proceduralist view presumes no capacity limitation to the activation of long-term memory stores, although activated representations are prone to loss through decay or interference (Cowan, 1995, 1999). The activated portion of long-term memories that are not held in the direct access region (or the focus of attention) are maintained outside of conscious awareness, and require ‘retrieval structures’ to bring them into the region of direct access (Ericsson and Kintsch, 1995).

Baddeley has for long speculated on a ‘general retrieval system’ run by the central executive, which “should be able to encode and retrieve information both from the slave systems and temporarily activated components of long-term memory” (Baddeley, 1996, p. 23). In so doing, he expressed the notion that the relationship between working memory and long-term memory processes might involve interplay via shared neuroanatomical mechanisms related to common control processes. An elaborated theoretical account of this notion has recently been added to the working memory model, in terms of a new component; the ‘episodic buffer’, which is conceived of as a temporary storage buffer capable of binding together information from the two slave systems with long-term memory information, thus functioning as an interface between working and episodic memory systems.
Furthermore, the shared patterns of PFC activity between working memory and episodic memory have encouraged some authors to posit general executive and/or mnemonic control processes to serve purposes applicable to both memory functions (Wagner, 1999). Proposed candidate roles for these prefrontally mediated control processes have involved controlled selection of task-relevant information (Fletcher and Henson, 2001), monitoring and manipulation of information held on-line (D’Esposito et al., 1998; Petrides, 1994) and top-down biasing functions that facilitate processing of context-relevant representations in posterior neocortical association areas (Miller and Cohen, 2001). These ideas might be bundled together and discussed as representing a general framework that primarily regards the commonalities that bridge working memory and long-term memory as related to executive control functions.

**Exploring the points of intersection: Human brain mapping**

The empirical studies of the present thesis have utilized PET (study I) and fMRI (study II and study III) techniques, which both provide measures of regional brain activation underlying the cognitive component processes invoked by cognitive tasks (for review, see Raichle, 2001). More than two decades ago, PET became the first brain mapping method to gain popularity among cognitive psychologists as a reliable method for indexing whole-brain activation in vivo by measuring regional blood flow changes or changes in glucose metabolism during cognitive task performance. However, a clear disadvantage inherent in the early PET experiments due to very coarse temporal resolution is the obligatory use of a blocked design format which necessitates cerebral blood flow changes to be integrated across long time periods (i.e. 60 – 120 seconds). This severe limitation of temporal precision makes detailed analysis regarding specific component processes problematic by preventing, for example, analytical strategies based on separate types of memory trials (e.g. trials being partitioned and compared according to whether stimuli represented “new” or “old” items). On similar grounds PET data do not permit dissociation among component processes that are associated with different temporal dynamics (i.e. temporally extended or phasic short-term modulation) of their underlying neural response (e.g. retrieval mode versus stimulus-synchronous retrieval attempt). The introduction of rapid event-related paradigms in fMRI studies (Buckner et al., 1996; Dale and Buckner, 1997; Rosen et al., 1998), enabled by the superior temporal resolution afforded in fMRI as compared to PET, allowed for the development of more intricate experimental designs where such issues could be addressed. Other advantages of fMRI over PET include its non-invasive methodology and that it is a relatively inexpensive technique, which has afforded an increasing accessibility of brain mapping equipment in laboratories around the world.
A typical brain imaging experiment is designed to identify task-specific brain activity associated with single cognitive functions or processes by directly contrasting the neural activation evoked by two different cognitive tasks (i.e. one experimental versus one control condition) which are assumed to differ only with respect to the cognitive process of interest. By utilizing such so called ‘subtraction’ methodology (and other more sophisticated designs), the general aim of the vast majority of neuroimaging studies have been to identify neural networks differentially recruited by specific cognitive functions. For this type of approach overlapping neural activation is typically discarded as redundant to the function of interest.

However, as a progressive number of studies continuously keep on providing more and more functional brain data of increasingly more specific cognitive component processes, the need to take a step back for seeing the “whole picture” or at least to get a broader perspective on the extensive bulk of extant imaging data has been emphasized (Cabeza and Nyberg, 2000). That is, the degree to which brain activation patterns evoked by different cognitive functions exhibit regional commonalities has become a question on its own. Inherent to this more global perspective on analysis is the question of what the appropriate functional interpretation(s) of intersecting sites of activation should be, in terms of underlying (shared) cognitive component processes.

The mixed fMRI design

Studies devoted to cross-domain functional imaging has mostly used either event-related (e.g. Ranganath et al., 2003) or blocked designs (e.g. LaBar et al., 1999; Braver et al., 2001; Collette et al., 2005) to assess similarities in brain activity patterns between different functions or domains. These approaches used in isolation are capable only of assessing a limited range of the full spectrum of the temporal dynamics inherent in the neural patterns induced by cognitive task performance. However, the recent introduction of a novel ‘mixed design’ that combines blocked and event-related procedures in the context of fMRI has substantially extended the temporal facets of neural activity than can be extracted from a single functional imaging experiment (Donaldson, 2004). The logic behind the ‘mixed design’ approach, which was used in study II and study III, rests upon the assumption that performance on any conceivable experimental task can be decomposed into two fundamental and complementary cognitive components; (1) ‘cognitive mode’ or ‘mental state’ assigned to task set configuration and maintenance, which relates to tonic control processes that provide the neural and cognitive context within which task-specific cognitive operations are to be implemented in terms of (2) phasic stimulus-locked item processes that operate in concordance with the given context. These two processes are ‘superimposed’ on each other and they are concurrently interacting dynamically throughout task
performance. At the core of performance on any given task resides what constitute the cognitive task set of the experimental subject, which is induced by task instructions and involves mechanisms that instantiate and maintain task set (i.e. intentional representation of ‘what to do’ during a specific task, including, but not limited to, stimulus-response mappings) (Allport and Wylie, 2000). Theories have proposed that task set governs the orchestration of item-specific cognitive processes (i.e. processes that become operative on a trial-by-trial basis) by means of biasing processing in favor of currently context-relevant cognitive operations and processing pathways for the duration of task performance (Miller and Cohen, 2001). Hence, maintenance of task set should depend on tonic control mechanisms, the neural implementation of which should exhibit sustained activation throughout a task, independent of stimulus onsets. Item-related processes on the other hand implicate the cognitive operations that are selectively triggered by the individual events or trials within a task. Since these processes are directly related to stimulus processing such as coding, evaluation, decision making and response execution, they evoke brain activity that is transient in nature and hence distinct from the prolonged changes in brain activity that reflect the tonic control processes underlying task set maintenance.

Mixed fMRI designs combine (i) standard event-related fMRI procedures designed to explicitly measure stimulus-synchronous and transient neural activity changes evoked during processing of individual items, and (ii) epoch-related blocked procedures that index the average neural activity changes that occur throughout entire task blocks as compared to control blocks (Donaldson and Buckner, 2001). Importantly, mixed designs allow the simultaneous assessment and separation of temporally independent brain responses. Generally, mixed paradigms alternate task blocks of cognitive performance with control blocks comprising periods of some low-level baseline (e.g. resting) (see Fig. 1). A critical feature of the mixed design is that the inter-stimulus-intervals (ISIs) that are interspersed between stimulus presentations must be of varying time duration or ‘jittered’, including some prolonged ISIs approximating 20 seconds, in order to keep down the correlation between task-induced sustained and transient fMRI signals. This is a prerequisite for an adequate separation of sustained and transient neural responses. To date several studies have successfully utilized mixed fMRI designs to simultaneously measure and isolate sustained and transient brain activity associated with cognitive tasks (Donaldson et al., 2001b; Braver et al., 2003; Burgund et al., 2003; Visscher et al., 2003).
A Brief Review of Previous Findings

Functional neuroimaging of sustained attention

Attention is of compound nature and many taxonomies and divisions of attentional processes have been proposed (e.g. Posner and Petersen, 1990; Mirsky et al., 1991; Stuss et al., 1995). Among the multiple component processes and conceptualizations implicated in the attention literature, several have been used interchangeably in relation to executive control and attention (Lyon and Krasnegor, 1996), such as inhibition, monitoring, and selection. In the present thesis, these concepts will be dealt with under the heading of executive functions (e.g. Miyake et al., 2000). Component processes that will be referred to attention include focusing, sustained attention/vigilance and shifting. Of particular interest in terms of generic mechanisms underlying cognitive task performance is the concept of sustained attention (Parasuraman, 1984; Sarter et al., 2001). Brain imaging studies of sustained attention have primarily been conducted by using vigilance tasks that require participants to maintain a selective attentional focus during an extended period of time. In general, vigilance tasks involve detection of subtle modality-specific changes that occurs only on rare occasion. There is ample evidence for the persistent activation of a predominantly right-lateralized fronto-parietal network in tasks of sustained attention (Cohen et al., 1988; Pardo et al., 1991; Paus et al., 1997), and focal lesions within the right PFC are known to cause sustained attention deficits (Wilkins et al., 1987; Rueckert and Grafman, 1996). Additionally, sustained attention have been found to activate areas along the midline of the frontal lobes comprising the dorsal portion of the anterior cingulate cortex (ACC) (BA 24/32) (Pardo et al., 1991), and this medial area is purported critical to attention functions in general (Mesulam, 1981; Posner and Petersen, 1990). The ACC and right PFC have been emphasized as control areas for upregulating tonic levels of intrinsic alertness (Mottaghy et al., in press), which ultimately is carried out by specific brain stem nuclei (e.g. Foote et al., 1991; Kinomura et al., 1996).

With respect to the neural systems underlying selective attentional focus and attention-shifting, numerous brain imaging studies have employed spatial cueing paradigms for their exploration (e.g. Coull and Nobre, 1998; Gitelman et al., 1999). Focusing and shifting of attention have been described in terms of two separate attentional networks, mediating orienting or visual selection and re-orienting of attention or shifting, respectively (Corbetta and Shulman, 2002). The neural substrates of the ‘orienting network’, which is believed to contribute to both directed visual attention and constitute the endogenous attention component of working memory (see section on brain activation similarities across domains below), have been proposed to involve bilateral regions of the intraparietal sulcus and the frontal eyefields (e.g. Corbetta, 1998), whereas the ‘re-orienting network’ or shifting component is posited to involve right-lateralized areas in the vicinity of
the parieto-temporal junction and the VLPFC (Corbetta and Shulman, 2002). A recent event-related fMRI study provided evidence for a specific role of posterior parietal cortex in attention-shifting, rather than sustained attention, as this area elicited transient activity increases associated with the presentation of visuo-spatial direction cues, but no sustained activation during the maintenance of focus (Yantis et al., 2002).

**Functional neuroimaging of working memory**

Brain mapping investigations of human working memory have yielded findings that corroborate and extend prior evidence from cognitive neuropsychology (Smith and Jonides, 1996) and single-unit recordings in nonhuman primates (Fuster and Alexander, 1971; Funahashi et al., 1989) by implicating regions within the prefrontal cortex (PFC) in various working memory processes (D’Esposito et al., 1998; Smith and Jonides, 1999). Much work has focused on identifying and characterizing neuroanatomical correlates of the different subcomponents in the working memory model proposed by Baddeley and Hitch (1974). The original tripartite model constituted two separate material-specific buffers responsible for temporary storage / maintenance of verbal information (the phonological loop) and visual and spatial information (the visuospatial sketchpad), respectively, both of which were considered as slave systems under the control of a domain-general central executive (Baddeley and Hitch, 1974; Baddeley, 1986). More recently, the working memory model has been updated to additionally constitute a complementary episodic buffer, responsible for the integration of material-specific representations held in the different slave systems and long-term memory representations (Baddeley, 2000). Neuroimaging studies have shown that tasks entailing temporary maintenance of verbal information within working memory over a delay typically evoke sustained neural activity in regions of the left ventrolateral part of PFC (VLPFC) (BA 44/45/47), involving activation at or adjacent to Broca’s area, as well as premotor regions (BA 6/8) (D’Esposito et al., 1998). The activation of these areas has been taken to reflect the operation of active subvocal rote rehearsal within the phonological loop (Smith and Jonides, 1999). The verbal or phonological storage component of the phonological loop has generally been associated with neural activation within the left parietal cortex (BA 40/19/7) (Awh et al., 1996; D’Esposito et al., 1998). The neural correlates of temporary retention of visual or spatial information, on the other hand, has been associated with a separate short-term buffer, the visuospatial sketchpad (Baddeley and Hitch, 1974), which appear to involve homologues frontal and parietal areas in the right hemisphere (D’Esposito et al., 1998; Owen et al., 1998). Medial frontal areas have consistently been shown to activate during working memory delays, irrespective of type of representation held on-line, including the ACC (BA 24/32) and pre-SMA (BA 6/8) (for review, see Petit et al., 1998). Moreover, the central executive component of working memory, postulated to mediate higher-level
control operations such as manipulation or transformation of temporarily retained information, has predominantly been posited to involve dorsolateral regions of PFC (DLPFC; BA 9/46) (D’Esposito et al., 1999; Smith and Jonides, 1999).

It should be emphasized that no single brain region is considered to be solely responsible for any higher-order function, such as the overarching and supervisory functions associated with the central executive. Rather, results from functional imaging studies that have focused on isolating the neural substrates of putative subcomponents of executive control suggest that these functions are not exclusively related to the frontal lobes (e.g. Collette and Van der Linden, 2002). Instead, they seem to be mediated by distributed large-scale networks involving regions of both the PFC and posterior neocortical areas as well as subcortical structures, with rather specific network nodes being activated as a function of the particular executive requirements of a given task (Funahashi, 2001). Accordingly, to reconcile such findings with the functional concept of a unitary central executive, Baddeley (e.g. 1996) emphasized the need for its fractionation. Today, there is an emerging consensus that the cognitive and neural mechanisms underlying the central executive might correspond to the dynamic and flexible interactions among multiple control processes of (relative) functional independence (e.g. Andrés, 2003). Nonetheless, taken as a whole, extant imaging data have substantiated the widely held view of the frontal lobes as a key structure for working memory and executive control.

