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Episodic memory in the human prefrontal cortex

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Stockholm, 2007

This thesis was typeset with the ConTEXt macro package (http://www.pragma-ade.nl) for the TEX typesetting system (http://www.ctan.org) developed by Donald Knuth. The text font is Gentium (http://scripts.sil.org/Gentium_download) and the math font is Euler (distributed with TEX and designed by Hermann Zapf to look like 'the handwriting of a mathematician with very good handwriting'). The illustrations on pages 20, 59 and the front coverwere created with MetaFun (which is integrated with ConTEXt) and those on pages 21, 23, 44 and 45 were created with R (http://www.r-project.org). All of these tools are open source.

ISBN 978-91-7357-136-4

Abstract

This thesis consisting of five papers examines the relationship between haemodynamic activation in the prefrontal cortex with episodic memory function in the healthy human brain. Brain function is measured with positron emission tomography (PET) and functional magnetic resonance imaging (FMRI) and episodic memory for words as well as visuo-spatial material is examined. The first paper consists of two experiments using either verbal or visuo-spatial material and examines the effects of practice on episodic memory in repeated cycles of encoding and retrieval. Subjects are scanned with PET during retrieval. It is found that before practice, the tasks activate fronto-parietal networks and that this activity diminishes with practice in favour of paracentral brain activity, perhaps reflecting decreasing demands on working memory. The second paper examines incidental encoding of figurative and non-figurative drawings while processing of the drawings takes place in different levels of processing (LOP). Subjects are biased toward either 'deep' or 'shallow' by rating agree-ability or graphical quality of the drawings respectively. A behavioural experiment is undertaken in the first part of the paper, establishing that the LOP effect extends to visuo-spatial material. PET scanning then shows increased activity for deep encoding compared to shallow encoding in left prefrontal, parietal and anterior temporal regions, while comparing shallow encoding to deep encoding yielded right prefrontal, parietal and posterior temporal activations. The third paper continues to examine effects of practice in another setting. Subjects are taught a specific aid to memory, a mnemonic known as the method of loci. They are scanned with PET while encoding a list of words both with and without use of the mnemonic as well as during acquisition of the mnemonic. Use of the mnemonic is associated with increased activity in left frontal and occipito-parietal networks. Acquisition of the mnemonic compared to baseline is associated with increased activity in lateral and medial parietal cortex while activity in the left medial

temporal lobe increased with practice. In the fourth paper, FMRI is used to expand the findings from the second paper by applying the greater temporal resolution of event-related FMRI to separate activity for the figurative from the non-figurative drawings. Only some of the results from the second paper are replicated. In the last paper, the 'remember'/'know' paradigm is used. This means that subjects are given a recognition test of previously seen words and asked to indicate the quality of a recognition experience as either 'remembered', meaning that the subject can recall the encoding event, or 'known', meaning that the subject finds the word familiar but has no recollection of the encoding event. The recognition test as well as the attribution of the recognition experience as 'remembering' or 'knowing' is scanned using event-related FMRI. Recognised words that are later 'remembered' compared to words that are later 'known' are associated with increased activity in the posterior part of the right hippocampus and comparing later 'remembered' words with correct rejections revealed activations in the left inferior parietal lobule and in the right middle frontal gyrus. We conclude that practice in an episodic memory task represents a change from controlled to automatic processing; that the strong form of the hemispheric encoding retrieval asymmetry hypothesis (HERA) is not sufficient to account for the patterns of activity in the frontal cortex associated with episodic memory; that levels of processing can be shown with visuo-spatial material and that levels of processing are reflected in differently lateralised frontal and parietal activity.

Sammanfattning på svenska

Denna avhandling undersöker förhållandet mellan hemodynamisk aktivering i frontalloben och episodisk minnesfuntion i den friska mänskliga hjärnan i fem artiklar. Hjärnfunktionen mäts med positronemissionstomografi (PET) och funktionell magnetresonansavbildning (FMRI) och episodiskt minne för såväl ord som visuo-spatiellt material studeras. Den första artikeln består av två experiment där antingen verbalt eller visuo-spatiellt material används och övningseffekter studeras i upprepade cykler av inkodning och avkodning. Försökspersonerna undersöks med PET under avkodning. Innan övning aktiveras frontoparietala nätverk och denna aktivitet avtar med övning och övergår till paracentral aktivitet, vilket möjligen avspeglar minskande anspråk på arbetsminnesfunktionen. Den andra artikeln undersöker incidentell inkodning av föreställande och icke-föreställande teckningar under det att inkodningen sker i olika bearbetningsnivåer (levels of processing). Försökspersonerna leds att bearbeta bilderna 'djupt' eller 'ytligt' genom att de får bedöma hur tilltalande respektive grafiskt kvalitativa bilderna är. Ett beteendeexperiment där det visas att bearbetningsnivåeffekten utbreder sig även till visuo-spatiellt material utgör första delen av artikeln. PET-avbildning visar sedan ökad aktivitet för djup inkodning jämfört med ytlig aktiverar vänstersidiga prefrontala, parietala och främre temporala områden medan ytlig inkodning jämfört med djup inkodning aktiverar högersidiga prefrontala, parietala och bakre temporala områden. Den tredje artikeln fortsätter att undersöka övningseffekter på ett nytt sätt. Försökspersonerna får lära sig ett minneshjälpmedel som kalla loci-metoden. De undersöks med PET under inkodning av en lista med ord såväl med som utan minneshjälpmedlet samt när de lär sig loci-metoden. Bruk av minneshjälpmedlet förknippas med ökad aktivitet i vänster frontala och occipito-parietala nätverk. Att tillägna sig metoden jämfört med baslinjen visar aktivitet i laterala och mediala parietala områden medan aktiviteten i vänster mediala temporallob ökar med övning. I den fjärde artikeln används

FMRI för att fördjupa fynden från den andra artikeln genom att tillämpa den högre upplösning i tiden som fås i händelserelaterad (*event-related*) FMRI och separera aktivitet vid bearbetning av föreställande teckningar från aktivitet vid bearbetning av icke-föreställande teckningar. Endast vissa resultat från den andra artikeln replikeras. I den sista artikeln används 'ihågkommet'/'bekant'-paradigmet (*remember/know*). Med detta avses att försökspersonerna får ange om de känner igen tidigare visade ord och dessutom får ange om upplevelsen vid igenkänning var av typen 'ihågkommet' (*remember*), alltså att försökspersonen minns inkodningsögonblicket, eller av typen 'bekant' (*know*) där försökspersonen känner igen ordet såsom tidigare visat, men inte kommer ihåg när det visades. Såväl igenkänningstestet som skattningarna av typ av upplevelse under igenkänning skedde under det att mätningar med händelserelaterad FMRI utfördes. Ord som kändes igen och där försökspersonen angett att minne av inkodningsögonblicket finns kvar ('ihågkomna') jämfört med ord som kändes igen utan sådan detalj ('bekanta') är associerat med aktivitet i högra bakre hippocampus och igenkända ord som angetts vara 'ihågkomna' jämfört med korrekt förkastade ord förknippades med aktivitet i vänster nedre lobulus parietalis och i högra mellersta gyrus frontalis. I avhandlingen drar vi slutsatserna att övning i en episodisk minnesuppgift representerar en förändring från kontrollerad till automatisk bearbetning; att den starka tolkningen av hypotesen om hemisfärisk inkodnings- och avkodningsasymmetri (HERA) inte är tillräcklig för att förklara mönstret av aktivitet i frontalloberna vid episodiska minnesuppgifter; att bearbetningsnivåer kan påvisas med visuo-spatiellt material och att olika bearbetningsnivåer avspeglas i olika lateraliserad aktivitet i frontallober och parietallober

List of publications

I. Karl Magnus Petersson, Johan Sandblom, Jens Gisselgård, Martin Ingvar (2001). Learning related modulation of functional retrieval networks in man. *Scandinavian Journal of Psychology, 42*, 197—216, reprinted with permission from Blackwell Publishing

II. Karl Magnus Petersson, Johan Sandblom, Christina Elfgren, Martin Ingvar (2003). Instruction-specific brain activations during episodic encoding: a generalised level of processing effect. *NeuroImage, 20*, 1795—1810, reprinted with permission from Elsevier

III. Lars Nyberg, Johan Sandblom, Sari Jones, Anna Stigsdotter Neely, Karl Magnus Petersson, Martin Ingvar, Lars Bäckman (2003). Neural correlates of training-related memory improvement in adulthood and aging. *Proceedings of the National Academy of Sciences of the USA, 100*, 13728—13733, reprinted with permission from the National Academy of Sciences of the USA

IV. Johan Sandblom, Karl Magnus Petersson, Martin Ingvar (2007). Levels of processing investigated with fMRI. *In manuscript*

V. Johan Sandblom, Håkan Fischer, Karl Magnus Petersson, Peter Fransson, Lars Bäckman, Martin Ingvar (2007). Remember/know revisited: recollection activates the MTL. *In manuscript*

Contents

Abstract i

Sammanfattning på svenska iii

List of publications v

Contents vii

Abbreviations ix

1 Introduction to the study of brain and memory 1
1.1 Different brains 2
1.2 Multiple memory systems in the brain 3
1.2.1 Concepts in memory experiments 3
1.3 Episodic memory 5
1.4 Episodic memory in the frontal cortex 5
1.4.1 Levels of processing 6
1.4.2 Loci 11
1.4.3 Source memory 11
1.4.4 Hemispheric encoding retrieval asymmetry 12

2 Aspects of episodic memory: question and aims 15
2.1 Paper 1 15
2.2 Paper 2 15
2.3 Paper 3 15
2.4 Paper 4 16
2.5 Paper 5 16

3 Methods for studying human brain function 17
3.1 The basis of blood flow measurements 18
3.2 Positron Emission Tomography (PET) 20
3.3 Functional Magnetic Resonance Imaging (fMRI) 22
3.4 Analysis of functional imaging data 24
3.4.1 Realignment and anatomical normalisation 25
3.4.2 Spatial filtering 26
3.4.3 Acquisition (slice) time correction 27
3.4.4 Statistical modelling and estimation 27
3.4.5 Specific difficulties in the study of learning 28
3.4.6 The general linear model 29
3.4.7 Hypothesis testing and statistical inference 30
3.4.8 General issues related to statistical inference 32
3.4.9 Random field theory 33

3.5 Specific methods of the studies 34

4 Results 37
4.1 Paper I 37
4.1.1 Object location of visuo-spatial material 37
4.1.2 Free recall of pseudo-words 40
4.2 Paper II 42
4.2.1 Behavioural data from paper II and paper IV 42
4.2.2 PET results 46
4.3 Paper III 48
4.4 Paper IV 48
4.5 Paper V 50

5 Discussion 51
5.1 Encoding in the frontal cortex 51
5.2 Retrieval in the frontal cortex 55
5.3 Hemispheric encoding retrieval asymmetry and retrieval mode 56
5.4 Automaticity and effects of practice 57

6 Conclusions and future perspectives 61
6.1 Conclusions 61
6.2 Unresolved issues 61

Acknowledgements 63

Abbreviations

ACC	anterior cingulate cortex
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATP	adenosine triphosphate
BA	Brodmann's area
BOLD	blood oxygenation level dependent
CT	computerised tomography
EEG	electroencephalogram
ERP	event-related potentials
FEF	frontal eye field
FMRI	functional magnetic resonance imaging
GLM	general linear model
HERA	hemispheric encoding retrieval asymmetry
ITC	inferior temporal cortex
LOP	levels of processing
MEG	magnetoencephalogram
MR	magnetic resonance
MTL	medial temporal lobe
PCC	posterior cingulate cortex
PET	positron emission tomography
PFC	prefrontal cortex
PPC	posterior parietal cortex
REMO	retrieval mode
ROI	region of interest
SPM	statistical parametric mapping
STG	superior temporal gyrus
SVC	small volume correction
TR	repetition time

“What is needed is not the will to believe,
but the will to find out, which is the exact opposite”

— Bertrand Russell

1 Introduction to the study of brain and memory

THE HUMAN brain is an information processing device for sensory input and a control device for the human body. It is a versatile system that can adapt to new information and process many types of information in more or less specialised ways. Below is a small list of relevant facts about the human brain (a selection from Churchland and Sejnowski (1992)). The brain exhibits

- specialisation of function, so that different regions of the brain are different in functional as well as cellular properties,
- a number of synapses that is roughly 10^{15} and a number of nerve cells of about 10^{12}, and there is approximately 1 synapse/μm^3,
- unevenly distributed connections between nerve cells, and connections from a cortical neuron to only about three percent of the neurons in the surrounding millimeter cube of cortex,
- neurons that take analog inputs (on a continuous scale) but have discrete output (to fire or not to fire),
- neurons whose output comprises only some 1–5 percent of the firing threshold for the receiving neuron,
- massively parallel information processing architecture.

