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Genetic influences on long-term memory control – COMT and retrieval-induced forgetting

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Abstract

In order to retrieve stored long-term memories, the human brain needs to select goal-relevant against interfering, irrelevant information. The prefrontal cortex is thought to support this ability. The catechol-o-methyl transferase (COMT) Val158Met polymorphism is found here as well. Here the homozygous expression of methionine causes, due to a thermolabile enzyme a reduced enzymatic degradation and higher concentrations of cortical dopamine. However the influence of the COMT gene on the neural mechanisms of memory inhibition in the prefrontal cortex remained unclear.

Functional magnetic resonance images (fMRI) were recorded from fifty-four subjects, eighteen per genotype, while they performed the retrieval practice paradigm (Anderson et al. 1994). In this paradigm subjects learn categorized word lists and repeatedly retrieve some of the words from some of these categories. This repeated retrieval typically involves the inhibition of interfering memories from the same category, which can be observed as retrieval-induced forgetting (RIF) on a later recall test.

The experiment revealed significantly larger amounts of RIF in the Met/Met genotype (8,5%) compared to the Val/Val genotype (2,6%) and replicated previous findings (Kuhl et al. 2007) of decreasing activation in prefrontal areas across retrieval practice cycles. Notably, Met/Met carriers showed the largest RIF, with a significant genotype by retrieval cycle interaction in the right inferior prefrontal (BA 47/10) cortex.

In conclusion our study expands knowledge concerning the linkage of the prefrontal cortex to dopaminergic systems and showed a dopaminergic influence on long-term memory control for the first time.

Kurzreferat

Um Inhalte des Langzeitgedächtnisses abzurufen, muss das menschliche Gehirn relevante gegenüber interferierenden und irrelevanten Informationen auswählen. Es wird angenommen, dass der präfrontale Kortex jene Fähigkeit unterstützt. Der Catechol-O-Methyl Transferase (COMT) Val108/158Met Polymorphismus ist ebenfalls in dieser Hirnregion zu finden. Die homozygote Expression von Methionin führt dabei, durch eine thermolabileres Enzym, zu einem reduzierten enzymatischen Abbau von Dopamin und erhöhten kortikalen Konzentrationen. Der Einfluss des Polymorphismus auf die die Inhibition von Gedächtnisinhalten im präfrontalen Kortex blieb dabei bisher unklar.

Funktionelle MR-Bilder wurden von 54 Probanden, 18 pro Genotyp, aufgenommen, während sie das sogenannte Abrufübungsparadigma durchführten (Anderson et a. 1994). Probanden lernten kategorisierte Wortlisten und riefen später einzelne Wörter aus einem Teil der Kategorien zweimal ab. Der wiederholte Abruf führt dabei zur Inhibition störender Gedächtnisinhalte und dem Effekt des abrufinduzierten Vergessens im späteren Test.

Das Experiment ergab signifikant mehr abrufinduziertes Vergessen in dem Met/Met Genotyp (8,5%) im Vergleich zu der Val/Val-Gruppe (2,5%) und replizierte eine abgeschwächte Aktivität im präfrontalen Kortex nach zusätzlichen Abrufübungen (Kuhl et al. (2007)). Probanden mit der homozygoten Expression von Methionin zeigten, gekoppelt mit einer signifikanten Genotyp x Abrufübungs-Interaktion im rechten inferioren präfrontalen Kortex (Brodmann Areal 47/10), das stärkste abrufinduzierte Vergessen.

Die Studie erweitert somit bisheriges Wissen zur Kopplung des präfrontalen Kortex zum dopaminergen System und weist erstmals einen dopaminergen Einfluss auf kognitive Kontrolle im Langzeitgedächtnis nach.

Key Words

Retrieval induced forgetting, COMT Val108/158Met polymorphism, inhibition, retrieval, prefrontal cortex

Schlüsselwörter

Abrufinduziertes Vergessen, COMT Val108/158Met Polymorphismus, Inhibition, Abruf, präfrontaler Kortex

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III List of Abbreviations

ACC	anterior cingulate cortex
BA	Brodmann area
C+	items from unpracticed categories with low normative strength
C-	items from unpracticed categories with high normative strength
COMT	catechol-o-methyl transferase
DA	dopamine
DLPFC	dorsolateral prefrontal cortex
IFC	inferior frontal cortex
IFG	inferior frontal gyrus
P+	retrieved items from practiced categories
P-	not retrieved items from practiced categories
PFC	prefrontal cortex
RIF	retrieval- induced forgetting
RP	retrieval practice
SD	standard deviation
VLPFC	ventrolateral prefrontal cortex

1 Introduction

1.1 Human memory

Human memory does not contain a single unitary system, but can be classified according to the quality of certain memory contents, or according to point of time when they have been stored. Short-term memory refers to the storage of current representations for the time they remain in our consciousness. Working memory temporarily contains and holds information that is currently processed and manipulated in order to fulfil a task. Long-term memory itself contains knowledge that has been stored minutes or years ago and has to be brought back into consciousness (see Eysenck and Keane 2006).

Memories themselves are classified into short-term memory, working memory and long-term information such as explicit and procedural memory (Tulving 1972). The content of the so-called explicit memory is additionally divided into semantic and episodic information. The former refers to the storage of facts, dates, general knowledge of our environment and language. The latter includes the storage of specific personal experiences and events. Apparently the medial temporal lobe is a neural correlate to the episodic memory itself. In that case patient studies support this argument. Exemplarily, patient H.M. required a resection medial temporal lobe after suffering from a head injury and subsequent epilepsy. After this operation and due to the lesion of the hippocampus he suffered from an anterograde amnesia that affected his episodic but not his procedural memory (Milner et al. 1998).

Several distinct processes are pre-requisite to store and bring memory back into mind. As an example encoding is required. It refers to the acquisition and the reorganisation of information that are received from the outside into memories. After a successful consolidation of memory contents retrieval actively recovers them from the storage systems of the human brain. Various studies indicate a prefrontal engagement that additionally distinguishes, as explained in the following sections between both hemispheres (Tulving et al. 1994, Shallice et al. 1994, Desgranges et al. 1998). Recognition means the identification of new information to be similar with previously perceived data.

The present work is concerned with cognitive and neural processes that control retrieval from episodic long-term memory, as introduced in the following sections.

1.2 Retrieval-Induced Forgetting

1.2.1 Cognitive Bases of Retrieval-Induced Forgetting

In order to remember past information, the human brain is confronted with a multitude of memories. Most of them are not being relevant at this point of time, and distract the retrieval of the correct memory item. In particular, memory traces, originating from previous similar experiences, can interfere, and thus impair the correct retrieval of the relevant experience. Interference can be caused either by similar memories that have been stored before the sought-after memory, which is known as proactive interference. Or the retrieval of information is impaired due to a later storage of similar memory traces, resulting in retroactive interference (Anderson et al. 1996). Both of the mechanisms are, among many others, major reasons for forgetting in long-term memory. Given that interference poses such a problem for our memory, it is reasonable to assume that there are mechanisms that help us to remember specific information from a vast number of similar memories. Inhibition might be one such mechanism, and is thought to produce retrieval-induced forgetting for the inhibited memories.

Retrieval-induced forgetting refers to the finding that the active retrieval of some memories causes related, non-retrieved information to become less available and accessible for recall (Anderson 2003, McCulloch et al. 2008). For a review on cognitive control of memory retrieval see Levy and Anderson (2002). This phenomenon has been investigated with help of the retrieval-practice paradigm, which is shown in Figure 1 (Anderson et al. 1994). The typical experiment contains an encoding phase, during which subjects study a word list with several categories and the corresponding items. In a following retrieval practice phase, only half of the items from half of the categories are retrieved by showing the category's name and the exemplar's first few letters. This procedure results in 3 subgroups of items: practiced items from practiced categories (P+), unpracticed items from practiced categories (P-) and unpracticed items from unpracticed categories (C). The effects of retrieval practice on these 3 item types are then tested in a category-cued recall. As a result, practiced items from practiced categories (P+) benefit the most and consequently are recalled better than baseline C items. Items without retrieval practice (P-) from the same category usually become less accessible and are recalled worse than baseline items from completely unpracticed categories. Note that this effect occurs even though both item types (P- and C items) are not retrieved during

retrieval practice. The only difference between these items is that P- items share the category with some practiced items. This effect is known as retrieval induced forgetting (RIF).

Concerning the mechanisms producing RIF, it is believed that the selective retrieval practice facilitates recall of P+ items and aggravates the remembering of associated P- items, the latter through inhibition (Anderson 2003, McCulloch et al. 2008, Anderson et al. 1994). Inhibition means that the internal representation of P- items in an active process become less available (Anderson et al. 2000). The interference these items cause would otherwise distract and complicate successful item retrieval. Recent studies nevertheless investigated whether retrieval- induced forgetting could also be due to blocking. This alternative account supports the view of an increased inaccessibility, rather than unavailability, of items that have not experienced repetition (P- items), in face of other retrieved items. Hereby P- items are not truly weakened, but the presence of the strengthened P+ items in the same category increases the difficulty for successful retrieval of the related P- items (Williams and Zacks 2001).

Previous studies found supporting evidence for the inhibition account (for a summary see Anderson et al. 2003) and are not in accordance with a blocking account. One of the findings is the so called cue-independence. In a typical retrieval practice paradigm, subjects are given the same retrieval cue in the final recall test as in the retrieval practice phase. Usually this is the category cue. According to the blocking view, because the strengthened P+ items are also linked to this same cue, they might block access, via this cue, to the unpracticed P- items. In case new test cues are given for P- items, retrieval-induced forgetting can still be observed (Anderson et al. 1994, Anderson and Spellman 1995). For example in case the pairing "Fruit_Kiwi" is recalled in the retrieval practice phase (P+ item), it typically causes forgetting of the corresponding P- pairing of "Fruit_Apple". Hence this pairing is recalled worse. If new, independent test cues like "Red_A___" are presented in the final recall, this impairment (RIF) is still found. This finding stands in opposition to the blocking theory, because with the new retrieval cue "Red", no stronger associated item blocks the target item from being retrieved. Another finding providing evidence for the inhibition account is retrieval specificity. Retrieval-induced forgetting only occurs if P+ items were actively retrieved during the practice phase. The repeated presentation of the complete pairing ("Fruit_Kiwi") during practice does not result in retrieval-induced forgetting (Anderson and Spellman 1995, Bäuml and Aslan 2004). This speaks against a blocking hypothesis because further studying should also strengthen the corresponding target items, which should then equally block access to the unpracticed items in the same category. The fact that active retrieval induced more forgetting of associated items is not consistent with the blocking account. Further evidence for the

inhibitory account comes from experiments showing that the mere attempt to retrieve goal-relevant items is sufficient enough to induce forgetting of the related items, even if there are no target items corresponding to the cue that is provided (Storm et al. 2006). This finding can also not be explained in terms of blocking, because no items in the practiced category are strengthened by this "impossible retrieval practice". Additionally, as outlined in the next section, retrieval-induced forgetting showed specific cortical responses in regions associated with inhibitory processes.

1.2.2 Neurocognitive bases of Retrieval-Induced Forgetting

Functional imaging studies investigating episodic memory have previously demonstrated that prefrontal activation is generally associated with the engagement of several distinct control processes during retrieval (Badre and Wagner 2007). Hereby, the retrieval practice paradigm has only recently been investigated using functional imaging methods. On the one hand, the existing studies have examined brain activity during retrieval practice, the phase during which inhibition is thought to operate. This resulted in knowledge about the neural substrates of experienced interference, inhibition and selective retrieval. On the other hand, imaging of brain activity during the final recall phase has revealed distinct neural processes related to retrieval-induced forgetting and enhancement, providing neural evidence against blocking and in favour of the inhibition account.

