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Mood related insights : functional and structural MRI studies in depression and anxiety disorders

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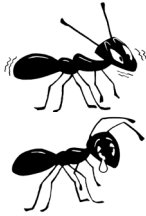
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CHAPTER 4

FUNCTIONAL MRI CORRELATES OF VISUOSPATIAL
PLANNING IN OUTPATIENT DEPRESSION AND ANXIETY

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Background: Major depressive disorder (MDD) has been associated with executive dysfunction and related abnormal prefrontal activity, whereas the status of executive function (EF) in frequently co-occurring anxiety disorders and in comorbid depression-anxiety is unclear. We aimed to study functional MRI correlates of (visuospatial) planning in MDD and anxiety disorders, and to test for the effects of their comorbidity.

Methods: Functional-MRI was employed during performance of a parametric Tower of London task in outpatients with MDD (n=65), MDD with comorbid anxiety (n=82), or anxiety disorders without MDD (n=64), and controls (n=63).

Results: Moderately/severely depressed MDD patients showed increased left dorsolateral prefrontal activity as a function of task load, together with subtle slowing during task execution. In mildly depressed and remitted MDD patients, in anxiety patients and in patients with comorbid depression-anxiety, task performance was normal and no activation differences were observed. Medication use and regional brain volume were not associated with altered visuospatial planning.

Conclusion: Prefrontal hyperactivation during high planning demands is not a trait characteristic, but a state characteristic of MDD without comorbid anxiety, occurring independent of SSRI-use. Disturbances in planning or the related activation are probably not a feature of anxiety disorders with or without comorbid MDD, supporting the current distinction between anxiety disorders and depression.

Executive functions are essential for successful adaptation to daily life and comprise a complex set of cognitive function, dysregulation of which may result in changes in coordination, organization, and inhibition of behavior (Elliott, 2003). Executive deficits have been repeatedly associated with Major Depressive Disorder (MDD) (Rogers et al., 2004). However, MDD frequently co-occurs with anxiety disorders, such as panic disorder, and social anxiety disorder (Ressler & Mayberg, 2007). Executive impairments in these common anxiety disorders (panic disorder, social anxiety disorder, and generalized anxiety disorder) are less well established and findings may have been confounded by the presence of comorbid MDD (Kaplan et al., 2006). Notably, the comorbid condition of depression and anxiety disorders has been associated with more severe psychopathology (Kessler et al., 2005; Roy-Byrne et al., 2000; Rush et al., 2005), increased disability (Fichter, Quadflieg, Fischer, & Kohlboeck, 2010; Gorman, 1996; Spijker et al., 2004), and worse outcome compared with patients with only a diagnosis of MDD or anxiety disorders (Bruce et al., 2005; Gorman, 1996; Gorman & Coplan, 1996; Melartin et al., 2004; Roy-Byrne et al., 2000; Rush et al., 2005). Nevertheless, the neural correlates of executive functions in comorbid depression-anxiety disorders have not been investigated yet.

A key aspect of executive functioning is planning (i.e. the process of making a plan when facing a problem, and performing the plan, while monitoring its execution), associated with recruitment of a dorsal prefrontal-parietal-striatal network during functional Magnetic Resonance Imaging (fMRI) in healthy controls as measured with the Tower of London visuospatial planning task (van den Heuvel et al., 2003; Wagner et al., 2006). In MDD, conflicting findings have been reported: Whereas two emission tomography studies (i.e., PET (Elliott et al., 1997) and SPECT (Goethals et al., 2005)) observed reduced prefrontal and subcortical perfusion coupled with impaired performance, in the only fMRI study to date increased dorsolateral PFC activation was found in depressed subjects relative to healthy controls (Fitzgerald et al., 2008). However, the size of the included depressed groups was rather small, limiting the power of the studies and the generalizability to the depressive population at large. Also, inconsistencies in results may have arisen owing to differences in scanning modalities and clinical characteristics of patient groups, including medication use and the presence of comorbidity.