At 1500 grams the brain comprises some 2 percent of the body mass. Its consumption of oxygen and nutrients require 20 percent of cardiac output at rest. It is a very sensitive organ and situated as it is at one extreme of the body, on the end of a multi-jointed trunk, it is at great risk. Being lodged in a bony compartment offers some protection, but head trauma accounts for a great number of deaths and life-long debility. Despite these risks the brain has given

humans an unmistakable evolutionary advantage. Learning in an information processing system has occurred when reprocessing the same input generates different output. In a system such as the human brain, learning occurs constantly. The brain is constantly developing and the function of the brain is always a function of its history (Petersson, 2005b). The brain has functional subdivisions on many levels (Ingvar and Petersson, 2000). Individual neurons are organised in groups that are organised in columns, that comprise cortical regions.

1.1 Different brains

Not only do people think differently, their brains are physically different. Brains have different sizes and shapes, and the patterns of the cortical folds (the *gyri*, and *sulci*) are unique for every brain. Causes for these variations include genetic differences, development in different environments and random variation. Nevertheless, students of brain function are forced to compare parts of one brain with parts of other brains. Some conventions have been invented to facilitate this. Korbinian Brodmann observed differences in the cellular architecture (the cytoarchitecture) of the brain and devised a system of cortical areas that still bear his name (Brodmann's area, BA) and are widely used. These have the drawback that they vary between people perhaps just as much as gyri and sulci, and it is not possible to determine what BA a given location belongs to until the individual is dead and the brain can be examined under the microscope. Still, Brodmann's areas are a very popular way of describing functional neuroimaging results.

Locations are commonly given as three-dimensional co-ordinates in a co-ordinate system originating in a central structure in the brain, the anterior commissure of the corpus callosum. This system was popularised by Talairach

and Tournoux (1988) and is still the standard way of recording neuroimaging results.

1.2 Multiple memory systems in the brain

The individual that is capable of making the best predictions about the surroundings has the highest likelihood for survival and procreation. With a very simple memory system only very simple predictions can be made, so there is a strong evolutionary drive for the development of more sophisticated memory systems. Earlier forms of memory are limited in their context, notably limited in time. Skills, habits, priming are all locked in the now. These systems have arisen at different times during human evolution (Gazzaniga, 1999), and the episodic is the latest form of memory to be added. Episodic memory makes it possible to process and retrieve events with a context, which in turn facilitates predictions on a larger scale both temporally and spatially than possible before since it is possible to recognise and interpret much larger patterns. A taxonomy of human memory (Eichenbaum, 2002, Squire and Zola, 1996 and Squire, 2004) is presented in table 1.1.

declarative	episodic	events
	semantic	facts
non-declarative	procedural	riding a bicycle
	priming, perceptual learning	differentiating unfamiliar speech sounds (l/r)
	simple classical conditioning	Pavlov's dogs
	non-associative learning	reflexes

Table 1.1 Distinct but interacting memory systems in the human brain. Episodic was the latest addition, and also the subject of this thesis

1.2.1 Concepts in memory experiments

The ecological relevance of memory experiments can be cast in doubt when one considers that memory in real life rarely occurs from lists and different materials are not in any particular order, and yet memory researchers tend to make claims that are relevant to living people. However, just as a work

of art can capture what is fundamentally relevant in the human condition in the relative locations of a few sticks, good experimental models can capture the relevant facets of the subject matter without being burdened with the problems of a noisy reality. Whether an experimental model is good is another matter, and one commonly debated in the field where it is use (and sometimes beyond that). In human memory research, the models are quite close to reality, compared to other fields.

	old	new
yes	hit	false alarm
no	miss	correct rejection

Table 1.2 The four possible outcomes in recognition tests

In memory experiments, at least three phases can be identified: encoding, storage and retrieval. Experimental manipulations affects one or more of these. Encoding denotes the acquisition of some information, eg. words on a list. Encoding may be taking place during the performance of some task such as counting the number of letters in the words and *intentional* if the subject has the intention to remember the words or *incidental*, if he does not. Storage can be during any length of time, and with any type of interfering task. Retrieval implies that memory is accessed from storage. Subjects may be asked to name the words he remembers (*free recall*) or be given clues and asked to name the words (*cued recall*) or be allowed to see the words again and indicate the ones that had been shown before (*recognition*) or being shown a pair of words and indicate which had been shown before (*forced choice recognition*). In tests of recognition, there are four possible outcomes (table 1.2). Measuring only hits runs the risk of regarding a subject who answers 'yes' to everything a good subject. Therefore, it is necessary to incorporate the subjects response bias in the assessment. A simple way is to subtract the false alarm rate (fa) from the hit rate (h). A slightly more complicated way (although not necessarily more efficient) is to calculate $d' = z_{fa} - z_h$ (Green and Swets, 1966).

1.3 Episodic memory

Episodic memory is unique in that information is encoded and stored together with specific contextual information or meta-information, including the circumstances of encountering the information (Schacter and Tulving, 1994b and Tulving and Markowitsch, 1998a). The place and time of the encoding event, as well as the persons involved and how the encoder felt are examples of information that might be encoded as source information. The integrity of the meta-information can be assessed experimentally for instance by having subjects study words from two lists and asking them from which list they later recognize the word (Dobbins et al., 2002). The difference between episodic memories with intact and degraded meta-information may be referred to qualitatively as the difference between 'remembered' and 'known' (Tulving, 1985a) items where 'remember' refers to full recollection including meta-information and 'know' refers to a report of familiarity, but no contextual information. Synonymously, the phenomenon has been referred to as the difference between 'recollected' and 'familiar' items (Yonelinas, 2001).

1.4 Episodic memory in the frontal cortex

As previously published from the group, the activity of the MTL decreases during repeated free-recall of abstract designs (Petersson et al., 1997, 1999a). In parallel with the MTL decreases, decreases were also observed in the prefrontal (PFC), the anterior cingulate (ACC), the posterior parietal (PPC), and parts of the inferior temporal (ITC) cortices (Petersson et al., 1999a). These learning related changes have tentatively been related in part to different demands for attentional and working memory resources, reflecting different adaptive processes related to a transition from a non-automatic to a more

automatic mode of processing. In paper I we extend these investigations of learning related modulation of functional retrieval networks in two different PET studies of episodic recognition of object-location conjunctions as well as free recall of pseudo-words. The learning related modulation has previously been conceptualised in terms of the interaction between attentional/control processes and learning or memory as well as the development of automaticity or reduced processing complexity. In the first experiment we used the recognition tasks and adapted the experimental paradigm Owen et al. (1996). This experiment was divided into two sub-experiments, the first being a replication of the study of Owen et al. (1996) and the second using a sensory-motor baseline state without explicit demands on encoding or retrieval. In the second experiment we used the paradigm described by (Petersson et al., 1999a, 1999b). Our primary anatomical focus of interest was the MTL (Desgranges et al., 1998, Fletcher et al., 1997 and Tulving and Markowitsch, 1997). Secondly, and in light of our previous results (Petersson et al., 1999a), we also explored the dynamic changes related to practice in the rest of the brain during recognition of object location conjunctions and free-recall of pseudo-words. We were particularly interested in the dorsolateral prefrontal, middle frontal/frontopolar, anterior cingulate, anterior insula/frontal opercular, posterior parietal, and occipital-occipitotemporal regions (Buckner et al., 1996, Fletcher et al., 1997 and Tulving and Markowitsch, 1997). In paper I, both PET studies represent multi-trial learning paradigms, the first exploring retrieval of object-location associations while in the second we explore the free-recall of apparently meaningless pseudo-words.

1.4.1 Levels of processing

Information selection for memory formation is based in part on attributed relevance of the incoming information. As a means of manipulating how

relevant the stimuli was to the subjects, paper II and paper IV used levels of processing. LOP (levels of processing) have been observed in encoding human memory research (Craik and Lockhart, 1972). Levels are evident when remembering is better after stimulus material is processed in an elaborate meaning-based or conceptual manner, so-called deep processing than when the initial, the material will be better remembered or more effectively retrieved than when the same material is processed with an emphasis on superficial or perceptual features, so-called shallow processing. It is possible to bias the mode of processing in experimental situations. The foundation of this effect has been studied vigorously. In the framework formulated by Craik and Lockhart (1972), it is suggested that a deeper, more semantically based processing of the encoded information yields more extensive associations with previously acquired general knowledge of the subject (Anderson and Reder, 1979 and Craik and Tulving, 1975). It is hypothesized that the richness and number of the associations that results from the processing of the stimulus determine the durability of the memory trace. Consequently, encouraging a processing strategy that leads to the formation of relatively more associations will prolong the life expectancy of the memory trace and generate more associative access pathways for later retrieval (Anderson and Reder, 1979, Craik and Lockhart, 1972 and Craik and Tulving, 1975). Another related hypothesis regarding the foundation for the LOP effect suggests that the effect depends on the distinctiveness of the memory trace compared to other memory traces (Baddeley, 1998 and Moscovitch and Craik, 1976). According to this hypothesis, recognition depends on the selection from any number of memory traces to match the stimulus. Hence, the likelihood of a memory trace being correctly selected is a function of its distinctiveness. One might expect that whether encoding is incidental or intentional would be greatly predictive of the effectiveness of encoding, but it appear to be of little consequence for the occurrence of the LOP effect (Craik and Tulving,

1975) or indeed the quality of encoding in general. Craik and Tulving (1975) also provided data indicating that the LOP effect could not be dismissed as a difference in terms of task demand. Manipulating task difficulty and time on task while holding the difference in semantic processing constant between deep and shallow processing did not suffice to replicate the effect. A similar conclusion was reached in Otten et al. (2001). In addition, experimental evidence indicated that the effects do not simply spring from the fact that semantic contexts are more accessible at retrieval by demonstrating the LOP effect also in cued recall (Moscovitch and Craik, 1976). In an effort to shed light on posterior parietal function Shannon and Buckner (2004) found activations in the left frontal cortex and medial parietal lobes when comparing deep (abstract vs. concrete judgment) with shallow (upper vs. lower case) encoding. It has been suggested that neuroimaging studies of the levels of processing phenomena have provided a means of connecting the functional role of the prefrontal cortex and encoding processes (Buckner et al., 2000). Direct evidence for a link between prefrontal activity and behavioral performance in episodic memory performance has been established by showing that the level of activity in the left prefrontal (BA 44/6 and 45/47) on average predicts whether information later will be retrievable or forgotten (Wagner et al., 1998b). Similar observations have been made concerning the medial temporal lobe (Brewer et al., 1998, Fernández et al., 1998, Petersson et al., 2003 and Wagner et al., 1998b). In deep vs. shallow incidental encoding, (Kapur et al., 1994) observed left middle-inferior prefrontal (PFC) activations (BA 45/46 and 47). In addition to left middle-inferior PFC activations (BA 9, 44), Rugg et al. (1997) observed activations including left anterior cingulate (ACC BA 32), left medial superior PFC (BA 8), left superior temporal (BA 22), and medial temporal lobe (MTL) activations. These findings were essentially replicated in the study of Otten et al. (2001). In most cases, verbal stimuli have been used in previous studies. Miller et al. (2002) however used split-brain patients to establish

that there was a material-dependent benefit from a LOP manipulation. When words were presented to the left hemsisphere and faces to the right there was a noticable When words were presented to the left hemsisphere and faces to the right there was a noticable increase in successful encoding, but not when words were presented to the right hemisphere or faces were presented to the left hemisphere.