**Functional neuroimaging of episodic memory**

Brain imaging of the various component processes contributing to episodic memory retrieval or ‘remembering’ has consistently revealed neural activation in prefrontal, parietal and medial temporal lobe circuitry (for review, see Cabeza and Nyberg, 2000). Initial evidence for a link between PFC and human long-term memory abilities came from two early positron emission tomography (PET) investigations of episodic memory (Shallice et al., 1994; Tulving et al., 1994). In parallel, these studies revealed pronounced activation of the PFC while participants were engaged in episodic encoding and recognition tasks. This finding was quite unexpected, since patients with PFC damage typically show only modest deficits for episodic recognition (for review, see Wheeler et al., 1995), although they display impaired source memory (Janowsky et al., 1989), and free recall (Incisa della Rocchetta and Milner, 1993). Even more intriguing was the lateralization effect regarding the pattern of PFC activity shown between the memory acquisition phase and the subsequent retrieval phase (Shallice et al., 1994; Tulving et al., 1994). In both studies it was shown that right PFC was preferentially engaged during episodic retrieval, whereas left PFC was preferentially engaged during encoding (Tulving et al., 1994; Nyberg et al., 1996a). A similar lateralization of PFC activity was revealed for retrieval of episodic versus semantic information, engaging right versus left hemisphere, respectively, independent of material (Buckner and Petersen,
The right PFC involvement in episodic retrieval typically involves a posterior region of VLPFC (BA 45) and a region in the anterior-most extent of the PFC referred to as the frontopolar cortex (BA 10) (Nyberg, 1998). These regions of the right PFC, with a special emphasis on the frontopolar cortex, have been linked to the instantiation and maintenance of the mental set known as ‘retrieval mode’, which is characterized by orienting attention inwards to guide the act of episodic retrieval (Tulving, 1983). Retrieval mode is described as “a state in which the cognitive system is prepared for or expects memory construction and recollection, i.e. networks are dysfacilitated or decoupled from other processing sequences in which they currently run and reassembled into interlocked networks primed for memory generation” (Conway, 2001, p. 1379). In line with this hypothesis, right and sometimes left frontopolar cortex (BA 10), and right VLPFC/frontal operculum (BA 44/45/47) has evoked sustained activation during episodic retrieval tasks (Donaldson et al., 2001a; Velanova et al., 2003). The dorsal ACC (BA 24/32) is another area implicated in retrieval mode (Lepage et al., 2000).

Recently, several event-related fMRI designs have employed clever task designs to demonstrate that the distinct areas in PFC (and other structures) that activate during the performance of an episodic memory task are highly dependent on task demands and the specific aspect of retrieval queried. For example, many investigations have associated left-lateralized PFC activity with retrieval tasks entailing recollection-driven recovery of contextual details (Henson et al., 1999, Johnson et al., 1997, Ranganath et al., 2000, Rugg et al., 1999), whereas right-lateralized PFC activity has been associated with familiarity-driven memory judgments (Buckner et al., 1998, Dobbins et al., 2004, Henson et al., 1999).

Neuroimaging data also corroborates evidence from human lesion studies (cf. Squire and Zola-Morgan, 1991) that structures within the medial temporal lobes, such as the hippocampus and the parahippocampal gyrus, are essential for episodic memory, by showing activation within these areas during episodic recollection (Nyberg et al., 1996b; Eldridge et al., 2000). Furthermore, activation in the parietal cortex during episodic memory tasks has become known as a signature of successful recovery of episodic information (e.g. Konishi et al., 2000). This neural effect has been termed the “parietal old/new effect”, since direct comparisons of event-related fMRI responses that accompany retrieval of “old” items with those that accompany correct rejection of “new” items have consistently yielded increased left parietal brain activity (Konishi et al., 2000), and similar findings are also well-established in human studies recording event-related potentials (ERP) from the scalp (Rugg and Allan, 2000).

**Brain activation similarities across domains**

In a large-scale meta-analysis involving 275 PET and fMRI studies from several different cognitive domains, both similarities and differences in activation patterns
were considered (Cabeza and Nyberg, 2000). The data set included studies of attention, perception, working memory, semantic memory retrieval, episodic memory encoding, and episodic retrieval across verbal, object and spatial stimulus-materials. Although specific activation patterns were identified for each cognitive function, the aggregated activation data also revealed a high degree of overlap in regional cerebral recruitment across diverse arrays of cognitive tasks, including tasks of working memory and episodic memory (Cabeza and Nyberg, 2000). The most consistent site of across-function similarities was the frontal lobes.

Concerning the generality of PFC involvement in different working memory and long-term memory processes, other ‘meta-analyses’ and reviews were specifically conducted to evaluate the extent to which distinct subregions within PFC could be identified as commonly recruited across forms of memory (Christoff and Gabrieli, 2000; Duncan and Owen, 2000; Fletcher and Henson, 2001). In a survey of ‘between-study’ similarities associated with encoding and retrieval aspects of working memory and episodic long-term memory, a selective set of PFC areas including VLPFC, DLPFC and anterior PFC were indicated to be commonly engaged (Fletcher and Henson, 2001). Another ‘meta-analysis’ highlighted task-general recruitment in regions of VLPFC, DLPFC and ACC across multiple cognitive domains, encompassing five different cognitive demands; response conflict, novelty, working memory load, working memory delay and perceptual difficulty (Duncan and Owen, 2000). Collectively, the various ‘meta-analyses’ point to regions in VLPFC (BA 44/45/47), DLPFC (9/46), frontopolar cortex (BA 10) and ACC (BA 24/32) as generic to different mnemonic demands.

These across-study findings were soon complemented by within-study comparisons that directly assessed similarities and differences of brain activity associated with episodic long-term memory and working memory within the same set of subjects (Braver et al., 2001; Cabeza et al., 2002; Nyberg et al., 2002; Ranganath et al., 2003). The findings of such within-study experiments confirmed the results of meta-analyses by revealing a high degree of overlapping activation patterns across tasks and domains.

For example, a direct comparison of the neural correlates of encoding and retrieval phases during episodic and working memory was carried out by Ranganath and colleagues using an event-related fMRI design (Ranganath et al., 2003). The stimulus material consisted of unfamiliar faces. Several PFC subregions showed increased activity in association with both episodic and working memory across encoding and retrieval processes. These regions were located in bilateral ventrolateral PFC (BA 44/45/47) and bilateral posterior frontal areas (BA 6). In addition, common activations differentially related to retrieval across domains were found in bilateral dorsolateral PFC (BA 9 and 46), left anterior PFC (BA 10/46), and ACC (BA 24).

Another event-related fMRI study by Cabeza and colleagues also yielded similar findings of PFC commonalities between episodic and working memory (Cabeza et al., 2002). This experiment measured brain activity during two separate phases of
task performance. During episodic retrieval, the first phase in each trial consisted of an instruction to think back to a previous study list. In the second phase, a retrieval cue was presented, to which subjects were to respond by making a Remember-Know-New judgment. During the first phase of a working memory trial, four ‘to-be-remembered’ words were presented simultaneously in two columns. The second phase consisted of a single word probe, to which subjects were to respond by making a ‘Right-Left-New’ judgment. Episodic and working memory trials were randomly ordered. Overlapping activations were found in both prefrontal and parietal cortices. Common frontal lobe activity was revealed in the left dorsolateral PFC (BA 9), bilateral ventrolateral PFC (BA 45), ACC (BA 32) and the dorsomedial PFC (BA 6). All regions evoked increased activity during retrieval (phase 2), but only the dorsomedial area was also activated during maintenance/encoding (phase 1).

An fMRI study that compared neural activation patterns associated with verbal working memory and spatial attention also revealed common neural networks (LaBar et al., 1999). Even though the task paradigms involved verbal versus spatial material in a deliberate attempt to minimize processing overlap, a substantial degree of regional activation commonalities were reported. Brain regions similarly activated by working memory and spatial attention were located in the posterior dorsomedial PFC (BA 6), parietal (BA 7/40) and left temporal regions (BA 21/37) (LaBar et al., 1999).

Another study used a ‘two-phase’ task design and event-related fMRI to examine similarities in evoked brain responses during tasks of episodic memory and visual attention (Cabeza et al., 2003b). For trials in each task, phase 1 consisted of a 3 second presentation of a three-choice response display (‘Remember-Know-New’ in the memory task; and ‘One-Two-None’ Blips in the attention task), which informed subjects of what task they were to perform. Following this task instruction, phase 1 also encompassed a fixation gap (memory task) or a continuous display of a symbol (attention task), during which subjects performed a vigilance task (i.e. monitoring for the occurrences of ‘blips’). The second phase constituted a retrieval cue (memory task) or the question ‘blips?’ (attention task), to which subjects made a three-choice response in accordance with the instructions. This study demonstrated a common network including right-lateralized regions in DLPFC (BA 9), and VLPFC (BA 47), bilateral parietal cortices (BA 7), ACC (BA 24/32), and cerebellum, which points to the involvement of general attentional processes as part of the large-scale neural network typically associated with episodic retrieval (Cabeza et al., 2003b).

In summary, recent studies have begun to explore cross-functional similarities, the findings of which have revealed a fair degree of cross-domain activation overlaps, most notably within the PFC. However, this new area of neuroscientific exploration has predominantly focused on direct comparisons between two domains at a time, and the experimental designs used has been limited to standard event-related or blocked task paradigms.
RESEARCH OBJECTIVES

The main goal of the empirical papers in the present thesis was to assess cross-functional activation patterns associated with episodic and semantic long-term memory, working memory, attention, and executive control, with the purpose of distinguishing unity and diversity within devoted neurobiological mechanisms. This was done in an attempt to delineate and characterize shared neural substrates in terms of distinct component processes on the basis of (i) the extent and nature of domain-generality, (ii) the underlying temporal dynamics, and (iii) the sensitivity to different executive load manipulations. Toward this end, three functional brain imaging studies were conducted with the following study-specific prospects of exploration:

I. To examine functional activation overlap across multiple measures of working memory, and episodic and semantic long-term memory.

II. To delineate activation overlap with respect to sustained and transient neural modulations evoked by working memory, declarative long-term memory, and sustained attention.

III. To identify overlapping brain patterns that modulate with increased executive demands within the domains of episodic and working memory.

SUMMARY OF EMPIRICAL STUDIES

Study I: Common prefrontal activations during working memory, episodic memory, and semantic memory.

This study was based on functional imaging data from two large-scale PET experiments that comprised multiple tasks of working memory, episodic long-term memory and semantic long-term memory (Nyberg et al., 2002). The objective was to examine the extent to which commonalities in regional recruitment exist between these different memory systems. The rationale was that findings of overlapping neural activity would implicate shared component processes, the identification and specification of which might contribute to enhance our understanding of how mnemonic functions are implemented in the human brain. To accomplish this, the overall data were re-analyzed to identify brain regions that were significantly activated across all tasks. Altogether, the two experiments incorporated three measures indexing each memory system. Working memory was tapped into by the tasks; one-back, two-back, and random number generation, episodic memory was indexed by the tasks; ‘yes/no’ item recognition, cued recall, and autobiographical memory, and semantic memory was measured by the tasks; living/non-living categorization, fact retrieval, and synonym generation.
Furthermore, the processing demands were varied as to response output. Tasks with emphasis on either ‘generation’ processes or ‘categorization’ processes were included for each domain. These two types of processes have been associated with separate neural correlates (Cabeza and Nyberg, 2000) and were considered to constitute a possible alternative basis of activity-related task division (Nyberg et al., 2002). Regarding the current focus on identifying task-general activation patterns, the inclusion of these different response demands as to processing requirements, in addition to the multiple measures employed within each domain, makes findings of shared neural mechanisms even more noteworthy. The statistical analysis included two steps to isolate a common network of brain activity. First, two overall activation maps were created by conducting a weighted contrast of all memory tasks relative to a ‘reading’ baseline for each experiment, independently. Next, the activation map associated with Experiment 1 was used as an inclusive mask for the overall activation map of Experiment 2, with the purpose of identifying common regional activation patterns across both experiments. In a second step, each region in the generated “overall” activation map was investigated with respect to the effect evoked by each individual memory task. This was done to assure that overall effects were not driven by only a subset of the memory tasks. The results converged in showing four anatomically distinct regions within the frontal lobes that were conjointly activated in all memory tasks relative to baseline (Fig 1). Common regions were located in left hemispheric VLPFC (BA 45/47), DLPFC (BA 9/44/46) and frontopolar cortex (BA 10), as well as midline ACC (BA 24/32). Thus, the revealed commonalities corroborate previous findings of a prefrontal predominance in cross-functional overlaps of brain activity, which implicate the engagement of common control processes (e.g. Wagner, 2002; Sylvester et al., 2003) or more basic attentional processes (e.g. Posner and Petersen, 1990). The question of what specific component process(es) could be attributed to this overlap was further addressed in study II.

![Figure 1. Commonly recruited PFC areas in Study I: ACC (BA 24/32) (sagittal view on the left), left frontopolar cortex (BA 10) (anterior view in the middle), and regions in the left DLPFC (BA 44/9/46), and VLPFC (BA 47/45) (lateral view on the right).]
Study II: Sustained and transient neural modulations in prefrontal cortex related to declarative long-term memory, working memory, and attention.

