Paper III

Increased parietal and frontal activation after remission from recurrent major depression: A repeated fMRI study

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Short title: Two-year fMRI follow-up of depressed patients

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Abstract

Nine patients with unipolar major depression were scanned with MRI twice over a two-year period, and compared with twelve healthy control subjects. All patients fulfilled criteria for major depressive disorder, recurrent type, at first scanning. Level of depressive psychopathology was assessed by the Hamilton Depression Rating Scale. The participants had to work on a mental arithmetics/working memory task while in the MR scanner. The task consisted of single digits (1 to 9) that were shown to the participant, who had to add the numbers in successive pairs and press a response button when the sum was 10. Neuronal activation was recorded based on the BOLD contrast phenomenon in a functional MRI protocol. The results showed significant increase in activation for the patients in the inferior frontal gyrus and the superior and inferior parietal lobule at the second compared with the first MR scanning session. There were also significant correlations between the HDRS scores and neuronal activation which showed a negative correlation particularly in the inferior frontal and parietal lobe areas, which overlapped with similar areas activated in the healthy control participants. This may indicate normalization of brain activation in depressed patients as a function of time from an illness phase to a remission / recovery state.

Introduction

Major depression is the most common psychiatric disorder and lifetime prevalence has been estimated to between 15-17 % (Angst, 1992; Kessler, McGonagle, Zhao, & et, 1994; Mintz, Mintz, & Arruda, 1992, Kringlen, Torgersen & Cramer, 2001). It is estimated that at any time 5% of the population suffers from depression (Murphy, Laird, Monson, Sobol, & Leighton, 2000). In addition to the major symptoms of depression, recent neuropsychological studies have revealed that patients diagnosed with major depression frequently show cognitive deficits (see (Shenal, Harrison, & Demaree, 2003)). These deficits seem to involve many key cognitive functions and processes, such as attention, memory, language, and executive functions(Den Hartog, Derix, Van Bemmel, Kremer, & Jolles, 2003; Elliott, 1998; Landrø et al., 2001; Veiel, 1997; Zakzanis, Leach, & Kaplan, 1999) (Burt et al. 1995; Goodwin, 1997; Beats et al., 1996; Purcell et al., 1997; Murphy et al, 2001, Grant et al., 2001), also including cognitive effort (Hartlage, Alloy, Vazquez, & Dykman, 1993; Hasher & Zacks, 1979) and increasing cognitive load (Veiel, 1997; Zakzanis et al., 1999; Austin et al., 2001).

It has also been reported that depressed patients show changes in brain function both in resting state (Liotti & Mayberg, 2001; Mayberg, 2002), and in response to cognitive challenges or neuropsychological tests (Beauregard et al., 1998; Elliott, 1998; Elliott & Dolan, 2002; Merriam, Thase, Haas, Keshavan, & Sweeney, 1999). The brain imaging literature has revealed altered neuronal activation in the prefrontal cortex, insula and anterior/posterior cingulate (Bench, Friston, Brown, Frackowiak, & Dolan, 1993; Bench et al., 1992; Dolan, Bench, Brown, Scott, & Frackowiak, 1994; Drevets et al., 1992; Hugdahl et al., 2004; Menon, Anagnoson, Mathalon, Glover, & Pfefferbaum, 2001), which are areas involved in attention, working memory and executive functions.

Most PET and fMRI studies, with a few exceptions (Mayberg et al., 2000; Mayberg et al., 1999) have been cross-sectional in nature, providing a snap-shot view into neuronal correlates of depression. No study has investigated brain activation in response to cognitive challenges in depressed patients over time, as correlates of clinical improvement. It could be hypothesized that neuronal activation in brain areas implicated in depression would be normalized as patients recover clinically. The opposite hypothesis could however also be possible, namely that clinical improvement is dependent on normalization of blood perfusion and activation in critical brain areas. In this study, we used functional magnetic imaging (fMRI) measuring BOLD contrast to investigate depressed patients with a time span of two years between the scanning sessions.

We chose a simple mental arithmetic task (see Hugdahl et al., 2004) with adding numbers as the cognitive challenge while the patients were scanned. The reason for this is that mental arithmetic is a task that captures both key aspects of attention, working memory and executive functions in the same task, and at the same time it is a very basic everyday task that has high ecological validity. In addition, it is a task that carries with it a layman notion of effortfulness and cognitive difficulty, two critical aspects of cognitive impairment in depression (Hammar, Lund, & Hugdahl, 2003a, 2003b; Hammar, 2003; Hartlage et al., 1993; Hasher & Zacks, 1979). Interestingly, despite the importance of the ability to perform simple number calculations in everyday life, this basic cognitive function has not been the target for neurocognitive or brain activation studies of psychiatric disorders. To our knowledge, there has not been a longitudinal study comparing both clinical and brain activation changes over a two-year period.

Methods

Participants

Nine patients with recurrent non-psychotic unipolar major depression (mean age 36 years at the first MR scanning) and 12 healthy control participants (mean age 31 years) were included in the study. Mean education was 14.33 years (SD 2,87) in the depressed group, and 15.00 years (SD 3.02) in the control group. There were 5 females and 4 males in the depressed group and 7 females and 5 males in the control group. The patients were out- or inpatients recruited for research purposes from four psychiatric clinics in the Bergen and Oslo areas in Norway. Mean lifetime duration of illness at the time of the second MR scanning was 17.43 years (SD 8.10). The patients were on different types of medication including SSRIs, mianserin, nefazodone, venlafaxine or moclobemide. None of the patients were on tricyclic antidepressant medication. Total lifetime duration of antidepressant treatment was 17.86 months (SD 12.59).