A number of previous functional neuroimaging studies have investigated episodic encoding and retrieval of word material under levels of processing manipulations (Kapur et al., 1994, Otten et al., 2001 and Rugg et al., 1997). It has been suggested that the neuroimaging studies of the LOP phenomena have provided a link between the functional role of the prefrontal cortex and encoding processes (Buckner et al., 2000). Direct evidence for a link between prefrontal activity and behavioral performance in episodic memory performance has been established by showing that the level of activity in the left prefrontal (BA 44/6 and 45/47) on average predicts whether information later will be retrievable or forgotten (Petersson et al., 1999a and Wagner et al., 1998b). Similar observations have been made concerning the medial temporal lobe (Brewer et al., 1998, Fernández et al., 1998, Petersson et al., 1999a and Wagner et al., 1998b). In the deep versus shallow incidental encoding, Kapur et al. (1994) observed left middle-inferior prefrontal (PFC) activations (BA 45/46 and 47). In addition to left middle-inferior PFC activations (BA 9, 44), Rugg et al. (1997) observed activations including left anterior cingulate (ACC BA 32), left medial superior PFC (BA 8), left superior temporal (BA 22), and medial temporal lobe (MTL) activations. These findings were essentially replicated in the study of Otten et al. (2001). In the present study we investigated the LOP effect using two visual materials, that is, figurative and non-figurative line drawings, in two experiments. First, we characterized the LOP effect in a behavioural study, and then, in a second study, we investigated the network of

brain regions related to incidental episodic encoding of visual material under a levels of processing manipulation contrasting judgments of pleasantness with judgments of graphical quality using positron emission tomography (PET). The former aspect may be thought of as a means to bias the processing of the stimuli toward an inherently meaningful encoding mode, in which the stimuli were associated in a meaningful way with an inner subjective state, while the latter provides richer encoding opportunity. In a 2×2 factorial design with the type of encoding instruction (ie. deep versus shallow) and type of visual material (figurative versus non-figurative line drawings) as the experimental factors, we investigated whether the LOP effect at the behavioral level generalized to our particular experimental setting. By using pleasantness and perceptual quality judgments in figurative as well as non-figurative drawings in the encoding situation, we investigated whether the semantic content of the encoded material interacted with the LOP effect. In the PET study we characterised the activation patterns in the brain along two dimensions: semantic content in the stimulus material as well as meaningful processing, here in the general sense of pleasantness judgment, through an explicit instruction. The first objective with the PET study was to investigate to what extent the LOP-related brain activations found with word stimuli under standard LOP manipulations (Kapur et al., 1994 and Rugg et al., 1997) generalised to our situation. In addition, the type of material manipulation may be viewed as a complementary way of manipulating meaning-based processing triggered by the semantic content of the stimulus material. The second objective was thus to investigate to what extent the encoding-related activations were similar when using line drawings with or without apparent semantic content, which hitherto remains an open question (Buckner et al., 2000). The primary anatomical foci of interest, given previously reported results (Kapur et al., 1994, Otten et al., 2001 and Rugg et al., 1997), were several relevant regions of the PFC and the MTL (Buckner et al., 1999, Buckner

and Koutstaal, 1998, Desgranges et al., 1998, Fletcher et al., 1997, Mayes and Montaldi, 1999, Nyberg L, 1998, Nyberg et al., 1996 and Tulving and Markowitsch, 1997).

1.4.2 Loci

According to Yates (1966), the method of *loci* and *imagines* as a way of memorising things was first described by Cicero and has been used by monks and scholars until quite recently. The method entails using previous knowledge of some set of places (the *loci*, for instance, the rooms in one's home) and then, while walking through them in in one's mind, placing the items to be remembered (the *imagines*) in different rooms. In the context of paper III, however, it represents a way to manipulate the relevance signal associated with the otherwise uninteresting word lists.

1.4.3 Source memory

Source memory refers to the ability to correctly attribute the source of an item that has been retrieved. Putatively, it is the unique feature of human episodic memory. The neural infrastructure supporting recognition in the medial temporal lobe has been the object of some study. It has been proposed that retrieval of 'remembered' items depends crucially on the hippocampus while retrieval of 'known' items rests on the perirhinal cortex (Aggleton and Brown, 1999 and Petersson et al., 2001). Eldridge et al. (2000) indeed found that the left hippocampus was activated more for recognition events classified as 'remember' than those classified as 'know', and the right hippocampus showed the same pattern although at a sub-threshold level. Yonelinas et al. (2005) and Wheeler and Buckner (2004) as well as Daselaar et al. (2006) found

bilateral hippocampal activations for 'recollection' more than for 'familiarity'. Building on the idea of context-dependent and dynamic processing in the medial temporal lobe (MTL; Petersson et al., 1999b), Fernández and Tendolkar (2006) regards the rhinal cortex as a familiarity detector which controls the nature of further processing. In addition, there have been reports suggesting that source memory depends on the frontopolar and dorsolateral parts of the prefrontal cortex (Dobbins et al., 2002 and Henson et al., 1999a). Previous papers did not separate recognition activity from activity related to source processing, since recognition and source testing were in immediate temporal contact. In paper V we attempted to separate the two by placing recognition activity and 'remember'/'know' judgments in different sessions.

1.4.4 Hemispheric encoding retrieval asymmetry

x	y	z	BA	region	side
-26	56	8	10	frontal pole	sin
-34	18	8	45/47	frontal operculum	sin
30	46	8	10	frontal pole	dx
32	24	0	45/47	frontal operculum	dx
38	18	32	8/9	dorsal prefrontal cortex	dx
2	22	40	32	anterior cingulate	

Table 1.3 The six sites proposed to make the foundation for the retrieval mode (Lepage et al., 2000)

The observation that functional neuroimaging experiments of encoding commonly revealed activations on the left side of the frontal cortex, and retrieval experiments commonly activated the right side led to the formulation of the HERA hypothesis (hemispheric encoding retrieval asymmetry Tulving et al., 1994 and Nyberg et al., 1996). The debate that followed contained strong arguments on both sides. The original formulation only referred to verbal stimuli, but in the following years a stronger proposal was put forward according to which the asymmetry applied to any type of stimuli (Nyberg L, 1998 and Nyberg et al., 2000). Criticisms included the suggestion that the apparent laterality difference based on task was in fact based on the materials used (Wagner et al., 1998a). A reformulated hypothesis was put forward by Habib et al. (2003)

which differed from the original in that encoding and retrieval must be tested on the same material in order to test the HERA hypothesis. As a further development, retrieval mode (REMO) was invented to capture one part of the HERA in a new way. REMO consists of six regions in the brain (table 1.3) that represent a the neural foundation for a 'retrieval-biased' mode of processing stimuli.

2 Aspects of episodic memory: question and aims

THE OJECTIVES of this thesis were to examine the role of the human prefrontal cortex in episodic memory and learning as well as the interaction of the prefrontal cortex with other regions of the brain.

2.1 Paper 1

The aim of the first study was to characterise the effect of practice on the functional anatomy of episodic memory retrieval of verbal and visuo-spatial material as well as replicate the findings of Raichle et al. (1994) and Owen et al. (1996).

2.2 Paper 2

The aim of the second study was to characterise the effect of semantic content of material as well as the effect of a levels of processing manipulation on episodic memory encoding of visuo-spatial material.

2.3 Paper 3

The objective of the third study was to illuminate whether explicit teaching of a mnemonic strategy could influence functional anatomy. We investigated the effects of training using a specific mnemonic (the method of loci) in young and older adults during an episodic memory task. Differences in network activity were sought between those who benefited from the mnemonic and those who did not as well as between young and older adults.

2.4 Paper 4

The aim of the fourth study was to separate aspects of the results from paper 2 by application of a method with a better temporal resolution than PET.

2.5 Paper 5

The aim of the fifth study was to refine search for episodic meta-information (source memory) by differentiating recognition processing from source processing by dividing the experiment into different sessions.

3 Methods for studying human brain function

The study of human brain function requires non-invasive methods that do not interfere with normal brain function. Such interference must be avoided on the tissue level as well as on the behavioural level. Consequently, the study of human brain function is undertaken mostly using methods that do not access the brain directly. The electrical currents generated by neuronal work can be detected on the scalp, which is the foundation for continuous recordings in the electroencephalogram (EEG) and time-locked recordings with event-related potentials (ERP). Furthermore, these currents, small as they are, generate fluctuating magnetic fields which can be detected with magnetoencephalogram (MEG). This group of methods are usually referred to as electro-physiological. Marta Kutas and Anders Dale described the foundations and practice of these methods succinctly in Kutas and Dale (1997).

The maintainance of membrane potentials requires energy turnover and hence neurons and other brain cells require transport of oxygen, nutrients and waste in order to function. This is mediated by blood flow. The brain consumes one fifth of the heart's output of blood at rest. When a region in the brain requires more blood, blood vessels (small arteries) in that region dilate, so that blood flow increases. The measurement of such differences in blood flow is another indirect means of measuring brain function. Two methods of this kind have been used in this thesis (PET and FMRI), and will be described in detail below.

3.1 The basis of blood flow measurements

The neurophysiological basis of functional neuroimaging is the relatively tight and roughly linear coupling between the regional cerebral blood flow, the metabolic activity, and the neural activity as measured with electrophysiology (Siesjö, 1978, Gusnard et al., 2001, Logothetis et al., 2001, Rees et al., 2000 and Scannell and Young, 1999). Oxygen is used in the oxidative metabolism of glucose to supply the brain with energy in the long term (Raichle, 1998). Brief increases in neural activity of a brain region implies that the energy and oxygen requirements in the region increases and is accompanied by an increase in blood flow as well as glucose consumption that exceed the increase in oxygen consumption (Fox et al., 1988). This means that the relationship between oxygen consumption and blood flow is not proportional. In a region of transient activity, the increase in glucose is partly broken down anaerobically by glycolysis despite of an overcompensation in blood flow. As a result there is a lowered extraction fraction of oxygen which causes an increased oxygen content locally in the blood (Raichle et al., 2001). The robust empirical relationship between changes in brain activity and blood flow has been known for over a century (Raichle et al., 2001).

The mismatch with a proportionaly higher blood flow and a lower oxygen consumption is the basis of the blood oxygenation level dependent (BOLD) contrast used in FMRI. The work of Logothetis and colleagues (Logothetis et al., 2001, 1999) suggests that a spatially restricted increase in the FMRI signal directly reflects an increase in neural activity. They recorded action potentials and local field potentials in parallel with the BOLD signal. Both these measures correlated with the observed BOLD signal, the local field potentials somewhat better than the action potentials. Local field potentials arise from the dendritic input as well as integrative processes within neurons. These findings are

consistent with autoradiographic measurements of glucose consumption by different brain regions in rats (Raichle et al., 2001).

The energy turnover in the brain is necessary in order to maintain ionic concentrations and membrane potentials at the appropriate levels. The dominant energy expenditure results from maintenance of these membrane potentials. Neuronal signalling evokes ionic fluxes across membranes, and these fluxes need to be restored. Most such fluxes are supported directly or indirectly by the 3Na/2K-ATPase[1] and other ionic pumps (Siesjö, 1978). Raichle et al. (2001) suggests that the glutamate cycle acts as a local driver for metabolism based on the abundance of glutamate as a transmitter. Thus the generation of ATP will be supplied anaerobically and lactate will be produced upon increases in neuronal work. This means that PET measures of regional cerebral blood flow will indicate proportionally higher increases in signal than the actual local increase in oxygen consumption. In FMRI, the sensitivity of the measured signal is based on the related increase in oxygenated blood locally. As noted, the BOLD signal correlates well with local field potentials and to a large extent these are generated in the post-synaptic dendritic component where large ionic fluxes that need restoration are generated from the neuronal input. There remains an unresolved question regarding the relationship between the type of brain activity and the signals measured with FMRI and PET. Are they related to excitation, inhibition, or both? The signal is a composite net-activity and it is difficult to imagine any regional activity that is not a mixture of excitatory and inhibitory components. However, given that inhibitory signals give rise to hyper-polarisation and less ionic leakage post-synaptically,

[1] An enzyme that swaps 3 sodium ions (Na^+) for 2 potassium ions (K^+) across cell membranes at the cost of energy (adenosine triphosphate, ATP). Cellular integrity demands that the concentration of sodium inside the cell is low and the concentration of potassium is high, while the opposite is true outside the cells

it is possible that the recorded signal might be more closely related to local excitatory activity (Shinohara et al., 1979).

3.2 Positron Emission Tomography (PET)

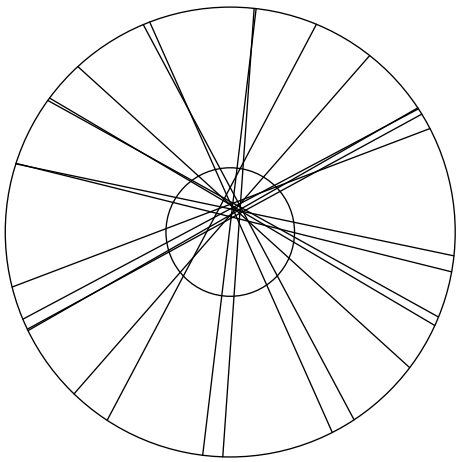


Figure 3.1 The photons emitted from the annihilation of a positron and an electron are detected by a ring of detectors surrounding the subject's head. 'Lines of response' are reconstructed from simultaneously detected photons. An area that is crossed by more lines has received more blood.

An emitted positron travels a very short distance before encountering an electron. The encounter results in annihilation of the positron and electron and the release of two photons in almost exactly opposite directions. Since these travel at the speed of light, when both are detected simultaneously in a ring of detectors, they describe a line on which the interaction must have occurred (a 'line of response', see figure 3.1). This is the way that PET (positron emission tomography) works. A positron-emitting isotope, such as ^{15}O, is incorporated into a molecule, such as water, and injected into (a vein of) the subject. It travels with the blood, and if the subject is using a certain part of the brain, small arteries will dilate and more blood (carrying the isotope) will flow through that brain region. The ^{15}O isotope has a half-life of just over 2 minutes, meaning that the activity is no longer measurable after 10 minutes (which equals five half-lives). In cognitive experiments, the subject is given a task to perform during the first minute after being given an injection with radio-labelled water (see figure 3.2). The subject is allowed to lie on a gurney and his head is placed in a PET scanner, which basically is a ring of photon detectors, and measurements of radioactivity are made. Since every persons cranium is unique, it offers

a unique pattern of attenuation to the emissions from the injected decaying radio-isotope. A transmission scan, where radiation is transmitted through the head of the subject from an external source rotating around the subject's head and measured on the opposite side, was made for each subject to make it possible to compensate for differences in cranial shape and thickness.