This study used a novel mixed blocked/event-related fMRI design which enabled separation of task-induced brain activity that have a sustained temporal profile from brain activity with a stimulus-locked transient response. The logic behind this approach is that the performance of a cognitive task not only depends on the transient neural responses directly related to stimulus processing such as coding, evaluation, decision making and response occurring during individual trials, but also task-related changes in sustained neural activity that is induced by task instructions. This change in sustained activity is thought to encompass tonic control processes that coordinate task performance in a goal-relevant and context-appropriate manner. By using this design we attempted cognitive decomposition of the revealed commonalities in regional recruitment during tasks of episodic and semantic long-term memory, working memory, and sustained attention. To more fully understand how shared PFC mechanisms contribute to long-term memory, it is important to explicate the temporal nature of common activations in terms of sustained versus transient components, which has as of recently remained an elusive query due to limitations in available imaging methodologies. In order to elucidate the nature of putatively shared component processes as implicated by the consistent findings of cross-functional patterns of activation overlap, specific knowledge of regional differences in temporal dynamics may be informative.

Figure 2: A schematic illustration of the mixed blocked / event-related fMRI design in study II.
Two main objectives were outlined for study II. First, we aimed to use the described mixed event-related/blocked fMRI-design to dissociate common activation patterns for episodic and semantic long-term memory with respect to tonic control processes/sustained neural responses versus phasic item-related processes/transient neural responses. Second, the overlapping pattern of sustained activity associated with episodic and semantic long-term memory task performance was directly compared with the patterns of sustained activity evoked by a two-back working memory task and those evoked by an attention/vigilance luminance detection task, respectively. The incorporation of these multiple measures, in addition to the design, enabling delineation of the temporal characteristics of evoked neural responses, permitted a unique chance to differentiate the neuroanatomical correlates shared between long-term memory tasks with regards to relative contributions of component processes putatively reflecting working memory processes and/or sustained attention.

The results yielded a fair degree of overlap in the sustained activity increases associated with the two long-term memory tasks, although the activity pattern was more extensive in the semantic memory task. Overlapping prefrontal activations were elicited in bilateral ventrolateral PFC (BA 47/45), medial frontal gyrus at the border of ACC (BA 8/32), and right anterior PFC near the polar cortex (BA 46/10). More posterior regions that showed common sustained activity included left middle temporal cortex (BA 21) and left parietal cortex (BA 40/39). In a next step, we inspected the peak loci of this generic long-term memory pattern of sustained activity with respect to brain responses evoked during the working memory and attention tasks, respectively. By this procedure we obtained relative indicators of the regional contribution of processes putatively devoted to these functions to the neural network shared by episodic and semantic memory processes.

The main finding was that tonic component processes associated with sustained activity showed a closely corresponding response pattern for long-term memory and working memory (see Fig. 3). A subset of the regions that showed overlapping sustained increases across long-term memory tasks elicited sustained increases in association with the attention/vigilance task. However, these regions were activated during the working memory task as well (see red areas in Fig. 3). Transient, as compared to sustained activity increases, were characterized by relatively higher degrees of domain-selectivity.

The results of study II indicate that dissociable component processes underlie the shared neural circuitry between episodic and semantic long-term memory. Specifically, within the common circuitry, we distinguished regionally specific contributions associated with sustained activity in the ACC, and bilateral [predominantly right] VLPFC (BA 45/47), assumed to reflect general attentional processes that putatively operate during many different kinds of cognitive tasks, from sustained activity in the frontopolar cortex (BA 10), assumed to subserve task set maintenance.
Figure 3. Common sustained activity increases relative to baseline and temporal signatures of the neural responses in a region of dorsal anterior cingulate cortex/pre-SMA. Numbers below the anatomical images denote the z-coordinate of each displayed transversal section.

Figure 4. Common transient activity increases in all memory tasks relative to attention (for colour mappings of task-specific BOLD response changes relative to baseline, see Fig. 3).
Moreover, other regionally specific contributions shared between the memory tasks, relative to attention, were associated with overlapping transient activity in left DLPFC (BA 9/44) (see Fig. 4), left superior parietal cortex (BA 7), and medial cerebellum. These areas were posited to participate in general-purpose phasic control mechanisms conceivably more directly related to aspects of item-specific mnemonic processing.

**Study III: Unity and diversity of tonic and phasic executive control in episodic and working memory.**

This study employed the mixed blocked / event-related fMRI design to dissociate sustained and transient neural responses that modulated with increased executive demands in tasks of working and episodic memory. By manipulating executive demand across two levels in each domain (source versus item episodic memory, and two-back versus one-back working memory) we aimed to address the question of whether executive control functions are best described in terms of unitary control mechanisms supported by a critical set of common brain circuitry, tentatively shared by multiple cognitive functions, or in terms of fractionated control processes that rely on different (subsets of) brain structures, the recruitment of which critically depends on, and differentially modulates with, the domain-selective executive demands encountered.

The results yielded mainly domain-selective control modulations in both sustained and transient regional response increases with augmented executive load. However, there was also support for unitary executive control components in terms of both sustained and transient control modulations.

*Figure 5.* The three regions demonstrating common sustained control modulations with increased executive demands.

A common fronto-striatal-cerebellar circuitry was found to exhibit domain-general sustained activity increases in response to the increased executive demands, which might reflect a shared tonic executive component that mediates task performance in highly demanding tasks. The incrementing executive demand also induced domain-
general transient recruitment of bilateral areas of the parietal cortices, located along the posterior intraparietal sulcus (BA 7), which might reflect inhibition/shifting of the ‘focus of attention’ in complex tasks that require a dynamical interface between stimulus and mnemonic information prior to response selection (e.g. Corbetta and Shulman 2002). Despite the implicated high degree of regional and functional heterogeneity within PFC and other structures, with respect to the increased demands on executive control processes, the results of study III provide evidence in support of theoretical models of executive functions that posit both diversity and unity among executive control processes (Miyake et al., 2000).

Taken at face value, none of the regions of the generic PFC network showed modulatory effects related to increased executive demand. For sustained effects this may indicate that a set of generic PFC regions are commonly recruited across a wide variety of cognitive tasks to certify a context-appropriate adoption, maintenance, and implementation of task set (subserved by the frontopolar cortex) and the sustained allocation of focal attention (subserved by the ACC, and right VLPFC), for the duration of task performance. This might be considered to represent a ‘core’ context processing system associated with sustained neural activation, largely independent of executive and response selection demands. As the cognitive effort and task control requirements are staggered along some dimension, the executive load may reach some critical level that overload the hitherto adaptable control processes above their threshold of sufficiency, which results in the need for additional and new regions to come into play. It is hypothesized that the component processes mediated by such apparently binary ‘on-off’ regions might reflect higher-order layers of executive control responsible for ‘bootstrapping’ the currently running cognitive system by ensuring enhanced processing efficiency via active top-down biasing that serve to prioritize context-relevant pathways over irrelevant pathways. Based on the current findings of the shared involvement of both the DLPFC (BA 44/9/46) and the basal ganglia (i.e. the caudate nucleus) to comply with increased executive load across episodic and working memory, such higher-order control of context processing might be mediated by selective gating mechanisms, which consistently have been linked to prefrontal-striatal circuitry in many neurocomputational models of working memory and executive control (e.g. Frank et al., 2001; Hazy et al., in press).

Interestingly, the sustained control modulation found in the left DLPFC overlaps with the area of DLPFC that was found to exhibit common transient item-related responses in study II. An inspection of the transient effects associated with each task relative to ‘resting’ baseline in study III replicated this prior finding by showing common item-related activity of similar magnitude for all tasks in the same DLPFC region that also exhibited common sustained modulation with increased executive load. In the next section, this and other findings from the three functional brain imaging studies will be further investigated.
The overarching purpose of the present thesis was to explore overlapping and selective brain activation patterns across different forms of memory with a primary focus on episodic and working memory. In order to identify, dissociate and characterize shared neural substrates with respect to underlying component processes, three functional brain imaging studies were conducted in which the experimental design of each study was intended to provide increasing leverage for cognitive decomposition. First, a large-scale re-analysis of PET data from two experiments was conducted to identify reliable common activations across multiple measures of working memory, and episodic and semantic long-term memory. Thereafter, a novel fMRI design was utilized to assess the temporal dynamics underlying common brain activity, in terms of sustained and transient neural modulations, as well as the relationship between memory-related activity and attention-related activity. Finally, similarities and differences in the neural substrates of executive control between working and episodic memory was examined by manipulating the demands for executive processing within each domain, independently.

In keeping with previous cross-function imaging studies that incorporated tasks of working memory and (episodic) long-term memory for direct within-study comparisons (Braver et al., 2001; Cabeza et al., 2002; Nyberg et al., 2002; Ranganath et al., 2003), common activations were found in a distributed network of brain areas, with the most salient points of intersection occurring within the frontal lobes. In study I, commonalities were exclusive to four discrete PFC areas; left VLPFC (BA 45/47), DLPFC (BA 9/44/46), frontopolar cortex (BA 10), and ACC (BA 24/32). However, this initial re-analysis of the data from two blocked design PET experiments suffered from similar limitations as many prior studies investigating these two memory functions or ‘systems’ together. That is, they have exclusively focused either on comparisons based on the neural activity triggered by distinct types of events (event-related designs), or comparisons based on the average relative change in neural activity evoked by the total number of trials (including the ISIs) during blocks of task performance (blocked designs).

The neural mechanisms and different component processes evoked during performance of cognitive tasks are arguably represented throughout a spectrum of different time scales. Investigations using either a blocked or event-related design in isolation cannot provide information on the full spectrum of the brain activation dynamics that underlie task performance. This is because blocked designs confounds the two types of responses, whereas event-related designs selectively index only item-specific transient changes and ignore temporally extended sustained responses. Mixed fMRI designs as the one exploited here (in study II and III), are unique because they allow researchers to dissociate and concurrently measure transient item-related responses induced on a trial-by-trial basis and item-
independent sustained neural activity that occur throughout entire task blocks (Visscher et al., 2003; Donaldson, 2004).

In the following sections, theoretical implications of overlapping brain activation patterns between episodic and working memory, with respect to underlying temporal profiles and the degree to which commonalities further overlapped with the activation patterns associated with semantic memory and attention/vigilance, respectively, will be elaborated upon. I start out by considering the PFC regions that exhibited common sustained activity across episodic and working memory, and tentatively propose hypotheses as to the candidate component processes that may be attributable to each of the implicated areas.

**Overlapping sustained neural activity: Common control processes related to maintenance of an attentive state and task set representation**

Compared to a low-level resting baseline, sustained activity that was common for episodic and working memory was manifested within a network of primarily frontal and parietal cortices. In study II, the areas of commonality within PFC encompassed bilateral ventrolateral PFC (BA 47/45), anterior PFC (i.e. frontopolar cortex; BA 10), and a midline portion of frontal cortex encompassing parts of dorsal ACC (BA 32) and the pre-supplementary motor area (pre-SMA) (BA 6). Beyond PFC, both tasks additionally exhibited sustained activation in the left parietal cortex (BA 40/39), and left temporal cortex (BA 21).

The sustained activation pattern shared by episodic and working memory involved three out of the four PFC areas that were identified in study I as showing common recruitment in two large-scale PET experiments that together comprised multiple measures of working memory, episodic memory, and semantic memory. These regions involved left VLPFC, frontopolar cortex, and the dorsal ACC, all of which (in particular VLPFC and ACC, and to a lesser degree frontopolar cortex) have been highlighted in a number of comprehensive reviews of across-study similarities in PFC activity (Cabeza and Nyberg, 2000; Christoff and Gabrieli, 2000; Duncan and Owen, 2000; Fletcher and Henson, 2001; Ramnani and Owen, 2004). This further corroborates the generality of their involvement in a wide spectrum of memory tasks and other cognitive challenges.

Despite extensive research, it remains unclear how to best characterize the precise functional contribution of each of these regions, although several candidate processes have thus far been proposed. Nevertheless, many prior accounts regarding the nature of the component processes mediated by these commonly recruited areas have proposed domain-specific contributions and stimulus-synchronous processes (e.g. claims that posit a selective role of left VLPFC in item-related transient processes associated with controlled semantic retrieval (Wagner et al., 2001) or
selection among competing semantic representations (Thompson-Schill et al., 1997). Such accounts are rather incompatible with current data as study II and III clearly demonstrated (primarily) item-independent sustained activity within many of the regions, and predominantly no transient neural activity changes.

**Basic attentional processes** In the overall task comparison of study II, covering semantic categorization and sustained attention beyond episodic and working memory, both the right VLPFC (BA 47) and a medial PFC/ACC (BA 6/32) region were found to yield a similar sustained effect across all four tasks relative to the low-level baseline (resting while maintaining the gaze upon a small circle in the centre of the visual field). This suggests a role of these areas in basic attentional processes such as maintaining an attentive state pertaining to the current cognitive focus throughout task performance. Also, an enhanced level of alertness might be required during ongoing tasks as compared to the resting baseline. The right lateralization of the common VLPFC response converge with findings from prior imaging studies demonstrating right PFC to be engaged in vigilance tasks (e.g. Pardo et al., 1991), as well as neuropsychological evidence showing that damage to the right PFC disproportionately impairs sustained attention (e.g. Wilkins et al., 1987). Another, yet closely related interpretation is that this task-general pattern relates to the apprehension of upcoming events, a feature pertaining to all tasks. Such a notion concurs with numerous findings of activation in right VLPFC/anterior insula and medial PFC in association with task preparation in studies exploiting different kinds of cueing paradigms (Brass and von Cramon, 2002; Luks et al., 2002; Curtis et al., 2004). All of these processes may be partly or entirely subserved by a generic attention network (Pashler et al., 2001), and the ACC in particular has been considered a key structure in an anterior attentional system (Posner and Petersen, 1990).