General intellectual abilities (IQ) were assessed at the first MR scanning using the Similarities and Picture Completion from the Wechsler Adult Intelligence Scale (WAIS-R (Wechsler, 1981). Mean raw score for the Picture Completion sub-test was 14.78 (SD 3.49), and 18.33 (SD 6.10) for the Similarities sub-test. The patients were scanned twice with a mean interval of 25.10 months (SD 4.86) between the first and second scan. The control subjects were scanned once, at about the same time as the first patient scanning.

Patients with alcohol or drug abuse as primary diagnosis, somatic disorders, recent ECT treatment or patients that had major hearing or vision difficulties, were excluded from the study, as were patients with schizoaffective and bipolar disorder. Present or past history of psychiatric disorder, or having been treated for alcohol or drug abuse were

reasons for being excluded from the control group. Participants in both groups were excluded if they had a history of neurological disorder.

The initial diagnostic interviews were conducted by clinically experienced psychiatrists and consisted of collection of relevant clinical and demographic information, including current and past medication. The Structured Clinical Interview (SCID I, Norwegian version 2.0, 1995) for DSM-IV Axis I Disorders was used. Severity of depression was measured by Hamilton Depression Rating Scale (HDRS), 17-items (Hamilton, 1960). To be included in the depression group at the first MR scanning, all participants had to score a minimum 18 points on the HDRS, reflecting a moderate to severe depression. Mean HDRS score at the first MR scanning was 23.88 (SD 3.27), and at the second MR scanning 13.00 (SD 5.87), reflecting that the patients were in remession or totally remitted/recovered at the second scanning. The mean HDRS score reduction from the first to the second MR scanning was 45.56%, which was statistically significant with the Mann-Whitney U-test, two-tailed, $p < .001$. All patients were on medication at the first scanning, while eight patients received medication treatment at the second MR session. This may have affected the results, and medication control should be built into future studies.

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Stimuli and procedures

The stimuli were the numbers "1" through "9" that were presented on a LCD-screen mounted in special goggles (Magnetic Resonance Technology Inc.) that the subjects wore during the MR scanning.[1]There were 16 trials with digit stimuli presented during each ON block, thus the total number of trials was 48. Each digit stimulus was

[1] The paradigm included three runs with different instructions. Only data from the third run are presented. Data from all three runs, comparing different patient groups have previously been presented (Hugdahl et al., 2004; Landrø et al., 2001).

presented for 300 ms, with 2200 ms blank interstimulus intervals (ISIs) in between. Each ON block lasted 120 sec, followed by a 60 sec OFF block. The ON and OFF blocks were, thus, alternated within a run. The digit stimuli were presented with the Micro Electronic Laboratory (MEL2) software (Psychology Software Tools Inc.). The OFF blocks consisted of resting with no stimulus presentations. A response button was placed on the participant's chest and he/she was instructed to press the button according to the specific instructions for each run.The participants were instructed to "add each consecutive number to the previous one, and press the button whenever the sum was 10". The MEL software recorded both response accuracy and response time. There were 6 presentations where the sum was "10" among the 16 trials for each ON block. Thus, the total number of target presentations, across the three ON blocks, was 18.

MR-scanning

Functional MR images were acquired using a 1.5 Tesla Siemens Vision MRI system. The slices for the functional imaging were positioned parallel to the AC-PC line, with reference to a high-resolution anatomical image of the entire brain, obtained by using a strongly T1-weighted FLASH sequence. The parameters for the anatomical sequence were as follows: TR 22ms, TE 6ms, 30^{o} flip angle, one excitation per phase encoding step, FOV 256 mm, 256×256 matrix, 128 sagittal slices with 1 x 2 mm in-plane pixel size and with 1.41 mm single slice thickness. For functional imaging, 100 images were acquired; each contained 40 axial slices, which were oriented in the anterior-posterior commissure (AC-PC) plane, covering the whole brain and most of the cerebellum. The parameters of the functional EPI sequence were as follows: gradient echo EPI, TR 6.0s, TE 60ms, 90^{o} flip angle, FOV 220×220 mm^2, 64 × 64 matrix. This resulted in a voxel size of 3.44×3.44×3 mm^3 in an ascending slice order. For reaching maximum signal

equilibrium, the first ten images of each session were rejected in the subsequent analysis.

fMRI data preprocessing and statistical analysis

The functional images were realigned, coregistered with the anatomical scan and normalized into the stereotactical MNI reference space using SPM99 (http://www.fil.ion.ucl.ac.uk/spm). The scans were normalized to a cubic voxel size of 4mm and smoothed by a Gaussian kernel of 8mm.