In a first study by Kuhl et al. (2007) a modified retrieval-practice paradigm was used to show the costs and benefits of retrieval during practice cycles. During retrieval practice subjects had to covertly complete a given category plus word stem three times overall and indicate their successful retrieval. Functional images were analysed by contrasting the first with the third repetition of retrieval practice. Concerning this contrast, the authors argued that the need for inhibition should decrease across retrieval practice cycles, as interfering items become less and less interfering if successfully inhibited during earlier practice cycles. This contrast revealed a general decrease in cortical activity in the bilateral ventrolateral PFC including the inferior frontal cortex and the right dorsolateral prefrontal cortex. Related to the individual amount of RIF, cortical engagement was found in the anterior cingulate cortex (ACC, BA 32) and the right VLPFC (BA 47).

In another study by (Wimber et al. 2009) investigating the retrieval practice phase, subjects were either re-exposed to a complete category-item pairing (restudy practice) or had to covertly retrieve the corresponding item, with a given word stem as retrieval cue (retrieval

practice). Comparing both conditions, cortical activity in the selective retrieval condition revealed activity in the medial (BA 8) and lateral (BA 9) prefrontal cortex. Therefore, the haemodynamic response in these areas likely reflects cognitive control demands due to interfering memories in the retrieval practice condition, compared to the restudy baseline that does not involve competition (see retrieval specificity). In this experiment, the DLPFC and the ACC correlated with forgetting. In line with the findings of Kuhl et al. (2007) the left lateral PFC functioning could reflect a decrease in cognitive control demands as a consequence of successful previous suppression during retrieval.

Notably, Kuhl et al. (2007) split their subjects, according to their RIF scores, in high and low forgetters. High forgetters engaged the ACC and the left anterior VLPFC (BA 47) strongly during first retrieval practice, with a strong decrease across repetitions. Low forgetters did not show a similar decrease, with a constant low level of activity in the ACC, and a constant high level of activity in the right VLPFC. This decrease also correlated with the amount of RIF. The authors consequently interpreted this decrease as a sign of successful suppression of interfering items during the first retrieval practice, leading to reduced competitor strength during later practice cycles. This interpretation is consistent with a wealth of previous findings showing that the ACC and VLPFC are involved in inhibition in other areas like response inhibition and task switching (Aron et al., 2004).

The neural correlates of inhibition have additionally been investigated during the final test, that is, during the phase when subjects are trying to recall all items from the given word list. These studies can give some indication of the neural traces that inhibition leaves on the previously competing items. For example haemodynamic response suggests such functioning in the right VLPFC (e.g. Kuhl et al. 2008), and in the left VLPFC (e.g. Wimber et al. 2008), too. In the case of retrieval-induced forgetting the left anterior VLPFC (BA 47) predicted amounts of forgetting, whereas the mid-VLPFC (BA 45) did not.

Because of the differential activation of multiple subregions of the ventrolateral (BA 44, 45, and 47/12) and regions in the dorsolateral prefrontal cortex (BA 46 and 9), Badre and Wagner (2007) assume a two-process model including controlled retrieval and post-retrieval selection. The latter indicates a process where long-term information is retrieved, then edited and checked for relevance in respect of competing information. The former mechanism located in the left anterior VLPFC and right VLPFC is assumed to be responsible for conducting retrieval processes to specialized areas in order to regain goal-relevant information from these domains (Wimber et al. 2008, Kuhl et al. 2008). Furthermore it could be shown that left anterior VLPFC (BA 47/45) is only sensitive to associative strength and responds to

monitoring tasks when cues are insufficient to activate relevant knowledge (Badre et al. 2005). Concerning pars triangularis of the inferior frontal gyrus (BA 45) post-retrieval selection was found. Greater activation has been detected and correlated to conditions with an increased number and strength of to be retrieved competitors (Badre et al. 2005, Badre and Wagner 2007). In conclusion the VLPFC is seen as site processing information in face of irrelevant competing knowledge and should therefore be directly involved during retrieval-induced forgetting, as supported by the above imaging studies

1.3 Genetic Polymorphisms and Cognitive Control

1.3.1 The COMT Polymorphism

The COMT gene is located on the long (q) arm of chromosome 22 between positions 11.21 and 11.23 and containing several single nucleotide polymorphisms (SNP). (GenBank number: Z26491). The G-to-A transition at codon 158 of the COMT gene would be the most common and explored functional polymorphism (Val108/158Met). The transition itself results in a change from guanine to arginine and a valine to methionine amino acid substitution, respectively. (Lachman et al. 1996, Lotta, Vidgren et al. 1995)

As an enzyme catalyzing the transfer of a methyl group from S-adenosylmethionine to catecholamines the catechol-methyl-transferase (COMT) inactivates neurotransmitters such as epinephrine and norepinephrine. Dopamine (DA) as a fundamental transmitter in the human brain is converted into 3-methoxytyramine. Due to an expression of methionin, the COMT enzyme suffers thermal instability and up to a fourfold decrease in enzyme activity at body temperature, relative to an expression of valine (Syvanen et al. 1997, Lachman et al. 1996). With a synthesis of valine resulting in a highly-active and thermostable enzyme, less catecholamine transmitters like dopamine are found. The heterozygous genotype shows an intermediate amount of COMT activity.

The neurotransmitter itself originates from the Substantia Nigra and the ventral tegmental area. Projections originating from these areas build the mesostriatal, mesolimbic and the mesocortical pathway (Björklund and Dunnett 2007). The latter conducts mostly ipsilateral dopaminergic fiber systems from the Substantia nigra pars compacta and the VTA to the medial frontal and the anterior cingulate cortex. Hereby the PFC receives input from the

medial part of the Substantia nigra, the ACC from dorsal regions of the SN (Fallon 1988, Lindvall et al. 1974).

1.3.2 Neurocognitive bases and effects of the COMT gene

As a major site of cognitive functions such as executive cognition and working memory, the PFC is impacted through the COMT polymorphism (Egan et al. 2001). This prefrontal cognitive modulation might, on the one hand, be affected by various dopamine receptors (DR). There are D1- (D1, D5) and D2-like (D2, D3, D4) receptors, whereas the former are more, except for the inferior frontal gyrus, extensively expressed in the PFC (e.g. Hurd et al. 2001). For a review on characteristics of dopamine in the PFC see Seamans and Yang (2004). While an intermediate dopamine concentration in the prefrontal cortex induces an activation of D1 receptors and a deficit in varying between highly active states elicited during task processing (Weinberger et al. 2001, Seamans and Yang 2004), D2 receptors are usually activated due to high or low amounts of dopamine and reduce difficulties in switching between activity states. Hence, D2 states enable faster switching between tasks and flexible task processing. In case of the dominance of D1 receptor functioning, robust working memory performance accompanied by the lacking sensitivity to distractors is found (review by Durstewitz and Seamans 2008).

Another factor modulating cognitive performance could be tonic vs. phasic dopamine action. According to the tonic-phasic dopamine hypothesis, dopaminergic regulation is performed by a low degree of tonic DA that arises from constant background firing of DA neurons and other glutamatergic afferents. The phasic part originates from burst firing of dopaminergic neurons (Grace 1991, Floresco et al. 2003, Bilder et al. 2004). While this DA from fast burst firing is re-uptaken by the few dopaminergic transporters (DAT), into the presynaptic terminal, it has been hypothesized that constant low-level DA in the PFC is removed by diffusion to noradrenergic terminals (Wayment et al. 2001). While this neurotransmitter lingers in the synaptic cleft it stimulates the tonic system of D1-receptors. Also it is more available for degradation per the COMT enzyme (Floresco et al. 2003). Due to the reduced enzyme activity, higher amounts of DA in prefrontal cortices of Met/Mets subjects are found. Previous research suggests that this leads to an increased tonic and decreased phasic DA transmission through autoregulation (Bilder et al. 2004, Floresco et al. 2003). Consequently this high concentration activates D1 receptors. Therefore, Met/Met carriers should suffer the aforementioned difficulties in updating or switching between cognitive tasks but score better

in stability demanding tasks. Here stability is seen as the potential to maintain current working memory tasks without being vulnerable to distractors. It has also been hypothesized that this equals greater efficiency in cognitive processing (Egan et al. 2001). Subjects homozygous for the COMT Val allele are assumed to show opposed dopaminergic transmissions and consequently do better on flexibility demanding tasks. At the same time they score worse concerning their cognitive stability (Bilder et al. 2004).

In previous research, subjects homozygous for methionin usually showed better performance in various working memory tasks (Savitz et al. 2006). In a review by Heinz and Smolka (2006) carriers of the Met allele additionally score better in executive tasks and attentional control.

Studying working memory and executive functioning with a Wisconsin Card Sorting Test (WCST), Egan et al. (2001) found better memory performance in the homozygous methionine genotype. Val/Mets usually still score better than Val/Val subjects. The homozygous valine genotype scores equally or worse especially concerning perseverative errors. In this test subjects have to successfully match a currently shown game card to a set of cards with differing item features like colour, design or quantity. Hereby an unknown task rule, from the subjects' perspective, has to be detected, which changes from time to time. The perseverative errors indicate the needed trials to adapt to a covertly changed task rule. This experiment consequently requires and indicates their ability to attend to and flexibly adapt their cognitive set.

Adapted to the dopamine hypothesis, the results could indicate, due to an increased ability for flexible task switching, a more successful adjustment to changing task requirements in Val/Vals. However higher amounts of perseverative errors in this genotype speak against this assumption. For this reason Val/Val subjects are rather thought to suffer from diminished task maintenance and therefore are possibly not capable to develop a solid plan for solving the task. Further research on working memory tasks revealed advantages for the Met/Met genotype in 1-back and 2-back tasks that require the stable online maintenance of information (Shallice et al. 1994). In an episodic memory task, subjects homozygous for methionine show an improved explicit memory performance, especially on a free recall (compared with recognition) test that poses increased demands on selection in the face of distraction (Frias et al. 2004). Beside these findings, studies showed that Met/Met subjects also perform better concerning other executive functions (Reuter et al. 2009). Overall, the differing COMT genotypes are assumed to explain about 1% of variance of cognitive task performance in children (Barnett et al. 2007) and about 4% in adults (Egan et al. 2001, Malhotra et al. 2002).

However, there are studies showing no association between the COMT genotype and cognitive performance (Meyer-Lindenberg et al. 2006).

On the other side the Met/Met genotype is assumed to suffer from emotional instability leading to an impaired processing of affective information (Drabant et al. 2006). Besides these findings, the COMT gene is thought to be predisposing for mental and behavioural illnesses such as depression, anxiety, bipolar disorders and schizophrenia (e.g. see Tunbridge et al. 2006). In the latter case Val/Val carriers are thought to have a slightly increased risk for this disease (Glatt et al. 2003, Egan et al. 2001). Applied to schizophrenia Durstewitz and Seamans (2008) patient's negative symptoms are thought to result from dominant D1 receptor effects. Positive symptoms are thought to be due to D2 receptor functioning. The former mechanism could hereby explain symptoms like perseverative errors. The latter, with an inability to stick to current tasks, results in symptoms like thought derailment. Regarding the control of memory retrieval, it was shown that schizophrenic patients showed reduced RIF due to a lacking ability of inhibition, pointing to a possible involvement of dopamine in inhibitory control (Soriano et al. 2009).