In order to construct a 3D image from the collections of raw response-lines (called a *sinogram*), a reconstruction algorithm called back projection was used as well as scatter correction to correct for random detector events. The temporal resolution of PET is determined by the half-life of the radio-isotope in use. Since ^{15}O has a half-life of just over 2 minutes, scanning is done for one minute and that is the temporal resolution. Spatial resolution in haemodynamic measures of brain function is bounded by the distribution of capillaries and the reach of tissue signals resulting in dilation of capillaries. In the case of PET, resolution is further (albeit slightly) affected by the distance a positron can travel before it annihilates with an electron. Spatial resolution is in the order of ten millimetres.

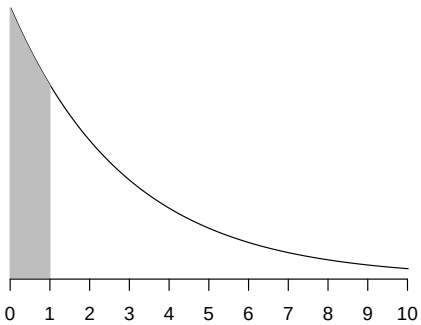


Figure 3.2 The half-life of ^{15}O is 122.2 seconds. Bound to hydrogen atoms as water in an appropriate saline solution it is injected into the subject. After ten minutes, roughly three percent of the injected activity remains. Some thirty percent of the decay between scans occurs in the first minute after injection, and this is the time during which measurements are made.

A PET scanning session consists of multiple measurements and the subject is therefore provided with an intravenous access cannula before getting into the scanner. Since subject movement presents a potential problem for subsequent data analysis, great care is taken to make sure the subject is comfortable and still for the roughly two hours of scanning ahead. When the subject's head is resting comfortably in the head cradle, an attenuation correction

(transmission) scan is undertaken, followed by ten to fifteen injections ($H_2^{15}O$, saline, each containing some 400–500 MBq or 10–15 mCi) and emission scans during which the subject is given relevant cognitive tasks. In total, the subject receives maximally 7 mSv of radiation in a scanning session, roughly the same as in a CT scan of the abdomen.

3.3 Functional Magnetic Resonance Imaging (fMRI)

Magnetic resonance imaging relies on applied quantum mechanics. For a thorough description the reader is referred to other sources (eg. Jezzard et al., 2001). Briefly, some atomic nuclei (notably those with an odd number of nucleons such as hydrogen, but also some others) have a *spin* which give them an intrinsic magnetic moment. When placed in a strong magnetic field (known as the B_0-field), these hydrogen spins align with the axis of magnetic field and may be perturbed with a electromagnetic signal (a radio-frequency pulse), resulting in the axis of the spin being temporarily misaligned with the axis of the B_0-field. During the relaxation process, when the axes return to alignment, an electromagnetic signal is emitted and detected by coils in an MR scanner. Orbiting electrons provide the nuclei with some shielding from the external magnetic field, and the positions of the nuclei in different molecular settings determine the configurations of orbiting electrons. This means that hydrogen nuclei in different molecular contexts or environments (and therefore different types of tissue) will give rise to different signals. In popular terms, water swimming in water sends a different signal than water swimming in fat.

In functional magnetic resonance imaging, the different molecular settings that generate the contrast are caused by haemoglobin. Whether a haemoglobin molecule carries oxygen alters its magnetic properties and the signal

emitted from hydrogen nuclei (oxy-haemoglobin is paramagnetic). In parts of the brain where more nutrients and oxygen are required, blood vessels dilate, allowing a greater inflow of oxygenated haemoglobin with the blood. The inflow increase overcompensates the local metabolic need, leading to an increase of oxy-haemoglobin in the small post-capillary veins, and the consequent small difference in signal is referred to as blood oxygenation level dependent (BOLD) contrast.

The resolution of FMRI surpasses that of PET both temporally and spatially. With modern scanners, physiology provides the limit of temporal as well as spatial resolution. The haemodynamic response to a neural event is sluggish and delayed (see figure 3.3), and extends spatially for an unknown distance of several millimetres beyond the origin of the signal for blood vessels to dilate. However, FMRI is also prone to problems that do not occur with PET, notably susceptibility artifacts that lead to signal drop-out in areas where tissue is in close proximity to air such as near the sinuses, nasal cavity or the mastoid bone as well as an increased sensitivity to artifacts caused by subject movement.

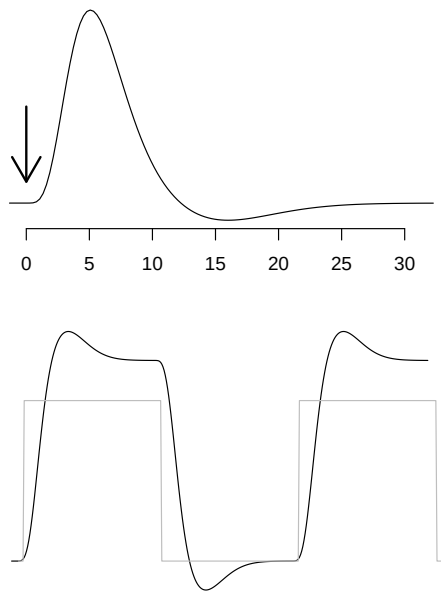


Figure 3.3 An approximation of the typical temporal outline of the haemodynamic response function after a brief intense stimulus. Note the delay until the maximum at 5–6 seconds. In the analysis of FMRI data what is known as a canonical haemodynamic response function is used in the model, and the experimental design (ones when stimulus is on, zeros when it is off, grey line in lower plot), is 'convolved' with it.

A scanning session in FMRI typically starts with a security work-up to make sure the subject does not have any implanted metallic material or any implanted device which may be susceptible to

magnetic fields. Also, the possibility of a pregnancy precludes scanning, not because of knowledge of any risk to the foetus or mother but in order to err on the side of safety. The experimental procedure may be described to the subject after which the subject is allowed to enter the scanner.

3.4 Analysis of functional imaging data

There are several issues related to functional imaging data which need to be addressed in order for them to be successfully analysed. Subjects will move during the scanning session, no matter how comfortable or padded they are. Any human brain is as unique as a fingerprint, so in order to make any useful comparison between individuals or groups a method of describing brain regions in spite of structural differences is needed.

During the last two decades a body of well described theories and empirically validated methods have been developed for the analysis of functional imaging data. These methods provide a framework for investigating functional neuroimaging data and making scientific inferences based on statistical analysis. Statistical models make explicit as well as implicit assumptions about the data. What is of importance in this context is not the assumptions or approximations per se but how well these are fulfilled by empirical data and the robustness of the methods used, when these assumptions or approximations are not fully met (Petersson et al., 1999a, 1999b). The general outline of functional neuroimaging data analysis proceeds as follows: the functional images are realigned, anatomically normalised, and spatially and temporally low-pass filtered, a statistical model for the data is specified, model parameters estimated and a test statistic is chosen in order to make statistical

inferences, taking into account the multiple non-independent comparisons (from Petersson et al. (1999a, 1999b).

3.4.1 Realignment and anatomical normalisation

In a functional neuroimaging experiment, a time-series of volumes (or 3D images) are acquired of a given participant in the different experimental conditions. For example, in our PET studies, 10 - 15 PET scans were acquired for each subject. In spite of the fact that the head of the participant was lightly fixated to the head cradle, small head movements still occurred (in the order of 1 - 3 mm). As a means of compensation for this movement, the reconstructed PET images are automatically realigned (cf. Ashburner and Friston, 1997). The brain in each volume of the time-series of a given individual will thus occupy the same position in image space.

The brains of different individuals are anatomically different. A necessary requirement for group studies in functional neuroimaging is to represent data in a standardised anatomical space. This requires a method to transform, or warp, individual data into the standardised space, so called anatomical normalisation. The procedure used transforms the image time-series of the individual participant into a standardised anatomical space and allows data from different subjects to be compared. In our studies we have commonly used the stereotactic space as defined by the SPM template (`http://www.fil.ion.ucl.ac.uk/spm`, Evans et al., 1993), an approximate Talairach space (Talairach and Tournoux, 1988), as specified and sometimes in combination with the Karolinska Brain Atlas (Greitz et al., 1991).

3.4.2 Spatial filtering

The inter-individual residual variability in functional anatomy generally exhibits spatial structure and is dependent on the algorithm used for normalisation. Simulation studies have indicated that a reduction of registration (realignment) error and a minimisation of the residual anatomic variability can significantly improve the signal detection sensitivity (Worsley et al., 1996). In the presence of residual functional-anatomical variability the effect of inter-subject averaging amounts to a spatial filtering or smoothing effect. Thus, if the spatial-scale of the filter matches the inherent scale of functional-anatomical variability in the population, no (or little) spatial information is lost. In general, when using a voxel-based approach, it is important to reduce the impact of misregistration and inter-individual residual functional-anatomical variability. A common strategy is to low-pass filter, or smooth, the data either at reconstruction or with a suitably chosen convolution kernel (e.g., an isotropic 3D Gaussian kernel). Spatial filtering, which in effect is a local weighted averaging procedure, also increases the local equivalence of the voxel data across measurements and individuals and thus the validity of voxel-based statistical models.

There have been several attempts to assess the residual functional-anatomical variability after realignment and anatomical normalisation in more or less low-pass filtered data (Petersson et al., 1999a, 1999b). These attempts have often used the variability in location of the local maximum statistic (peak location). Several studies estimate inter-subject standard deviations of the peak coordinates to be on the order of 5-10 mm (Fox and Pardo, 1991, Hasnain et al., 1998, Hunton et al., 1996 and Ramsey et al., 1996). When, for example, PET data from different laboratories are compared, this variability increases

and indicating that activation foci that are less than 10 mm apart cannot always be reliably distinguished (Petersson et al., 1999a, 1999b)

3.4.3 Acquisition (slice) time correction

In studies with FMRI, data are collected sequentially slice by slice. Hence, in the attempt to improve accuracy in the time domain, a correction for these differences in time relative to stimulus may be applied in the analysis of the data (Frackowiak et al., 2003). However, since this is only an interpolation and there are also other reasons for imperfections in the time estimates, there is a risk that such a compensatory measure may introduce artifacts. This seems especially important if the repetition time (TR) is long (SPM manual, `http://www.fil.ion.ucl.ac.uk/spm/doc/manual.pdf`). In our case, the TR was 4.2 seconds and hence considered to contraindicate an implementation of slice time correction, based on a small examination of the data from paper IV using both methods, although the differences were small.

3.4.4 Statistical modelling and estimation

Functional neuroimaging data are typically analysed in terms of a specific linear model, parameters are estimated, and subsequently various null-hypotheses are tested. Under the assumption that the activation and reference conditions differ in some relevant specific aspect of cognitive processing, the locations of statistically significant differences in signal between conditions presumably define brain regions that are related to this difference. This approach is crucially dependent on an adequate choice of conditions to compare. For example, in a simple subtraction, only parts of the underlying functional network may be observed, since common components activated to

a similar degree will not be observed. Furthermore, results obtained with the subtraction approach can only be interpreted as relative differences since, at present, a canonical reference state or baseline condition seems difficult to define (Petersson et al., 1999a, 1999b).

A closely matched control condition ideally differs only in a single aspect from the condition of interest and can be used to test for specific effects. Instead a low-level control condition, for example rest with eyes closed or visual fixation, can be used to detect many, most, or all of the brain areas involved in a given task. Thus the simultaneous use of both closely matched and low-level control conditions can provide complementary information (Petersson et al., 1999a, 1999b).

3.4.5 Specific difficulties in the study of learning

Learning takes time to occur, and this is relevant beyond the trivial sense. When a person is practising a task, time passes between the first and the second time, so the difference between the first and tenth performance of the task is not only nine practise rounds, but also that it is later in the day. In an experimental setting this may be a confounding factor that must be separated from the object of study, the learning that may have occurred (Petersson et al., 1999a). In functional neuroimaging experiments, the situation is quite constrained and artificial, meaning that the subjects ability to concentrate on the task is likely to diminish over time. Also, non-specific effects of time may occur in measuring devices such as a scanner (Petersson et al., 1999a). There are several ways to deal with this, including using different statistical models and altering the experimental design. The linear (or polynomial to the n-th degree) effect of time may be included in the statistical model. However, this will to some degree confound the learning that may have occurred,

and thereby decrease sensitivity to the factor of interest. A better way may be to design the experiment so that such post-hoc statistical compensation is not necessary. Including baseline measurements in close temporal proximity to the experimental measurements and basing analysis on differences between the two measurements allows experimental control of non-specific time effects. This may be called an interaction approach, since the statistical analysis is based on finding an interaction between the experimental measurement and its associated baseline measurement. The success of this approach depends on the baseline being truly equal and the temporal proximity to the experimental measurements being sufficient.

