Contextual memory in patients remitted from their first episode of depression: An fMRI study

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Background: **Memory problems are a well known symptom of major depressive disorder (MDD). Recollection of past experiences is thought to be more impaired than familiarity in MDD. We investigated whether these memory problems are still persistent in remission. Furthermore, we tried to delineate the neural correlates of memory processing in remission.** *Methods:* **13 remitted patients (non medicated, remitted from first episode) and 13 matched controls participated in a contextual memory task while lying in a fMRI scanner.** *Results:* **Behavioural performance did not differ between remitted patients and controls. We did find a difference between remitted patients and controls in brain activation during encoding.** *Conclusions:* **Although the sample size is small, there is striking evidence that MDD patients even when being in remission from their first episode already form declarative memories differently.**

1. Introduction

Major depressive disorder (MDD) is a common mental disorder affecting approximately 121 million people worldwide (Dutch lifetime prevalence is 15%, (Bijl, 1997)) Symptoms of MDD include memory problems. For instance, depressed patients report to have a memory bias towards negative, mood-congruent information (Williams, 1997). Also, patients tend to 'overgeneralize' their personal experiences (Williams, 1996), which means that they retrieve less specific and more general autobiographical memories following the presentation of a cue word than a matched control group would do (Mackinger, 2000).

Also reported are problems with contextual memory. This is a part of the declarative memory system which allows one to remember events embedded in a specific context. Sometimes, a distinction is made between items that are remembered with and without a specific context. This is best explained by an example. Sometimes you meet someone in the street and you know you have met the person before, but you cannot remember any specific feature of the where and when you met this person before. This is called familiarity based recognition. Some say familiarity based recognition and recollection are two separate processes (Mandler, 1980; Yonelinas, 2005). These dual-process models suggest that while recollection relies purely on episodic memory, familiarity is not necessarily based on this, since it is only based on a feeling of knowing. Others think they are part of the same process, lying on the same continuum (Haist, 1992). With respect to the brain regions mediating these processes, studies also diverge, in particular with respect to the engagement of the medial temporal lobe (MTL).

According to some studies, familiarity and recollection, is based on separated MTL structures. This distinction is shown in lesion studies, in which lesions often cause amnesia (Vargha-Kadem, 1997). Neuroimaging methods, like PET and fMRI, have made it possible not only to examine structural changes due to a disorder, but allow us to investigate brain processes in an organism under changing conditions. This results in a knowledge about functional activity which correlates with a certain disorder. One can also look at different conditions. In memory for instance, one can differentiate between the neural correlates of encoding or retrieval. Neuroimaging studies have tried to segment familiarity and recollection as well. Some report a qualitative distinction, in which familiarity could be associated with the perirhinal cortex, recollection with the hippocampus (for example Davachi, 2003, Ranganath 2004). Also, left prefrontal cortex would be associated with source (contextual) memory as well (Cansino, 2002). Another line of research, however, suggests that there is no division of labour within the MTL (Squire 2004 for review, Kirwan 2004, Gold 2006).

What is the relevance for MDD? In MDD, many brain regions that are normally involved in these memory processes are affected, right from the onset of the disease. The hippocampus is such a region, and it is reported to become smaller with repeated episodes of MDD (Sheline, 2003). There are several reasons for this shrinkage: neuronal loss through chronic hypercortisolemia, glial cell loss, stress-induced reduction in neurotrophic factors, stress-induced reduction in neurogenesis (Sheline, 2003). Also, the prefrontal cortex is impaired in depression. It is reported to be smaller and functionally different than in controls.

In MDD declarative memory is reported to be impaired. Recognition is intact, but recollection is impaired (Ilsley, 1995). According to Richard Davidson, these problems in MDD are very important in understanding and treating MDD. He thinks of MDD as a disorder in the context regulation of affect, which means that depressed patients show normative affective responses, but in an inappropriate context (Davidson, 2000). So, understanding the way in which depressed patients acquire new memories of particular contextual information, will help understanding the pathophysiology of the disorder. Note, that with respect to this question it seems particularly interesting to investigate patients being in remission from MDD, because this will help identifying the trait markers of the disease and eventually add to the question which brain regions are involved in the maintenance of the disease (given that MDD is highly recurrent).