1.4 Hypotheses

In a previous study investigating RIF, Kuhl et al. (2007) assumed that there are "high and low forgetters" grouped according to their behavioural inhibition scores. High suppressors showed a high initial activation of the dorsal ACC and the right VLPFC during the first retrieval practice phase, followed by a large decay across repeated practice cycles. In contrast, low suppressors showed no comparable engagement of the ACC, or decay in the right VLPFC.

In this study I wanted to test the hypothesis that there is a genetic influence of theVal108/158Met polymorphism of the catechol-o-methyltransferase gene on the ability to inhibit irrelevant memory information, as indicated by retrieval-induced forgetting. I used functional magnetic resonance imaging (fMRI), scanning subjects during retrieval practice phases. I predicted that due to different amounts of prefrontal dopamine, the three genotypes will show differential behavioural results and cortical activation patterns. I hypothesized greater RIF in the Met/Met genotype due to higher dopamine levels and a stable task processing, in line with the tonic-phasic dopamine hypothesis. On the contrary, Val/Val carriers should show the lowest RIF due to a lower amount of DA and the accompanying capability of flexible task switching. Consequently they should suffer from an increased distraction by interfering information. On a neural level, stronger initial haemodynamic activation in the prefrontal cortex and especially inferior frontal areas should be found in Met/Met subjects. This would not only reflect different selection demands, but also speak for the expected larger mnemonic control in this genotype. A greater decrease in these areas from the first to the second retrieval practice phase is thought to indicate the benefits of successful inhibitory mechanisms, and should therefore be found in Met/Met carriers.

2 Methods

2.1 Participants

Fifty-six participants (18 per homozygous genotype) were recruited at the University of Magdeburg or from the IfN (Leibniz-Institute for Neurobiology) subject database, and were paid for participation. For further information on gender, age and handedness see Table 1. For this study we disregarded usual genotype frequency in the population and examined an almost equal number of subjects in each group. I also matched groups for gender, mean age and handedness to avoid potentially confounding influences on our results.

	Val/Val	**Met/Met**	**Met/Val**
male	9	8	8
female	9	10	10
mean age	26,2	25,3	24,3
SD	4,2	2,2	2,3
right handed	16	17	16

Table 1: Participants grouped for genotype.

The experiment was realised following the guidelines of the Ethics Committee of the University of Magdeburg - Faculty of Medicine. All of the participants gave informed consent, had no known history of neurological or psychiatric disease and normal or corrected to normal vision.

2.2 Genetic Analysis

DNA was gained from venous blood probes and tested for COMT-Val108/158Met-polymorphism. Approximately one third of the samples had to be recruited and genotyped newly. Others were available from an existing database at the Leibniz Institute for Neurobiology, Magdeburg, and had been genotyped earlier in an analogous manner.

Genotyping was performed with the COMT-f (5'-GCCCGCCTGCTGTCACC-3') and COMT-r (5'-CTGAGGGGCCTGGTGATAGTG-3') primers described by (DeMille, Kidd et al. 2002). Each PCR dilution was made with 5 µl genomic DNA (100 ng/ml), 0.5 µl Taq polymerase, 5 µl Q solution, 2.5 µl Taq Buffer, 2.5 µl of the COMT-f and COMT-r primer, 0.5 µl dNTP and 6.5 µl H_2O. Denaturation was accomplished with 1 min preheating with 94°C. After 42 cycles with 30 sec to denature (94°C), 30 sec to anneal (60°C) and 30 sec to elongate (72°C) a final elongations lasting 10 min (72°C) took place. For three hours PCR products were digested with NlaIII at 37°C. This resulted in three fragments (114, 70 and 54 base pairs long) for the Val allele and four fragments (96, 70, 54 and 18 bp) for the Met allele. The restriction fragments were separated on an agarose gel containing 4,5% ethidium-bromide. Visualized under UV light Val carriers were defined by a 114 bp long fragment and Met alleles by a 96 bp long fragment. For a similar description of this analysis see Schott et al. (2006).

2.3 Task Procedures

The experiment included nine runs, with three runs per scanning session. Each run consisted of a study phase, a retrieval practice phase, a Flanker Test used as a distracter task and a final recall phase (Figure 1). Scanning sessions were separated by short breaks during which participants remained in the scanner. During each study phase, 24 items like Apple or Tennis belonging to four different semantic categories like Fruit or Sport (6 items per category) were presented successively, together with the category name.

Overall 216 German nouns were used, taken from (Schmolck et al. 2002) and (Scheithe and Bäuml 1995). All items per category had unique first letters and therefore unmistakeable cues. The category name and the corresponding item were shown for 2000 msec with a 1500 msec fixation interval in-between. In the following retrieval practice phase, only half of the categories (e.g. Fruit) with half of the items (e.g. Fruit_Mango and Fruit_Kiwi) were practiced. This was done covertly in order to minimize movement artifacts. Each practiced items stayed on the screen for 2500 msec, followed by a fixation interval lasting 1000 msec. Hereby only the items' word stems (e.g. Fruit_Ma …) were displayed. Subjects were instructed to silently remember the adequate item. This retrieval practice was done twice for each of the three items with the lowest normative association to the category name, but only for half of the studied categories (e.g. Fruit).

A Flanker Test followed the retrieval practice as a distracter task (Eriksen and Eriksen 1974). Participants had to decide, via a button press, whether the middle arrow was directed left or right, ignoring the surrounding two arrows on each side. These could either point in the same or to the opposite direction. Pictures where shown for 1500 msec, with a fixation cross interval varying from 500 to 2500 msec (average 1500 msec). Every answer was given as quickly as possible via button press. The index finger indicated the left, the middle finger an arrow to the right side.

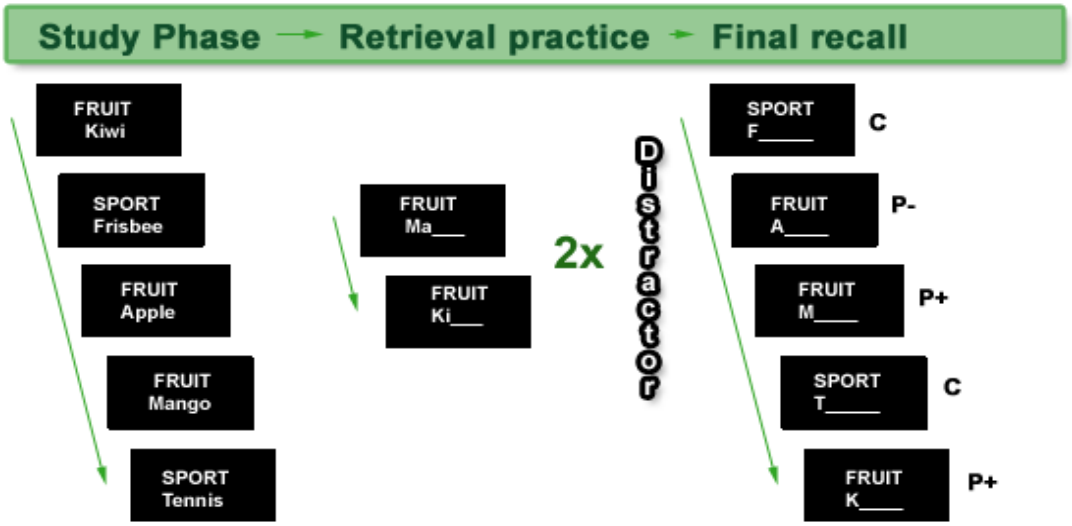

Figure 1: Task Prodecure Scheme

In the final memory test all initially studied words had to be retrieved. Due to the task procedure every run consisted of 6 normatively weak practiced items like Fruit_Mango (P+ items), 6 normatively strong unpracticed items from practiced categories like Fruit_ Apple (P- items), as well as 6 normatively weak (C+) and 6 normatively strong (C-) control items from completely unpracticed categories (e.g. Sport)

Subjects were given the category name and the first letters of the item they had to retrieve for 2000 msec. Subjects were asked to covertly remember the corresponding word at first and respond verbally as soon as three exclamation marks were shown for another 1500 msec. In case participants didn't remember the correct answer they were asked to say "Weiter". Fixation intervals between the trials lasted 1000 msec. Answers were recorded via a microphone attached to the head coil. Items were checked for correctness and classified as remembered or forgotten. Only exactly matching items were scored as remembered.

2.4 FMRI Data Acquisition

Functional images were acquired using a 1.5-Tesla-MRI (General Electrics Signa LX) scanner belonging to the University of Magdeburg - Faculty of Medicine. An ascending interleaved EPI sequence with a repetition time of 2000 ms and an echo time of 35 ms was used. 188 brain volumes were acquired per session. From that 48 volumes were acquired in each study phase, 21 volumes for the following Flanker task, 39 volumes per retrieval practice phase and 60 volumes during the final test phase. Overall 20 volumes were acquired in two fixation blocks. One was positioned between the flanker test and retrieval practice, the other one after the final recall. For the later analysis, I discarded the first three volumes from each session to attain tissue magnetization equilibration. A single image consisted of 23 axial slices. Slice thickness was 6 mm including a 1 mm gap, in-plane resolution 3.15x3.15 mm. T1-weighted anatomical images were acquired in the same MRI scanner. To avoid head movement the participants were instructed to move as little as possible, especially in the final recall phase where they had to verbally respond. Additionally, head movement was limited per pillows and foams inserts.

2.5 FMRI Data Analysis

Functional and statistical data analyses were performed with SPM 5 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London) and Matlab 7 (The MathWorks, Inc., Natick, MA). The functional images were temporally and spatially realigned and unwarped. T1 images were bias corrected and coregistered with the mean functional images. Functional and structural images were later normalized to a structural T1 MNI (Montreal Neurological Institute, Montreal, Quebec, Canada: http://www2.bic.mni.mcgill.ca/) template image and smoothed with an 8mm Gaussian Kernel. Gathered coordinates were, with the Talairach Client (http://www.talairach.org/), transformed into anatomical label information.

For the first level (single subject) statistical analysis, a general linear model (Friston et al. 1995) was set up including eight covariates corresponding to study events (P+, P-, C+ and C- items, separately for later remembered and forgotten items), two covariates modelling first and second retrieval practice trials, and eight covariates corresponding to the final recall events (P+, P-, C+ and C- items, again separately for remembered and forgotten items).

Additional covariates were included for the four possible flanker trials (congruent left, congruent right, incongruent left, and incongruent right), for speech events, button presses, and fixation periods. Covariates were, except for fixation periods, formed by convolving delta stick functions at the onset of each event of interest with the theoretical shape of the haemodynamic response function. Head motion that derived from realignment was included as a covariate of no interest.

In each genetic group both retrieval phases were analysed by contrasting them against fixation blocks. The comparison of interest in the present study was the contrast between brain activity during the first and the second cycle of retrieval practice, which was expected to differ between genotypes. The single-subject t-maps contrasting first and second retrieval practice with fixation were therefore entered into a two-by-three factorial mixed ANOVA including the within-subjects factor retrieval practice cycle (RP1 vs. RP2) and the between-subjects factor Genotype (Met/Met, Val/Met, and Val/Val). Planned comparisons within this model were then done by contrasting RP1 with RP2 separately in each group and a RP cycle x Genotype interaction contrast. The latter only included homozygous participants. Unless mentioned otherwise, all contrasts were calculated using an alpha level of .001, uncorrected for multiple comparisons.

All cortical activity patterns are calculated and displayed using an imaging mask that excludes the cerebellum. For an additional description of activation patterns in a region of interest (ROI), weighted means of a functional ROI (eigenvariate) were extracted using EasyROI (http://www.sbirc.ed.ac.uk/cyril/cp_download.html). Calculated means of all eigenvectors per genotype and retrieval practice cycle were graphically displayed. Statistical analyses on these results were performed to outline significant differences between the retrieval practice cycles. An outlier mean estimate from one Met/Met subject was excluded (see Supplemental Table 9).