3.4.6 The general linear model

The general linear model (GLM) is a framework that encompasses all basic univariate models, including the ANOVA/ANCOVA and the multiple regression models. In the GLM framework n observations from a single image voxel are represented as column vector of length n, Y; the p effects and predictor variables are represented as p column vectors also of length n, forming an $n \times p$ matrix X called the design matrix. The fixed regression parameters are represented as a column vector β of length p; the residual random error is written as the column vector e of length n. With the assumption of mean zero, independent and identically distributed error of magnitude s^2, the concise representation of the GLM is:

$$E(Y) = X\beta \quad \text{and} \quad Var(Y) = \sigma^2 I,$$

where I is the $n \times n$ identity matrix. Note that we have made no specific distributional assumptions; the usual normality assumption is only needed for statistical inference. Using only the general assumptions above, according to

the Gauss-Markov theorem (Bickel and Docksum, 1977, Bilodeau and Brenner, 1999 and Brockwell and Davis, 1991), the linear unbiased estimates of b and s^2, that are best in terms of minimising the squared estimation error, are given by:

$$b = (X'X)^{-1}X'Y \quad \text{and} \quad s^2 = 1/(n-p)(Y-Xb)'(Y-Xb),$$

where b and s^2 are the estimate of the unknown β and σ^2, respectively. The form of b can be found from algebraic manipulation of $Y = Xb$. Note that $Y - Xb$ is the residuals, so that the form of s^2 is just the mean squared residuals (the $n - p$ reflecting the dimensionality of the residuals that are left after fitting p independent effects). Tests of linear combinations of the parameters can be made under the normality assumption, which gives:

$$Cb \sim N(C\beta, C(X'X)^{-1}C'),$$

where C is a row vector of length p, often called a contrast (Frackowiak et al., 2003).

3.4.7 Hypothesis testing and statistical inference

The model parameters are always assessed in relation to their uncertainty in a statistical hypothesis-testing framework. Informally, we wish to know if the magnitude of the parameter (or contrast of parameters) is substantial with respect to its uncertainty (i.e., its standard deviation). Hypothesis testing proceeds as follows: the null hypothesis is assessed with a test statistic, a function of the data that is sensitive to deviations from the null hypothesis and reflects the effects of interest; the observed statistic is compared to its distribution under the null hypothesis, yielding a P-value. A small P-value is interpreted as indicating that there is little support for the null hypothesis,

though its interpretation is more subtle. The P-value is the probability of observing a statistic value as large or larger, under an identical replication of the experiment, and under the assumption that the null hypothesis is true. Hence, the P-value is a statement about the data under the null hypothesis, not the null hypothesis itself.

The regression approach in functional neuroimaging fits univariate models at every voxel (the number of voxels is typically on the order of 10^5), and effects of interest are tested in each individual model by generating and assessing a statistic image. Usually an image regression approach is used, which implies that the same univariate model is fitted at each voxel. The common test procedures in functional neuroimaging conform to the standard structure of hypothesis testing. If a particular, pre-specified voxel is of interest, then standard univariate theory can be applied. Otherwise the statistic image is searched for, for example, voxels of significant magnitude using the local maximum statistic, or, given an intensity threshold, significant clusters using the supra-threshold cluster size statistic.

3.4.7.1 The use of weighted contrast vectors

When doing experiments where the number of events of different types cannot be known until the experiment is done, as was the case in paper V and paper IV, there is a risk that the numbers of events differ greatly. This is detrimental to the statistical model because the estimated variance becomes quite different. The parameter estimates for event types with very few representatives are associated with a greater uncertainty. In order to compensate for this it is possible to give weights to the different parameter estimates to reflect the underlying certainty. Estimates that are very uncertain because they are based on few measurements can be given a lower weight. In our case,

in paper V and paper IV, the weights were based on $\sqrt{n}$, that is, the contrast vectors were multiplied with this number within session.

3.4.8 General issues related to statistical inference

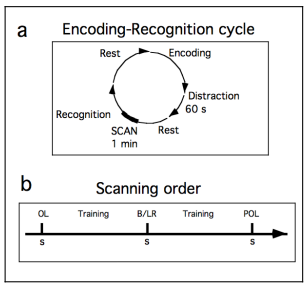
The statistical analysis of functional neuroimaging data is massively univariate and therefore gives rise to a multiple comparisons problem. It is therefore necessary to appropriately control the false positive rate, yet avoiding any unnecessary loss of sensitivity and statistical power. Given the null hypothesis H_0 and a test statistic $T(X)$ of the data X, the test is said to be liberal, conservative, or exact, if for any given level α and rejection region $R(\alpha)$, the probability that $T(X)$ belongs to the rejection region $R(\alpha)$, $P[T(X) > R(\alpha))|H0]$, is greater than, less than, or equal to α, respectively. Appropriate control of the false positive rate requires an exact or conservative test. In general, the more conservative the test is the lower the sensitivity of the test.

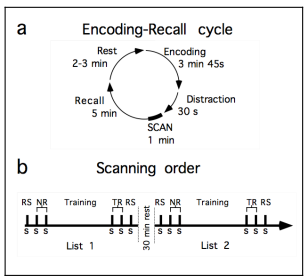
Functional neuroimaging data are often characterised by spatial auto-correlation, meaning that adjacent voxels are correlated, due to the point spread function of the imaging system, physiological factors, as well as image smoothing. Given a non-trivial spatial auto-correlation in the statistic image, it is implied that multiple comparisons are non-independent and a simple Bonferroni correction would be unnecessarily conservative. There are several approaches to handle this problem and these divide into parametric, non-parametric, and Monte-Carlo simulation approaches (Petersson et al., 1999a, 1999b). The parametric approaches used in functional neuroimaging are usually based on some type of random field theory (Adler, 1981, Friston et al., 1995 and Worsley et al., 1996) generating distributional approximations.

3.4.9 Random field theory

In our studies we have used the GLM framework for modelling and estimation, while we have based our hypothesis testing and statistical inference on parametric approaches founded in smooth random field theory. Random field theory has proved versatile in testing a number of test statistics (e.g., local maximum, cluster size statistic, or the number of regions with size greater than a given size). The smooth random field theory approach has been extensively validated on simulated data and empirical studies using real null data have indicated that this approach gives accurate results (Aguirre et al., 1997 and Zarahn et al., 1997). In addition, investigations of the robustness and characterization of inherent limitations of the random field theory approach with respect to the various assumptions and parameters have been carried out extensively; including, for example, with respect to degrees of freedom (Worsley et al., 1992), smoothness estimation (Poline et al., 1995), and variance heterogeneity (Worsley et al., 1996). In addition, non-parametric methods have been used as benchmarks for cross-validation of the random field theory approach and these investigations have also shown that the approach provides accurate results (e.g., Ledberg et al., 2001). Essentially, the random field theory approach allows for spatial correlation between voxels in the statistic image when correcting for multiple comparisons, thereby improving on the Bonferroni correction and thus preserving statistical power. The approach has been developed to accommodate several statistical fields, such as Z, t, X^2 and F fields, where all non-Gaussian random fields are derived from Gaussian random fields. For further discussion of assumptions, approximations, and limitations in functional neuroimaging, see Petersson et al. (1999a, 1999b).

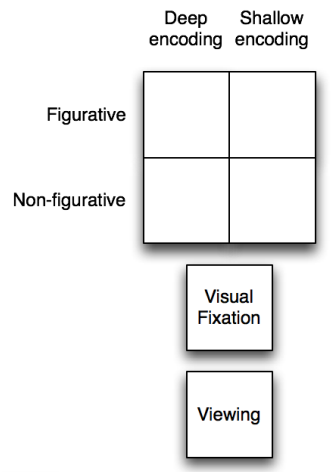
3.5 Specific methods of the studies



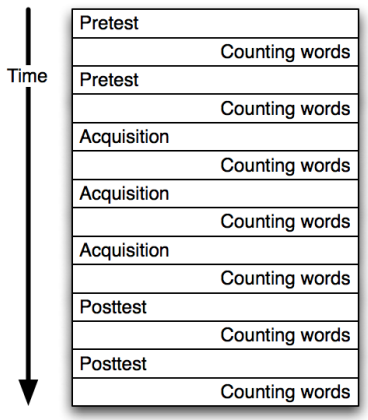


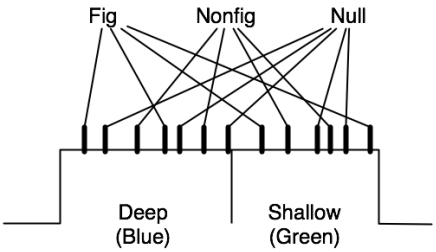
In the first experiment of paper I, the effects of practice were studied and scans were performed during the recall phase of multiple encoding-retrieval cycles of non-figurative drawings and pseudo-words. In 'OL' and 'POL', subjects indicated which of two objects presented in different locations on a computer screen had been seen in that location during encoding. There were 16 subjects, divided in two groups which differed only in the reference condition used. Half were scanned while indicating which of two squares contained an 'X' ('B' condition), and half while indicating which to two empty squares had been seen before ('LR' condition). The second experiment was similar, but instead of non-figurative drawings, pseudo-words were used, and instead of a recognition test, subjects recalled the words freely.

Encoding was manipulated along two axes and two low-level reference conditions were used in paper II. Subjects were scanned as they were incidentally encoding drawings while following either of two instructions: judging to what degree the drawing or any imagery the drawing evoked was pleasant ('deep' condition, 'yes', 'neutral' or 'no') or judging the graphical quality of the drawing ('shallow' condition, 'high', 'medium' or 'low'). In addition, the drawings were either figurative or non-figurative. A separate behavioural experiment was performed as part of the paper.

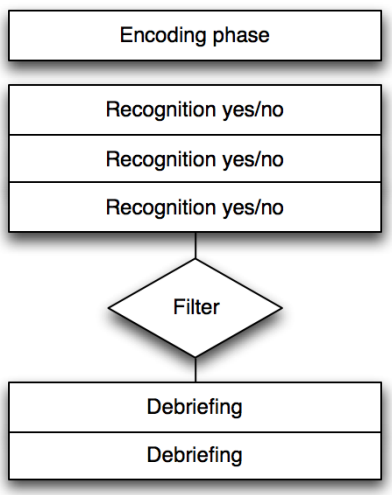


The effects of practice on serial recall were examined in paper III where we scanned subjects during a sequence of testing memory for a word list, acquiring the loci mnemonic consisting of a list of imagined places in which to 'place' the items to remember and testing use of the mnemonic on a new list. 14 scans were undertaken. The data was analysed using an interaction approach since each scan was followed by a baseline scan. In this way it was possible to avoid confounding and irrelevant effects of time.





The paradigm of paper two was modified in paper four so that figurative and non-figurative drawings were displayed in random order. The deep and shallow encoding conditions were described to the subjects prior to scanning and conveyed to the subjects during scanning by the color of the drawings. The specific mapping between color and condition was randomised over subjects. Data was analysed without the use of slice timing correction and using weighted F contrasts in order to compensate for differences in the number of occurrences of the different event types.



The last paper allowed subjects to study a word list and to be scanned during a recognition test. After the recognition test, subjects were shown the hits from the recognition test and asked to indicate what the quality of the recognition experience had been, whether it had been one of 'remembering' (meaning that they had a specific recollection of the encoding moment), 'knowing' (meaning that they recognised the word but did not specifically recollect the encoding moment) or if they no longer were certain about the recognition experience. Data was analysed without the use of slice timing correction and using weighted F contrasts in order to compensate for differences in the number of occurrences of the different event types.

4

Results

RESULTS below are presented in text and occasionally in tables. For p-values, coordinates and statistics the reader is referred to the original papers. An exception is made for the medial temporal lobe since distances are small and coordinates may be of greater interest. Coordinates, when given, refer to millimeters right of (x), anterior to (y) and superior to (z) the anterior commissure of the corpus callosum in the center of the brain. In the tables, anatomical region and Brodmann's area is reported. A finding on a left is indicated with 'sin' after the BA number, and a finding on the right is indicated with 'dx' in the same manner. If there is neither 'sin' nor 'dx', the finding is on or near the mid-line. When a Brodmann's area is mentioned, it is not implied that the entire area has been observed, merely that a finding had at least one peak in the mentioned BA. Numbers separated with a slash indicates that a finding was on the border between the areas.