The fMRI data for each participant were analyzed within a single-subject fixed-effects statistical model, implemented in the statistical SPM99 software package, using a box-car model convolved with a hemodynamic response function (HRF) to adjust for the hemodynamic delay of the BOLD signal. For each condition, a single contrast was estimated. The resulting images, containing the size of the estimated parameters, were entered in a second-level random-effects analysis. Therefore, the final results were based on a three group, one-way ANOVA model, containing the pre- and post-investigation of the patients and the control subjects. In this model, the two investigations of the patients were treated as independent measurements which was considered reasonable in this case, since there were 1-2 years between the measurements with individual histories of treatment, medication and rehabilitation. A correlated variance between the two measurements is therefore unlikely and the main differences can be studied by exploring only the group-means. Since the activation pattern for this tasks has been well-characterised (Hugdahl et al., 2004; Landrø et al, 2001), we explored the results on an uncorrected level of $p<0.001$ and displayed only clusters with at least contiguous 10 voxels. Further, the differences between the pre- and post-

treatment investigation were explored in more detail on a threshold of $p<0.001$ and the same criteria for the cluster size.

Since we were particularly interested in the activation changes between the first and second scanning in the depressed participants, we tested first the comparability of both scanning sessions. This was done in order to exclude the possibility of a general trend for differences in levels of activation between the two measurements, as an extra control procedure since we did not have clearing for scanning of the control subjects twice. For this purpose we performed a conjunction analysis that involved both measurements. Such an analysis is based on the assumption of independency of two measurements and would highlight only those areas which were consistently activated in both measurements (cf. Price & Friston, 1997).

In a further analysis, based on region of interest (ROI), we explored the different levels of activation for the two occasions and the control group in more detail. The ROIs were extracted from the results obtained for the control group (see Figure 1).

Insert Figure 1 about here

The regions comprised the anterior cingulate gyrus, the inferior frontal gyrus, the parietal lobe and the cerebellum. For each region, the averaged estimated parameter from the single subject analysis was extracted, by averaging all voxels, which showed a positive effect for the main contrast. We also investigated the correlation between the HDRS score and the activation levels, reached in the second investigation of the subjects. This regression model was explored at a significance level of $p<0.01$ and cluster size of at least 10 voxels.

Due to a technical error, no behavioral data were collected at the second scanning session. This would, however, not impair the interpretation of the activation data. In the Hugdahl et al. (2004) study, using the same task, depressed patients in an acute state (HDRS > 18), showed hypoactivation in frontal and parietal areas while their performance scores were significantly lower than the healthy controls. The response accuracy scores from the first scanning session were 88.9%, std 13.0 for the control subjects, and 68.5%, std 16.8 for the depressed patients. The corresponding reaction time data were 696 ms, std 148 and 622 ms, std 143. The differences for both measures were significant when tested with paired t-tests ($p < .05$).

Results

The control group showed the expected activation pattern with bilateral responses in the inferior and superior parietal lobes and inferior frontal gyri, as well as in the anterior cingulate gyrus and the cerebellum (Figure 2, Table 1).

Insert Figure 2 and Table 1 about here

Overall, the patient group showed a less significant activation pattern than the control group in the first scanning session. Like controls, they showed bilateral activation in the parietal lobes and the inferior frontal gyri. There were, however, no significant activations ($p<.001$) in the cingulate gyrus and cerebellum. Intensity of activation increased in most of the areas from the first to the second scanning in the patient group (see Figure 3 and Table 1). The conjunction analysis across the first and second patient measurement demonstrated significant and consistent activations for both scanning

sessions in the above mentioned areas and, in addition bilaterally in the ventral part of the inferior frontal gyrus as also seen in Figure 3 and Table 1).

Insert Figure 3 about here

When the groups were compared statistically, there were two regions that showed a significant difference between the groups. Compared to the control group, the medial portion of the cerebellum was less activated in the patients in the first scanning session, while areas in the middle temporal gyrus, including the Heschl's gyrus, were less activated in the second scanning session.

Since we were particularly interested in recovery / remission effects in the patients, we re-explored the differences between the patient group at the two time-points with a lower threshold of $p < 0.01$. This showed increased activations bilaterally in the parietal lobe and in the right frontal cortex at the second relative to the first scanning session when contrasting the two MR scanning sessions. This is seen in Table 2.

Insert Table 2 about here

The posterior cingulate gyrus also showed increased activation at the second compared with the first MR scanning session. The opposite comparison revealed attenuated activity in the second session in the left precentral gyrus and cerebellum, as well as the right Heschl’s gyrus.

Comparing the second minus first scanning for the patients, the region of interest (ROI) - analysis, as described in the Methods section, was performed. Figure 4 shows the results.

Insert Figure 4 about here

Confirming the results from the difference-contrast analysis, we found increased activations bilaterally in the parietal lobe and the right prefrontal cortex as well as in the right cerebellum. By contrast, the left prefrontal cortex, the anterior cingulate gyrus and the left cerebellum showed a slight decrease. However, with the exception of the cerebellum, neither the differences between the two occasions of the patients, nor the differences between the patients and the controls reached a significance level of $p<0.05$ (t-tests).

To explore relationships between the HDRS scores and activation, we correlated the individual activations from the second MR scanning session with the HDRS-score, obtained at the second session. See Table 3.

Insert Table 3 about here

We found a negative correlation between depression severity and neuronal response in the right parietal and frontal lobe, overlapping the regions found to be activated in the healthy controls. These activations included the left inferior occipital gyrus, right inferior parietal gyrus, right inferior frontal gyrus, and the right cingulate gyrus. A positive correlation was seen in the left middle frontal gyrus and bilaterally in the posterior cingulate.