**Task set maintenance** The frontopolar cortex (BA 10) also evoked common sustained activity increases during episodic and working memory tasks, but in contrast to the ACC and right VLPFC, no response was found in this area during the attention/vigilance task. In the literature, the frontopolar cortex has been intimately linked with episodic memory, and more specifically, the instantiation and maintenance of retrieval mode, which reflects a specific cognitive state or task set that supports recovery of episodic event information (Tulving, 1983; Lepage et al., 2000). Although this account fits well with the sustained temporal signature, it cannot readily explain the parallel effects demonstrated for both working memory (study II and III) and semantic memory (study II). The common sustained effect obtained across all memory tasks (but not attention/vigilance) clearly indicates a more general role of this anterior-most cortical region than endorsed by the retrieval mode hypothesis. This might putatively correspond to cognitive control processes related to task set maintenance and context representation in general (Braver et al., 1999; Allport and Wylie, 2000). Some authors have considered such control processes as constituting procedural working memory. However, such
accounts appear to merely encompass a subset of the control processes that conceivably subserve task set maintenance.

Task set or ‘task set configuration’ refers to the task goal, strategic and procedural directives and constraints, stimulus-response mappings, and putatively an abstract model of the appropriate set of operational component processes to be utilized in order to achieve the current task goal. Indeed, task set representations can be defined as temporary and arbitrary ‘schemas’ in its most abstract form, in that the represented conglomerate of context-appropriate component processes (whose co-ordinated execution are performed by distributed large-scale neural systems) giving rise to task completion is not directly accessible to conscious awareness. Although the concept of task set implicates very fundamental higher-order control mechanisms that should be engaged in the service of practically any type of experimental task, it is proposed that the task set-related control processes represented within the anterior PFC may diverge from those being exploited in very basic tasks contexts (e.g. attention/vigilance tasks). Their engagement may conceivably depend on task requirements that involve some degree of flexible interplay between mnemonic representations and online processing of current perceptual input. In congruence with the cognitive control theory put forward by Cohen and colleagues (Cohen and Servan-Schreiber, 1992; Braver et al., 2002), in which context representations (i.e. task sets) are contingent upon sustained neural implementation, the frontopolar control processes operate throughout the duration of task performance as indicated by the sustained activity. Frontopolar cortex plausibly maintains a mental state of tonic ‘intentionality’ and ‘anticipation’ related to current and future goal states, which is consistent with claims that prospective memory is being subserved by this region (Burgess et al., 2001).

Theories concerning contextual representation and top-down modulation in the service of goal-directed behaviour have typically focused on the DLPFC (BA 9/46) as the principal brain structure responsible for such ‘higher-order’ control processes (e.g. Frith and Dolan, 1996; Fuster, 1997; Braver et al., 2002; Curtis and D’Esposito, 2003). A primary influence to this strong emphasis on the DLPFC in contemporary models of cognitive control and working memory comes from experimental studies of nonhuman primates. For example, single-unit recordings have demonstrated sustained neuronal firing within DLPFC during delayed-response tasks (e.g. Funahashi et al., 1989). Furthermore, local and reversible lesions of neural tissue in DLPFC have yielded detrimental effects on performance in similar tasks and performance errors have been associated with reduced delay-period activity (Fuster, 1973; Bauer and Fuster, 1976; Funahashi et al., 1993). Suggestive evidence has also indicated rule representations to be maintained in the DLPFC as revealed from electrophysiological recordings of behaving nonhuman primates (Wallis et al., 2001).

Human neuropsychological studies of patients with selective damage to the DLPFC have not always been able to establish a similarly strong link between DLPFC and working memory/executive processes (e.g. Müller et al., 2002). This lack of
conclusive findings seems to suggest that working memory and executive processes (e.g., manipulation and monitoring) often specifically assigned to DLPFC in many theoretical models of PFC function may not be strictly dependent on this area. However, lesions comprising both DLPFC and VLPFC have been found to cause impairments in even simple working memory tasks (Müller et al., 2002). Nevertheless, the central importance of DLPFC in diverse executive control processes is by no means questioned. It is merely posited that the specific control processes associated with task set maintenance might be subserved by the frontopolar cortex, at least in task contexts that do not critically challenge the cognitive system by inducing excessive demands on executive control.

As previously mentioned, prior imaging studies have noted prominent activity in the right frontopolar cortex in tasks of episodic retrieval (Cabeza and Nyberg, 2000; Lepage et al., 2000). This activity appeared to be independent of the level of retrieval success, which served to inspire the attribution of activation in this area to the adoption and maintenance of retrieval mode (Lepage et al., 2000), and results from evoked brain potentials associated with an episodic memory task indicated tonic frontopolar activation (Duzel et al., 1999). Adding further credence to this notion, two imaging studies investigating episodic retrieval with the mixed fMRI design demonstrated sustained, but not transient activity in the frontopolar cortex (Donaldson et al., 2001b; Velanova et al., 2003). Nonetheless, as noted above, the retrieval mode hypothesis cannot account for the present findings of identical frontopolar activations evoked during semantic categorization and working memory as those elicited for episodic memory. The results of study II are not unique, however. There are several reports of anterior PFC involvement in working memory (Braver and Bongiolatti, 2002; Cabeza et al., 2002; Nyberg et al., 2002) and frontopolar activation has also been observed in tasks indexing semantic monitoring (MacLeod et al., 1998), cognitive branching (Koechlin et al., 1999) and prospective memory (Burgess et al., 2001; Burgess et al., 2003; den Ouden et al., 2005).

Recent evidence for a general role of frontopolar cortex in the establishment and maintenance of task set configurations was obtained by Sakai and Passingham (2003). They aimed to investigate preparatory neural activity evoked prior to the first trial in a number of different working memory tasks. Sustained activity was demonstrated in the frontopolar cortex during the delay intervals following a short presentation of a ‘pre-task’ cue that merely informed participants of what specific task they were going to perform. In a mixed blocked/event-related fMRI study that explored the temporal dynamics underlying task switching, the right frontopolar cortex was found to selectively elicit sustained activity during mixed-task blocks (i.e., no frontopolar state effects were seen for single-task blocks). This sustained effect was taken to reflect augmented demands on tonic control mechanisms that subserve the maintenance of multiple concurrent task set configurations and regulate the need for flexibility (Braver et al., 2003). Ramnani and Owen (2004) have proposed that the frontopolar cortex is selectively engaged when there is demand to integrate
the outcome of two or more different cognitive operations in a coordinated fashion to meet task requirements. However, this view cannot readily explain the general finding of sustained frontopolar activity in simple item recognition tasks and semantic classification.

On the basis of current findings and prior data it is tentatively proposed that tonic control processes subserved by the anterior PFC (BA 10) might be recruited in task situations that require the integration of mnemonic information not externally accessible (e.g. conceptual knowledge, episodic memoranda, working memory content), with some anticipated aspect of the immediate or intermediate future. More specifically, an abstract means-end goal representation might be established in the frontopolar cortex, by which critical parameters for task completion are determined and specified. This task set configuration might include a discrete set of necessary cognitive operators or computational manoeuvres (e.g. classification, memory search, matching, updating, selection processes) and the setting of response criteria in accordance with an appropriate set of ‘if-then’ rules. In other words, the frontopolar cortex is posited to play a role in task set control processes that might be preferentially engaged in tasks that involve working memory, and/or declarative long-term memory. This implies a putatively distinct conception of a particular kind of task set configuration that might be referred to as a ‘general retrieval mode’.

Selective sustained neural activity: Distinct processes related to active maintenance and monitoring within working memory.

As would be expected, there was a set of frontal areas that exhibited sustained neural activity in the delay intervals during the two-back working memory task, in the absence of activation during the episodic memory task. These regions involved the left mid-DLPFC (BA 9), right posterior superior PFC (BA 6) and the medial frontal cortex including dorsal ACC (BA 6/32). Conversely, no region was selectively engaged in association with maintenance of the task set assumed to be uniquely devoted to ‘retrieval mode’ (see the above section). It should be noted, though, that the apparent lack of process-specificity in the sustained activation pattern associated with episodic retrieval might be eloquently linked to the pertinent differences in processing load across the two functions.

Taking into consideration system-specific neurocognitive component processes generally found to evoke sustained neural activity in respective task, the episodic task concurs principally with ‘retrieval mode’ related to the cognitive state of directing attention toward anticipation of remembering of things past, whereas the two-back working memory task involves constant on-line processing related to active maintenance, and continuous monitoring of the two most recently presented items. Hence, with respect to processing demands, the inter-stimulus intervals
(ISIs) in the episodic retrieval task must be considered relatively process vacant as compared to the two-back task. Although sustained neural activity was found in regions classically associated with retrieval mode during the episodic task (i.e. right-lateralized frontopolar cortex and VLPFC), they were also activated in the two-back task (see above section).

A quite unexpected result in study II was the finding that the pattern of sustained activity elicited during the semantic categorization task showed such an extensive overlap with the activation pattern exhibited during the two-back working memory task. Only the region of left hemispheric mid-DLPFC (BA 9) prevailed as selective to working memory after taking into account or disregarding sustained activity that was shared with the semantic memory task. Although the type of semantic task employed inherently involves a working memory component since the target category must be retained online as a comparison template, and the fact that all distractor items were members of a conceptually similar category instance to that represented by the target category (e.g. fruit versus vegetables) may compel interference resolution, it was still surprising that only a single region remained selectively engaged in the two-back task.

The functional contributions generally ascribed to this left mid-DLPFC region have been closely linked to the type of control operations generally associated with the central executive (e.g. D’Esposito et al., 1998; Petrides, 2000). Two major perspectives related to DLPFC functions can be distinguished in the imaging literature. One view holds that DLPFC is preferentially linked with the mechanisms underlying active maintenance of task-relevant information within working memory (e.g. Fuster, 1995; Goldman-Rakic, 1995). The other view postulates a higher-order role of mid-DLPFC in subserving multiple executive processes that monitor, co-ordinate and manipulate/act upon representations held on-line within working memory while attributing active maintenance processes to the VLPFC (Smith and Jonides, 1997; D’Esposito et al., 1998; Owen et al., 2000). Brain imaging studies specifically designed to dissociate the brain regions involved in maintenance versus manipulation processes have provided inconsistent results regarding the specific roles of mid-DLPFC and VLPFC (e.g. D’Esposito et al., 2000; Ragland et al., 2002; Veltman et al., 2003).

Successful two-back task performance requires the combined deployment of processes underlying maintenance and manipulation/monitoring. Regarding the selective sustained activation of mid-DLPFC observed for the two-back task of study II, there are a number of distinct task properties that differentiate this task from the other tasks (episodic item recognition, semantic classification, and vigilance) with respect to control processes expected to operate throughout the ISIs. For example, the requirement to constantly hold in memory the two most recent items and keep track of which item was most recently presented is specific for two-back. These task demands are assumed to concurrently engage processes of active maintenance and monitoring of item information (representations of item identity and their inter-relational order), which generally activates the mid-DLPFC
(Petrides, 1994b; Owen et al., 1996) (see also section on domain-selective control modulations below).

**Overlapping transient neural activity: Shared control processes related to response selection or context-integrative item coding**

In study II, overlapping transient activity between episodic and working memory were assessed after first controlling for sensory and motor activity by subtracting out the transient responses elicited by target detection in the attention/vigilance task. Common transient activity was found in three frontal sites including the left posterior DLPFC (BA 44/9), a small area of the left VLPFC (BA 47), and the ACC/pre-SMA (BA 32/6). Other areas exhibiting shared transient engagement during item processing were located in left superior parietal cortex (BA 7) and medial cerebellum. Furthermore, it was found that all of the transiently activated regions that were shared between episodic and working memory also exhibited similar transient responses during item processing in the semantic memory task.

The finding of shared involvement of the left posterior DLPFC (approximating an area at the conjunction of BA 44/9/46) across all memory tasks is of special interest. Noteworthy, the focus of this activation is identical to the area of commonality that was observed in study I to elicit overlapping activation across all nine memory tasks (i.e., triplets of tasks indexing working memory, episodic memory, and semantic memory, respectively) (Nyberg et al., 2003). However, since PET data (and blocked designs in general) do not permit inferences with respect to differential temporal properties of neural activity changes, the data from study I made detailed functional interpretations of the reported common DLPFC activity problematic.