4.1 Paper I

4.1.1 Object location of visuo-spatial material

Performance levels in all conditions were high, the lowest recorded was 96 percent. The task was well matched to the subjects ability to perform it. Maintenance of a high and constant performance avoids the confounding effect of performance differences across groups or over time or in parallel to

Region side	*BA*
PFC	10 dx, 46 dx, 10 dx, 11 dx
FEF	6 dx, 8 dx
ACC	24 dx, 32 dx
insula	14 dx, 15 dx
insula	14 sin, 15 sin
parieto-occipito-temporal	18 sin, 18 dx, 19 sin, 19 dx, 7, 39 sin, 40 sin, 40 dx, 37 sin, 37 dx, 36 dx

Table 4.1 Object location vs. baseline

changes in blood flow and so makes interpretation easier. Several regions were significantly activated when comparing recognition of combined objects and locations with baseline, including the right prefrontal cortex, right frontal eye field, anterior cingulate, bilateral anterior insular cortices, and a large cluster encompassing occipito-parietal regions and an occipito-temporal cluster extending into the MTL as well as the medial cerebellum.

Region	*BA*
occipito-temporal	17 sin, 17 dx, 18 sin, 18 dx, 19 dx, 20 sin, 35 dx, 36 dx, 28 sin
PCC	23 sin, 31 sin
central gyrus	2 sin, 5 sin

Table 4.2 Object location vs. location recognition

In the object location vs. location recognition comparison, bilateral occipital and occipito-temporal regions were activated, as would be expected when the stimuli differ so obviously in visual complexity. There were also activations in the posterior cingulate region and left paracentral region.

Region	*BA*
middle PFC	6 dx, 8 dx
inferior PFC	44 dx, 45 dx
frontopolar	10 dx, 46
parietal and occipital	7 dx, 39 dx, 40 dx, 19 dx
inferior temporal	19 dx, 37 dx

Table 4.3 Location recognition vs. object location

In the reverse comparison, right sided activations included the right inferior frontal, middle frontal and frontopolar regions. The right parietal activation included the precuneus and the superior parietal lobule extending in to the right inferior parietal lobule and superior occipital region. There were also separate right inferior temporal and left cerebellar activations.

Practice related decreases (object location vs. practised object location) were observed in the superior, middle, middle-inferior frontal and the orbital regions and also in the anterior cingulate cortex, as well as in the left anterior insular or frontal opercular regions. Some of this, notably the ACC finding may perhaps be explained by difficulty maintaining interest in the task and straying attention. Practice related decreases were also observed bilaterally in the occipito-parietal and occipito-temporal regions.

Region	*BA*
PFC	10, 11, 45 dx, 10, 11, 46
ACC	24, 32
frontal operculum, insula	14 sin, 15 sin, 49 sin
parieto-occipito-temporal	7, 40 dx, 40 sin, 19 dx, 19 sin, 18 dx, 18 sin, 37 dx, 37 sin

Table 4.4 Object location vs. practised object location

In contrast, increases as a result of practise (practised object location vs. object location) were observed in the perisylvian parieto-temporal and posterior insular or parietal opercular regions, in the paracentral-midcingulate, and left middle-inferior temporal regions. Practice related increases were also observed in a right paracentral region and in a left medial superior frontal region, as well as in the pulvinar of the left thalamus.

Region	*BA*
midcingulate gyrus	6, 32
superior temporal gyrus	41 dx, 41 sin, 42/22 dx, 42/22 sin
posterior insula	13/16 dx, 13/16 sin
inferior parietal lobule	40 dx, 40/43 sin
central	4 dx
inferior temporal	20/21 sin
thalamus, pulvinar	n.a.

Table 4.5 Practised object location vs. object location

In the object location vs. baseline and practised object location vs. baseline comparisons there were bilateral occipito-temporal activations extending into the most posterior parts of the MTL. The MTL was also activated bilaterally in practised object location vs. location recognition.

Region	*BA*	*x*	*y*	*z*
MTL	28, 36	32	-2	-18
MTL	28, 36	30	-22	-22
MTL	36	-22	-24	-8

Table 4.6 Object location vs. baseline

Region	*BA*	*x*	*y*	*z*
MTL	34 dx, 36 dx	30	-8	-30
MTL	28 sin, 34 sin, 35 sin, 36 sin	-32	-12	-22

Table 4.7 Object location vs. location recognition

Clear MTL activations were observed in object location vs. location recognition, including robust bilateral occipito-temporal activations extending throughout the MTL.

Region	*BA*	*x*	*y*	*z*
MTL	28 dx, 34 dx, 35 dx, 36 dx	36	-8	-30
MTL	28 sin, 34 sin, 36 sin	-28	2	-24

Table 4.8 Object location vs. practised object location in the MTL

Decreases related to practice were observed bilaterally in the anterior parts of the occipito-temporal cortex and the MTL. For greater sensitivity and given previously established interest in the MTL, these were examined using a ROI from the object location vs. location recognition contrast

4.1.2 Free recall of pseudo-words

Region	*BA*
superior frontal	6, 8, 9, 10, 46
inferior frontal	44, 45, 47, 49
insula	14 sin, 14 dx, 15 sin, 15 dx
ACC	24, 32, 33
PCC	23, 26, 29, 30
precuneus, superior parietal lobule	7 sin, 7 dx, 39 dx, 40 sin, 40 dx, 37 sin

Table 4.9 Novell recall vs. reference condition

In the relatively less practised novel recall compared to the reference condition, several brain regions were activated, including prefrontal, anterior insular and anterior cingulate regions. More specifically, bilateral posterior parts of superior and middle frontal extending into left the inferior frontal or frontal opercular regions. The frontal operculum was activated bilaterally extending into the anterior insular cortices. Also the mid-posterior cingulate cortex was activated bilaterally. Other areas that were activated included parieto-temporo-occipital, infero-temporal and cerebellar regions, encompassing the precuneus and superior parietal lobule bilaterally, extending into the superior parts of inferior parietal, supramarginal right angular and superior-middle

occipital regions. The activated region also included the bilateral inferior occipital gyrus and the posterior parts of left inferior temporal gyrus.

Similar activations were observed in the relatively more well practised trained recall compared to reference condition including prefrontal, anterior insular and anterior cingulate. The prefrontal activations included the middle frontal or frontopolar the posterior parts of middle frontal extending bilaterally into the inferior frontal-frontal operculum and the anterior insular cortices. In addition to the anterior cingulate there was a mid-posterior cingulate cortex was activated. Other areas that were activated included parieto-temporo-occipital, occipital, right occipito-temporal, and cerebellar regions. These activations included the precuneus extending into parietal and posterior cingulate areas. There were also bilateral activations in inferior parts of the superior parietal lobule extending on the right into the superior parts of superior-middle occipital gyri. The occipital and occipito-temporal activations encompassed posterior parts of the superior occipital gyrus bilaterally and a small activation in the left lingual-fusiform gyri.

Region	*BA*
frontopolar	10, 46
middle frontal	45
inferior frontal	44 dx/sin, 45 dx/sin, 46 dx/sin, 49 dx/sin
anterior insula	14, 15
PCC	23, 31 dx
superior parietal lobule	7 dx/sin
occipital	18, 19
lingual fusiform	19 sin, 37 sin

Table 4.10 Trained recall vs. reference condition

Region	*BA*
ACC	24 sin, 32 sin
superior frontal gyrus	6 sin, 8 sin
inferior frontal gyrus	44 sin, 45 sin, 47 sin, 49 sin
anterior insula	14 sin, 15 sin
lateral orbitofrontal	11 sin/dx
middle frontal gyrus	10 sin
inferior temporal gyrus	20 sin, 21 sin, 37 sin
inferior parietal	40 dx

Table 4.11 Novel recall vs. trained recall

Practice related decreases (comparing novel recall vs. trained recall) were observed in the left anterior cingulate extending to the left superior frontal gyrus, and in the left middle-inferior frontal-frontal opercular extending into the anterior insular region. Prefrontal decreases were also observed in the lateral orbitofrontal bilaterally and a left middle frontal region. In addition, practice related decreases included two smaller left middle-inferior temporal and a right inferior parietal region.

Region	*BA*
mid-cingulate	24, 31
precuneus	5, 7
STG	22 dx

Table 4.12 Trained recall vs. novel recall

Practice related increases were observed in midcingulate-paracentral lobule (BA 24, 31), anterior precuneus (BA 5, 7), right superior temporal gyrus (BA 22), lentiform nucleus, and right cerebellar regions.

4.2 Paper II

4.2.1 Behavioural data from paper II and paper IV

Since papers II and IV have so much in common, behavioral results are presented together. As can be seen in figure 4.1 there was a significant main effect of materials, figurative or non-figurative. There was also a significant main effect of instruction deep or shallow. The simple main effects of instruction in both types of materials were also significant. The interaction of materials

and instruction was not significant, which perhaps can be guessed from the plot. We also stratified the subject responses in terms of subject ratings (i.e. positive, neutral and negative) and analysed the data as a repeated-measures three-factor analysis of variance with Greenhouse-Geisser non-sphericity correction including the factors instruction, material, and subject rating. The results showed similar significant main effects of materials and instruction. The effect of subject ratings of the stimulus material was not significant in the behavioural experiment that was part of the PET study, but it was significant in the FMRI study. In the FMRI experiment we used a linear mixed effects model (Pinheiro et al., 2006a and R Development Core Team, 2006), which may be more sensitive to this type of data and we specified rating as a random effect. Reanalysing data from the PET study with the same mixed-effects model used in the FMRI study revealed that the ratings indeed were significant with this model. The reaction times did not differ significantly due to instruction or material in the PET study, but were significantly longer for neutral judgments than for positive or negative ones. In the FMRI data, this effect was replicated but additionally, reaction times were significantly longer for non-figurative drawings and for the shallow instruction. They were also marginally (but significantly) slower for subsequent misses than hits. Reanalysing the reaction times for the PET data revealed significant effects for material and instruction but none for the random effect of rating. This likely reflects the greater sensitivity of the mixed effects model (see figure 4.2) as well as the apparent decrease in sensitivity that may be the consequence of regarding a factor as random instead of fixed.

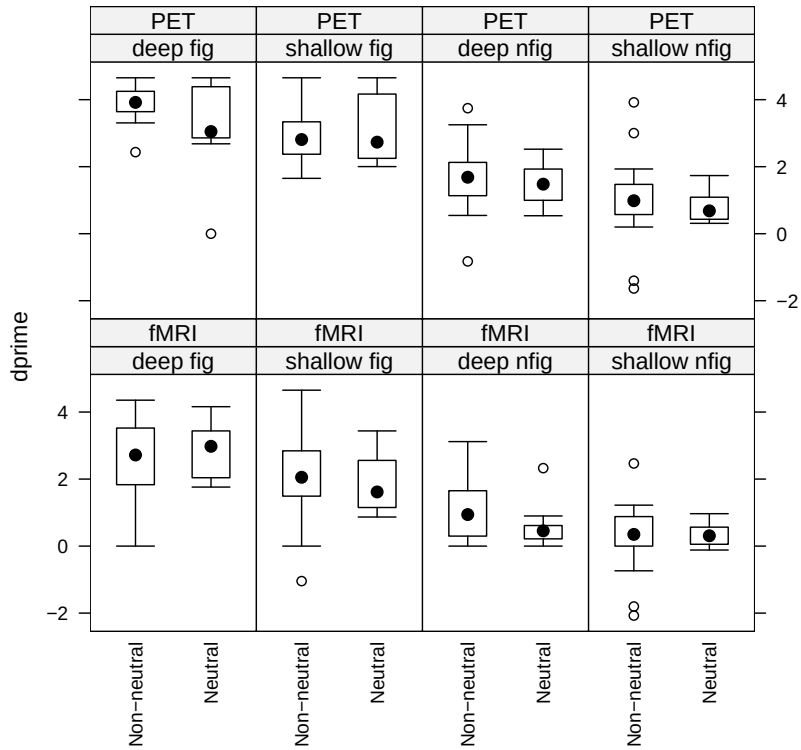


Figure 4.1 The levels of performance in the PET and FMRI studies of the LOP effect. Negative and positive responses were collapsed and compared with the neutral ones.