2.6 Behavioural Data Analysis

For the behavioural analysis, RIF was calculated by subtracting recall rates of C- from P-items from each participant. Correspondingly, enhancement was calculated as the difference in performance between P+ items and C+ items. To test for significance we performed two-tailed t-tests with a 0,05 alpha threshold.

3 Results

3.1 Behavioural Results

In a combined analysis for all genotypes, subjects showed significantly higher recall rates for previously retrieved P+ items (81,79%, SD 8,2, $t(53)= 22,65$ $p < 0,05$) than for control items C+ out of unpracticed categories, which were remembered in 49,90% (SD 12,77). Non-practiced items out of practiced categories P- were recalled at 61,21% (SD 10,54), whereas matching C- items were, with 66,84% (SD 9,65) significantly better recalled ($t(53)= -5,2$, $p < 0,05$). These data generate an overall retrieval-induced forgetting effect ((C-) – (P-)) of 5,62% (SD 7,94) and a retrieval-induced enhancement effect ((P+) – (C+)) of 31,89% (SD 10,35). For a graphical overview see Figure 2 and Table 2.

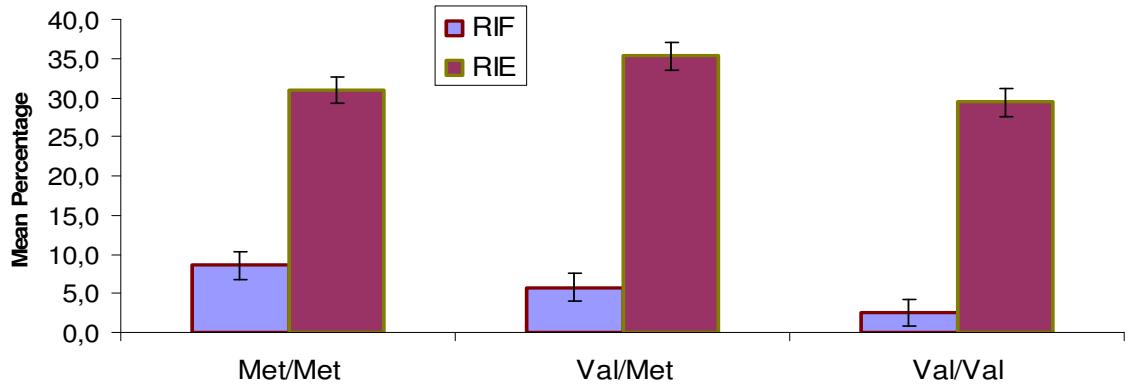

Figure 2: Graphical depiction of our behavioural results from the final recall

Analysed separately, significantly larger RIF was found in the Met/Met group (8,54%) compared to Val/Val genotype with 2,57% ($t(34) = 2.14$, $p < 0.05$). These results emerge from a less successful retrieval of P- items in Met/Met carriers, with no difference in control item performance. The heterozygous genotype showed an intermediate amount of RIF (5,76%). RIF in the Val/Val genotype itself was not significant ($t(17) = -1,43$, $p = 0,09$), whereas RIF was significant in the remaining two groups ($t(17) = -4,02$, $p < 0,05$ for the Met/Met genotype; $t(17) = -3,97$, $p < 0,05$ for the Val/Met genotype).

	P+	C+	P-	C-	C(mean)	RIF	RIE
Met/Met	81,38	50,41	59,77	68,31	59,36	8,54	30,97
Val/Val	82,82	53,40	66,15	68,73	61,06	2,57	29,42
Val/Met	81,17	45,88	57,72	63,48	54,68	5,76	35,29

Table 2: Behavioural results from the final recall test with mean percentages arranged by groups (standard deviation in brackets).

Our results are consistent with previous findings concerning the costs and benefits of retrieval. I could show higher recall rates for practiced P+ items in comparison with C+ items equated for normative strength (Anderson et al. 1994). Furthermore, I were able to demonstrate an influence of the COMT-polymorphism on retrieval-induced-forgetting. In doing so results show the lowest amount of RIF in the Val/Val group and the highest RIF in the Met/Met group. RIF in Val/Met subjects was found at an intermediate level. Val/Met subjects show the greatest retrieval induced enhancement (35,29 %) and benefit the most from further retrieval practices. However I did not find significant differences in retrieval-induced enhancement between the two homozygous genotypes ($t(34) = 0.42$, $p > .05$).

3.2 Functional imaging results

This study focused on the comparison between the two retrieval practice phases for all genotypes separately, and on the corresponding interaction effects. Nevertheless functional images were collected throughout the sessions. If not described otherwise results were calculated with a threshold of $p < 0{,}001$ (uncorrected) and an extent threshold of 10 voxels.

3.2.1 Retrieval practice phases

Comparing the first and the second retrieval practice (RP1>RP2) within all genetic groups, I found widespread bilateral activity. Beside precentral activation in the primary motor cortex BA 6, I found responses in parietal and late visual areas (BA 18, BA 19). Frontal haemodynamic responses include the inferior frontal gyrus (BA 47) and spread out to Brodmann area 46 and 9 into more ventro- and dorsolateral prefrontal regions. Grouped according to genotypes, the exact coordinates revealed by the contrast RP1 > RP2 can be found in Supplemental Table 2, 3 and 4.

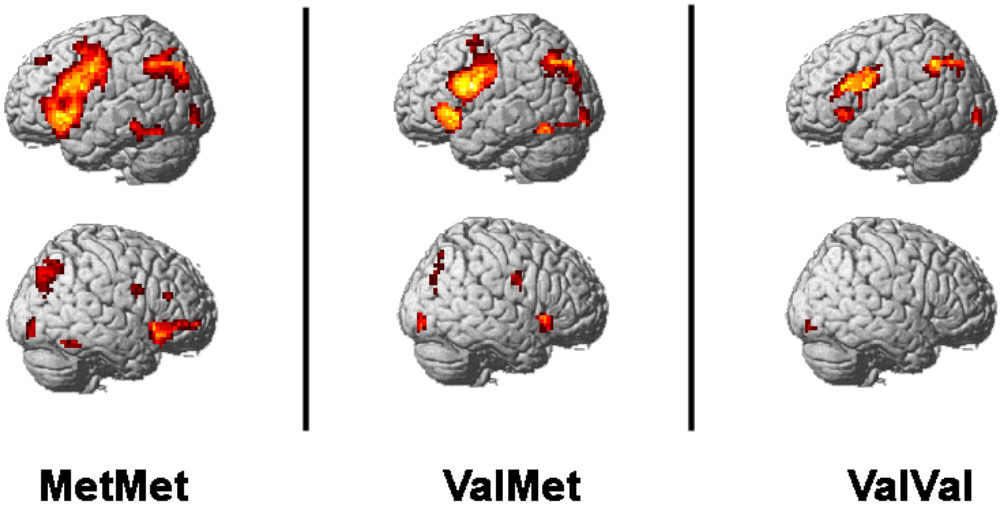

Figure 3: BOLD response from first to second retrieval practice phase (RP1 > RP2)

Figure 3 reveals differences in haemodynamic responses between all three genotypes. Met/Met subjects show extended left sided activation reaching from the VLPFC to the DLPFC and the precentral gyrus. The smallest left lateralized prefrontal haemodynamic response can be found in the Val/Val genotype. The latter group showed no significant activation in the dorsolateral prefrontal gyrus (BA 47) of the left hemisphere, and, importantly, in the prefrontal cortex on the right hemisphere.

3.2.2 Interaction between Genotype and Retrieval phase

Testing for a positive interaction (threshold $p < 0.005$, uncorrected) between both homozygous genotypes and the retrieval practice cycles, I found responses in the inferior frontal gyrus (BA 10; x= 39, y= 42, z= -3) and BA 47 (x= 39, y=18, z= -18) of the right hemisphere (see Table 3).

Positive Interaction							
Anatomical Label		**BA**	**X coor**	**Y coor**	**Z coor**	**t**	**size**
R	Inferior Frontal Gyrus	BA 47	39	18	-18	3,20	17
R	Inferior Frontal Gyrus	BA 10	39	42	-3	3,87	31

Table 3: Active regions calculated for positive interaction between Met/Met carriers and Val/Val subjects (threshold p < 0,005, extended threshold 10 voxels, cube range +/- 3mm)

Extracting eigenvariates for both areas, haemodynamic response in the right frontopolar cortex (BA 10) decreased in Met/Mets from first (0,65 beta estimate) to second (-0,03 beta estimate) retrieval practice (for detailed numbers see Supplemental Table 9). In Val/Val subjects, only a weak initial haemodynamic response (0,07 beta estimate) could be shown, whereas in the second retrieval phase BA 10 showed a relatively stronger response (0,25 beta estimate). In Val/Met carriers a decrease in activation could be shown between the two phases. Cortical activation during first and second retrieval practice phase revealed a decrease in the right BA 47 in methionine subjects. Val/Val subjects did not show any differential activation during both retrieval phases (-0,17 to -0,14 beta estimate). For further information on the dynamics of both cortical areas in between the two retrieval practice phases, contrasted against fixation see Figure 4.

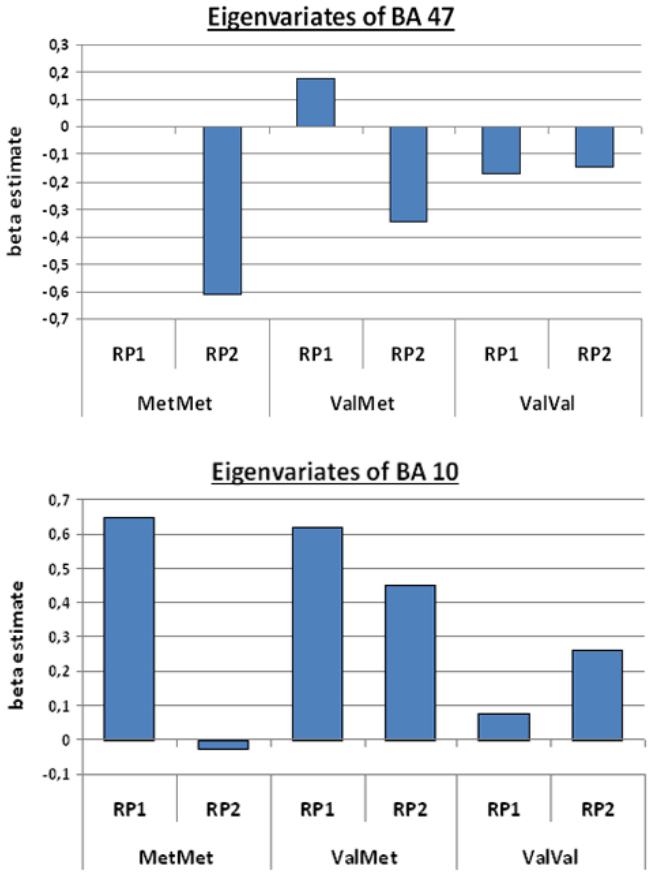

Figure 4: Mean estimates (beta estimates) for BA 10 and BA 47

The right anterior VLPFC (BA 47) showed significant declines in haemodynamic response in the Met/Met ($t(17) = 3,70$, $p < 0,01$) and the Val/Met genotype ($t(17) = 3,56$, $p < 0,01$), whereas there was no significant difference in the Val/Val group ($t(17) = -0,15$, $p = 0,44$). The frontopolar cortex (BA 10) showed a significant decrease in the homozygous methionine

group (t(17) = 3,32 , p < 0,01), but not in the heterozygous (t(17) = 0,75 , p = 0,23) or Val/Val group (t(17) = -1,03 , p = 0,16). For a graphical overview concerning the differences between cortical activities from RP1 and RP2, contrasted against fixation blocks see Figure 5.