Discussion

The major findings in the present study were significant increases in activation in the patient group in the inferior frontal gyrus and the superior and inferior parietal lobule at the second compared with the first MR scanning session. These increases involved Brodmann areas 40, 44, 45 in the frontal lobe and area 7 in the parietal lobule. There was also an increase in activation in the posterior cingulate at the second scanning session. The change in activation in the inferior frontal gyrus (BA 44 and 45) and the inferior parietal lobule (BA 7) may be directly linked to a change in information processing capacity between the two sessions due to clinical remission. Increased activations at the second session may reflect enhanced capacity for both mental arithmetic and working memory. We have previously shown that the same task activates both prefrontal and parietal areas in healthy controls (Hugdahl et al., 2004; Landrø et al., 2001). Of particular interest in this context is the suggestion that while the prefrontal areas may relate more to working memory, the parietal lobe areas may relate more to mental arithmetic (Chochon, Cohen, van der Moortele, & Dehaene, 1999). Processing of continuously presented number stimuli would seem especially critical in a mental calculation task, where the participant has to actively keep the last digit in memory, while at the same time disposing of the previously presented digit. The patients showed increases in areas in the vicinity of the supramarginal and angular gyri, respectively, areas that have been found to be activated in simple calculations and number processing respectively (Warrington, James, & Maciejewski, 1986). However, we would prefer not to over-emphasize differences in activation patterns between the process of working memory and mental arithmetic, or calculation. Working memory is intrinsically interwoven with mental calculation in a task such as the present one, and we would rather stress the notion of effortful processing and cognitive load (Hartlage et al., 1993; Hasher & Zacks, 1979). The task used here clearly draws on effortful cognitive

processes and the enhanced activation at the second session suggests that patients experienced restored aspects of effortful and cognitively demanding processing associated with clinical remission. The increase in activation in the cingulate gyrus in the second compared to the first scanning is in agreement with previous studies (e.g. (Drevets, 2001; Drevets, 2003; Mayberg, 2002) which have pointed to a neuronal network underlying pathological processing in depression that involves the prefrontal and parietal cortex, the striatum, thalamus, and anterior and posterior cingulate gyrus. Mayberg (e.g.(Mayberg, 2002); see also (Liotti & Mayberg, 2001) has suggested, on the basis of resting brain metabolism studies with PET, that hypometabolism in the cingulum is a hallmark of major depression, and that this may be a characteristic of mood changes. In the 2002 study, Mayberg showed that normalization of glucose metabolic activity in this region of the brain followed response to treatment and remission. In a similar vein, Pfleiderer (Pfleiderer et al., 2003) found that electroconvulsive therapy normalized glutamate/glutamine levels in the cingulum in depressed patients. Thus, the cingulum plays an important role in regulating mood through glutamate/glutamine regulation. Increase in activation in this area in the present study may therefore be indicative of normalization of neuronal responding in depressed patients when in a remission state compared to a acute depressed state (cf. (Hugdahl et al., 2004)).

As stated in the Methods section, the scores on the HDRS decreased significantly from the first to the second MR scanning, i.e. a reduction from "severe depression" to "mild depression", that is in the sub-threshold range. However, two of the nine patients still scored in the "severe" range, while two patients were scored as totally recovered, and five were scored as "mild depression". The correlation with neuronal activation showed a negative correlation particularly in the inferior frontal and parietal lobe areas, which

overlapped with similar areas activated in the healthy control participants. This may indicate a tendency towards normalization of brain activation in the patients as a function of time from an illness phase to a remission state. Hammar et al. (Hammar et al., 2003a) found improvement in performance on a cognitively demanding attention task in depressed patients over a 6 month's follow-up period. Interestingly, the patients in the Hammar et al. (Hammar et al., 2003a) study still were in the range of mild depression on the HDRS scale which is similar to the HDRS data obtained in the present study at the second MR scanning. There was also a positive correlation between the HDRS scores and activation in the left prefrontal area. This would thus confirm the region of interest (ROI) analysis in this area, which showed strong activations in both the first and second MR scanning. This was an unexpected finding, but could be caused by lowered threshold sensitivity in these areas in an acute depressed state.

A weakness in the present study is the absence of performance data which makes direct comparisons between localization of neuronal activation and cognitive processing possible. There are however two reasons why this may not seriously impair the conclusions drawn. First, patients in an acute state, scoring above 18 on the HDRS scale show clear hypoactivation in frontal and parietal areas despite a performance accuracy above 75% on the same task as the one used in the present study (Hugdahl et al., 2004). Thus, performance is not a critical factor in this task. Second, the increase in brain activation at the second MR session clearly overlaps areas shown in other studies in depressed patients when in remission (Mayberg, 2002). Thus, the activation data are not confounded through the absence of performance data. A word of caution should also be in place regarding the fact that we could not re-test the control subjects. We have, however, previously re-tested 5 healthy subjects in this task with 6 months interval between sessions (unpublished data) and could not see any changes in the activation

patterns in these subjects. Thus, we feel that this could not explain the changes in activation seen in the remitted patients. Moreover, the comparison between the first and second measurement in the patients was based on the assumption of obtaining reliable activations in both measurement occasions. Although activation reliability at the group level is relatively unknown (cf. McGonigle et al., 2000), Specht et al. (2003) found high test-retest reliability for tasks with high attentional load. Similarly, Fernandez et al. (2003), Rombouts et al., 1998, and Machielsen et al. (2000) have all reported high intra-subject reliability for both auditory and visual tasks related to mapping of language and memory functions. Thus, it seems safe to assume that the differences observed in the patients between the first and second measurements were reliable and meaningful effects with regard to activation data.