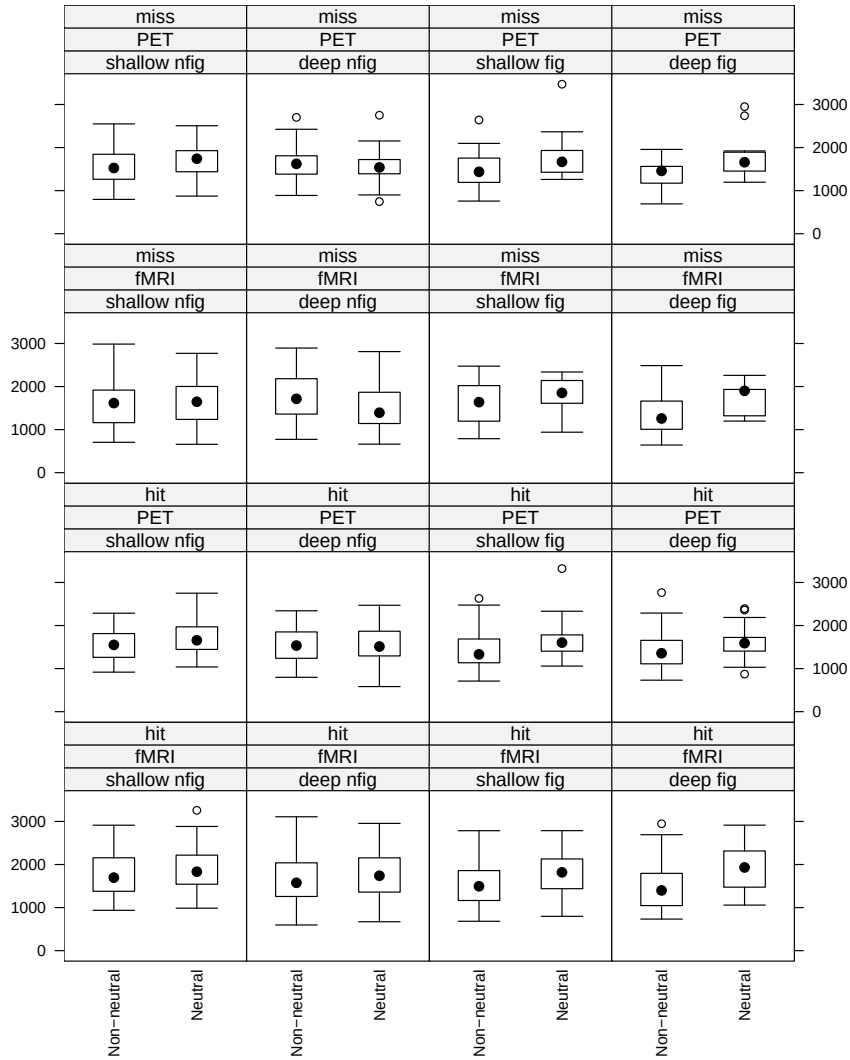


Figure 4.2 The reaction times in the PET and FMRI studies of the LOP effect. Negative and positive responses were collapsed and compared with the neutral ones.

4.2.2 PET results

Region	*BA*
superior frontal	6, 8, 9, 10
middle frontal	6/8 sin
inferior frontal	47 sin
inferior parietal	39/22 dx, 39/40 sin
anterior temporal	20/21 dx, 20/21 sin

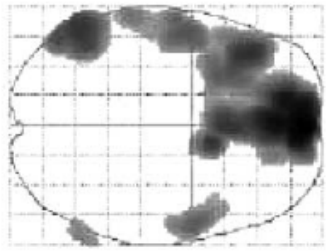


Figure 4.3 Deep vs. shallow encoding

In the comparison of deep and shallow encoding, a significant network of 8 regions was activated. The network encompassed several regions that were significant at the cluster level, including medial-left prefrontal, bilateral inferior parietal, and anterior temporal clusters: the prefrontal cluster consisted of medial and bilateral superior as well as left lateralised middle and inferior frontal regions, extending into medial orbitofrontal. The inferior parietal clusters consisted of a right angular-superior temporal and a left angular-supramarginal region. The temporal clusters included bilateral middle-inferior temporal regions extending into the temporal polar region.

Region	*BA*
middle prefrontal	10 dx
inferior prefrontal	44/6 dx
precuneus, superior parietal lobule	7 sin, 7 dx
supramarginal gyrus	40 dx, 40 sin
inferior temporal	37 dx

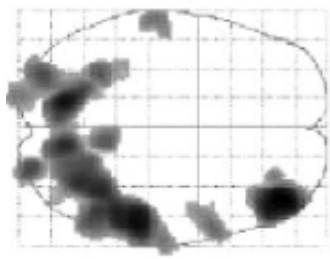


Figure 4.4 Shallow vs. deep encoding

In the shallow vs. deep encoding comparison a significant network of 11 regions was activated. This network included several regions that also were

significant at the cluster level, including right middle-inferior prefrontal, bilateral superior, and left inferior parietal as well as inferior temporal, bilateral occipital, and cerebellar clusters: the prefrontal clusters consisted of a right middle frontal and a right inferior frontal region. The superior parietal cluster included the precuneus and superior parietal lobe bilaterally extending into the superior parts of supramarginal gyrus and the right inferior parietal (or superior occipital) region. In addition, a left inferior parietal cluster was observed The temporal and occipital clusters consisted of a right inferior temporal and a right middle-inferior occipital region, both regions extending into the right fusiform gyrus. Cerebellar activations included a right anterior medial and a more posterior left mediolateral region.

When encoding of figurative drawings was compared with encoding of non-figurative pictures a significant network of 16 regions was activated. The activated network included prefrontal, left inferior parietal, left anterior temporal, right posterior inferior temporal, and medial temporal clusters that were significant at the cluster level: the prefrontal clusters included a left lateralised medial superior frontal and a left middle frontal region. The activation in the inferior parietal cluster was localised to the posterior angular gyrus. The left anterior temporal and right posterior inferior temporal clusters included an anterior middle-inferior temporal region extending into the temporal pole and a posterior inferior temporal. The left medial temporal activation included the left parahippocampal cortex extending posteriorly and laterally into the anterior fusiform gyrus.

Region	*BA*
superior frontal	6, 8, 9
middle frontal	6/8 dx
inferior parietal	39 sin

Table 4.13 Encoding of figurative drawings vs. encoding of non-figurative drawings

Greater increase in blood flow for deep than shallow encoding for the figurative drawings was observed in the left anterior medial superior frontal gyrus

(BA 9, 10). In the reverse interaction contrast, greater increase in blood flow for deep than shallow encoding for the non-figurative drawings was observed in the right posterior parietal lobe on the border between BA 7 and 40, in the inferior temporal BA 37, and bilateral fusiform/posterior medial temporal regions.

4.3 Paper III

Increased activity was observed in the bilateral parietal cortex and medial parietal cortex when comparing acquisition to baseline. We tested for learning-related changes by contrasting late acquisition with early acquisition (acquisition 3 vs. 1) and found learning-related changes involving the left hippocampal region, where activity increased across acquisition trials.

When comparing use of the loci mnemonic with serial recall without the mnemonic we used an interaction approach (Petersson et al., 1999a) in order to control for non-specific effects of time. Differences were found in the left occipito-parietal cortex (BA 7, 39) and left dorsal frontal cortex (BA 6/8).

4.4 Paper IV

First a global search was performed and after that a directed search based on the analogous contrasts from paper II. Since we used F contrasts in this study, the directionality of contrasts must be gleaned from individual parameter estimates, which are given in the original paper.

The most prominent activation was found on the medial aspect of the frontal lobe in the orbitofrontal gyrus bordering on the most inferior part of the superior frontal gyrus. In addition, there were small activations at the bottom of the right superior temporal sulcus on the slope toward the middle temporal gyrus and in the left middle orbital gyrus. Using 10 mm spherical regions of interest with small volume correction (SVC) around the coordinates found in the deep vs. shallow contrast in the PET study (paper II) two additional activations were identified in the left inferior frontal gyrus and the medial orbitofrontal gyrus.

Region	*BA*
orbitofrontal gyrus	11
middle temporal gyrus	21 sin
middle orbital gyrus (paper II: deep vs. shallow)	11 sin
medial orbitofrontal gyrus (paper II: deep vs. shallow)	11/25

Table 4.14 Deep vs. shallow and shallow vs. deep

Region	*BA*
angular gyrus	39 sin
PCC, precuneus and calcarine	30 sin
lingual	18 sin
orbitofrontal	11 sin
insula	49 sin
fusiform and inferior temporal gyri	19 dx
medial superior frontal	9
occipital	18 dx
frontal pole	10
calcarine	17 sin
ACC	32
superior frontal (paper II: figurative vs. non-figurative)	8 sin, 9 sin
superior parietal lobule (paper II: non-figurative vs. figurative)	7 dx
occipital (paper II: non-figurative vs. figurative)	18/19 sin

Table 4.15 Figurative vs. non-figurative and non-figurative vs. figurative

4.5 Paper V

Here also F contrasts were used so directionality is not known unless parameter estimates are investigated. Contrasting hits that were later 'remembered' with hits that were later 'known' revealed an activation in the posterior part of the right hippocampus assessed with small volume correction using an anatomically defined region of interest (WFU Pickatlas, Maldjian et al., 2003). There were two differences between 'remember' events and 'correct rejection' events above the threshold. They were in the left parietal cortex (inferior parietal lobule, BA 40), and in the right frontal cortex (middle frontal gyrus, BA 10).

5 Discussion

THE BASIS for this thesis is the five papers that investigate different aspects of episodic memory in man. The primary aim was to clarify the role of the frontal regions in episodic memory function as it has been established to be of importance in the previous literature (Schacter and Tulving, 1994b). Prominent theories, with a massive experimental basis, posits an interaction between the medial temporal lobe and the frontal cortex as the basis for episodic memory (Squire and Zola, 1996). Paper I, paper III and paper V concerned retrieval while the two variations on the LOP theme, paper II and paper IV concerned encoding. It was shown that the LOP effect generalises to visuo-spatial material, and that the side preference for frontal activation was dependent on the encoding instruction (paper II, paper IV). The frontal activation in retrieval reflects controlled processing in that it wanes with practice (paper I). The introduction of a mnemonic strategy induced increased frontal and parietal activation during retrieval (paper III). Contrasting 'remember' events with 'correct rejection' events yielded right frontal (and left parietal) activations in study of word recognition and contrasting 'remember' with 'know' showed activation in the posterior hippocampus (paper V).

5.1 Encoding in the frontal cortex

We observed activity in the left middle-inferior region (BA 44, 45, 46, 47) when comparing activity during 'deep' (elaborate, meaning-based) encoding with 'shallow' (perceptually oriented) encoding. This may be interpreted as semantic processing of the stimuli, induced by the instruction that was

given to the subjects. In the reverse comparison, shallow versus deep, we expected a right lateralisation of the prefrontal activation independent of whether the material was figurative or non-figurative, given the emphasis on visuo-perceptual feature-based processing during the shallow encoding of the stimulus material (Golby et al., 2001 and Kelley et al., 1998). Two regions of the PFC were significantly activated, the right middle frontal (BA 9, 10, 46) and more posterior, the right inferior frontal region (BA 6, 44). Altogether, this shows instruction-specific left middle-inferior and medial PFC regions associated with meaning-based as well as right middle and inferior frontal PFC regions associated with perceptual feature-based processing independent of whether the material was figurative or non-figurative.

Conversely, we observed that during shallow encoding compared with deep encoding, there was a marked right-sided activation along the middle and inferior frontal gyri. This is in line with feature-based on-line processing, ie. processing of visuo-spatial material that is not semantically based (Jonides et al., 1993). Since the only difference between these two conditions is the instruction (the material is randomised across subjects), it is difficult to reconcile these findings with the stronger version of the HERA hypothesis (see page 12). The results also do not easily lend themselves to explanation in purely material-specific processing terms. Instead, it appears likely that the instruction biases the processing of the stimuli in different directions. These different biases are not equally likely to lead to encoding of the stimuli. In the sense that semantic processing occurs in the left frontal lobe and semantic processing promotes encoding, the encoding part of the HERA hypothesis is given some support by this finding.

In parallel with the observed prefrontal lateralization, there was a corresponding side difference in activation in the posterior parietal cortex when com-

paring processing based on pleasantness with that based on graphical quality. Parallel neuroanatomical frontoparietal networks have been described by Goldman-Rakic (1988) and the hypothetical functional correlate of this seems to be represented as co-occurring activations in certain parietal and frontal regions (Cabeza and Nyberg, 2000 and Fletcher et al., 1997). In the deep versus shallow comparison, the left inferior parietal region (angular-supramarginal BA 39, 40) was dominating although a small right angular or superior temporal activation was also observed. It has been suggested that the left parieto-temporo-occipital region is part of a unitary semantic network (Vandenberghe et al., 1996). Our observation of a left inferior parietal (angular gyrus BA 39) activation in the comparison of figurative and non-figurative drawings is consistent with this suggestion. In the comparison of shallow versus deep, the posterior parietal activations were clearly dominating on the right side and included the precuneus, the superior parietal (BA 7) extending into the right inferior parietal and superior occipital regions (BA 19). This is in line with the emphasis on visuo-perceptual feature-based processing and stimulus-controlled visuo-spatial attention (Corbetta and Shulman, 2002, Gitelman et al., 1999 and Mesulam, 1998) and that we observed greater parietal activations on the right compared to the left in the non-figurative versus figurative contrast.