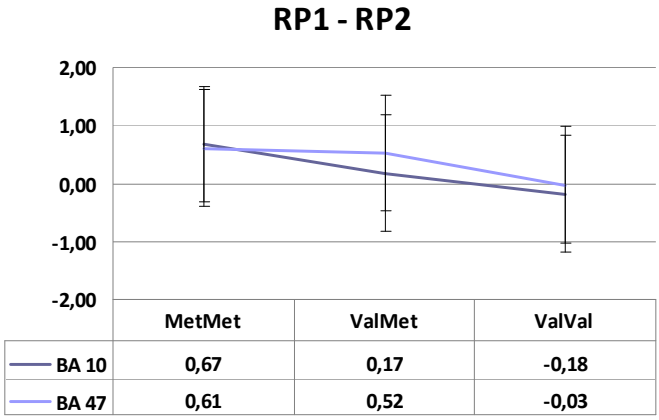

Figure 5: Differences of the mean averages of activation during both retrieval practice phases calculated for BA 10 and BA 47 (mean estimates on y-axis, standard deviation displayed as columns)

4 Discussion

In this study, I investigated the genetic influence of the COMT polymorphism on inhibition in long-term memory. I assumed a differential processing and retrieval of task relevant information in the presence of competing memory information. I found differences in behavioural inhibition scores, and in functional imaging results acquired in the retrieval practice phase. The neural substrates I found indicate dopaminergic influences on inhibitory brain areas. Furthermore, the results support an inhibitory account of retrieval induced forgetting.

Previous research investigated retrieval-induced forgetting on a neural and behavioural basis, examining diverse conditions. With our genetically based approach, I could replicate Andersons et al.'s (2003) RIF finding when calculated across all genotypes. Similarly, our study showed significantly larger differences in the retrieval of C- and P- items within genotypes. The costs (retrieval-induced forgetting) and benefits (retrieval-induced enhancement) of retrieval are displayed in Table 2.

Concerning the individual amount of RIF, Kuhl et al. (2007) classified their subjects into "high and low suppressors". The Met/Met genotype showed RIF amount of 8,54%, the Val/Val genotype showed 2,57% of RIF. Therefore our results might suggest that the COMT polymorphism not only impacts our behavioural results. They might also explain, in terms of genetic factors influencing the dopaminergic signalling in the PFC, behavioural and neural differences between Kuhl et al's (2007) high and low forgetters. Apart from the COMT genotype I did not consider other genetic factors and physiological mechanisms in this work. Previous studies have shown that COMT exerts its influence on cognitive and brain function in interaction with other dopamine genes like DAT. However, our results do not allow conclusions about a possible modulatory role of these other genes.

4.1 Neural correlates of retrieval

Using functional imaging, Kuhl et al. (2007) investigated the mechanisms of forgetting and cognitive control during retrieval practice phases using the retrieval-practice paradigm (Anderson et al. 1994). Comparing the first against the second retrieval-practice phase, decreasing activation has been found in the frontoparietal, the ventrolateral prefrontal cortex as well as in the right dorsolateral PFC (approximately BA 10, BA 9 and BA 46). To clarify

further differences between a successful cognitive control, meaning the inhibition of non-retrieved interfering items, Kuhl et al. (2007) median-split their sample into subjects with high and low amounts of RIF. High suppressors did not show differential cortical response in the right VLPFC (BA45) compared to low forgetters during RP1. However they showed a larger decrease in haemodynamic response from the first to the second practice phase. This might reflect a more effective use of inhibition during the first retrieval. Consequently, following practices do not require further strong activation as seen in the low suppressor group. Also, the activation decrease in areas related to memory suppression in the ventro- and dorsolateral cortex as well as in the ACC, predicted later forgetting of interfering items (Anderson et al. 1996, Cools et al. 2010). At the same time, in between high and low-forgetters no significant difference concerning the retrieval of P+ items was found, suggesting that the differences were specific to memory suppression, not enhancement.

Contrasting first against second retrieval practice phase in the present study, all subjects showed benefits of repeated retrieval practice in premotor and extended prefrontal areas, as well as in late visual areas in the occipital lobe. For detailed information see Supplemental Table 1. Our study showed larger prefrontal activation decreases in the Met/Met group, relative to Val/Met carriers or Val/Val subjects. The basic differences between all three genotypes are displayed in Figure 3 and in Supplemental Table 2 to 4.

Testing a significant interaction effect I found right sided cortical activation in BA10 and BA 47 (see Table 3). The latter region is subsumed to the inferior frontal gyrus or likewise the VLPFC (BA 44, 45, 47). Importantly, these areas closely overlap with the areas that were related to individual differences in memory suppression in the previous study by Kuhl et al. (2007). It is believed that these areas take over specialized roles within the functioning of the prefrontal cortex, depending on the paradigms and their difficulty. Hereby hierarchical structures are assumed (Björklund and Dunnett 2007, Badre and Wagner 2007). In general, recent studies consistently showed activation of the VLPFC during retrieval from long-term memory. It is thought that these areas located on the right hemisphere either support attention to relevant items, or solve competition per inhibition (for a review see Aron et al. 2004, Kuhl et al. 2008). Concentrating on left lateralized functioning, Badre and Wagner (2007) reviewed two possible mechanisms within episodic memory retrieval, the so-called controlled retrieval and post-retrieval selection. On the one hand, activation of the anterior VLPFC (BA 47) is thought to reflect increased demands on controlled retrieval (Wimber et al. 2008, Badre and Wagner 2007, Badre et al. 2005). BA 47 tends to increase activation as soon as, in a goal-directed task, retrieval is not easily possible due to an unsatisfactory activation of stored

knowledge by the given cue. In this case, cognitive control helps to maintain and combine various cues in order to retrieve the relevant target memory. On the other hand, it is often the case that, besides the target item, interfering information is also co-activated by a retrieval cue. To solve this problem the inferior frontal gyrus/ mid- VLPFC (BA 45) is activated and thought to select the to-be-retrieved information from a bulk of competing memories, a process termed post-retrieval selection.

As mentioned above, previous work also suggested right lateralized selection and inhibiting processes in the inferior frontal cortex including BA 44, 45, 47 (Aron et al. 2004). Here, mechanisms like response inhibition, task set switching, inhibition in the presence of interfering memories, and inhibition during retrieval are attributed to this area. In particular, paradigms testing episodic memory connected suppression and inhibition to the VLPFC (Cools, et al. 2010, Kuhl et al. 2008, Kuhl et al. 2007). Another considerable function is the selective orientation of attention that has been tested contrasting engagement during the retrieval of previously practiced and non-practiced items. Thereby, on the one hand, overcoming the interference elicited by practiced P+ items has been associated with the right anterior VLPFC (Kuhl et al. 2008, Malhotra et al. 2002). Consequently, on the other hand, this increased interference demands increased selective attention towards the previously non-retrieved items (P-) and cortical activation in order for them to be successfully retrieved in the later test phase (Lindvall et al. 1974).

As can be seen in Figure 4, all three genotypes show differing cortical response of BA 47 between the two retrieval practices. The Met/Met genotype shows no initial activation with a strong decrease towards RP2. The heterozygous genotype showed an intermediate amount of decrease and the highest initial response. When I interpret Figure 4 in combination with the aforementioned inhibition theory, homozygous valine carriers show a constant activation in the right BA 47 over both retrieval practices, which can be thought of as reflecting higher requirements in mnemonic control. Heterozygous subjects benefit from a further practice phase and the successful retrieval of the P+ items seems easier upon repetition. The results of the Met/Met genotype would implicate, that no explicit demands on cognitive control are needed. Here I cannot explicitly distinguish activation that evolves from the selection of target P+ or from the inhibtion of non-target P- items during retrieval practice. Nevertheless activation of the VLPFC might indicate higher requests to overcome distraction in the Val/Val genotype. The heterozygous genotype hereby seems to be able to benefit from a second practice phase, whereas the requirements on the Met/Met carriers from the outset do not seem that large.

The Met/Met genotype showed retrieval-induced forgetting of 8,54%, and their decrease in BOLD signal across retrieval cycles is similar to Kuhl et al.'s (2007) VLPFC engagement in the high forgetter group. In Val/Val group the activity in BA 47 only slightly increased between the two practice phases. The results of our experiment might be unequal to Kuhl et al.'s (2007) in several respects, including the different classification criteria used to split the participant sample into distinct groups. I a-priori created three groups, based on the subjects' genetic polymorphisms, and therefore theoretically based on differential prefrontal dopamine concentrations. The amount of retrieval-induced forgetting was essential for assigning a subject to one of the two different suppression groups in the previous study (Kuhl et al., 2007). Nevertheless both experiments show, as soon as successful suppression of interfering items took place in BA 47, this region benefits during the second retrieval practice. In fact the need for further cognitive control is diminished and a strong activation is no more necessary. In case distracting information cannot be inhibited, like in the homozygous valine carriers, the demands on cognitive control and the corresponding cortical response remain on a similar level.

Figure 4 also displays the mean activation patterns of a right-lateralized cluster in BA10 that showed a significant interaction effect. The frontopolar cortex in general does not show a right or left lateralized specific functioning, such that all assumptions concerning its capabilities include both hemispheres (Gilbert et al. 2006). As concluded by the authors of a recent review, this cortical area seems to contribute to multiple cognitive functions. For example, activation indicated emotional processing, working memory or episodic retrieval. As it is described in this work, the distinction of the lateral versus the medial portion of BA 10 revealed a close association to episodic memory tasks, and multitasking and mentalizing, respectively. Recent studies also associated the (right) frontopolar cortex (BA 10) with multitasking abilities, such as the integration and combination that is required while processing multiple tasks simultaneously (Badre et al. 2009). An increase in cognitive control demands is thought to hierarchically activate prefrontal and frontal areas, with the frontopolar cortex as the highest abstraction processing area. In a review by (Owen and Ramnani 2004) functions like the processing of internal states, memory retrieval models, prospective memory, branching and reallocation of attention, relational integration and the integrating the outcomes of two or more separate cognitive operations are attributed to this region.

Turning to our study, I found a lateral activation peak (see Supplemental Figure 1). Here the highest haemodynamic response in RP1 with later cortical depression in the Met/Met genotype. Haemodynamic response in Val/Val carriers did not show significant differences

between both retrieval practice phases. Using the inhibitory account, cortical depression might follow due to successful inhibition in other cortical areas and a lacking need of dual task processing. The small but insignificant increase of cortical activation from the first to the second retrieval phase in the Val/Val genotype might indicate unsuccessful inhibition. Following the assumption that this area activates depending on cognitive control loads, our results suggest that Met/Met subjects might show a greater ability to reduce interference, to attend to and to operate with higher task processing requirements. The Val/Val genotype might not be able to respond to these requirements and cannot benefit from their treatment. Nevertheless, due to the vast amounts of hypothesis, I cannot clearly account one theory to be responsible for our results, exclusively. Moreover the found activity pattern in BA 10 resembles the one in the right IFG (BA47) of Kuhl et al. (2008). It is therefore possible, considering the exact BA 10 localisation, that we found an anterior activation attributable to the inferior frontal gyrus.

A linear decline of the activation differences between both retrieval practice phases depending on the COMT Val108/158Met genotype is depicted in Figure 5. Here homozygous methionine carriers show the largest decreases in BA 47 and BA 10 in a comparison of RP1 and RP2. Both methionine expressing groups thereby show significantly different haemodynamic responses, whereas Val/Val carriers do not. Consequently Met/Met carriers show a rather flexible cortical response. The results mirror a greater cognitive control and inhibition, as well as a better resistance against interference. Val/Val subjects do not show neural correlates of successful inhibition and hence do not benefit from a further practice phase.