The new finding in this study was normalization of brain activation in depressed patients as a function of time from an illness phase to a remission state, using a longitudinal design. The clinical improvement correlated with increases in neuronal activation in the inferior frontal, parietal, and occipital areas, in addition to the cingulate cortex.

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Table 1

Cluster size	T-value	Coordinates x	y	z	Hemisphere	Anatomical structure	Brodmann area
Controls							
252	6,90	-40	-48	52	Left	Inferior & Superior Parietal Lobule	BA 40 / 7
30	6,65	40	-68	-28	Right	Cerbellum / Fusiform Gyrus	BA 37
79	6,20	52	-64	-20	Left	Cerbellum / Fusiform Gyrus	BA 37
73	6,11	-8	-72	-20	Left	Cerebellum	
240	6,10	44	-48	52	Right	Inferior & Superior Parietal Lobule	BA 40
78	6,03	-48	20	16	Left	Inferior Frontal Gyrus	BA 44/ 45
99	5,68	48	8	36	Right	Inferior Frontal Gyrus	BA 9 / 44/ 45
12	5,35	-4	28	40	Left	Medial Frontal Gyrus / Cingulate Gyrus	BA 6 / 32
15	4,89	40	20	-16	Right	Inferior Frontal Gyrus	BA 47
12	4,60	-8	-68	52	Left	Precuneus	BA 7
10	3,96	36	-52	-36	Right	Cerebellum	
Patients Scan I							
56	5,29	-32	-48	44	Left	Inferior Parietal Lobule	BA 40
11	4,74	-48	8	32	Left	Inferior Frontal Gyrus	BA 44
15	4,53	44	8	28	Right	Inferior Frontal Gyrus	BA 44
23	4,20	32	-64	52	Right	Superior Parietal Lobule	BA 7
Patients Scan II							
226	6,98	32	-48	44	Right	Inferior & Superior Parietal Lobule	BA 7 / 40
269	6,46	-36	-52	48	Left	Inferior Parietal Lobule	BA 40
58	6,42	40	4	28	Right	Inferior Frontal Gyrus	BA 44
21	5,52	40	32	16	Right	Inferior Frontal Gyrus	BA 45
11	4,03	-48	12	28	Left	Inferior Frontal Gyrus	BA 44
(Controls) – (Patients Scan I)							
19	4,21	-8	-63	-10	Left	Cerebellum / Lingual Gyrus	
(Controls) – (Patients Scan II)							
13	4,82	36	-20	-2	Right	Heschl's Gyrus	BA 41
12	4,04	48	-47	-1	Right	Middle Temporal Gyrus	

Uncorrected threshold $p<0.001$, Cluster level =10 voxels

Table 2

Cluster size	T-value	Coordinates x	y	z	Hemisphere	Anatomical structure	Brodmann area
(Patients Scan II) – (Patients Scan I)							
26	3,84	-8	-52	36	Left	Posterior Cingulate Gyrus	BA 31
64	3,58	-28	-52	28	Left	Inferior Parietal Lobule	BA 40
14	3,28	32	-44	40	Right	Inferior Parietal Lobule	BA 40
10	3,03	40	4	12	Right	Inferior Frontal Gyrus	BA 44
(Patients Scan I) – (Patients Scan II)							
18	3.95	-56	-4	40	Left	Precentral Gyrus	BA 4 / 6
15	3.64	36	-20	0	Right	Heschl's Gyrus	BA 41
25	3.47	-12	-44	-4	Left	Cerebellum	

uncorrected threshold p<0.01, Cluster level =10 voxels

Table 3

Cluster size	T-value	Coordinates x	y	z	Hemisphere	Anatomical structure	Brodmann area
positive correlation with HDRS-score							
14	7,41	-24	25	28	Left	Middle Frontal Gyrus	BA 9
12	5,01	-4	-49	21	Left	Posterior Cingulate	BA 30
13	4,25	20	-49	21	Right	Posterior Cingulate	BA 30
negative correlation with HDRS-score							
11	6,28	-40	-82	-6	Left	Inferior Occipital Gyrus	BA 18
10	4,91	20	-29	42	Right	Cingulate Gyrus	BA 31
14	4,72	40	9	25	Right	Inferior Frontal Gyrus	BA 44
14	4,65	40	-44	46	Right	Inferior Parietal Lobule	BA 40

uncorrected threshold p<0.01, Cluster level =10 voxel

Figure legends

Figure 1: Selected regions of interest (ROI) based on the overall activatikon pattern observed in the control group

Figure 2: Renderings of significant activations in the healthy control group

Figure 3: Renderings of significant activations in the depressed patients at the first (upper panel) and second (lower panel) scanning session, comparable to pre- and post treatment.