Therefore, the main aim of this study is to examine declarative memory formation with and without contextual information in the form of a source memory paradigm in remitted MDD patients. These patients have recovered from their first episode of depression and receive no ongoing treatment. While suffering from depression, they were treated with SSRIs. These patients will be compared with matched normal control subjects on a source memory task which they will perform in a fMRI scanner. In this study we want to ask the

following questions.

1. First, are remitted patients behaviourally impaired in a source memory task investigating item based recognition and recollection of contextual information? This will answer the question whether memory problems in depression are state or trait related? Given the early stage of the disease, it may very well be the case that there are no behavioral differences. Yet, this does not mean that the underlying neural activity is not altered.

2. Hence, our second focus in this article will be on brain activity during encoding. Therefore we will investigate neural activity during declarative memory formation in the aforementioned source task and dissociate brain activity according to whether it is later remembered or forgotten (i.e subsequent memory effect). We will look at brain activity predicting retrieval of information with and without contextual information indexing that retrieval is either based on recollection or familiarity. Are these brain processes different for both groups? We hypothesize that remitted patients, due to MDD-related changes in the brain, will activate a compensatory network of brain regions to fulfil the task.

2. Methods

2.1 Study sample characteristics

13 remitted patients and 13 healthy controls (matched for gender, handedness, years of education and age) participated in the study (table 1). All remitted patients were recovered from their first episode of depression, for at least half a year. During their depressive episode they used selective serotonin reuptake inhibitors (SSRIs). At the time of this study, none of them was using any medication for at least one month (in case of fluoxetine, at least 2 months). Exclusion criteria for both groups were neurological illnesses, psychiatric illnesses (except a history of depression in case of the depressed patients), and the abuse of alcohol or drugs. Also, subjects had to meet the criteria for participating in an fMRI experiment (attachment 1). All subjects were paid for their participation and signed an informed consent form prior to their participation.

2.2 Experimental material and procedure

Stimuli included photographs of buildings and landscapes, presented in three colors (red, green and blue) in the study phase, and in grayscale in the test phase (previously used by Weis, 2004 and Takashima, 2006). Examples of stimuli are given in figure 1.

6 study-tests blocks (in total ~ 1 hour) were used in this study. Scanning took place during study and test phases. Each study phase consisted of 180 pictures (in each of the three colors) and each test phase consisted of the same 180 pictures (now in grayscale) randomly intermixed with 90 new pictures, that weren't presented during the study phase. The order of blocks was randomized over subjects. In both study and test phase, stimuli were intermixed with null events. During these null events, a fixation cross was presented on the screen. The subjects were asked to elaborately encode the picture in this time. These null events (15 during encoding, 23 during retrieval) were also used as a baseline in the fMRI analysis. For the study phase, right after this 'null event' three squares appeared on the computer screen, one in red, one in green and another in blue. Each of these squares corresponded to a button on the button box. Subjects had to indicate by button press in which color the picture they just encountered was presented. After each study session, a test session was presented to the subjects. In these test sessions, subjects had to indicate whether the pictures (now

Table 1 Study sample characteristics

	Remitted patients	Controls	Significance
Age	35,231	34,538	NS
Gender	5 male / 8 female	5 male / 8 female	NS
Education	14,846	15,538	NS
ZBV State	29,182	36,385	0,021
ZBV Trait	29,545	42,462	0,001
HDRS	0,615	3,615	0,000

ZBV State = Zelfbeoordelingsvragenlijst 'State', ZBV Trait = Zelfbeoordelingsvragenlijst 'Trait', HDRS = Hamilton Depression Rating Scale.

presented in grayscale) were familiar or not. If not, subjects had to press a button on another button box held in the other hand. If they did recognize the picture, they were asked to immediately indicate what color the picture was presented in (the so-called source), on the same button box they used in the study phase. This resulted in four possible answers: three for recognized pictures (old-red, old-green and old-blue), and one for new pictures (new). Button presses were counterbalanced across subjects. This was done by varying the hand with which the 'color' response had to be given from left to right.

2.3 Behavioral data analysis

Responses were sorted in 5 categories: 1) colorhit, 2) colorfalse, 3) miss, 4) false alarm and 5) correct rejection.

For the old items, the categories were 'colorhit' (correctly identified old item + correct context), 'colorfalse' (correctly identified old item without context) and 'miss' (old items incorrectly identified as new). For the new pictures, there were two categories: 'correct rejection' (new item correctly identified as new) and 'false alarm' (new item incorrectly identified as old). For all categories, the number of responses was calculated as well as the reaction times. Furthermore, a relative percentage hits minus false alarms and a relative source memory percentage was drawn up from the data. For all subjects, d prime was calculated as well, to see whether subjects performed above chance level. Subjects from both groups were compared with regard to these statistics in separate ANOVAs.