In summary, these results show clear instruction-specific lateralisation in parallel frontoparietal networks reflecting the manipulation of the encoding instruction. The bilaterally distributed, frontal cortical activations in both encoding levels complement the HERA model (Tulving et al., 1994) as well as the observation of a material-specific PFC activation in encoding observed previously (Kelley et al., 1998 and Wagner et al., 1998b). However, holding the material constant, the left prefrontal activation in deep versus shallow and the right prefrontal activation in shallow versus deep is difficult to reconcile

with the HERA model. Our findings indicate that the prefrontal pattern of activation is processing sensitive and depends on task instructions (paper IV, Petersson et al., 2001), in this case a LOP manipulation.

Our results also demonstrate an extensive medial and bilateral superior (BA 6, 8, 9, 10) cluster extending into the very anterior and inferior parts of the anterior cingulate cortex (BA 24, 32) and medial orbitofrontal cortex (BA 11, 25). These latter activations were not observed in the study of Kapur et al. (1994). Rugg et al. (1997) observed a medial superior frontal activation (BA 8) and the results of Otten et al. (2001) indicate an anterior medial superior frontal activation similar to the one observed in this study.

In the comparison between deep and shallow, the FMRI results replicated some of the findings from paper II. There was an activation in the left inferior frontal cortex and the orbitofrontal extension of the medial frontal cortex with a higher BOLD signal in deep vs. shallow. As in paper II, it might be speculated that this represents introspective activity as subjects are scanning internal cognitive-evaluative states when judging whether they like what a drawing evokes (Gusnard et al., 2001 and Raichle et al., 2001). A recent study of encoding of socially relevant pictures (Harvey et al., 2007) makes findings along this line.

Our generalisation to visual material of the left middle-inferior PFC results reported by Kapur et al. (1994) and Rugg et al. (1997) independent of whether the material was figurative or non-figurative lends support to the suggestion by Kapur et al. (1994) that these activations are related to elaborate meaning-based processing. However, in our experimental setting this conceptualisation may need to be given a broader interpretation since we used pleasantness judgements in the deep encoding condition, meaning that the

subjects were associating the stimuli in a meaningful way with an inner subjective state (Craik and Tulving, 1975). The human orbitofrontal cortex has been related to affective processing in both lesion and functional neuroimaging studies (Elliott et al., 2000), including pleasant touch (Francis et al., 1999) as well as abstract reward and punishment (O'Doherty et al., 2001) and also in theoretical models of the interaction between mood and memory (Rolls and Stringer, 2001). We therefore suggest that the observation of activations during deep encoding in the inferior parts of the ACC and the medial orbitofrontal cortex, with both figurative and non-figurative line drawings, indicates that the subjects meaningfully engaged in the pleas- antness evaluation of the stimuli regardless of whether the stimuli contained any explicit semantic content or not (see Frey and Petrides (2002)).

5.2 Retrieval in the frontal cortex

In paper III, increased activity was observed during retrieval in the left dorsal frontal cortex when the loci structure was used for word encoding (when comparing posttest and pretest). Task-relevant processes that have been linked to the dorsal frontal cortex include feature binding (Mitchell et al., 2000), creation of an organisational structure (Fletcher et al., 1998a), generation of images based on words (Mellet et al., 1998), and integration of information in working memory (Prabhakaran et al., 2000). A recent study of the loci method replicated this finding (Kondo et al., 2005) when comparing intentional encoding of photographs of inanimate objects before and after learning the loci method.

5.3 Hemispheric encoding retrieval asymmetry and retrieval mode

A large number of studies suggest the existence of a frontal asymmetry where a preference for encoding to the left side vs a right sided preference for recall, the HERA model (Tulving et al., 1994). Wagner et al. (1998b) introduced an alternative perspective to this and suggested that the basis for the asymmetry was material specific rather than representing a general phenomenon. In paper II our data do not support a strong version of the HERA model as we found a right sided activation in encoding of figurative and non figurative material. Also, during encoding the side preference for the frontal activations was dependent on the encoding instruction. Later the HERA model has been qualified by Habib et al. (2003) such that only a design with an intraindividual comparison and a design where both encoding and retrieval are studied could test the HERA hypothesis. The data presented here do not support HERA in its original formulation but the experiments have not specifically tested the reformulated, weaker, version of the theory.

The detailed functional role of the medial PFC territory in episodic memory is largely unknown. It is, however, well known in the processing of emotional states and has rich connections to insula and other parts of the limbic system (Adolphs, 2002). The more posterior parts of the observed medial PFC territory has been related to generative aspects of semantic memory and working memory (object, spatial, and problem solving), and more anterior, to episodic memory encoding, both for verbal material and objects/faces (Cabeza and Nyberg, 2000). That the medial superior frontal region was activated in the figurative versus non-figurative contrast, together with a left middle frontal region (BA 6, 8), suggests that this region is related to some aspects of semantic processing, perhaps reflecting semantic information being loaded

and manipulated in on-line working memory (Fletcher and Henson, 2001). We note that a subregion of the medial superior frontal cluster showed an interaction effect; that is, the deep versus shallow effect was greater in the figurative compared to the nonfigurative condition. Several studies have reported changes in activity of the medial frontal region as a result of identifying internal states (Frith and Frith, 1999 and Gusnard et al., 2001) and also as having a special function in the encoding of pictures with a social content (Harvey et al., 2007). Our LOP manipulation invoked a difference in the degree of self-reference. Specifically, the deep task required the subjects to reference the picture to an inner subjective state. The interaction [(DF>SF)>(DN>SN)] (where the difference between 'deep' and 'shallow' was bigger for figurative than non-figurative drawings) in the frontal lobe was most clearly expressed in the superior parts of the medial aspect of the left hemisphere (BA 9,10) and it seems probable that the opportunity for self-reference is greater in figurative than non-figurative drawings which may contribute to this effect.

In paper V, left parietal as well as right frontal activations were found by comparing 'remember' events with 'correct rejection' events during the recognition sessions. In this comparison, successful searches for memory traces matching the cue are contrasted with unsuccessful searches. This bears similarities with recent studies (Iidaka et al., 2006, Lundstrom et al., 2003 and Shannon and Buckner, 2004). Possibly the comparison reflects a purer form of 'retrieval mode' (Lepage et al., 2000) in that 'correct rejections' comprise an 'unfulfilled' retrieval mode.

5.4 Automaticity and effects of practice

In two of the papers (paper I and paper III), the effects of practice were studied, In the first repeated encoding and retrieval of object location conjunctions

were studied (recognition was done during PET scanning) and it was found that the large network of brain regions initially activated by the recognition task dwindled and was altered. Widespread frontal and parieto-temporo-occipital activity became a band of activity in the posterior insula bilaterally, extending dorsally and also frontopolar medial activity. Specifically, regions that showed decreased activity as a function of practice included the left middle-inferior prefrontal (BA 9, 45, 46), bilateral and middle frontal or frontopolar (BA 10), right anterior insular and frontal opercular, anterior cingulate, bilateral posterior parietal, occipital, inferotemporal, and cerebellar regions. Regions with in- creasing activity as a function of practice included bilateral posterior insula-opercular, mid-posterior cingulate-paracentral, and temporal regions. Similar practice related changes were observed in a free recall task of abstract designs (Petersson et al., 1999b). In Petersson et al. (1999a) it was shown that these practice related changes were not explained by differences in performance. The present result is consistent with this suggestion since the performance was almost perfect (96% correct) even in the less practiced object-location condition and so did not change between conditions.

The decreases in activity in the MTL observed with practice in the OL-POL comparison and in Petersson et al. (1997) indicate that there is no simple relation between retrieval performance and MTL activity. Instead it was suggested in Petersson et al. (1997) that there may be a positive correlation between retrieval success and the MTL activity at a given level of encoding strength. This and previous findings (Montaldi et al., 1997) suggest that there may be an inverse relation between the strength of encoding and the activation of the MTL during retrieval (Mesulam, 1998).

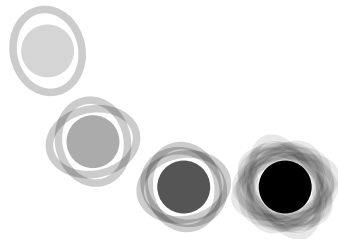


Figure 5.1 Schematic and speculative illustration of an episodic memory becoming more like a semantic one. The item being remembered is strengthened and clarified with each re-encoding, but the peripheral episodic meta-information is becoming blurred or overwritten.

Presumably, repeated encoding and retrieval would reactivate the neocortical representations and thereby strengthen the neocortical interconnections in such a way that the neocortical network eventually can support declarative retrieval with less dependence on the interaction with the MTL. Alternatively, repeated encoding and retrieval would transform an initial episodic memory into a more semantic-like memory. The changing role of the MTL might then be interpreted as an indication that the MTL is more critical for episodic memory retrieval than semantic memory retrieval. Slightly differently conceptualised this is consistent with findings concerning the role of the MTL (Eldridge et al., 2000). Specifically, initial episodic recognition judgements are mainly based on recollective remembering. With repeated encoding experiences, the stored information will gradually lose its spatio-temporal context, becoming more like a fact. Speculatively, one may suppose that the the central item being encoded remains the same, but for each new re-encoding event, a new spatio-temporal context is provided, and therefore blurred or even overwritten. In parallel the recognition judgements are increasingly being based on a familiar knowing.

Conclusions and future perspectives

6

6.1 Conclusions

The conclusions from this thesis are that

- practice in an episodic memory task represents a change from controlled to automatic processing evident in networks of associated brain activation patterns changing from frontal and parietal to paracentral, perhaps as an expression of less demand on working memory;
- the strong form of the HERA hypothesis (see page 12) does not suffice to explain all imaging experiments of episodic memory, specifically not ours;
- levels of processing can be shown with visuo-spatial material;
- levels of processing are reflected in differently lateralised regional brain activity in the frontal and parietal cortices;
- repeated episodic encoding and retrieval leads to re-encoding and the transformation of the memory trace to a semantic one.

6.2 Unresolved issues

A more precise description of the processing differences resulting in apparently different levels of processing and associated differences in successful encoding will require a series of new behavioral experiments. It is necessary to determine if it is simply the degree of 'semanticising' that determines the

probability for encoding or whether it depends on the degree of self-reference or on entirely different factors.

The propensity to attempt meaningful interpretations of everything that happens in the surrounding environment appears to be a fundamental part of the construction of the brain — the human brain is to a large degree a semantic machine, even to the extent of creating its own meaning. This function of the human brain as a 'semantic engine' depends on the stimuli that is presented to it but it might also be available to experimental manipulation by explicit instruction or training, opening up for future potentially profitable investigations. Also, meaning does not spring from nothing, even inside a human brain. Language, previous knowledge and current preoccupation presumably influence what the semantic engine produces.

Therefore it seems profitable to pursue these issues along the dimensions of language, meaning and memory, similar in spirit to the work of Hagoort et al. (2004)

The mechanisms involved in the transformation of memories from episodic to semantic through re-encoding deserves closer experimental scrutiny. Presumably not all kinds of information are available for re-encoding, so careful theoretical consideration and behavioral experiments are necessary for a deeper understanding of these phenomena.

Acknowledgements

I WISH to thank my supervisors, Dr Karl Magnus Petersson and Professor Martin Ingvar for support when it was sought and good advice when it was needed. Many other people have contributed in personal as well as professional ways to the completion of this thesis. Attempting to list them all will inevitably result in accidental omission of some, so I will refrain from that. Nevertheless, there are some whose contribution is so clear and unmistakable that failure to mention them would be silly. I do not imply that those mentioned made a bigger contribution, merely that it is easier to identify. The work was conducted at the PET unit and MR research centre at the Karolinska Hospital in Stockholm. The support staff at the PET center (notably Julio Gabriel and Vahid Jalouli) were crucial to the execution of the PET studies. The MR experiments could not have been done without the support of the clinical staff at the MR center. The statistical analysis in the scarcity of clear results could not have been performed without the fruitful discussions with Jesper Andersson. My fellow doctoral students during the years made the situation bearable: Katrina Carlsson, Predrag Petrovic, Christian Forkstam, Jens Gisselgård, Johanna Lind, Karin B Jensen, Carolina Ciumas and others. The amazing people at the support mailing lists for the various software that I used (R, ConTEXt, SPM) who seem to respond to my questions usually before I have thought to ask them. During the last period of thesis writing I have spent some time working at the Vårdcentralen Kronan in Sundbyberg and I thank the patients and staff there for keeping my head straight.

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