Figure 4: Activation effect sizes for the five different ROIs, split for the patients and controls. R = right, L = left, AC = anterior cingulum. Scan I = First scanning session, Scan II = Second scanning session

Figure 1

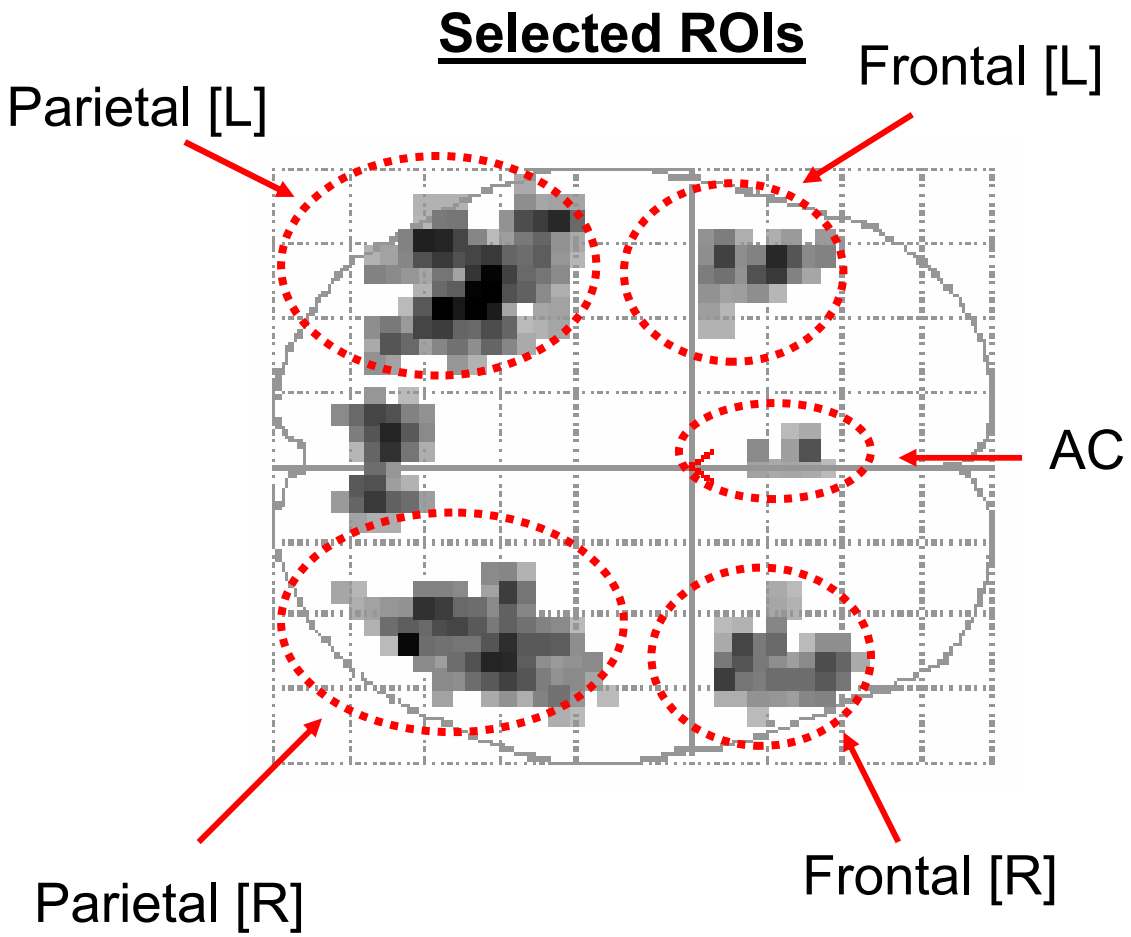


Figure 2

Healthy Controls

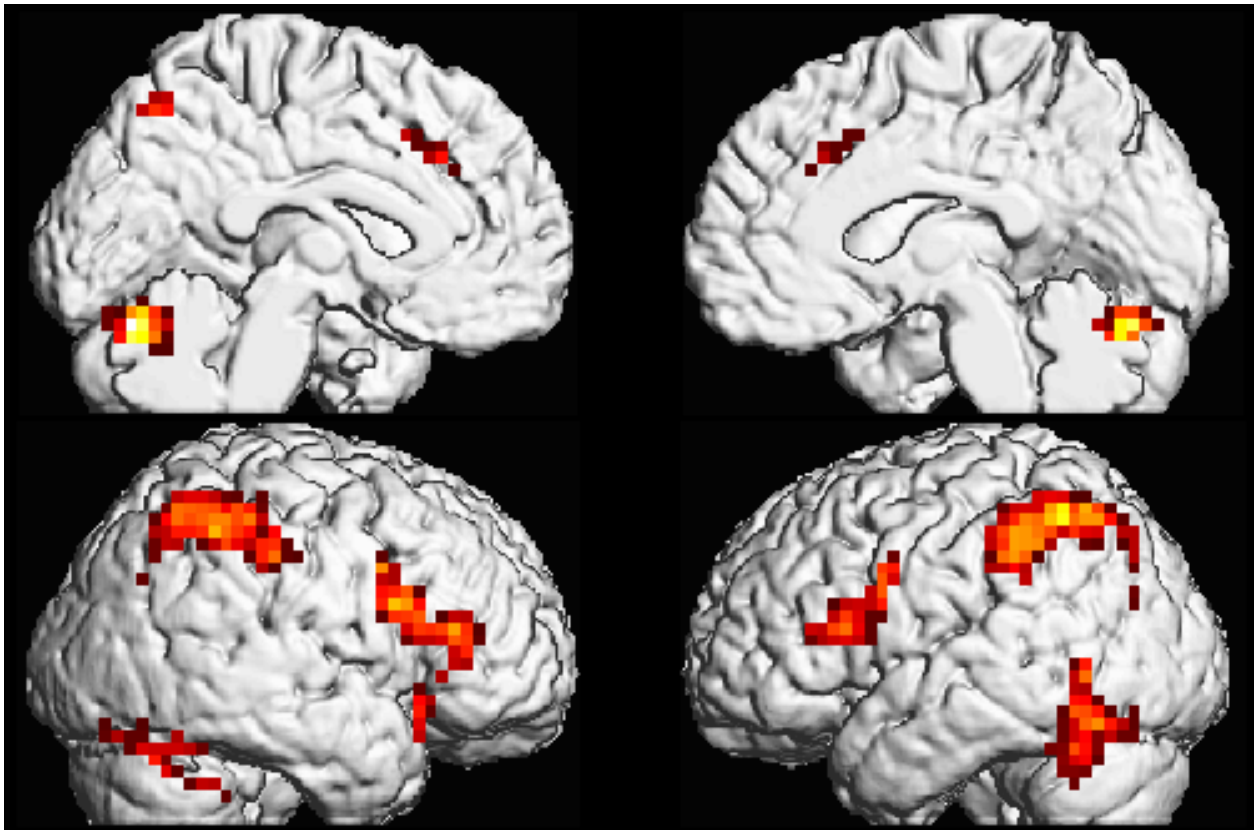
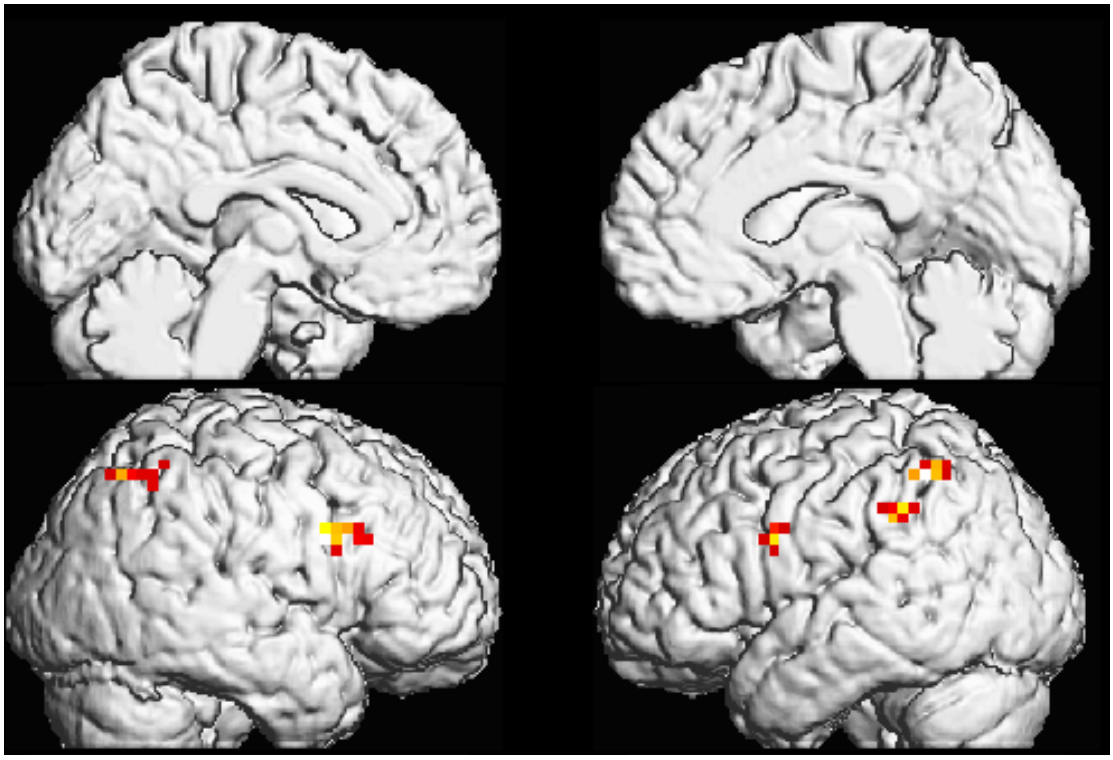
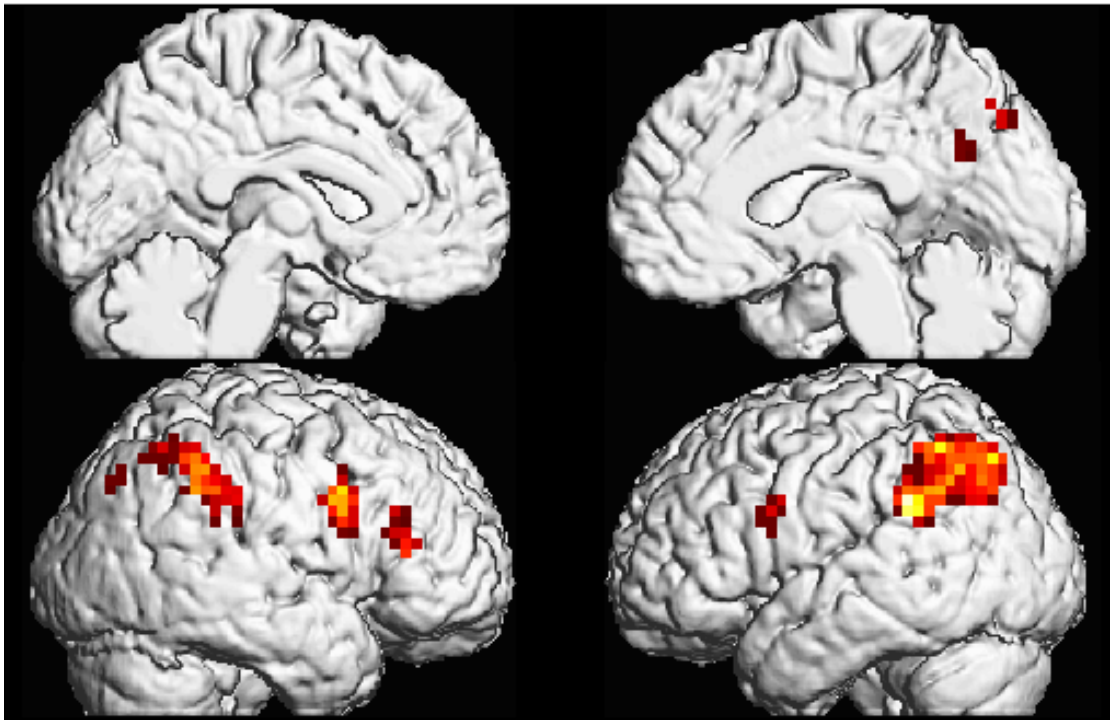