2.4 Questionnaires

Before participation, subjects were interviewed. Questions were asked regarding their psychiatric history and severity of depression (only for patients). Additionally, questionnaires were applied to examine the psychopathological status during the participation in the study. Questionnaires that were used were the mini international neuropsychiatric interview (MINI, Dutch version: cognitive mental status), Hamilton depression rating scale (HDRS, depression severity), Beck's depression inventory (BDI, depression index), ZBV (Zelfbeoordelingsvragenlijst state and trait anxiety), Questionnaire life events and a questionnaire to assess handedness. Relevant outcomes can be found in table 1.

2.5 (f)MRI data acquisition

A 1.5 Tesla Siemens Sonata MRI scanner was used in this study. We used standard gradients and a circular polarized phase array head coil to obtain T1-weighted anatomical volume images and twelve series of T2*-weighted echo planar images (EPIs). Each EPI volume consisted of 33 transversal slices which were 3 mm thick, a repetition time of 2.290 seconds and an echo time of 30 ms (slice matrix = 64 x 64; voxel size = 3 x 3 x 3 mm3; 90 degrees flip angle; slice gap 0.5 mm; field of view 224 mm). For structural MRI, we acquired a T1-weighted MP-RAGE sequence (volume TR = 2250 ms, TE = 3.93 ms, 15 degrees flip angle, 176 saggital slices, slice matrix 256 x 256, slice thickness = 1 mm, no gap, field of view = 256 mm). The six study phases consisted of about 105-125 volumes each, and the test phase of about 110-130 images each.

2.6 fMRI data analysis

All fMRI data was analyzed using SPM5 (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm). The first five volumes of each session were discarded to avoid T1 equilibration effects in the data. For each session, the volumes were realigned to the first image. The structural image then was coregistered with the mean realigned volume acquired in the realignment process. All images were slice time corrected. Each volume was normalized using a standard T1 template. Images were smoothed with an 8 mm full-width half maximum isotropic Gaussian kernel. fMRI data were statistically analyzed using the general linear model (GLM). The explanatory variables were temporally convolved with the canonical hemodynamic response function and its temporal derivative. Also, a high pass filter was applied to filter out low frequency components. Then, contrast images were created for each subject individually. These images were analyzed in a second level analysis for both groups and between groups analyses of conditions and contrasts were done.

We investigated the so-called subsequent memory effect or difference due to memory effect, where the focus is on brain activity at encoding whih predicts successful (source) memory formation. The conditions of interest (all for encoding) were source, item and miss. The contrasts of interest (all for encoding) were source vs miss, item vs miss, overall hits vs miss, source vs item.

Table 2 Behavioral data

	Remitted patients	Controls	p-value
D prime	1.268	1.717	0.070
Hits – False Alarms	41.483	54.701	0.074
Percentage source memory	53.222	58.466	0.330

Our analysis strategy was to first conduct a whole brain analysis to get an overall impression over significant results and subsequently conduct a regions of interest analysis when necessary. In this whole brain analysis, results were threshold at p = 0.01 and the cluster-size statistic was used as the test statistic. Only clusters significant at p < 0.05 (corrected for multiple non-independent comparisons) are reported. This exploratory analysis was taken as a confirmation of MTL activations as found previously. Given our regional specific hypothesis regarding involvement of the MTL, a region of interest (ROI) was defined separately for left and right MTL including the hippocampus and surrounding cortex (i.e., BA 26/28/29/30/34-37) using the WFU Pick Atlas toolbox for SPM, which provides a method for generating ROI masks based on the Talairach Daemon database (Maldjian et al., 2003). Local maximum test statistics were employed in this ROI analysis and all reported p-values were corrected for multiple non-independant comparisons based on the family-wise error correction (Friston et al., 1996).

3. Results

3.1 Behavior

Behavioral results are displayed in table 2. All p-values were considered significant if smaller than 0.05. D prime was calculated and did not differ between the remitted patients and controls. Also, the percentage of false alarms was subtracted from the percentage of hits. This measure also did not differ between groups. The percentage of colorhits divided by the total amount of hits (source memory) didn't differ either.