4.2 Dopaminergic influences

Our study used the Val108/158Met polymorphism of the COMT gene to investigate behavioural effects in combination with prefrontal dopaminergic functioning. Because the COMT enzyme reduces the concentration of dopamine in the cortex, differences between genotypes should theoretically be related to differing amounts of this neurotransmitter. More exact, the expression of methionine diminishes its enzymatic metabolism up to fourfold (Syvanen et al. 1997, Lachman et al. 1996). Hence the homozygous Met/Met genotype shows a higher concentration of DA, especially in the prefrontal cortex.

Recent studies widened knowledge about the functional consequences of this polymorphism. Thereby, depending on the linkage to the prefrontal cortex, executive functioning such as

response inhibition, working memory, decision making, attention and others are affected (Cools et al. 2007, Cools et al. 2006). In the case of working memory tests the Met/Met genotype usually shows better task performance (see Savitz et al. 2006, but see Cools et al. 2003). A study by Frias et al. (2004) investigated the influence of the COMT polymorphism on semantic and episodic memory testing various age groups. In distinguishing between episodic recall and recognition tests, Met/Met carriers could not clearly be distinguished from Val/Val subjects on simple recognition tests, but did show significant differences on free recall. In line with the present thesis, this result indicates that prefrontal dopamine plays a role for memory retrieval under conditions involving ambiguous cues and therefore increased interference, as present during free recall, but not recognition. The experiment also indicated an age-dependent memory performance, whereas the both oldest Met/Met groups (50–60 and 65–85 years), but only the oldest Val/Val subjects showed a decline over a 5 year period.

A common experimental set-up for testing executive performance is the Wisconsin Card Sorting Test (WCST). In connection to dopamine concentrations, this experimental set-up was firstly used by Egan et al. (2001). The measurement of perseverative errors showed an increasingly better task performance related to the amount of expressed methionine. Val/Val carriers scored the worst, a finding that could be replicated by (Malhotra et al. 2002). Since these early findings, a homozygous methionine expression has been thought to usually enable stable task processing. In contradiction to this solid task maintenance, Val/Val carriers are thought to show a rather flexible task processing with the ability to switch between changing cognitive demands (Cools et al. 2002). A better average executive memory performance in the Met/Met genotype in a WCST was replicated with results from healthy subjects and schizophrenic patients (Cools 2006). Using a different working memory measure, Egan et al. (2001) could also show an excessive activation of the DLPFC (BA 46) and the anterior cingulate cortex in Val/Val carriers during a 2-back task. In the light of similar task performance in both genotypes, this result can be interpreted as inefficient interference resolution.

Possible benefits of engaging these cortical areas are found in Met/Met carriers, who show strong haemodynamic response decays from first to second retrieval practice. Less decrease from the first to the second retrieval practice can be assumed to reflect the costs of inefficiency in the Val/Val genotype. Additionally, Bäuml and Aslan (2011) could predict, with the working memory capacity of their subjects, the resulting retrieval-induced forgetting amount. High capacities thereby resulted in greater RIF scores, suggesting a strong link between working memory capacity and long-term memory control.

In general, stable task processing, in the presence of distracting information or interfering memories, results in a better attention towards goal-relevant items and can therefore be assumed to also increase ability to avoid distraction caused by interfering memories (Durstewitz and Seamans 2008, Durstewitz et al. 2000). A flexible task processing within this long-term memory phenomenon leads, in the hypodopaminergic genotype, to less cognitive control associated with an easier activation and less inhibition of related, currently irrelevant memories. With a RIF of 8,54% for Met/Met carriers and 2,57% for the Val/Val genotype, our results support this theory. During both retrieval practices subjects were asked to process P+, while P- items served as distractors. The homozygous valine carriers hereby show to lack a mechanism to control and reduce the interference strength of not retrieved items from practiced categories, resulting in a significantly higher correct retrieval of P- items. On the contrary the Met/Met genotype is able to focus on the current task and to minimize interference by inhibition, resulting in forgetting of the distracting items

Apart from all these advantages, high prefrontal DA concentrations are also thought to have a certain negative impact. So the COMT gene has for example also been assumed to affect the processing of emotional stimuli. Here aversive stimuli cause stronger BOLD responses in the right amygdale, the hippocampus and the prefrontal cortex, especially in BA 47 in homozygous methionine carriers (Heinz and Smolka 2006).

Research on dopaminergic influences on cognition also used studies with patients, suffering from DA dysregulation (Tunbridge et al. 2006, Tan et al. 2007). In particular, the linkage to impairments in patients suffering from schizophrenia brought new knowledge. In this case, an incorrectly regulated DA signalling for example is thought to be centrally involved in producing the positive and negative symptoms, and the well studied impairment in executive functioning (Bertolino et al. 2004). Because of the genetically based impact of the COMT Val108/158Met polymorphism, it is likely to influence frontal lobe functioning. Increased activation might reflect an unsuccessful task processing, whereas a diminished cortical response possibly reflects a reduced capability to handle or the inability to attain to a specific cognitive requirement (Weinberger et al. 2001). With respect to a verbal working memory task an increased ventrolateral PFC activity was found in schizophrenic patients (Tan et al. 2006). However, using a N-back working memory task, Tan et al. (2006) could show a stronger VLPFC responses due to increased task requirements. This result was opposing to healthy subjects showing greater DLPFC activity response (Owen and Ramnani 2004). Consequently compensatory activation might not be the only factor for a differing haemodynamic response, and it remains unclear so far under which circumstances higher

dopamine concentrations are related to an increased or decreased BOLD signal. Turning to retrieval-induced forgetting in subjects suffering from schizophrenia, various results of RIF in patients could be found in (Soriano et al. 2009, Nolan et al. 2004, but see Joober et al. 2002). Thereby Soriano et al. (2009) investigated recall and recognition during the final test phase and support the theory of a defective inhibition in schizophrenic patients. This finding is consistent with the idea that intact frontal functioning is required in order to successfully inhibit distracting memories.

As another disease caused by a change in dopaminergic concentrations, studies have investigated patients with Parkinson disease (e.g. Bertolino et al. 2004). Hereby, studies using L-Dopa treatment attained similar effects of dopaminergic concentrations in the PFC in working memory tasks and could show an ameliorated functioning after medication (Mattay et al. 2003, Perlstein et al. 2003, AhnAllen et al. 2007). On the other hand (Callicott et al. 2003) found an increased distractibility in patients without medication, which would at first speak against higher prefrontal dopamine and a resulting higher cognitive function However these results might be due to a hypodopaminergic striatum and consequently upregulated frontal areas.

Adding on these results, prior investigations clearly indicate individual differences in prefrontal functioning due to the COMT genotype and dopaminergic concentration. While hyperdopaminergic states also evince certain detriments, the theory of D1 receptor activation depending of dopaminergic concentrations that follows an inverted u-function has been developed (Della Sala 2010). Under the assumptions of this model, Met/Mets subjects with a higher amount of prefrontal DA are found at the peak of the curve. In contrast, Val/Vals show less DA and are located at the ascending part of the curve (Williams and Goldman-Rakic 1995, Williams and Castner 2006). Mattay et al. (2003) manipulated cortical and behavioural responses with amphetamine that increases DA amounts due to the blockage of extrasynaptic uptake. They used N-Back tasks and the WCST. In the Val/Val subgroup, amphetamine induced, with no changes in overall task performance, a reduced reaction time coupled with a smaller haemodynamic response in the prefrontal cortex in the N-Back tasks. In the WCST, Val/Val participants showed less perseverative errors under drug administration. Concerning the Met/Met group, AMP did not affect prefrontal activation concerning the conducted imaging. However it lead to a worse task performance and longer reaction times in the 3-back task, also more errors were made in the WCST. Consequently higher dopamine concentrations per amphetamine are thought to relate to a shift, on the inverted u-curve, to the right. Val/Val subjects nevertheless profit from this higher position on the curve. In the

Met/Met genotype, amphetamine administration lead to a hyper-dopaminergic state that compromised task performance at high memory loads. In schizophrenic patient studies, inefficent hyperdopaminergic states are thought to be reached already at lower task requirements (Levy et al. 2010). Therefore the inverted u-curve is thought to be shifted to the left in these patients (Jansma et al. 2004, Perlstein et al. 2003). I believe that the current results, showing greater RIF scores in the Met/Met genotype, stand in line with this general theoretical approach, which might explain the behavioural results.

4.3 Genetic influences

What already has been proven experimentally or assumed due to computational models is the dependence of dopaminergic signalling on the concentration as well as the neurotransmitter's receptor binding. Regarding the relationship between dopaminergic signalling and cognitive functions, a considerable theory is the tonic and phasic dopamine hypothesis (Bilder et al. 2004, Floresco et al. 2003, Grace 1991). According to this model, short DA bursts, eliciting from the ventral tegmental area, release the neurotransmitter into the synaptic cleft. This phasic dopamine is quickly re-uptaken per postsynaptic receptors and so immediately reacts to given stimuli. Tonic release creates a certain steady neurotransmitter concentration in subcortical structures and does not react to temporarily changed task demands. Because tonic DA cannot be re-uptaken due to less DATs in PFC, and due to the extrasynaptic location of the COMT enzyme, tonic dopaminergic signalling is increasingly affected by COMT while it lingers in the extrasynaptic space (Floresco et al. 2003, Eysenck and Keane 2006).

Apart from the signalling itself, the density and type of the dopaminergic receptors contribute to PFC functioning. (Hurd et al. 2001) found higher mRNA expression levels of D1 receptors in the prefrontal cortex. The inferior frontal gyrus (BA 44, BA 45, BA 47), which widely showed different haemodynamic activity patterns during our experiment, offered a mRNA expression of both receptors at an equal low level. Therefore differential activation of BA 47 might not be due to the density of various receptor types. Otherwise an increased receptor thickness might have dominated with its characteristics in transmission and functioning, and would have produced opposite results. Regarding this, a possible explanation for a behavioural impact due to dopaminergic concentrations are specialized receptor activation states. As it is described in (Durstewitz et al. 2000, Seamans and Yang 2004, Meyer-Lindenberg et al. 2006) a broad PFC activation throughout multiple stimuli and their representations activates D2 receptors. In this state, a minimal inhibition of distractors is

possible. Active D1 receptors filter the vast amounts of incoming stimuli and possibly create a stable memory maintenance.

While levels of tonic DA suppress the phasic signalling, low enzymatic degradation in Met/Met carriers leads to higher tonic and lower phasic signalling. Given that high tonic, extrasynaptic dopamine concentrations rather activate D1 receptors, a rather stable task processing is found (Durstewitz and Seamans 2008). Consequently this tonic signalling would not be present to the same degree in the hypo-dopaminergic Val/Val genotype. Adapted to the retrieval-practice paradigm, this hypothesis is in accordance with our behavioural results, showing a significantly higher inhibition of distracting memory items in the Met/Met group.

5 Conclusion

Functional MR images were recorded from fifty-four subjects. Assembled into the three genotypes of the COMT polymorphism the subjects performed the retrieval practice paradigm of Anderson et al. (1994). As a result the amount of RIF in the test phase as well as the haemodynamic responses during the paradigm were analysed per genotype seperately.