As discussed in the prior section on overlapping sustained neural activity, several authors have considered DLPFC to represent an area of central importance in the service of different aspects of higher-order cognitive control and executive functions (e.g. Petrides, 2000; Braver et al., 2002). Reminiscent of the functions ascribed to the supervisory attentional system in Norman and Shallice’s model (1986), the DLPFC has been posited to influence the level of activation within multiple other brain systems via sustained (excitatory and/or inhibitory) top-down modulations to bolster context-appropriate processing pathways and goal-oriented behavior (Cohen and Servan-Schreiber, 1992). Although certainly a most prevalent region of activation in functional brain imaging investigations of the brain systems engaged in demanding working memory tasks and other tasks indexing executive control such as the Stroop task, the precise role of DLPFC in executive processing remains controversial. In the view of DLPFC as a sort of “task-process coordinator” that represents and maintains context-relevant information in the service of exerting top-down modulatory influence on the neural processing throughout the cortex to promote efficient and accurate task performance, this area might be expected to exhibit sustained activation (e.g. Curtis and D’Esposito, 2003).
The response selection hypothesis An opposing view holds that DLPFC is preferentially concerned with memory-guided phasic control processes that act in the service of response selection, rather than maintenance processes (Frith, 2000). Several recent imaging studies have provided evidence that support this claim (e.g. Schumacher and D’Esposito, 2002). For example, in an fMRI study of spatial working memory, where the task was explicitly designed to assure that selection of the relevant information held on-line in working memory could not be carried out until the trial was terminated (i.e. with the onset of a test probe) (Rowe et al., 2000), DLPFC was found to exhibit significant transient activity in association with the response phase, while showing no sustained activity during the maintenance phase. Consequently, it has been argued that brain imaging findings of persistent delay period activity in DLPFC may be attributable to control processes related to response preparation that may occur only to the extent that the employed experimental task design allows for response selection to take place during delays, i.e. in advance of its execution (Curtis et al., 2004).

According to the selection account, the DLPFC should be expected to evoke transient neural activity associated with control processes that may help to resolve response competition (e.g. evaluating the relevance of active internal representations with respect to task goal). The findings of study II converge with this account by demonstrating common transient activity in left posterior DLPFC across working memory and episodic memory in the absence of sustained activity. It should be noted that the common activation focus in the left posterior DLPFC is more caudal and ventral as compared to the mid-DLPFC (BA 46/9) area that has previously been proposed as a prime candidate for higher-order control processes linked with the ‘central executive’ (e.g. Curtis and D’Esposito, 2003). However, the location in posterior DLPFC is in complete concordance with the activation focus of a previous event-related fMRI study that also examined episodic and working memory together (Cabeza et al., 2002). Importantly, this regionally specific between-study overlap applied selectively to transient activity elicited during the retrieval phase of the episodic and working memory tasks, with no maintenance-related activation of the posterior DLPFC in either study. Hence, across two independent direct comparisons of episodic and working memory, active retrieval processes was associated with a topographically identical overlap in transient item-related left posterior DLPFC activity. This common effect could reflect selection processes.

Imaging studies of episodic retrieval has previously demonstrated increased transient activity in the left posterior DLPFC as a function of the executive requirements associated with memory search (Velanova et al., 2003; Wheeler and Buckner, 2003), which reasonably entail auxiliary increases on selection control processes. For example, Wheeler and Buckner (2003) observed significantly greater activity in the left posterior DLPFC for retrieval trials involving items studied only once as compared to retrieval trials involving either extensively studied (i.e. overlearned) or “new” items. This transient effect may conceivably be accounted for
by the selection hypothesis, since retrieval following shallow as opposed to deep encoding typically requires more elaborative evaluation and often less certain memory decisions, which should increase the demands on (response) selection (Craik and Lockhart, 1972).

Returning to the common transient effects obtained in study II, it was found that semantic classification activated the posterior DLPFC and VLPFC areas to a similar degree as the episodic and working memory tasks. Both the left posterior DLPFC (BA 44/9) and left VLPFC (BA 47) have in numerous previous studies been strongly linked with controlled retrieval and selection of information from semantic memory (Badre and Wagner, 2002) and corresponding left PFC regions have been proposed to subserve semantic working memory processes (Gabrieli et al., 1998). With respect to such “narrow” and domain-specific interpretations, which are typically inferred from studies of single cognitive functions in isolation, the current data point to the value of employing multiple tasks of different cognitive domains for cross-functional comparisons within the same ‘within-subjects’ study.

A more general account of left PFC function has been proposed by Thompson-Schill (Thompson-Schill, 2003; Kan and Thompson-Schill, 2004), who argues that regions within the left VLPFC (approximating BA 47/45/44), although representing the most replicated area of activation in semantic tasks (together with inferior temporal cortex), do not serve controlled semantic processing per se, but rather mediate a general control mechanism supporting selection processes independent of cognitive domain. This account fits well with the previously discussed response selection hypothesis.

**Context-integrative item coding** It should be noted that the shared recruitment of left DLPFC may contribute to phasic component processes other than selection. Courtney and co-workers have pointed out that “activation of the same areas by both long-term retrieval and working memory is consistent with the idea that retrieval produces an active representation of the recalled material much like the active representation of material held during working memory delay” (Courtney et al., 1997, p. 610).

Extending this notion, it might likewise be argued that externally presented stimulus items, especially in tasks that involve judgments based on mnemonic information (e.g. retrieval cues), need to be transiently (en)coded/maintained in a working-with memory state (Moscovitch, 1992) to provide a comparison template for matching purposes while context-relevant item attributes are evaluated with regard to stored representations. In addition to item coding for identity, such transiently maintained item representations might also encompass more context-integrative dimensions such as intentional purpose (e.g. matching the current item to the item presented n-back or as to previously memorized list of items or a semantic category) and relevant stimulus-response associations. It is this conception of context-integration with respect to purposeful and intentional stimulus-to-response processing that distinguishes and constrains the type of item coding processes proposed here from, for example, perceptual coding processes involved in
passive word reading (although multiple coding elements undeniably overlap between the two).

On the basis of the present data and several prior imaging studies of various cognitive domains showing a general pattern of item-related activation within the left posterior DLPFC, it is tentatively proposed that this area might play a role in generic control processes related to the operative integration of (1) codespecification of items, (2) transferring of salient cues (extracted during codespecification) to designated processing systems, and (3) linking computational outcome to stimulus-response associations and corresponding motor output. The running implementation of these item processes might produce a transiently coded internal representation that enters into a working-with memory state.

These purported control processes would serve to implement task set ‘intentions’ during each trial by enhancing context-salient item properties for the coding of transient internal representations optimized for current context-appropriate type of cognitive operations. Depending on the time required for completion of adequate item processing on each trial, the engagement of retention systems might become necessary. However, most tasks typically finalize stimulus-locked perceptual input-motor output cycles very quick leading to rapid decay of the transient unitized code unless effortful biasing is exerted to prolong the maintenance of the representation (Ruchkin et al., 2003).

This aspect relates to the idea that encoding processes mediated by left posterior DLPFC/VLPFC might entail working memory processes that enable access to and maintenance of item-specific phonological and semantic codes as well as associative connections, the only difference to “traditional” working memory maintenance being the briefer engagement of those processes during item encoding (Wagner, 1999). Findings of positive correlations between the time an item is retained online in working memory via rote rehearsal and subsequent recognition performance seem to parallel this hypothesis (Davachi et al., 2001).

However, the cognitive mechanisms subserving the transient context-integrative coding processes are assumed to be independent from the working memory mechanisms that support active maintenance. The posterior DLPFC appears to contribute primarily to the phasic operations involved in the encoding and retrieval aspects of working memory tasks in a fashion that seems to generalize to episodic and semantic long-term memory tasks (and presumably non-mnemonic tasks as well).

Accordingly, studies directly comparing brain activity between encoding and retrieval phases have consistently reported similar transient recruitment of the posterior DLPFC area during item processes related to encoding and retrieval (Wagner et al., 1998; McDermott et al., 1999b; Ranganath et al., 2000), and this has been taken to reflect incidentally evoked encoding processes during the process of active retrieval (attempts) (McDermott et al., 1999a). The incidental encoding
effects associated with active processing of episodic retrieval cues have also been explicitly demonstrated by Buckner and co-workers (Buckner et al., 2001).

Indeed, active retrieval mechanisms that involve elaborative search for memory traces should conceivably be intimately linked with semantic processes during the strategic probing and evaluation of recovered associative information potentially generated during the initial encoding. In fact, it might be argued that all episodic retrieval attempts involve an interaction between active mnemonic control operations in PFC and stored semantic information such as multiple associative links presumably held in posterior cortex. As already mentioned, the left posterior DLPFC/VLPFC has consistently been activated in tasks that require controlled retrieval of semantic associations (e.g. Badre and Wagner, 2002).

However, an intriguing finding not consistent with a role of left posterior DLPFC in context-integrative coding processes specific to memory functions comes from an fMRI study that assessed the neural effects of increased task difficulty in non-mnemonic tasks of response selection (complex versus simple response-stimulus mapping rules) and perceptual discrimination (fine versus coarse line length) (Jiang and Kanwisher, 2003). A closely located region in left posterior DLPFC showed increased neural activity with increased difficulty across both task manipulations. Moreover, this common effect was also seen in other task contrasts of high versus low task difficulty, including tasks of colour discrimination and lexico-semantic classification (Jiang and Kanwisher, 2003). This would seem to implicate a more general and broader functional contribution of the left posterior DLPFC extending beyond memory tasks. Possibly, left posterior DLPFC participates in many cognitive domains to implement context-integration of stimulus-to-response processing on an item to item basis, whereas in tasks that involve mnemonic or lexico-semantic coding of items the left VLPFC is engaged in tandem with left posterior DLPFC.

**Cognitive efficiency** If the common function reflected in the shared recruitment of posterior DLPFC is attributable to cognitive efficiency with respect to the degree of implementation of context-relevant item processing in a general sense, the magnitude of the neural response in this area should be positively correlated with behavioral indices of task performance. A practical means to obtain relevant measures for this type of assessment in the context of episodic memory is to use the subsequent memory paradigm (Brewer et al., 1998; Wagner et al., 1999). The set-up of this design allows event-related neural activity elicited during item encoding to be partitioned as to whether each item is later remembered or forgotten in an ensuing recognition test, which provides an excellent index of the neural correlates of encoding efficacy.

Several studies using this design have indeed demonstrated significantly greater neural response in the area of left posterior DLPFC during encoding of those items that were subsequently remembered than those that were forgotten (e.g. Otten et al., 2001). Viewed from the perspective that posterior DLPFC mediates top-down control to optimize context-contingent item processing these findings would be
expected. That is, the certified implementation of task set goals in the context of intentional encoding should indeed entail elaborative and successful encoding promoting higher levels of recovery for items endorsed by greater transient activation of this area as opposed to items not affording an equal degree of context-integrative control.

A more recent fMRI study manipulated an incidental study phase as to produce intermixed deep (semantic judgments) versus shallow (orthographic judgments) encoding and measured brain activity on an item by item basis during both encoding and retrieval phases (Henson et al., 2005). Of the relevant comparisons conducted in this study, only a single contrast showed a transient increase in the left posterior DLPFC. This selective activation reflected shallow encoding associated with subsequent hits relative to subsequent misses, which was attributed to familiarity-based recognition processes. By contrast, bilateral VLPFC (BA 47) activity associated with subsequent hits following deep encoding relative to shallow encoding was assumed to reflect processes underlying recollection memory (Henson et al., 2005). However, it might equally well be reasoned that more elaborative conceptual processing as compared to shallow processing at encoding should increase the relative degree of familiarity-based memory rather than recollection-based memory. Particularly so, as the study by Henson and colleagues employed a simple yes-no recognition test without the explicit demand to recover contextually detailed information. Also, the conclusion by Henson and colleagues appears to be at odds with other imaging evidence.

For example, this might be argued to be the case in an fMRI study that examined the effects of divided attention on the activation patterns associated with encoding and retrieval (Kensinger et al., 2003). This study employed secondary tasks to be performed concurrently with encoding. Two levels of secondary task difficulty were used to manipulate the attentional resources available for encoding operations. It was found that the encoding-related neural activity in the left posterior DLPFC was reduced by concurrent performance of the ‘difficult’ as compared to the ‘easy’ distraction task, as revealed by a significantly greater response evoked in the ‘easy’ encoding condition. This could be taken to reflect a greater detrimental impact of the harder concurrent task on the capability to integrate the component processes required for successful encoding. Accordingly, adequate context-integration during item processing is hampered to the extent that the secondary task impinges upon control systems that would otherwise be engaged in encoding.

Unfortunately, for the analysis of subsequent memory effects, the authors reported the stereotactic coordinates for only one of two observed left PFC regions associated with greater encoding-related activation for remembered than for missed items. These two left prefrontal regions (the reported region being located in the left VLPFC (BA 45/47) showed a response magnitude predictive only of successful retrieval of items encoded during the easy secondary task. On the other hand, the analysis of brain activity associated with the retrieval task found the left posterior DLPFC (BA 9/44/46) and left VLPFC (BA 45) to exhibit greater transient activity
for items that were encoded in the easy as opposed to the hard condition (Kensinger et al., 2003). By using a “remember-know” recognition paradigm, it could be determined that encoding during the easy secondary task produced a greater amount of ‘remember’ or recollection responses than encoding during the hard secondary task. In contrast to the interpretation by Henson and colleagues (2005), the findings of Kensinger and colleagues (2003) clearly indicated that the left posterior DLPFC was associated with recollection and retrieval of contextually detailed information. These results support the idea of interdependent functional roles being subserved by left posterior DLPFC and VLPFC in the service of context-integration and evaluation of conceptual associations during item coding operations in both encoding and retrieval tasks, which contributes to recollective processing and the activation of relevant representations of long-term memory.