The reaction times of all possible answers did not differ between groups (p=0.246). Within groups, there was a significant difference in reaction times (p=0.000, see figure 2), whereby colorfalse judgments took the longest, correct rejections shortest. Thus, any difference between the groups in functional activation could not simply be related to global psychomotor slowing.

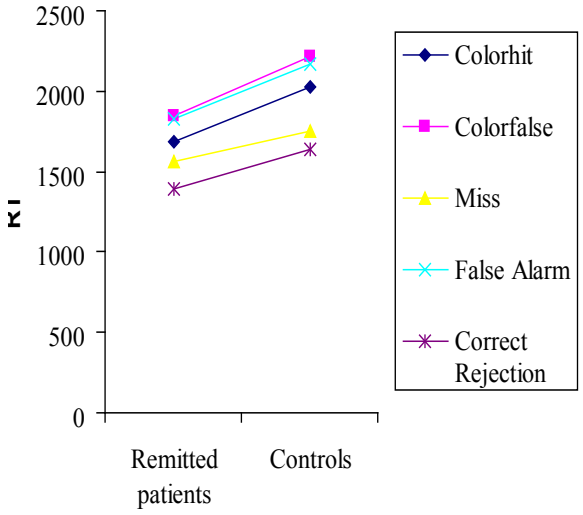


Figure 2 Reaction Times

3.2 fMRI results

First, single conditions are reported, to show principle group differences. Then, memory conditions are reported in order to investigate differences between groups. Results are displayed in table 3-4 and in figures 3-5.

3.3 Results conditions:

All results were obtained within a region of interested based on the Brodmann areas that were activated in the overall analysis (p<0.01). There was a significant between group contrast for the encoding of source information with more activity in the left IFG (see figure 3), anterior cingulate and operculum for controls and more activity in the parahippocampal gyrus (see figure 5) for remitted patients. For the encoding of item information, no significant results were found.

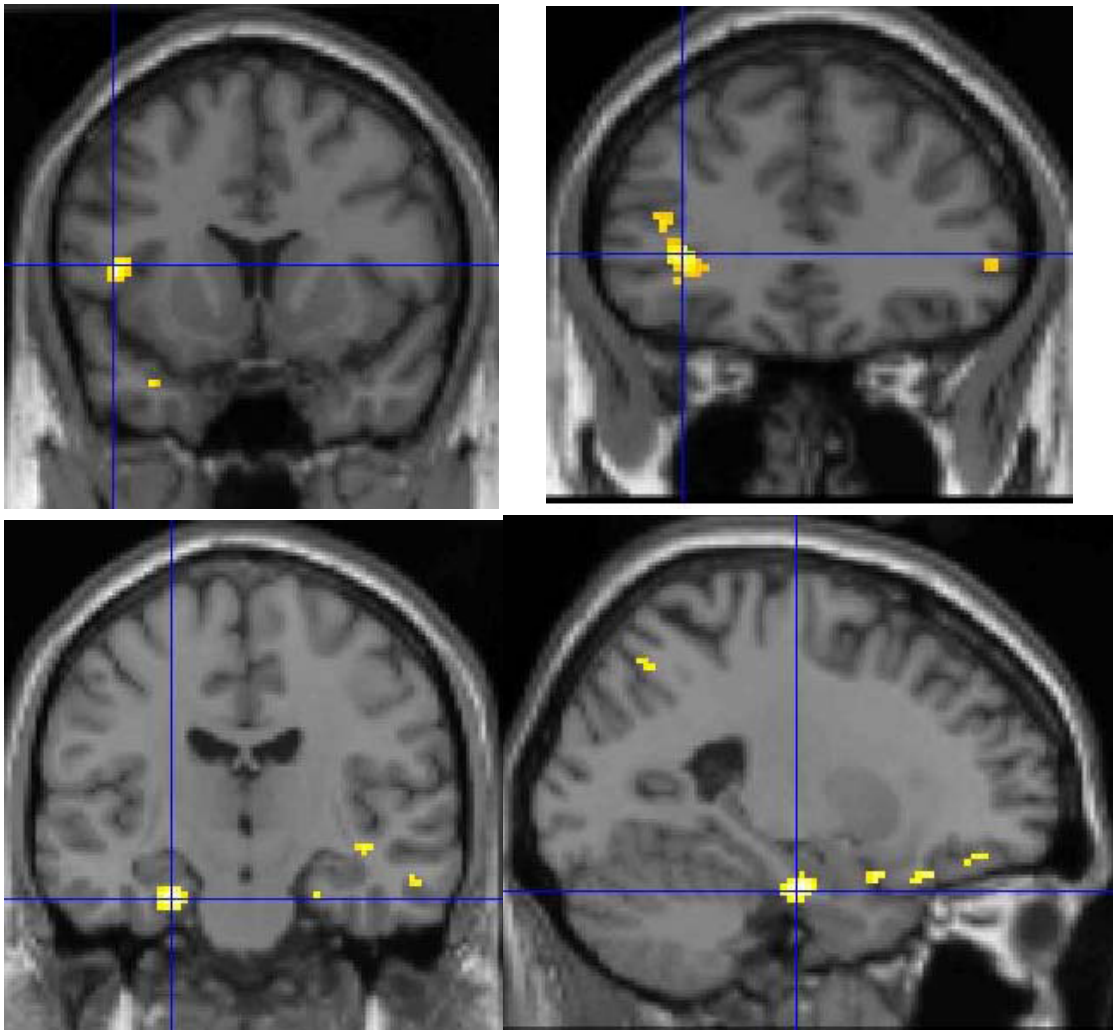
3.4 Results contrasts:

Overall remembered versus forgotten items was associated with a larger activation of the

Table 3 fMRI results encoding (single conditions)

		Structure	Coordinates			p-value
			x	y	z	
Colorhit (source)	c > r	L IFG	-46	12	10	0.055
		Anterior cingulate	-2	8	8	0.047
		Operculum	-30	-28	18	0.008
	r > c	Parahippocampal gyrus	-24	-26	-26	0.043
Colorfalse (item)	c > r	*				
	r > c	*				

IFG = inferior frontal gyrus. * = no relevant result
c > r – results where functional activations were bigger for controls than for patients
r > c – results where functional activations were bigger for patients than for controls



Examples of local maxima (as indicated in the results section) are shown superimposed on selected coronal slices of the mean high-resolution T1-weighted volume. All activated clusters were at least five voxels in size and significant at the cluster level (p(corrected) < 0.05)

Figure 3 Colorhit controls vs remitted patients: Regions activated more during encoding for later remembered items with context than later forgotten items.

Figure 4 Overall hits vs misses remitted patients vs controls: Regions activated more during encoding for later remembered items than later forgotten items.

Figure 5 Colorhit remitted patients vs controls: Regions activated more during encoding for later remembered items with context than later forgotten items.

Table 4 fMRI results encoding (contrasts)

		Structure	Coordinates			p-value
			x	y	z	
Colorhit vs miss	c > r	*				
	r > c	R MTG	62	-20	-10	0.006
		R MTG	54	-46	-6	0.049
Colorfalse vs miss	c > r	L rectal gyrus	10	38	-18	0.065
	r > c	L IFG	-34	34	4	0.020
		R IFG	40	4	24	0.064
		R MTG	60	-22	-8	0.009
		R MTG	66	-48	-2	0.042
		R SFG	18	52	-2	0.061
		L precuneus	0	-60	34	0.032
Overall hits vs miss	c > r	*				
	r > c	L IFG	-34	34	4	0.040
		R MTG	62	-22	-10	0.005
Colorhit vs colorfalse	c > r	L STG	-46	-40	14	0.003
		L MTG	-44	-60	8	0.005
		L cuneus	-10	-66	24	0.014
		L SMG	-2	38	52	0.029
		R IFG	42	22	30	0.054
	r > c	*				

IFG = inferior frontal gyrus, MTG = medial temporal gyrus, SFG = superior frontal gyrus, SMG = superior medial gyrus, STG = superior temporal gyrus. * = no relevant result.

anterior cingulate in controls, and the left IFG and right MTG in remitted patients (see figure 4). When comparing source with item encoding, the remitted patients did not show more activation in comparison with the controls, while the controls revealed more activation of the left SMG, left and right IFG, left cuneus and left MTG.

When encoding of source memory is contrasted with later forgotten items, only remitted patients show a significantly active area, the right MTG. When encoding of item memory is contrasted with later forgotten items, controls reval a bigger activation in the rectal gyrus whereas the remitted patients show more activation in the left and right IFG, the right MTG, the right SFG and the left precuneus.