In the present study, we aimed to investigate neural correlates of visuospatial planning in a large sample of outpatients with a half-year diagnosis of MDD, MDD with a comorbid anxiety disorder or an anxiety disorder without comorbid MDD, and in healthy controls. We also investigated whether illness severity (McDermott & Ebmeier, 2009) and use of antidepressant medication was associated with (abnormal) planning performance and its neural correlates. Executive processes including visuospatial planning have been shown to rely on cortical prefrontal cortex (PFC) regions, such as the ventrolateral PFC,

dorsolateral PFC, and anterior cingulate cortex (ACC) (van den Heuvel et al., 2003; Wagner, Koch, Reichenbach, Sauer, & Schlösser, 2006). Importantly, these regions have also been implicated in neuroanatomical models of mood regulation in psychiatric disorders (Drevets et al., 2008a; Phillips et al., 2003b) and some evidence exists that top-down regulatory brain regions are compromised in MDD (Heller et al., 2009; Johnstone et al., 2007). However, whether such deficient DLPFC and ACC involvement is implicated in the neuropathology of both depression and anxiety disorders has, to our knowledge, rarely been studied. Therefore, we aimed to examine executive function during a planning task in patients with MDD, anxiety disorders or comorbid depression-anxiety. We hypothesized that relative to healthy controls, outpatients with MDD with and without comorbid anxiety exhibit impaired visuospatial planning performance coupled with abnormal DLPFC and anterior cingulate cortex (ACC) activity, correlated with illness severity. Finally, we aimed to explore whether anxiety disorders were characterized by a similar pattern of visuospatial planning abnormalities.

PARTICIPANTS

Participants were recruited from the NESDA study (Netherlands Study of Depression and Anxiety), a large-scale, multi-site longitudinal observational cohort study (Penninx et al., 2008). NESDA has been designed to be representative of those with depressive and anxiety disorders in different health care settings and different stages of the developmental history of disorders (e.g., normal controls, high familial risk, subthreshold disorders, first and recurrent episodes). Therefore, the sample is stratified for setting (community, primary care, and specialized mental health) and set up to include a range of psychopathology. The rationale, methods, and recruitment have been described in detail elsewhere (Penninx et al., 2008).

Out of the 2981 NESDA respondents, participants aged between 18 and 57 years were asked to participate in the NESDA neuroimaging study if they met diagnostic and statistical manual for mental disorders (DSM) version IV criteria for MDD and/or anxiety disorder (panic disorder and/or social anxiety disorder and/or generalized anxiety disorder) during the last six months, or no lifetime DSM-IV diagnosis.

Exclusion criteria for patients were 1) the presence of axis-I disorders other than MDD, panic disorder, social anxiety disorder, generalized anxiety disorder, lifetime, 2) any use of psychotropic medication other than a stable use of SSRIs or infrequent benzodiazepine use (i.e., equivalent to 2x10 mg oxazepam 3 times a week, or use within 48 hrs prior to scanning). Healthy control participants had never met criteria for any DSM-IV disorder and were not taking any psychotropic drugs.

Exclusion criteria for all participants were: 3) presence of major internal and/or neurological disorders (including contusio cerebri), 4) dependency or recent

abuse (past year) of alcohol and/or drugs, 5) hypertension, 6) general MRI contraindications. Diagnoses according to DSM-IV algorithms were established using the structured Composite International Diagnostic Interview (CIDI) – lifetime version 2.1 (Robins et al., 1988), administered by a trained interviewer.

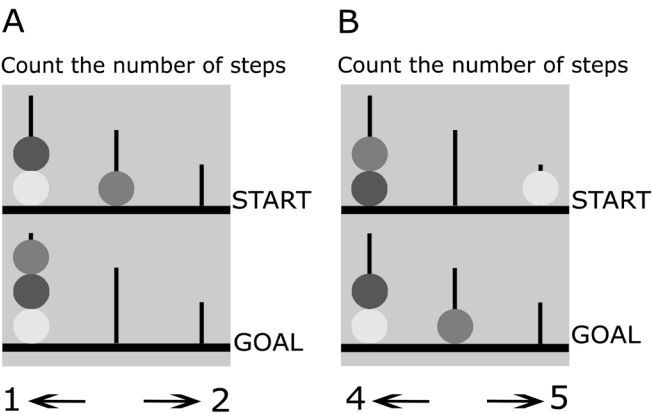
Overall, 301 native Dutch speaking participants (233 patients and 68 HC) were included and underwent magnetic resonance imaging in one of the three participating centers (i.e., Leiden University Medical Center [LUMC], Academic Medical Center [AMC], University of Amsterdam, and University Medical Center Groningen [UMCG]). The study was carried out in accordance with the Declaration of Helsinki. Also, the Ethical Review Boards of each participating center approved this study. All participants provided written informed consent after complete description of the study.

TASK PARADIGM

We used an event-related parametric version of the Tower of London, described in detail elsewhere (van den Heuvel et al., 2003). Briefly, participants were presented a starting configuration and a target configuration and were requested to work out the minimum number of steps (ranging from one to five) to reach the target (Figure 1). In the baseline condition, participants were instructed to count the number of blue and yellow beads. We used a pseudo-randomized, self-paced design with maximal response duration of 60s for each trial, presented using E-prime (Psychological Software Tools, Pittsburgh, PA, USA). Participants' responses and response times were registered through two magnet-compatible button boxes. No feedback regarding the answers was provided.