High dopaminergic concentrations, due to the homozygous expression of methionine, in the prefrontal cortex lead to higher RIF (8,5%) scores and a successful interference resolution compared to the Val/Val genotype (2,6%). While dopaminergic levels are thought to be predictive of a stable or flexible task maintenance, I could successfully transfer this theory to the field of long-term memory retrieval and forgetting. The calculation of a significant Genotype x Retrieval Practice interaction effect revealed a flexible cortical response in methionine carriers. Val/Val subjects did not show beneficial effects, such as a smaller haemodynamic response in the second RP, but achieve better retrieval rates for P- items.

Moreover, dependence of haemodynamic responses to dopaminergic concentrations was explicitly found in BA 47 and BA 10. Additionally, I found a linear decline in haemodynamic activation within the retrieval practice phases that correlated with the amount of expressed dopamine in these areas. Consequently genotypes differ in their ability to encode or retrieve goal-relevant in the face of distracting information as well as in the processing and monitoring of competition. While greater BOLD response in these locations is thought to reflect greater inhibition, I could therefore believe that the Met/Met genotype is more capable to inhibit distracting items implying a stable task processing.

Though all of this previous research associates enzymatic metabolism to these findings it remains questionable, whether this polymorphism is the only cause of the aforementioned individual differences.

6 Zusammenfassung

Es wurden Ergebnisse per funktioneller Magnetresonanz mittels 54 Probanden generiert. Unterteilt in die drei Genotypen des COMT-Polymorphismus führten die Probanden das Abruf-Übungs-Paradigma von Anderson et al. (1994) aus. Somit konnte die Stärke des Abrufinduzierten Vergessens sowie auch die hämodynamische Reaktion des Kortex während des Paradigmas in Abhängigkeit des Genotyp separat analysiert werden.

Hohe dopaminerge Konzentrationen, welche durch die Expression von Methionin entstehen, führen, in Vergleich zu dem homozygoten Val/ Val-Genotyp (2,6%), zu einem verstärktem Abruf-induzierten Vergessen (8,5%) und einer erfolgreichen Hemmung interferierender Informationen im präfrontalen Kortex . Bisher wurde die Dosis des vorhandenen Dopamins mit der Hypothese einer stabilen oder flexiblen Aufgabenlösung in Verbindung gebracht. Mit dieser Arbeit konnte diese Theorie erfolgreich auf den Bereich des Abrufes und des Vergessens von Informationen des Langzeitgedächtnis ausdehnt werden. Die Berechnung der Interaktion zwischen Genotyp und den Abruf-Übungen zeigte eine flexible kortikale Reaktion in Probanden mit der Expression von Methionin. Homozygote Val/Val-Probanden konnten durch diese Expression, im Sinne einer reduzierten hämodynamischen Antwort in der zweiten Abrufübung, nicht profitieren. Dabei zeigte sich aber ein erfolgreicherer Abruf von P- Items und die Fähigkeit zur flexiblen Aufgabenlösung.

Ebenfalls konnte eine Abhängigkeit der hämodynamischen Antwort zu vorhandenen dopaminergen Konzentrationen speziell in den Brodmann Arealen 47 und 10 nachgewiesen werden. In Korrelation zu dem gebildeten Dopamin in diesen Hirnregionen zeigte sich ebenfalls ein linearer Abfall der hämodynamischen Aktivität in den Abrufübungen. Folglich unterscheiden sich die Genotypen in ihrer Fähigkeit des Abrufes relevanter Information bei der Existenz störender Informationen, sowie auch in der Kontrolle konkurrierender Gedächtnisinhalte. Durch stärkere BOLD-Aktivität als Maß für Inhibition, wird angenommen, dass der Met/Met Genotyp besser zur Inhibition störender Gedächtnisinhalte und somit zu einer stabilen Aufgabenlösung befähigt ist.

Obwohl die bisherige Forschung die entsprechenden Ergebnisse mit diesem enzymatischen Metabolismus in Verbindung bringt, ist es bisher unklar ob jener Polymorphismus der einzige Grund für die gemessenen individuellen Unterschiede ist.

7 Publication biography

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8 Appendix

RP1 > RP2 (all genotypes)							
Anatomical Label		**BA**	**X coor**	**Y coor**	**Z coor**	**t**	**size**
L	Inferior Frontal Gyrus	9	-45	3	27	10,70	3098
L	Medial Frontal	6	-3	3	57	10,52	
L	Inferior Frontal Gyrus	6	-51	15	24	9,85	
L	Precuneus	19	-27	-72	39	9,62	907
L	Inferior Parietal Lobule	39	-33	-60	39	9,11	
L	Inferior Occipital Gyrus	18	-27	-90	-3	7,47	
R	Inferior Frontal Gyrus	47	36	18	-3	7,95	267
R	Inferior Occipital Gyrus	18	27	-90	-9	7,07	148
R	Declive	*	48	-57	-21	5,44	
R	Fusiform Gyrus	19	45	-75	-15	5,25	
R	Precuneus	19	27	-72	42	7,00	453
L	Fusiform Gyrus	37	-45	-60	-18	6,44	218
L	Culmen	*	-48	-45	-24	5,61	
L	Fusiform Gyrus	19	-42	-75	-12	3,91	
R	Nodule	*	0	-57	-27	6,01	12
R	Precentral Gyrus	6	51	-9	30	4,92	206
R	Precentral Gyrus	6	48	0	27	4,58	
R	Middle Frontal Gyrus	46	51	24	24	4,71	63
R	Middle Frontal Gyrus	9	42	30	33	3,58	

Supplemental Table 1: Locations showing significant haemodynamic responses from first to second retrieval practice phase (RP1 > RP2) calculated for all genotypes (p<0,001 threshold, extended threshold 10 voxels, L left hemisphere, R right hemisphere, BA Brodmann area, * No BA has been found)

RP1 > RP2 (MetMet)							
Anatomical Label		**BA**	**X coor**	**Y coor**	**Z coor**	**t**	**size**
L	Superior Frontal Gyrus	8	-3	18	48	7.11	1644
L	Inferior Frontal Gyrus	9	-45	6	27	6.97	
L	Inferior Frontal Gyrus	47	-42	27	-6	6.75	
L	Precuneus	19	-27	-75	36	5.77	479
L	Inferior Parietal Lobule	39	-33	-60	39	5.42	
L	Precuneus	7	-21	-72	51	3.53	
R	Superior Parietal Lobule	7	27	-72	45	5.43	219
R	Precuneus	19	30	-69	33	4.71	
R	Inferior Frontal Gyrus	47	36	24	-12	5.01	241
R	Inferior Frontal Gyrus	47	36	18	-6	4.93	
R	Inferior Frontal Gyrus	46	39	42	-3	4.57	
L	Superior Frontal Gyrus	8	-15	42	45	4.33	10
R	Inferior Occipital Gyrus	18	33	-87	-6	4.27	19
L	Inferior Occipital Gyrus	18	-27	-90	-3	4.18	36
L	Lingual Gyrus	17	-15	-96	-9	3.60	
R	Inferior Frontal Gyrus	9	42	3	27	4.15	29
L	Middle Temporal Gyrus	20	-57	-39	-12	3.95	55
L	Fusiform Gyrus	39	-48	-60	-18	3.82	
L	Fusiform Gyrus	39	-54	-54	-18	3.75	
L	Thalamus	*	-9	-18	0	3.83	67
L	Putamen	*	-12	-6	0	3.55	
R	Superior Frontal Gyrus	10	30	54	-3	3.70	16
R	Right Cerebellum	*	54	-51	-21	3.62	13
R	Right Cerebellum	*	48	-57	-21	3.53	

Supplemental Table 2: Haemodynamic responses (RP1 > RP2) calculated for Met/Met subjects (p<0,001 threshold, extended threshold 10 voxels, L left hemisphere, R right hemisphere, BA Brodmann area, * No BA has been found)

RP1 > RP2 (ValMet)							
Anatomical Label		**BA**	**X coor**	**Y coor**	**Z coor**	**t**	**size**
L	Medial Frontal Gyrus	6	-3	3	57	6.41	360
L	Superior Frontal Gyrus	6	-21	6	60	4.26	
L	Precuneus	7	-27	-66	36	6.02	415
L	Inferior Frontal Gyrus	9	-45	12	21	5.92	550
L	Inferior Frontal Gyrus	9	-42	3	27	5.81	
L	Precentral Gyrus	6	-51	0	33	5.64	
L	Inferior Frontal Gyrus	47	-45	30	0	5.71	265
L	Inferior Frontal Gyrus	47	-33	24	-6	5.27	
R	Inferior Frontal Gyrus	47	36	18	-3	5.03	93
R	Inferior Occipital Gyrus	18	27	-90	-6	4.58	44
L	Fusiform Gyrus	37	-48	-57	-18	4.55	53
L	Fusiform Gyrus	18	-21	-93	-12	4.16	34
L	Inferior Occipital Gyrus	18	-27	-90	-3	4.06	
L	Inferior Occipital Gyrus	18	-30	-84	-12	3.31	
L	Thalamus	*	-9	-15	0	4.01	85
L	Putamen	*	-12	0	9	3.88	
R	Precuneus	31	30	-72	24	3.73	86
R	Precuneus	19	27	-72	33	3.62	
R	Angular Gyrus	39	30	-60	36	3.46	
L	Fusiform Gyrus	19	-39	-75	-12	3.52	12
L	Fusiform Gyrus	19	-39	-66	-12	3.43	
R	Precentral Gyrus	6	45	-9	30	3.44	29
R	Precentral Gyrus	6	57	-3	24	3.22	
R	Lingual Gyrus	18	9	-72	3	3.40	17
R	Cuneus	18	0	-75	6	3.31	

Supplemental Table 3: Haemodynamic responses (RP1 > RP2) calculated for Val/Met subjects (p<0,001 threshold, extended threshold 10 voxels, L left hemisphere, R right hemisphere, BA Brodmann area, * No BA has been found)

RP1 > RP2 (ValVal)							
Anatomical Label		**BA**	**X coor**	**Y coor**	**Z coor**	**t**	**size**
L	Precentral Gyrus	6	-45	0	27	5.51	351
L	Middle Frontal Gyrus	46	-42	18	24	4.71	
L	Middle Frontal Gyrus	46	-48	27	21	4.67	
L	Inferior Parietal Lobule	40	-42	-54	39	5.28	290
L	Precuneus	7	-24	-72	39	4.70	
L	Medial Frontal Gyrus	6	0	3	60	5.25	333
L	Superior Frontal Gyrus	8	-6	15	48	4.93	
R	Medial Frontal Gyrus	32	9	12	45	4.31	
L	Inferior Frontal Gyrus	47	-36	24	-3	4.67	98
L	Cuneus	18	-24	-93	0	4.64	26
L	Inferior Occipital Gyrus	18	-27	-90	-9	4.57	
L	Lentiform Nucleus	*	-18	6	12	4.50	53
L	Thalamus	*	-9	-9	18	3.89	
L	Thalamus	*	-9	-18	0	3.95	30
R	Inferior Frontal Gyrus	47	36	18	-6	3.84	14
R	Inferior Occipital Gyrus	18	27	-90	-9	3.84	16
R	Thalamus	*	21	-21	3	3.77	13

Supplemental Table 4: Haemodynamic responses (RP1 > RP2) calculated for Val/Val subjects (p<0,001 threshold, extended threshold 10 voxels, L left hemisphere, R right hemisphere, BA Brodmann area, * No BA has been found)

RP1 < RP2 (all genotypes)							
Anatomical Label		**BA**	**X coor**	**Y coor**	**Z coor**	**t**	**size**
L	Anterior Cingulate	24	-6	30	3	7,32	594
R	Medial Frontal Gyrus	10	6	42	-9	5,99	
L	Postcentral Gyrus	3	-33	-33	48	6,78	230
R	Inferior Parietal Lobule	40	57	-30	21	6,42	540
R	Middle Temporal Gyrus	39	51	-57	9	6,09	
R	Superior Temporal Gyrus	22	57	-54	18	5,00	
R	Superior Frontal Gyrus	9	18	51	24	5,13	69
L	Cingulate Gyrus	24	-15	-6	39	4,83	61
L	Caudate	*	-21	-3	30	4,20	
R	Precuneus	7	6	-57	36	4,62	185
R	Posterior Cingulate	31	9	-54	24	4,39	
L	Precuneus	7	-9	-57	45	3,83	
L	Sub-Gyral	21	-45	-9	-9	4,62	69
L	Superior Temporal Gyrus	22	-48	-9	3	3,57	
L	Insula	13	-39	-21	-6	3,48	
L	Insula	13	-45	-33	18	4,54	95
L	Superior Temporal Gyrus	42	-57	-30	15	4,01	
R	Middle Frontal Gyrus	9	24	27	30	4,06	44
L	Medial Frontal Gyrus	10	-9	60	9	4,02	29
L	Superior Frontal Gyrus	9	-9	54	21	3,68	

Supplemental Table 5: Haemodynamic responses calculated for RP1 < RP2 in all genotypes (p<0,001 threshold, extended threshold 10 voxels, L left hemisphere, R right hemisphere, BA Brodmann area, * No BA has been found).