4. Discussion

The aim of the present study was to investigate the neural correlates of declarative memory formation with and without context in MDD patients being in remission compared to matched controls. In particular, we aimed at answering the following questions: First, are remitted patients behaviourally impaired in a source memory task investigating item based recognition and recollection of contextual information? Second, are brain processes at encoding of item/source information the same for both groups or are there any indices for an altered brain activity in MDD patients even when they are in remission?

First of all, a note has to be made regarding the interviews. Remitted patients and controls differ in their scores on the ZBV State, ZBV Trait and the HDRS. This means that they are more anxious while being a subject for this study, but also they have reported to be more anxious than matched controls regarding their personality. Hence, their anxiety seems not to be related to the scanning procedure but may have to do with the fact that MDD patients have higher anxiety levels even when being in remission (Kendler, 2003). Though there was a difference in the Hamilton rating scale between the groups, our patients did not exceed the threshold of 8 and hence were not actually

depressed but show slight mood differences. The HDRS mean score of the remitted patients was 3.75 (range 1-8).

Remitted patients (matched for age, gender, education and handedness with controls) didn't display any behavioural differences from controls and both groups differed significantly from chance even for the source memory task.

This finding is in line with previous research (Gallassi, 2006), which states that remitted patients are improved in memory tasks. In their study, Gallassi et al. investigated 48 depressed patients before and six months after medication (fluoxetine and reboxetine). After six months 33 'remitters' and 9 'non-responders' were left (6 drop-outs). Before medication, all patients performed worse than normal controls on the Wechsler memory scale and other memory tasks. The remitted patients significantly improved after six months on the Wechsler memory scale and other memory tasks, but they still differed from controls on effortful tasks (logical memory, associate verbal learning, autobiographical memory).

The results suggest a state, but also a trait component of memory problems in MDD. This trait marker of MDD concerns effortful tasks.

Our study even suggests that in the early course of the disease, there are no behavioural indications of a declarative memory deficit being a trait marker of the disease. However, this does not necessarily mean that there are no differences at all, just that it did not exceed certain threshold. But we would actually argue, that if at all a declarative memory deficit should be evident even after a first episode, it should be rather subtle and may only be detectable in a larger cohort.

Another study argues (Weiland-Fiedler, 2004) that subjects, which were remitted from depression would still have neuropsychological problems, although they are not depressed anymore. In this study, 28 remitted patients with past recurrent episodes of depression performed on tasks of the Cambridge Automated Neuropsychological Test Battery and the California Verbal Learning Test. The remitted patients performed worse than controls on sustained attention, suggesting this could be a trait marker for depression. They didn' t differ from controls on short-term verbal learning or longterm verbal memory suggesting intact hippocampal functioning in these remitted patients. This study also suggests a state component of memory for MDD, just like ours.

Most important, with respect to the aims of the study, we found significant different functional activations in patients and in controls. These differences did not consist of either a hyper-or hypoactivation in the patient group but resulted in both, depending on the brain region.

When investigating the single conditions, the main findings were:

1. no difference between remitted patients and controls could be found in the item memory encoding condition. This is as expected, because item memory is reported to be unaffected in MDD (Ilsley, 1995).

2.When investigating source memory, a difference between the two groups can be found. Controls are found to activate for instance the left inferior frontal gyrus, anterior cingulate and operculum more than remitted patients. The left inferior frontal gyrus and the anterior cingulate are reported to be involved in source memory encoding (Cansino, 2002; Gould, 2006).

Remitted patients report to activate the parahippocampal gyrus more than controls. The parahippocampal gyrus is also believed to be involved in source memory encoding (Brown and Aggleton, 2001). This activity in remitted patients could mean that remitted patients have to activate this region more than controls, in order to perform the same on the task.

When investigating the contrasts:

1. Controls do not activate more regions than remitted patients in the overall hits vs miss contrast. Remitted patients activate the left IFG and the right MTG more than controls. The left IFG and right MTG are involved in source memory encoding (Tsukiura, 2002), which could mean that remitted patients hyperactivate these regions in order to perform the same as controls.

2. Controls activate the left STG, left MTG, left cuneus, left SMG and right IFG more than remitted patients in the source vs item contrast. Remitted patients activate nothing more in this. This suggests that there is a larger activation for controls only in the contrast that is most related to the specific successful encoding of source information.

3. Remitted patients show more activity than controls in the colorhit vs miss contrast. Vice versa this is not the case. Remitted patients show more activations in the right medial temporal gyrus, which is already mentioned in the overall hits vs miss contrast. This difference is thus due to source encoding.