FIGURE 1:
EXAMPLE OF THE
TOWER OF LONDON

- A) example of a one-step planning trial.
- B) example of a four-step planning trial.



SCANNING PROCEDURE

Severity of depression and anxiety at the day of scanning was assessed using Beck Anxiety Inventory (Beck et al., 1988) and the Montgomery Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979). During the scanning session, we monitored anxiety levels using a Visual Analogue Scale (Huskinson, 1974) ranging from 0 to 100. Prior to scanning, participants underwent a brief training session (10 trials).

The Tower of London paradigm was performed as part of a larger functional imaging session, including a verbal memory task, an emotional faces paradigm, and 'resting state' imaging, results of which will be reported elsewhere. The Tower of London paradigm was administered as the first paradigm in each session.

IMAGE ACQUISITION

Imaging data were acquired using Philips 3-Tesla magnetic resonance systems (Best, The Netherlands) located at the Leiden University Medical Center, Academic Medical Center Amsterdam, and University Medical Center Groningen, equipped with a SENSE-8 (Leiden University Medical Center and University Medical Center Groningen) and a SENSE-6 (Academic Medical Center) channel head coil, respectively. For each subject, echo-planar images (EPI) were obtained using a T2*-weighted gradient echo sequence (repetition time [TR]=2300 ms, echo time [TE]=30ms [University Medical Center Groningen: TE=28 ms], matrix size: 96x96 [University Medical Center Groningen: 64x64], 35 axial slices [University Medical Center Groningen: 39 slices], interleaved acquisition, 2.29x2.29mm in-plane resolution [University Medical Center Groningen: 3x3mm], 3mm slice thickness). Echo planar images were scanned parallel to the anterior-posterior commissure plane.

Anatomical imaging included a sagittal 3-dimensional gradient-echo T1-weighted sequence (TR=9 ms, TE=3.5 ms; matrix 256x256; voxel size: 1x1x1mm; 170 slices).

DATA ANALYSIS

Task performance and clinical characteristics

Psychometric and performance data were analyzed with SPSS (SPSS Inc., Chicago, IL, USA). If the data did not meet the assumptions required to perform parametric analyses, and log-transforming did not resolve these problems, the appropriate non-parametric test was performed (Kruskal-Wallis multiple independent sample test [H] and subsequent Mann-Whitney test for two independent samples [U]). Performance was analyzed by means of a Repeated-Measures-ANCOVA, using the proportion correct scores and mean response times per trial type as dependent factors, group (1) MDD without comorbid anxiety disorders [MDD], 2) comorbid depression-anxiety [CDA], 3) anxiety disorders [ANX], healthy controls [HC]) as between subject factor, and age as a

covariate. Significance for behavioral analyses was set at 5%, and post hoc paired tests were Bonferroni-corrected for multiple comparisons.

Image processing

Functional imaging data were preprocessed and analyzed using Statistical Parametric Mapping software (SPM5; <http://www.fil.ion.ucl.ac.uk/spm/>) implemented in Matlab 7.1.0 (The MathWorks Inc., MA, USA). Preprocessing included slice time correction, image realignment, registration of the T1-scan to the mean EPI, warping to MNI-space as defined by the SPM5 T1-template, reslicing to 3x3x3mm voxels and spatial smoothing using an 8mm FWHM Gaussian kernel. Subject movement greater than 3mm in any direction resulted in exclusion of the data from further analysis.

The fMRI experiment was modelled in an event related fashion with regressors (i.e. explanatory variables) made by convolving each event-related stimulus function (baseline, 1-5 step trials) with a canonical haemodynamic response function and modulated using reaction times. In addition, error and no-response trials were included as a regressor of no interest. Low-frequency noise was removed by applying a high-pass filter (cut-off of 128s) to the fMRI time-series at each voxel.