RP1 < RP2 (MetMet)							
Anatomical Label		**BA**	**X coor**	**Y coor**	**Z coor**	**t**	**size**
L	Anterior Cingulate	24	-6	30	3	6,31	419
R	Anterior Cingulate	24	3	24	-6	6,11	
R	Medial Frontal Gyrus	10	6	42	-9	4,20	
R	Inferior Parietal Lobule	40	57	-33	24	4,29	68
L	Cingulate Gyrus	24	-15	-6	39	4,18	33
L		*	-21	-9	33	3,81	
L	Middle Temporal Gyrus	39	48	-60	12	4,05	45
R	Middle Frontal Gyrus	8	24	21	42	3,93	35
L		*	-21	21	21	3,88	10
R	Posterior Cingulate	31	9	-54	24	3,87	49
L		*	-21	6	27	3,67	13

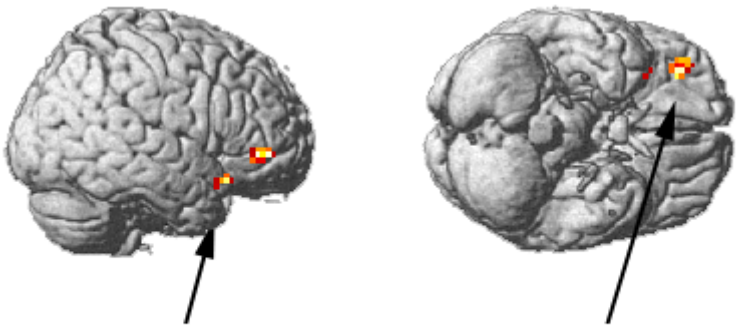
Supplemental Table 6: Haemodynamic responses calculated for RP1 < RP2 in Met/Met subjects (p<0,001 threshold, extended threshold 10 voxels, L left hemisphere, R right hemisphere, BA Brodmann area, * No BA has been found).

RP1 < RP2 (ValMet)							
Anatomical Label		**BA**	**X coor**	**Y coor**	**Z coor**	**t**	**size**
L	Inferior Parietal Lobule	40	-33	-33	42	5,39	137
L	Anterior Cingulate	24	-9	30	6	5,18	403
R	Anterior Cingulate	32	6	45	-6	4,91	
L	Medial Frontal Gyrus	10	-15	36	-3	4,69	
R	Inferior Parietal Lobule	40	57	-30	21	4,87	139
L	Insula	13	-45	-33	18	4,50	30
L	Caudate	*	-21	-3	30	4,25	34
R	Middle Temporal Gyrus	39	51	-57	9	4,03	105
R	Middle Temporal Gyrus	39	39	-57	9	3,86	
R	Middle Temporal Gyrus	37	39	-57	-3	3,42	
R	Superior Frontal Gyrus	9	15	51	24	3,98	20
L	Precuneus	7	-12	-54	45	3,94	23
R	Anterior Cingulate	32	24	30	18	3,43	10

Supplemental Table 7: Haemodynamic responses calculated for RP1 < RP2 in Val/Met subjects (p<0,001 threshold, extended threshold 10 voxels, L left hemisphere, R right hemisphere, BA Brodmann area, * No BA has been found).

RP1 < RP2 (ValVal)							
Anatomical Label		**BA**	**X coor**	**Y coor**	**Z coor**	**t**	**size**
L	Inferior Parietal Lobule	40	-36	-36	51	4,21	79

Supplemental Table 8: Haemodynamic responses calculated for RP1 < RP2 in Val/Val subjects (p<0,001 threshold, extended threshold 10 voxels, L left hemisphere, R right hemisphere; BA Brodmann area, * No BA has been found).



Supplemental Figure 1: BOLD responses calculated from positive interaction contrast (p<0,005 threshold, extended threshold 10 voxels)

BA 47	MetMet			ValMet			ValVal		
	RP1	*RP2*	*RP1-RP2*	*RP1*	*RP2*	*RP1-RP2*	*RP1*	*RP2*	*RP1-RP2*
mean average	0,00096924	-0,60733494	0,60830418	0,17578789	-0,34513944	0,52092733	-0,17112222	-0,14379378	-0,02732844
SD	0,71651339	0,76141864	0,67717344	0,61673267	0,85800668	0,62071311	0,75462878	0,84906471	0,73169554
	0,054717	-1,0609	1,115617	0,19323	-0,42257	0,6158	-0,62176	-1,678	1,05624
	-0,69682	-1,1424	0,44558	-0,56691	-1,2884	0,72149	0,14299	-0,030407	0,173397
	-0,04119	-1,1004	1,05921	1,3328	0,34783	0,98497	-0,12289	0,29896	-0,42185
	-1,1247	-0,8638	-0,2609	0,40915	-0,85489	1,26404	0,49707	-0,19498	0,69205
	-0,42751	-0,82177	0,39426	0,28826	-0,77731	1,06557	-0,16138	0,45254	-0,61392
	1,0212	0,058426	0,962774	0,57761	0,40534	0,17227	-0,066291	0,72259	-0,788881
	-0,052973	-4,115	4,062027	-0,38144	-0,17792	-0,20352	0,065601	0,72646	-0,660859
	1,1926	1,4544	-0,2618	-0,19569	-1,2968	1,10111	-0,87902	-0,30606	-0,57296
	-0,70653	-1,1422	0,43567	0,24345	-0,13862	0,38207	0,23174	0,41644	-0,1847
	-0,32378	-0,82088	0,4971	1,1317	0,19984	0,93186	-1,0498	-0,4369	-0,6129
	0,51483	-1,0557	1,57053	-0,61184	-2,0549	1,44306	0,48327	0,40446	0,07881
	0,45209	-0,42883	0,88092	-0,29413	-0,43549	0,14136	-0,48293	-0,65651	0,17358
	0,74126	0,86259	-0,12133	0,33062	-0,10133	0,43195	0,58456	-0,38979	0,97435
	-0,2356	-0,74565	0,51005	0,026332	0,92263	-0,896298	-0,46344	0,97589	-1,43933
	0,87514	-0,61403	1,48917	-0,76642	-0,71218	-0,05424	-0,39521	-0,65157	0,25636
	-0,71403	-0,59804	-0,11599	-0,26011	-1,4121	1,15199	1,5089	0,19125	1,31765
	-0,87307	-0,70791	-0,16516	0,63527	0,34626	0,28901	-1,9987	-2,4105	0,4118
	0,30787	-1,5976	1,90547	1,0723	1,2381	-0,1658	-0,35291	-0,022161	-0,330749

BA 10	MetMet			ValMet			ValVal		
	RP1	*RP2*	*RP1-RP2*	*RP1*	*RP2*	*RP1-RP2*	*RP1*	*RP2*	*RP1-RP2*
mean average	0,64763818	-0,02713665	0,67477483	0,62285383	0,45058833	0,1722655	0,07563333	0,25839111	-0,18275778
SD	0,64259004	0,67506855	0,83728854	0,8153449	1,18748767	0,97896758	0,71798396	0,80657162	0,74659557
	0,90715	0,17673	0,73042	0,76308	-1,3705	2,13358	0,34913	0,20528	0,14385
	0,63374	-0,53707	1,17081	-0,14523	-1,6257	1,48047	-1,2582	-0,8965	-0,3617
	-0,34434	0,0098269	-0,3541669	0,64367	0,99588	-0,35221	-0,35307	-0,53685	0,18378
	0,071289	0,43254	-0,361251	-0,97165	-2,3337	1,36205	-0,41639	-0,10459	-0,3118
	-0,2932	0,57625	-0,86945	0,73814	0,89701	-0,15887	0,20126	0,48306	-0,2818
	1,4403	-0,31057	1,75087	0,60584	0,82914	-0,2233	-0,48889	0,40954	-0,89843
	3,9428	-3,7168	7,6596	-0,42253	1,21	-1,63253	1,5849	1,1464	0,4385
	0,28901	0,21466	0,07435	0,70441	0,88998	-0,18557	0,40572	0,23935	0,16637
	0,24304	-1,7992	2,04224	0,56215	-0,18938	0,75153	0,52381	0,92495	-0,40114
	1,4038	0,46496	0,93884	1,0439	1,5224	-0,4785	-0,17515	2,1318	-2,30695
	-0,22615	-0,42378	0,19763	0,53992	-0,44638	0,9863	0,72336	0,51032	0,21304
	0,7056	-1,1145	1,8201	2,6534	1,866	0,7874	0,2388	-0,82876	1,06756
	0,83149	0,61791	0,21358	0,70426	0,1567	0,54756	-1,4025	-1,0078	-0,3947
	0,90882	0,03715	0,87167	0,46533	1,3321	-0,86677	0,34278	0,65089	-0,30811
	0,77891	-0,42783	1,20674	0,59271	1,3675	-0,77479	0,64726	0,96215	-0,31489
	0,43869	0,50325	-0,06456	-0,047031	0,76418	-0,811211	0,51691	-0,50286	1,01977
	1,4375	0,59581	0,84169	0,6607	0,88746	-0,22676	0,31326	0,48012	-0,16686
	1,7842	0,52254	1,26166	2,1203	1,3579	0,7624	-0,39159	0,38454	-0,77613

Supplemental Table 9: Calculated mean estimates for BA 47 and BA 10 for all subjects (excluded values are labelled in yellow, SD standard deviation)

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Ehrenerklärung

Ich erkläre, dass ich die der Medizinischen Fakultät der Otto-von-Guericke-Universität zur Promotion eingereichte Dissertation mit dem Titel

Genetic influences on long-term memory control – COMT and retrieval-induced forgetting

im Universitätsklinik für Neurologie

mit Unterstützung durch PhD Alan Richardson- Klavehn und
Dr. Maria Wimber

ohne sonstige Hilfe durchgeführt und bei der Abfassung der Dissertation keine anderen als die dort aufgeführten Hilfsmittel benutzt habe.

Bei der Abfassung der Dissertation sind Rechte Dritter nicht verletzt worden.

Ich habe diese Dissertation bisher an keiner in- oder ausländischen Hochschule zur Promotion eingereicht. Ich übertrage der Medizinischen Fakultät das Recht, weitere Kopien meiner Dissertation herzustellen und zu vertreiben.

Magdeburg, den

Franziska Wendler