4. Regarding item memory, remitted patients activated regions including the left and right IFG,

the right MTG, right SFG and the left precuneus relatively.

a. The left and right IFG are known to be involved in successful memory encoding (Gabrieli, 1998; Uncapher, 2005). Remitted patients might need to hyper activate this region in order to successfully encode item information.

b. The precuneus is reported to be involved in the encoding of spatial locations (Frings, 2006; Wallentin, 2006), which fits well with the processing of the stimuli used here. Hence our data suggest, that in order to come up with the same behavioral result, a larger activations of posterior regions is needed.

c. The right SFG is thought to be associated with monitoring and ordering of episodic information particularly during retrieval (Henson, 1999).

To conclude, if memory problems in depression are indeed trait related, they can be considered to be a permanent biological marker for depression, which may even be thought of in terms of representing an endophenotype, i.e. an internal phenotype that fills the gap between genes and depression (Hasler, 2004). In this study, the difference between remitted patients and controls was too small to become significant, but remitted patients did score lower on memory performance than controls. Of course , we have to take into account that the size of our group was still rather small so that any conclusions are only preliminary. Indeed, we are currently busy increasing our sample size. Yet, there is striking evidence that MDD patients even when being in remission from their first episode already form declarative memories differently. It is still to preliminary to associate this difference to particular brain regions, but this should be the focus of future studies.

References

Bijl R.V., Van Zessen G., Ravelli A. (1997). *Psychiatrische morbiditeit onder volwassenen in Nederland: Het NEMESIS-onderzoek.II. Prevalentie van psychiatrische stoornissen.* Ned Tijdschr Geneeskunde 141: 2453-60.

Bremner, J.D., Vythilingam, M., Vermetten, E., Nazeer, A., Adil, J., Khan, S., Staib, L., Charbey, D.S. (2002). *Reduced volume of orbitofrontal cortex in major depression.* Biol.Psychiatry Vol.51 Issue 4, 15 February 2002, 273-279.

Brown, M.W., Aggleton, J.P. (2001). *Recognition memory: what are the roles of the perirhinal cortex and hippocampus?* Nat Rev Neurosci. 2001 Jan;2(1):51-61.

Cansino, S., Maquet, P., Dolan, R.J., Rugg, M.D. (2002). *Brain activity underlying encoding and retrieval of source memory.* Cereb Cortex. 2002 Oct;12(10):1048-56.

Davachi L., Mitchell J.P., Wagner A.D. (2003). *Multiple routes to memory: distinct medial temporal lobe processes build item and source memories.* Proc Natl Acad Sci U S A. 2003 Feb 18;100(4):2157-62.

Davidson R.J., Jackson D.C., Kalin N.H. (2000). *Emotion, plasticity, context, and regulation: perspectives from affective neuroscience.* Psychol Bull. 2000 Nov;126(6):890-909.

Frings L., Wagner K., Quiske A., Schwarzwald R., Spreer J., Halsband U., Schulze-Bonhage A. (2006). *Precuneus is involved in allocentric spatial location encoding and recognition.* Exp Brain Res. 2006 Sep;173(4):661-72. Epub 2006 Mar 9.

Friston K.J., Holmes A., Poline J.B., Price C.J., Frith C.D. (1996). *Detecting activations in PET and fMRI: levels of inference and power.* Neuroimage. 1996 Dec;4(3 Pt 1):223-35.

Gabrieli J.D., Brewer J.B., Poldrack R.A. (1998). *Images of medial temporal lobe functions in human learning and memory.* Neurobiol Learn Mem. 1998 Jul-Sep;70(1-2):275-83.

Gallassi R., Di Sarro R., Morreale A., Amore M. (2006). *Memory impairment in patients with late-onset major depression: the effect of antidepressant therapy.* J Affect Disord. 2006 Apr;91(2-3):243-50.

Gold J.J., Smith C.N., Bayley P.J., Shrager Y., Brewer J.B., Stark C.E., Hopkins R.O., Squire L.R. (2006). *Item memory, source memory, and the medial temporal lobe: concordant findings from fMRI and memory-impaired patients.* Proc Natl Acad Sci U S A. 2006 Jun 13;103(24):9351-6.

Gould, R.L., Brown, R.G., Owen, A.M., Bullmore, E.T., Williams S.C., Howard R.J. (2006). *Functional neuroanatomy of successful paired associate learning in Alzheimer's disease.* Am J Psychiatry. 2005 Nov;162(11):2049-60.