Other studies have also focused on the activation patterns associated with episodic retrieval processes following either shallow or deep encoding, measuring brain activity in the subsequent recognition tests (e.g. Buckner et al., 1998). In an early blocked fMRI experiment, the left posterior DLPFC (BA 44/9) was found to elicit greater activation for retrieval processing following shallow encoding (co-occurring with low retrieval success) as compared to deep encoding (co-occurring with high retrieval success) (Buckner et al., 1998). However, since those results were obtained from blocked recognition conditions that comprised either items of shallow or deep encoding, the differential activation could relate to differences regarding effortful retrieval attempts and/or behavioral strategies adapted for low/high confidence memory judgments. In more recent studies using event-related and mixed fMRI designs (Wheeler and Buckner, 2003, Velanova et al., 2003), which allow individual retrieval attempts to be categorically divided into successful recovery, correct rejection, false alarm or miss, it has been found that a similar region of left posterior DLPFC is preferentially activated during controlled retrieval of shallowly encoded items. The utilization of strategic retrieval processes presumably required in such instances would entail the type of context-integrative control processes suggested to be implemented by the left posterior DLPFC (BA 44/9), and the subsequent memory effects associated with this area similarly agree with such hypothesis with respect to the mechanisms underlying elaborative encoding.

Imaging evidence from working memory studies appear to parallel the above findings from long-term memory by suggesting that task difficulty and increased load in working memory tasks is associated with increased activity in DLPFC during strategic encoding of items but not maintenance (Rypma and D'Esposito, 1999). In an early fMRI study, Courtney and colleagues (1997) employed an event-related design to index the neural correlates of face working memory in order to separate patterns of brain activity into distinct temporal phases of the task corresponding to encoding and maintenance operations. Their analysis revealed a neural response profile in keeping with a predominantly transient encoding-related recruitment of posterior DLPFC. Across three prefrontal activation sites reported in the study (DLPFC, VLPFC and anterior PFC) the posterior DLPFC area showed
the relatively strongest transient effect for encoding, combined with the relatively weakest sustained effect for active maintenance (Courtney et al., 1997).

Taken together, several previous fMRI findings may be interpreted as to confer with the idea that left posterior DLPFC (BA 44/9) might play an integrative role in contextual top-down biasing of initial perceptual processes that link input of currently relevant stimulus dimensions via a transiently coded internal representation to appropriate processing pathways in posterior cortical circuitry while accessing stimulus-to-response mapping rules (and related motor response set) presumably held in parietal cortex in anticipation of computational feedback.

In line with the assumption that this area exerts biasing of perceptual processing, Carter and colleagues (Carter et al., 2000) found bilateral posterior DLPFC regions to exhibit transient activity showing a very early peak response (compared with, for example, the ACC) which was assumed to reflect strategic item-by-item selection demands. These activations were stronger for unexpected congruent trials than other trials in the Stroop color task, and came before stimulus-related activation in the extrastriate cortex (BA 18/19) suggesting that DLPFC and ACC may interact to control and modulate posterior visual areas (Carter et al., 2000).

A common requirement across the tasks of working memory, episodic retrieval and semantic categorization comprise the need to compare external stimulus material with internal mnemonic information. This comparison process should to varying degrees require retrieval processes that actively probe internally stored information, retained in working memory or long-term memory. In keeping with a number of prior theories on the control of memory (Buckner, 2003), it is proposed that such matching and evaluation processes are subserved by the left VLPFC. This region conceivably act to disambiguate item saliency by exerting top-down biasing on processing in the posterior cortical areas that contain the actual subset of long-term memory representations required to be reactivated and recovered. The VLPFC have been postulated to entail item-related control processes underlying active retrieval, intentional encoding and decision making related to the evaluation of mnemonic information, regardless of whether held in working memory or stored in long-term memory (Petrides, 2005).

Pertaining to the generic context-integrative and/or selection control functions we propose to be subserved by the regions of posterior DLPFC and VLPFC, their anatomical locations are quite fitting. Being situated in the sulcus principalis of frontal cortex, they (especially the more caudal portions of DLPFC and VLPFC) are deemed “the initial recipients of information from posterior association areas and are the locus of the initial interaction of executive processing with short-term memory for modality-specific and multimodal information” (Petrides, 1994a). The posterior DLPFC has been suggested to be optimally situated to integrate premotor, PFC, and verbal information (Brass and von Cramon, 2004). The close structural relationship further indicates that the control mechanisms subserved by left posterior DLPFC and VLPFC are intimately intertwined as to their role in
selecting, co-ordinating and certifying the internal integration of stimulus input, appropriate cognitive operations, response selection and motor output.

**Selective transient neural activity: Updating and temporal coding of working memory items and active long-term memory probing for episodic traces**

Numerous prior event-related fMRI studies have investigated the differential functional activation patterns associated with working memory and episodic memory. In convergence with these studies, study II revealed selective transient activity in the left DLPFC (BA 9) for working memory and the right VLPFC (BA 47) for episodic memory. The activation of the left DLPFC region is more dorsal as compared to the DLPFC region that evoked common transient activation. With regard to item-specific component processes whose contribution should be of critical importance to performance in two-back tasks an obvious candidate is updating (Morris and Jones, 1990). Updating refers to the executive mechanism by which the working memory content is successively refreshed and modified in accord with the most recently encountered items and ‘refreshing’ actually refers to a specific control process postulated to be mediated by left DLPFC (Johnson et al., 2003). However, two-back task performance arguably necessitates complementary executive control processes. For instance, selective inhibition might serve to facilitate the updating process by disambiguating the two item representations held ‘on-line’ to ensure that the correct item is discarded from memory (a complementary discussion on updating is provided in the section on domain-selective control modulations below).

Another item-related control process claimed to be mandatory in the two-back task promotes temporal ‘tagging’ of items, which may be referred to as the operation by which the encoding of each item integrates representation of identity with temporal code-specification (Smith and Jonides, 1997). Such temporal coding has been explicitly related to activity in the left DLPFC (Smith and Jonides, 1997). An alternative account of the processes underlying coding of temporal order in two-back tasks propose spatial recoding of this inter-relational information (cf., (Courtney, 2004), which could explain the transient DLPFC recruitment in accordance with theories of the functional organization within PFC that postulate dorsal parts to predominantly engage in spatial processes and verbal parts to predominantly engage in nonspatial processes (e.g. Levy and Goldman-Rakic, 2000). Generally, activation of DLPFC is the most frequently reported finding in brain imaging studies that have assessed diverse executive control processes considered to be dependent upon the central executive (e.g. Smith and Jonides, 1999). A possible interpretation would be that the key operational characteristics of the transient control effect seen in left DLPFC may relate to the effective co-
ordination of other more specific computational units that promote the attainment of more specialized executive functions.

With respect to the episodic memory task the selective activation of the right VLPFC (BA 47) involving frontal operculum in the vicinity of the anterior insula may be considered as ‘prototypical’ for episodic retrieval. It has previously been hypothesized that right VLPFC is part of a network of regions responsible for establishing and maintaining ‘retrieval mode’ during the performance in episodic tasks (Lepage et al., 2000). In line with such accounts, study II revealed concurrent responses in the right frontal operculum in terms of both transient and sustained activity. The observation of this co-occurring pattern of item-related and tonic activation in this particular PFC region was in fact a replication of the findings of a previous mixed fMRI study that employed a highly similar episodic recognition task in which an identical area in right frontal operculum showed the same combination of transient and sustained neural modulations (Donaldson et al., 2001b). Since the mixed design fMRI experiment in study II incorporated multiple tasks within the same study protocol in order to identify common neural mechanisms across different tasks, we were able to show that the sustained activity in the right VLPFC was not specific to episodic memory. This result suggests that the domain-specificity ascribed to right VLPFC/frontal operculum in relation to retrieval mode (e.g. Lepage et al., 2000), may be in need for re-consideration as our analysis clearly showed similar levels of sustained activity in this area during working memory, semantic memory and attention.

An alternative possibility, however, that might still account of right PFC activity in terms of retrieval mode, although in terms of transient rather than sustained activation, relates to a feature of the mixed design used in the study. A prerequisite for the extraction of sustained and transient neural responses in this type of design is the obligatory use of a temporally ‘jittered’ stimulus presentation, i.e. varying length of time intervals between stimuli within task blocks, including a few rather extended time periods. This is necessary in order to increase the variance of signal magnitude in the activation data within respective task blocks (the same procedure is used for rapid event-related fMRI designs) and thus decorrelate the tonic and phasic regressors. Hence, within each task block a number of quite long inter-item periods without stimulus presentation need to be inserted. During these periods the retrieval mode might be “turned off” or at least diminish its influence on task-irrelevant processing (i.e. task-unrelated spontaneous thought processes become disinhibited) until the next item (i.e. retrieval cue) appears. According to this hypothesis, a retrieval mode might have been attained in a more item-selective manner, in case of which a transient neural response should be observed at stimulus presentation.
Control-modulation of overlapping regions by increased executive demands

In study III, the functional neuroanatomy underlying the recruitment of executive control processes in response to incrementing executive load was examined by task manipulations across working and episodic memory, independently. It was shown that the generic PFC regions associated with activation commonalities in study I and study II, did not (further) modulate with increased demand on executive processing, indicative of general-purpose control mechanisms to be mediated by this shared PFC circuitry (see above sections on overlapping sustained and transient neural activity, respectively). Common control modulations associated with increased executive demands were seen in both sustained and transient neural activity.

A distributed pattern of common sustained increases in response to executive load was noted in left hemispheric fronto-striatal-cerebellar circuitry, encompassing areas in the DLPFC, the caudate nucleus and the cerebellum. All of these regions have been implicated in mechanisms underlying higher-order control of task set and context processing on the basis of neuropsychological studies (Owen et al., 1993; Rogers et al., 1998; Ravizza and Ivry, 2001; Ravizza and Ciranni, 2002) and anatomical connections (Alexander et al., 1991; Middleton and Strick, 1994; Saint-Cyr, 2003). This fronto-striatal-cerebellar circuitry could tentatively reflect a unitary tonic executive top-down component that mediates task performance in highly demanding tasks, which might represent a candidate neural substrate corresponding to the shared variance seen among nine executive tasks (indexing shifting, updating and inhibition) in a latent-variable analysis conducted by Miyake and colleagues (Miyake et al., 2000). This posited neurocognitive control network may relate to the concept of context processing (Cohen and Servan-Schreiber, 1992; Miller, 2000; MacDonald et al., 2005) and be selectively recruited with augmented need for top-down selective attention among task-relevant representations retained ‘on-line’ in situations that involve a high degree of competing irrelevant information. Such an interpretation of the shared tonic executive component in left DLPFC (BA 46/44) and the basal ganglia corresponds to many neurocomputational models of cognitive control and working memory in which dopaminergic modulations promote top-down biasing of relevant information processing via frontostriatal circuitry (Cohen and Servan-Schreiber, 1992; Durstewitz et al., 1999; Braver and Barch, 2002; Durstewitz and Seamans, 2002; Ashby et al., 2005; Hazy et al., in press).

A functional account of the common sustained cerebellar activity increase in response to augmented executive requirements might relate to a global preparatory role based on predictive mechanisms (Courchesne and Allen 1997). According to this view, the cerebellum acts to “optimize” the internal configuration of context-relevant neural computations in advance of task execution. The fact that cognitive performance is reduced, rather than abolished, following cerebellar damage, and
selectively concerns effortful and speeded tasks of divided attention and working memory has been attributed to the disruption of such a preparatory process (Courchesne and Allen 1997). Hence, the cerebellum is tentatively recruited as a “supportive system” that promotes additional coordination of attention and anticipatory control in highly demanding tasks (e.g. Gottwald et al., 2003).

A common transient activation increase associated with augmented executive requirements was found in bilateral posterior parietal areas along the intraparietal sulcus (BA 7). A general executive control account of posterior parietal involvement in tasks with high executive demands might be hypothesized to entail an inhibitory/selective attention mechanism (supervised by the PFC), which would be compatible with findings that engagement of this area in visual attention seems dependent on the presence of irrelevant distractors (Desimone and Duncan, 1995; Wojciulik and Kanwisher, 1999). Assuming that this posterior part of the parietal cortex participates in demanding cognitive tasks by imposing an appropriate ‘focus of attention’ capable of dynamically switching between mental space and the external world could explain findings from cross-functional fMRI studies yielding overlapping activity in the intraparietal sulcus between tasks of verbal working memory and covert spatial attention (e.g. LaBar et al., 1999). Given the transient stimulus-synchronous increase in the intraparietal sulcus, the putatively underlying inhibitory/selective attention mechanism might re-align the attentional ‘focus’ for each stimulus onset, hence being phasically tied with item-related decision processes. This also agrees with the assumed role of the intraparietal sulcus in the specification and implementation of stimulus-response transformation rules (Rushworth et al., 2001). In study III this function could specifically aid in the evaluation and discrimination of retrieved information by allowing shifting among representations to be selective attended to, irrespective of whether information is currently retained in working memory or retrieved from long-term memory. In keeping with such a proposition the posterior parietal cortex at the intraparietal sulcus has demonstrated transient activation during attentional shifts (Yantis et al., 2002).

**Domain-selective control modulations by increased executive demands**

**Working memory updating** A prefrontal pattern of transient activity that was selectively devoted to control processes engaged in the two-back relative to one-back task involved the left DLPFC (BA 9). Relative to one-back, two-back task performance involves multiple control processes related to item updating: inhibiting and discarding of selective information from working memory, encoding and temporal ‘tagging’ of new information added to working memory, and repositioning active representations within working memory (Jonides et al., 1997; Postle et al., 2001). Although previous brain imaging studies have linked DLPFC
with updating processes (Salmon et al., 1996; Braver et al., 1997; Van der Linden et al., 1999), a recent event-related fMRI study, albeit demonstrating updating-related DLPFC activity, failed to differentiate this response from the activity elicited during stimulus encoding and maintenance (Postle et al., 2001). However, the experimental paradigm used by Postle and colleagues (2001) was the running memory span, which differs from the n-back paradigm used here, with respect to many computational constituents. For example, the running memory span task lacks concurrent demands on processes related to matching, evaluation, decision making and response execution, all of which constitute stimulus-locked processes preceding updating processes in the two-back task updating. These additional processing requirements conceivably make the two-back task more complex (although less process-pure) regarding the item processing stage (as the running memory span task “merely” requires discarding one item and adding another with each new stimulus presentation, i.e., updating). Hence, the binary “quantum leap” of DLPFC (BA 9) activity seen here and in previous imaging studies contrasting two-back with one-back task engagement (Cohen et al., 1997) and comparisons of two-back relative to item recognition working memory tasks (Smith et al., 1998), may reflect item-related auxiliary control operations required for selective attention within working memory, temporal coding and updating of stored items required only in the two-back task.