Figure 3

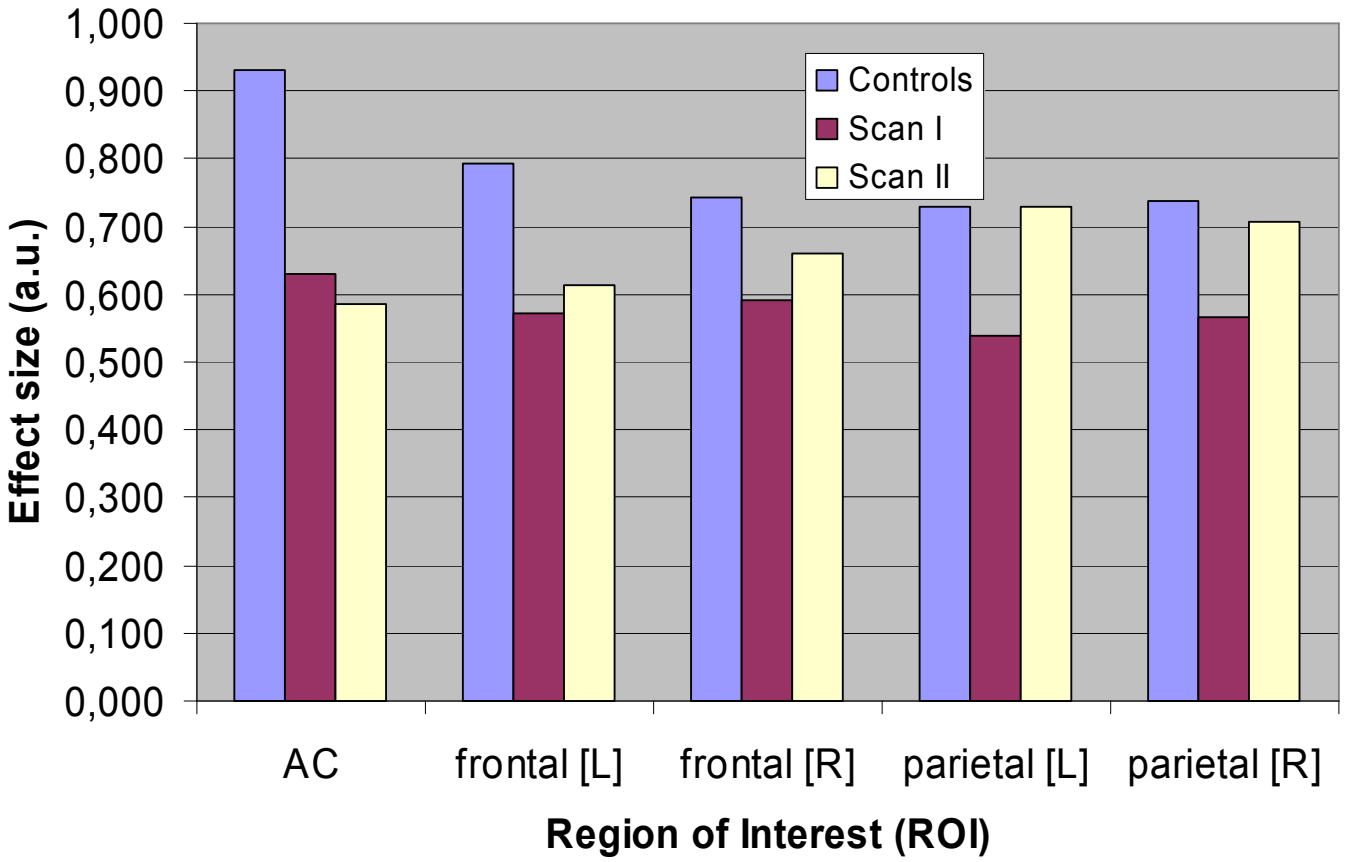


Patients Scan I



Patients Scan II

Figure 4


1,000
0,900
0,800
0,700
0,600
0,500
0,400
0,300
0,200
0,100
0,000
Effect size (a.u.)
Controls
Scan I
Scan II
AC
frontal [L]
frontal [R]
parietal [L]
parietal [R]
Region of Interest (ROI)