Haist, F., Shimamura, A.P., Squire, L.R. (1992). *On the Relationship Between Recall and Recognition Memory.* Journal of Experimental Psychology: Learning, Memory, and Cognition 1992. Vol. 18. No. 4. 691-702.

Hasler, G., Drevets W.C., Manji H.K., Charney D.S. (2004). *Discovering endophenotypes for major depression.* Neuropsychopharmacology 2004 Oct;29(10):1765-81.

Henson, R.N.A., Shallice, T., and Dolan, R.J. (1999). *Right prefrontal cortex and episodic memory retrieval: a functional fMRI test of the monitoring hypothesis.* Brain 122, 1367–1381.

Ilsley JE, Moffoot AP, O'Carroll RE. (1995). *An analysis of memory dysfunction in major depression.* J Affect Disord. 1995 Oct 9;35(1-2):1-9.

Kendler, K.S., Hettema, J.M., Butera, F., Gardner, C.O., Prescott, C.A. (2003). *Life event dimensions of loss, humiliation, entrapment, and danger in the*

prediction of onsets of major depression and generalized anxiety. Arch Gen Psychiatry. 2003;60:789-796.

Kirwan, C.B., Stark, C.E.L. (2004). *Medial temporal lobe activation during encoding and retrieval of novel face-name pairs.* Hippocampus 14:919-930.

Mackinger, H.F., Leibetseder, M.M., Pachinger, M.M., Fartacek, R.R., (2000). *Autobiographical memories in women remitted from major depression.* Journal of Abnormal Psychology 2000, Vol. 109, No. 2, 331-334.

Maldijan J.A., Laurienti P.J., Kraft R.A., Burdette J.H. *An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets.* Neuroimage. 2003 Jul;19(3):1233-9.

Mandler, G., (1980). Recognizing: The judgment of previous occurrence. *Psychological Review, 87,* 252-271.

Ranganath, C., Yonelinas A.P., Cohen M.X., Dy C.J., Tom S.M., D'Esposito M. (2004). *Dissociable correlates of recollection and familiarity within the medial temporal lobes.* Neuropsychologia. 2004;42(1):2-13.

Sheline Y.I., Gado M.H., Kraemer H.C. (2003). *Untreated depression and hippocampal volume loss.* Am J Psychiatry. 2003 Aug;160(8):1516-8.

Squire, L.R., Stark C.E., Clark R.E. (2004). *The medial temporal lobe.* Annu Rev Neurosci. 2004;27:279-306.

Tsukiura, T., Fujii, T., Takahashi, T., Xiao, R., Sugiura, M., Okuda, J., Iijima, T., Yamadori, A. (2002). *Medial Temporal Lobe Activation During Context-Dependent Relational Processes in Episodic Retrieval: An fMRI Study.* Human Brain Mapping 17:203–213(2002).

Uncapher M.R., Rugg M.D. (2005). *Encoding and the durability of episodic memory: a functional magnetic resonance imaging study.* J Neurosci. 2005 Aug 3;25(31):7260-7.

Vargha-Kadem, F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M. (1997). *Differential effects of early hippocampal pathology on episodic and semantic memory.* Science. 1997 Jul 18;277(5324):376-80.

Wallentin M., Roepstorff A., Glover R., Burgess N. (2006). *Parallel memory systems for talking about location and age in precuneus, caudate and Broca's region.* Neuroimage. 2006 Oct 1;32(4):1850-64.

Weiland-Fiedler P., Erickson K., Waldeck T., Luckenbaugh D.A., Pike D., Bonne O., Charney D.S., Neumeister A. (2004). *Evidence for continuing neuropsychological impairments in depression.* J Affect Disord. 2004 Oct 15;82(2):253-8.

Williams, J.M.G., (1997). *Cognitive psychology and emotional disorders.* Chichester, England: Wiley.

Williams, J.M.G., (1996). *Depression and the specificity of autobiographical memory.* In D. C. Rubin (Ed.),Remembering our past. Studies in autobiographical memory (pp. 244-267). Cambridge, England: Cambridge University Press.

Yonelinas, A.P., Otten, L.J., Shaw, K.N., Rugg, M.D. **(2005).** *Separating the Brain Regions Involved in Recollection and Familiarity in Recognition Memory.* **The** Journal of Neuroscience, March 16, 2005, 25(11):3002-3008.