**Episodic post-retrieval monitoring** An account that can explain our finding of significantly greater right DLPFC (BA 46) activation for source memory than item recognition is provided by the ‘monitoring hypothesis’ as proposed by Henson and colleagues (1999). This hypothesis builds on the idea of retrieval monitoring as a crucial component in the control of episodic retrieval (Koriat and Goldsmith, 1996) and postulates that the extent to which monitoring processes are required is determined by the degree of diagnostic ambiguity pertaining to an item and the corresponding memory judgment (Henson et al., 1999; Henson et al., 2000). By using event-related fMRI in conjunction with confidence ratings of each item response in a source memory task, Henson and colleagues recently demonstrated that right DLPFC was differentially recruited for low confidence memory judgments, irrespective of whether an item was decided on as “old” or “new”, and whether the given response was correct or false (Henson et al., 2005). It appears likely that the source task employed in our study, as compared to the recognition task, should have engendered a higher degree of uncertainty leading to a greater proportion of low-confidence judgments. Successful item recognition can principally rely on familiarity-driven processing which is generally associated with a relatively low level of monitoring demand. Source memory, on the other hand, is likely to entail additional monitoring before each veridical response, in that some of the recognized items must be rejected due to their belonging to the non-targeted of the two previously encoded word lists.

A complementary role in source memory putatively subserved by the right VLPFC area (BA 47) showing selective activation during this task could relate to this areas
postulated role in inhibitory control (Konishi et al., 1999; Aron et al., 2004). In contrast to recognition, source memory requires cognitive suppression of the task-irrelevant retrieval orientation and behavioural inhibition of veridical responses for the duration of post-retrieval monitoring. Such inhibitory control would be required for all items that initially signal familiarity to allow for appropriate evaluation and verification processes to take place before a response can be given. Hence, the right VLPFC may act to suppress premature and inappropriate “old” judgments due to feelings of familiarity. Differential activation of this area in source memory relative to item recognition may also be interpreted in terms of greater demands on “cue specification” processes (Fletcher et al., 1998). The control processes underlying monitoring, inhibition and cue-specification should arguably be intimately tied together during source memory judgments. The degree to which the implicated inhibitory process of right VLPFC constitute a mechanism that is uniquely concerned with controlled episodic retrieval might be questioned however (e.g. Badre and Wagner, in press).

A hierarchical neurocognitive model

The combined imaging data from the current studies (study I-III) are used to outline a tentative hierarchical cognitive architecture that attempts to give an account of the relative regional specialization within common core mechanisms and executive control circuitry, and how these different unitary neurocognitive component processes might dynamically work together during cognitive task performance (see Fig. 6). The current data (study I) corroborate prior evidence of common activation within a generic PFC network for a wide range of memory processes and other cognitive challenges (e.g. Duncan and Owen, 2000), by showing reliable co-recruitment of common areas in ACC, VLPFC, DLPFC, and frontopolar cortex across all nine different memory tasks used in two PET experiments (i.e. three tasks chosen to tap each of the three domains of working memory, episodic memory and semantic memory, respectively). Using the mixed fMRI design (study II) we were able to dissociate overlapping activations within the generic PFC circuitry in terms of both the temporal dynamics of the underlying neural modulations and the extent of overlap in regional activation with a sustained attention task. By manipulating executive load in working and episodic memory independently, in conjunction with using the mixed design (study III), it was established that none of the regions within the identified generic PFC network modulated with increased executive demands, indicating a role in tonic general-purpose control mechanisms of relatively ‘low-order’. Common regional control-modulations evoked under duress from augmented executive load were found in two unique sets of shared brain circuitry distinguished by the different temporal signatures of their underlying neural responses.

Taken together, these results provide a basis for an attempt to decompose the functional contribution of discrete areas within ‘common’ circuitry in terms of
putatively shared component processes. Below, the derived hypothetical componential infrastructure is arranged within a hierarchical neurocognitive architecture pertaining to memory processing tasks in particular (and tentatively, the model extends to cognitive task performance in general). The hierarchical model aims to segregate and characterize different levels of 'control' and/or representation attributed to the distinguished common regions and corresponding shared component processes are suggested (cf. Marklund and Nyberg, submitted). Examples of putatively task-specific brain regions and associated component processes are also outlined.

**Level I** The most fundamental and general layer of the architecture constitute brain mechanisms related to the establishment and maintenance of a heightened level of alertness coupled with an enhanced state of attentive focus and readiness. This most basic type of control is considered to be closely associated with vigilance in terms of the tonic state of activation and sustained attention it yields (Parasuraman, 1984).

A frontal network involving regions of (primarily right) VLPFC/anterior insula (BA 45/47) and medial PFC (BA 6) including portions of the dorsal ACC (BA 24/32) is thought to mediate such domain-general attentional processes which set the stage for a cognitive focus throughout task performance. This attentional circuitry is associated with sustained neural activity that extends the task period and it should be engaged in practically all types of task contexts, even though the degree of recruitment may be modulated with factors such as level of expertise and task difficulty (Dehaene et al., 1998). Both the ACC and right PFC are considered critically involved in the voluntary control of tonic endogenous alertness via top-down modulation of brainstem structures that enhance arousal levels (Mottaghy et al., in press). A specific contribution of the ACC may constitute continuous performance monitoring that index and signal the need for cognitive control adjustments (e.g. MacDonald et al., 2000; Ullsperger and von Cramon, 2004) (see level II). The ACC involvement at this basic level is in keeping with the long held view of this midline structure as an integral part of an anterior attentional network (Posner and Peterson, 1990), and it is believed to be the main coordinator of intrinsic alertness levels (Mottaghy et al., in press). A recent multivariate analysis of the functional connections between ACC and other cortical regions revealed different regional interactions depending on whether tasks preferentially tapped attention or memory processes (Lenartowicz and McIntosh, 2005). In parallel with the task-dependent changes in the functional connectivity associated with the ACC, the findings of that study also implicated that the functional contribution of this area was altered between tasks as indicated from divergent behavioural consequences in respective task (Lenartowicz and McIntosh, 2005). This might be interpreted as if the generic attentional control processes mediated by the ACC (and right VLPFC/anterior insula) participate in basic regulation of available attentional resources devoted to endogenous and/or exogenous processing demands.
Figure 6. Schematic outline of a tentative hierarchical neurocognitive model involving six layers or levels of component processes associated with different levels of attentional and control mechanisms as well as representational and task-specific operational levels. Depicted on the rendered views at the bottom are several common lateral PFC sites based on study II (each color corresponds to a shared level in the model; yellow = common sustained activity increases for attention, long-term memory and working memory; orange = common sustained activity increases for long-term memory and working memory; green = common transient activity increases for long-term memory and working memory, blue = common load-sensitive transient increases in parietal areas in study III).
**Level II** At the second layer of the model another form of fundamental control over behaviour is posited to operate, by which task set is represented and a basic context processing bias is provided and maintained throughout task performance. The common pattern of sustained activation revealed in the frontopolar cortex (BA 10) observed for all memory tasks across study II and III, but not for the attention/vigilance task (study II), implicate mechanisms of the anterior-most sector of PFC to subserve the core processes responsible for the instantiation and maintenance of such task set representations. As opposed to the above defined arousal/attention mechanisms that promote a general state of enhanced alertness and focused attention in any given task situation (in a fashion presumably independent of the specific task-context and devoid of representational content) the mechanisms that enable task set configuration is hypothesized to generate and represent an abstract form of current context representation including task goals (e.g. Braver et al., 1999).

Task set is concerned with more abstract types of information (e.g. intentions, motivation, strategies) as compared to the active maintenance of item-specific memoranda such as task-relevant stimulus features after removal of sensory input, which is accomplished by more “classical” working memory buffers (Courtney, 2004). Task set may be defined as abstract means-end representations by which an operational “blueprint” of the specific cognitive operations to be performed on the stimulus input are specified (e.g. Gallese, 2003). Such a notion is compatible with the purported role of frontopolar regions in prospective memory (Burgess et al., 2001). The current data furthermore indicate a potentially selective role of frontopolar cortex in what could be termed a ‘general retrieval mode’ subserving state-related control processes among tasks that require some type of mnemonic representation to be accessed and evaluated in order to generate the context-appropriate behavioural output, regardless of whether information is stored in working memory, episodic or semantic long-term memory.

Beyond these relatively load-insensitive tonic control processes (as indicated by the lack of frontopolar modulation with increased executive demands in study III) this level of the hierarchical model also harbors tonic control mechanisms of a more “executive” kind, which might be engaged when the running cognitive system is seriously challenged. Hence, the tonic top-down mechanisms implicated here are thought to be recruited in the service of ‘boosting’ and ‘insulating’ the abstract task set representation maintained within the frontopolar cortex (Sakai and Passingham, 2003) in the face of salient, irrelevant information and/or inappropriate and prepotent response tendencies, that left “unattended” (i.e. if allowed access to the focus of attention) would interfere with task performance.

The need to recruit this tonic ‘bootstrapping’ executive mechanism is surmised to be detected by conflict and response competition monitoring processes performed by the ACC (Botvinick et al., 1999; Carter et al., 1999) (see level I), which is also suggested to provide the necessary “alerting” signals when reliance on the currently deployed level of control may compel erroneous performance if not properly
adjusted (e.g. MacDonald et al., 2000). It is proposed that the implicated tonic top-down mechanisms come into play in situations when higher-order regulatory processes are expected to be required on a regular basis throughout a task (as opposed to the transient increases in control following the detection of a performance error due to reduced alertness, which typically expires after the subsequent trial (Kerns et al., 2005). Frontostriatal circuitry involving the left DLPFC (BA 44/9/46) and the caudate nucleus are posited to exert such persistent (supplementary) top-down biasing of processing to protect the cognitive focus and related processes from interference.

The posterior DLPFC (BA 44/9/46) is hypothesized to implement periodic refreshing of the task set by eliciting transient inter-trial ‘updating’ signals to “remind” more posterior cortices engaged in task-specific operations of the immediate goals. It is further speculated that the cognitive mechanism by which the DLPFC promotes such ‘boosting’ of relevant neural computations to be performed on upcoming items in effortful and highly demanding tasks, might in fact correspond to the ‘context-integrative’ coding process attributed to this area in the service of stimulus-locked processing (see level IV). However, at this layer the context-integrative biasing of processing pathways takes place in-between trials or item presentations. Given that the signal-frequency or temporal density of such phasic inter-item control is a function of the executive demands of a task the BOLD signal would be expected to merge and take on the appearance of a sustained response if invoked sufficiently often (cf. Cohen et al., 1997).

To further ensure the priority of context-appropriate processing pathways and to counteract disruptive influences during cognitively demanding tasks, it is hypothesized that the ‘core’ context processing bias and task set maintenance subserved by the frontopolar cortex (BA 10) might be tonically enforced in terms of ‘insulation’ from interfering elements via inhibitory mechanisms subserved by the caudate nucleus. Combined with the recurrent ‘boosting effect’ promoted via phasic DLPFC activation, such ‘task set insulation’ via sustained active suppression of competitive and context-inappropriate processing is compatible with recent neurocomputational models that emphasize a critical role of fronto-striatal networks in cognitive control (e.g. Braver et al., 1999; Frank et al., 2001; Braver et al., 2002).

Complementary to the tonic executive mechanism mediated by this PFC-basal ganglia circuitry, processes subserved by the cerebellum also appears to come into play in tasks that entail high executive load as indicated by the enhanced common sustained activity seen in this area exclusively for the high-load tasks of study II. The specific cerebellar contribution to tonic top-down control might reflect supportive and anticipatory influences on task-specific cognitive operations (e.g. Courchesne and Allen, 1997).

**Level III** In addition to generic tonic control processes subsumed at level I (i.e. sustained attention and general alertness), and level II (i.e. context representation
and task set maintenance, as well as top-down biasing processes that operate throughout effortful task performance), phasic executive control processes might become operative on an item to item basis. Such executive processes are associated with transient activity increases and are considered to be selectively recruited during demanding item processing. The third layer of the model is posited to constitute an array of such higher-order control processes, generally assembled under the umbrella concept of executive functions (as opposed to the concept of cognitive control which is used here to denote tonic top-down processes), each of which is attributed to a certain type of phasic control over stimulus-locked processing. Processes subsumed at this level include selection, inhibition, updating, shifting, and several other transiently invoked executive or attentional control functions whose primary role is to guide more specialized computations and cognitive operations (e.g. retrieval from long-term memory, material-specific temporary retention in working memory, see level IV). Hence, the selective recruitment of these processes depends on task-specific properties and the extent to which a task involves the need to exert control over context-appropriate behavior during individual trials. Important factors in determining whether phasic control processes are required in a cognitive task are the degree of competition and interference from irrelevant inputs or dominant but inappropriate processing pathways, the novelty or ambiguity of a situation, as well as the need to inhibit and override automatized behaviour or prepotent responses.

A number of phasic executive functions and discrete, tentatively critical regions in their neural implementation are outlined at level III (see Fig. 5), all of which are allegedly required for, but not specific to many tasks involving complex mnemonic processing demands. The degree of domain-generality of the various executive functions implicated here (and others) need further investigation in light of amounting evidence that both unity and diversity exists among different executive (phasic) processes at both the cognitive and neural level (e.g. Miyake et al., 2000; Friedman and Miyake, 2004; Collette et al., 2005).

**Level IV** The fourth layer constitutes the representational level. The model implicates generic PFC circuitry to mediate context-integrative processes that designate the manner by which external stimuli and mnemonic information are integrated and coded into task-appropriate representations held in posterior association cortices. The common transient activity elicited in left posterior DLPFC (BA 44/9), and left VLPFC (BA 47) across all types of mnemonic operations associated with item processing in study II and III (i.e. transient effects for one-back and two-back working memory, episodic item and source retrieval, as well as semantic categorization) is attributed to control of coding and retrieval of representational information. The common left posterior DLPFC (BA 44/9) region may be considered to mediate phasic control of task-set implementation on an item to item basis to optimize event-related behavioral outcome, which is referred to as context integration. The common region of VLPFC (BA 45/47) is generally associated with item-related mnemonic control processes that support retrieval,
evaluation and selection of active representations held in working or long-term memory stores (Buckner, 2003). Hence, the VLPFC may be considered to disambiguate context-relevant subsets of representations in long-term memory for selective activation and recovery.

It is tentatively proposed that the contributions of left posterior DLPFC and VLPFC might relate to an early frontal ERP component thought to be “elicited by items that can be represented in a unitized code, a format that represents an item within a particular domain of processing and by which it can be integrated in a task context” (Mecklinger, 2000, p. 568), which resonates well with the purported role of these areas in transient control of context-salient code-specification and stimulus-to-response integrative processing. The transiently coded representation of such items might encompass multiple associative links in long-term memory, the activation of which may predispose recognition in episodic memory tasks (Weiskrantz, 1997). Congruent with the current notion a recent event-related fMRI study of working memory (Mitchell et al., 2004) found that left posterior DLPFC was activated when task demands required activation of specific attributes pertaining to items that were maintained within working memory before a correct response could be given. This transient item effect was of equal magnitude in both immediate trials (when items were still actively maintained in working memory) and long delay trials that were assumed to require reactivation of items from long-term memory before responding (Mitchell et al., 2004). Also, the left posterior DLPFC has been demonstrated to exhibit significantly greater event-related responses for frequency judgments that require detailed analysis of perceptual traits/contextual item information as opposed to judgments that merely require familiarity assessment (Dobbins et al., 2004). Both of these findings converge with the view that the left posterior DLPFC contributes to context-integrative coding processes.

Interestingly, an equivalent event-related effect in left PFC is generally not observed for spatial location stimuli in either episodic retrieval tasks (e.g. Penney et al., 2000) or working memory tasks (e.g. Sala et al., 2003). The typically less pronounced item modulation in left PFC for spatial information is allegedly tied to the specific format which to some degree precludes representation along the conceptual dimension and requires instead a visual-structural representation format to be used (Mecklinger, 2000). Accordingly, certain types of materials such as objects, pictures and words, may be better suited than spatial information when it comes to enable contextual relationships to be embedded within their transiently coded internal representation. However, such stimulus-dependent involvement might primarily concern the VLPFC region, which has been associated with material-specific activity (e.g. Braver et al., 2001) and is closely linked with conceptual processing (Wagner et al., 2001).

At the first stage of stimulus-to-response processing the left posterior DLPFC (BA 44/9) may access the operational “schema” of the current task set in order to coordinate and certify a context-relevant item coding that transfers a transiently
coded internal representation of the most relevant stimulus features (permeated with current ‘intentional’ directives) into a working-with memory state providing a unitized/optimized input for the currently appropriate processing systems to operate on. Based on the outcome of the cognitive operations performed on each item (or rather its unitized representational code which may comprise a conglomerate of codes) the computational feedback provided by the context-relevant processing system may cause modulations of specific parameters related to task goal specifications which according to the current model were coded into the transient internal representation via context-integrative processes (along with task-salient item attributes and other codes). Such modulations should bias item-related response selection in accordance with current task priorities as to generate an appropriate behavioral response. Thus, the left posterior DLPFC (BA 44/9) may be considered to influence both item coding and response selection. In a similar vein as proposed here, it has been suggested that left hemisphere PFC areas might promote top-down disambiguation of the context-relevant item features that are most ‘diagnostic’ for an appropriate memory decision to be made (Ranganath, 2004).

The actual representations of mnemonic information are posited to be stored in posterior association cortices. For example, object information appears to be represented and processed in temporal and occipital areas along the ventral ‘stream’, whereas spatial information is primarily attributed to parietal areas along the dorsal ‘stream’ (e.g. Moscovitch et al., 1995; Köhler et al., 1998). Although not explicitly addressed in the present thesis, several previous imaging investigations that have incorporated diverse stimulus materials within the same study demonstrate that most of the common areas of PFC implicated here, are largely material-independent as regards their relative activation patterns (e.g. Braver et al., 2001; Ranganath et al., 2004; Khader et al., 2005; Woodruff et al., 2005).

For example, Khader and colleagues (2005) investigated associative memory for different stimulus materials (faces and visuo-spatial items) encoded together with single words. By employing an unusually long retention interval of two days between the initial encoding phase and the retrieval task, it was assumed that memory consolidation was allowed to take place. Of relevance to the present discussion, a region located in left posterior DLPFC (BA 44/9) demonstrated robust transient activity during cued-recall of both faces and visuo-spatial items, hence conceivably subserving a crucial role in content-independent retrieval control processes associated with context-biased reactivation of relevant long-term representations. Moreover, the transient effect in the left posterior DLPFC region showed a positive correlation with the number of retrieved item associates, again for both faces and visuo-spatial items, which might indicate that this area is critically involved in the actualization of each activated long-term memory representation, regardless of material type. The reported activation focus of this effect was principally identical to that of our demonstrated transient activity in the left posterior DLPFC that was observed in all memory tasks relative to the attention
task in study II. In line with our hypothesis that the left posterior DLPFC (BA 44/9) is engaged in item coding operations that bias context-relevant processing which might involve conceptual associations it should contribute to cue-specification processes that helps elicit the activation of relevant representations from long-term memory. It should be noted that the findings of Khader and co-workers also substantiated the claim that episodic long-term memories are stored in material-specific posterior association cortices (Khader et al., 2005).

**Level V** At the fifth level, more task-specific component processes are represented. For example, temporary retention of item-specific information in the absence of external input, which has been associated with sustained activity in the supplementary motor area (e.g. Petit et al., 1998), may be considered specific for tasks that require working memory storage for their completion. The vertical lines that connect the right-most units in Figure 6, across levels I - IV, illustrate the idea that successful performance on, for example, an item recognition memory task will depend on all these processes along with synchronized activity in the relevant regions.

The dotted line between levels IV and V implies that if the task set implemented at level II specifies a different task to be performed, for instance, two-back working memory instead of episodic retrieval, different processes would be invoked (the two-back task would additionally recruit a number of phasic executive processes at level III, presumably updating, inhibition, and monitoring functions would be obligatory. Differences might hence occur at the third executive level as well.

Different components will typically be engaged at level V as different task-specific processes will be added depending on task-specific requirements. In the present example, the process of episodic retrieval is added at level V. This process has been associated with activity in the medial temporal lobe regions (e.g. Squire, 1992b; Nyberg et al., 1996b) and the involvement of right PFC areas (Nyberg et al., 1996a).

Clearly, the proposed model is tentative and many details remain to be worked out and tested. It is quite likely that additional levels should be included in the model. For example, there is much evidence that a component process such as episodic retrieval at level V can be further decomposed into various subcomponents with putatively unique neural signatures (e.g. Henson et al., 1999). Such a scenario is indicated by the multiple layers indicated in the left-most unit at level V, which implicate that different sets of brain regions might be involved in particular subcomponents of task-specific processes. Interactions among levels, vertically as well as horizontally, must also be worked out (see future directives below).
CONCLUSIONS

The present thesis has explored similarities and differences between attention, memory and executive functions, with a special focus on shared elements between the concepts of episodic and working memory and their neural underpinnings. Based on the current findings and an overview of other relevant empirical data, we conclude that general-purpose control processes mediated by PFC is a common neural denominator across tasks of episodic and working memory. Findings of regional commonalities in brain activity between working memory and long-term memory might have theoretical implications for the way we classify human memory functions (Cabeza and Nyberg, 2000; Fletcher and Henson, 2001). That is, to further advance our understanding of the relative interdependence between working memory and long-term (episodic and semantic) memory processes, it is important to identify and characterize the neural substrates and component processes that are shared by these ‘systems’. Such similarities seem to involve general attentional processes, the structural basis of representational codes in posterior areas, and shared purpose-general neurocognitive control mechanisms in primarily PFC circuitry. In a broader perspective, all coherent forms of cognition may involve constant interactions between different forms of memory, the coordination of which may depend on temporally dynamic prefrontal control mechanisms for biasing the working memory processes that select, activate and integrate multiple currently relevant representations of long-term memory with aspects of the external world for input to the focus of attention.

Caveats and Directives for Future Research

A potential caveat concerning the brain imaging studies reported here might relate to their reliance on group-study designs and group-average measures. It has been argued that such designs could be sensitive to Type II errors in that individual differences within the population (e.g. with respect to task performance as well as brain activity) are treated as noise, which might result in conflated effects if the data comprise substantial variability (Kosslyn et al., 2002).

Another caveat might relate to the implicit assumption that overlapping functional neuroanatomy as indexed by fMRI and PET translates to the notion of shared component processes being recruited across tasks. Although a ‘sharing account’ of common brain activity is appealing as it provides a rather parsimonious account of brain function, the observed commonalities might be more apparent than real. It has been argued that a sharing view constitute only one of (at least) three possible interpretations of common activations across tasks (Cabeza and Nyberg, 2000). First, the relatively limited spatial resolution pertaining to PET and fMRI might not be able to discern the fact that, at the micro-level, adjacent yet domain-specific neuronal cell assemblages contribute to what, at the macro-level, appears to be
regionally overlapping brain activity. Also, taking into account that spatial smoothing of the registered BOLD signal during preprocessing of the fMRI data and the use of group-average analysis would further conceal such tentative subdivisions, makes it difficult to refute this possibility altogether. Second, a ‘network’ interpretation would posit that the functional specialization of a commonly activated brain area might vary considerably between different tasks depending on the specific ‘neural context’ within which it operates (McIntosh, 1999). Thus, according to this view, the process mediated by a single area is greatly influenced by its current functional interconnections with other brain areas, and such functional networks are believed to modify with task instructions (Nyberg and McIntosh, 2001).

A future prospect that could extend the scope of the present thesis, involves an individual differences approach in the context of the combined fMRI data of study II and study III. This would allow analysis of differences in both item-specific effects (e.g. differential neural activity evoked for specific responses, such as ‘hits’ and ‘correct rejections’), as well as sustained effects associated with high and low performers. In brief, the idea would be to exploit individual differences within behavioural indices of task performance to further explore the nature and functional significance of common and load-sensitive brain regions illuminated here. For example, such a method could shed light on the issue of whether (or which) common and/or load-dependent brain regions contribute to component processes whose degree of recruitment might predict better task performance (i.e. based on behavioural measures of relative task efficacy (accuracy) or neural efficiency (RT) among individuals). Behavioral studies comparing subjects with high and low working memory span have shown the former group to outperform the latter at retrieving information from long-term memory, which implicates shared elements in efficient task performance across domains (e.g. Cantor and Engle, 1993). It has recently been argued that taking into account individual differences in the context of functional brain imaging studies might be especially productive if used in conjunction with a theory of generic neural and cognitive mechanisms (Kosslyn et al., 2002). This resonates well with the currently posited hierarchical model of unitary control components that are assumed to generalize across diverse cognitive domains.

Another approach that might assist in clarifying the functional significance of common regions could be to explore the effective connectivity among these areas and between each area and other anatomically linked parts of the brain, as well as to perform analyses of changes in such functional integration across tasks and/or manipulations of executive demands. To use an analytic method that combines such inter-regional interaction changes with an individual differences approach (Mechelli et al., 2002) has proven a worthwhile enterprise with respect to defining effective connectivity (e.g. increased regional co-operation) that predicts more efficient task performance on object-location learning (Buchel et al., 1999) and working memory tasks (Kondo et al., 2004).
In conclusion, the present thesis puts emphasis on the value of examining cross-functional activation commonalities for deepening our understanding of the higher-order cognitive organization of the brain. It is further suggested that, only after considering both similarities and differences regarding the anatomical foci and temporal dynamics of neural activity across multiple cognitive domains it is possible to draw (relatively sensible) inferences about regionally specific contributions to the cognitive architecture reflected within the intricate mosaic of brain patterns associated with one specific domain.
REFERENCES


Coull J.T., & Nobre A.C. (1998). Where and when to pay attention: the neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI. *Journal of Neuroscience, 18*, 7426-7435.

Coull J.T., & Nobre A.C. (1998). Where and when to pay attention: the neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI. *Journal of Neuroscience, 18*, 7426-7435.


and arousal during the performance of an auditory vigilance task. *Journal of Cognitive Neuroscience, 9*, 392-408.


68