Main effects of task and between group comparisons

Following the summary statistics approach, contrast images for task load (with trial types 1-5 having weights [-1.5 -1 -0.5 1 2]) were calculated per subject on a voxel-by-voxel basis and entered into second-level analyses for between-group [MDD, CDA, ANX, HC] comparisons (1x4 ANCOVA), with age as covariate. Additionally, 'center' was added as a regressor by means of two dummy variables. We repeated this analysis after exclusion of the SSRI using patients and also directly compared the functional maps of SSRI using patients to SSRI-non using patients. To test for the impact of depression severity on planning activity we formed 3 clinical relevant subgroups (Muller et al., 2000) and compared them to HC: 1) remitted (MADRS 0-8), 2) mild (MADRS 9-18), 3) moderate/severe depressed (MADRS>18). We performed an ANCOVA with age and center as covariates within MDD, CDA, and HC, and repeated these analyses with BAI scores as additional covariate. Separately, we tested for the effects of anxiety severity within group by performing a linear regression analysis with BAI scores as regressor of interest, and age, MADRS score, and center as covariates, masked with a binary mask derived from the relevant main effect at $p < .005$, uncorrected.

The main effect of task is reported at a threshold of $p < .05$ whole brain corrected for Family Wise Error ($p_{FWE_wholebrain}$). For the between-group comparisons, we choose the dorsolateral PFC and anterior cingulate cortex (ACC) as regions of interest (ROI). To restrict the search for interaction effects to voxels which were identified in the main effect, group comparisons were masked with the orthogonal relevant main effect at $p < .005$ (uncorrected).

Group by task interaction effects were inspected at $p < .001$, uncorrected ($p_{\text{uncorrected}}$). To further protect against Type-I error, Small Volume Correction (SVC) was applied for the main comparison (effect of diagnosis), by centering a sphere with a 16mm radius around the peak voxel (i.e., twice the size of the smoothing kernel and equivalent to 17.2 ml). The resulting volumes of interest had to meet $p < .05$, FWE voxel corrected ($p_{\text{FWE_SVC}}$), to be considered significant. Non-ROIs had to meet $p < .05$, whole brain FWE corrected ($p_{\text{FWE_wholebrain}}$).

In a previous study, we reported decreased ACC volumes in both patients with MDD and anxiety disorders (van Tol et al., 2010). Therefore, we used the statistical toolbox Biological Parametric Mapping (BPM; Wake Forest University School of Medicine) to test whether between-group effects were affected by variations in regional grey matter volume (Casanova et al., 2007).

SAMPLE CHARACTERISTICS

Data from 12 participants were excluded because of poor imaging data quality or incomplete data. In addition, task involvement was considered insufficiently reliable when overall performance was below 75%, (including baseline accuracy) in order to maximize the likelihood of analyzing planning-related activity and to reduce possible bias due to non-task related processes. Distribution of sufficient/insufficient performance was similar over groups (MDD: 65/4; comorbid depression-anxiety: 82/3; panic disorder and/or social anxiety disorder: 64/4; healthy controls: 65/2, $X^2_{3,289} = 1.12$, $p = .77$). We excluded insufficient performers from further analysis ($n = 13$). Finally, two healthy controls were excluded because of Montgomery Åsberg Depression Rating Scale scores > 8 (Muller et al., 2000).

Our final sample consisted of 274 participants, i.e. 65 patients with a half-year diagnosis of MDD (MDD), 82 patients with MDD plus panic disorder and/or social anxiety disorder and/or generalized anxiety disorder (comorbid depression-anxiety [CDA]), 64 patients with panic disorder and/or social anxiety disorder, and/or generalized anxiety disorder without MDD (ANX), and 63 healthy controls (HC). Group characteristics are listed in Table 1. All diagnostic groups showed higher Montgomery Åsberg Depression Rating Scale and Beck Anxiety Inventory scores than the healthy controls. In addition, comorbid depression-anxiety patients showed higher Montgomery Åsberg Depression Rating Scale and Beck Anxiety Inventory scores than patients with MDD or anxiety disorders, and patients with anxiety disorder showed higher Beck Anxiety Inventory scores than MDD (Montgomery Åsberg Depression Rating Scale: all $z > -4.26$, $p < .001$; Beck Anxiety Inventory: all $z > -3.01$, all $p < .003$). The sample was highly representative of the main NESDA sample (see supplemental material). Depression severity scores decreased during the interval between baseline assessments (T1) and subsequent MRI sessions (T2) (Table S-1). Splitting of the depressed groups into severity groups based on their symptom severity at T2

RESULTS

TABLE 1: DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF THE TOTAL SAMPLE (N=274)

MADRS= Montgomery Asberg Depressive Rating Scale; BAI: Beck Anxiety Inventory; rem=MADRS scores indicative of a remitted depressive state (0-8); mild=MADRS scores indicative of a mild depressive state (9-18); modsev=MADRS scores indicative of a moderate to severe depressive state(>18); 1yr diagn MDD: Diagnosis of MDD in the last year; lifetime MDD: life time diagnosis of MDD; lifetime ANX: life time diagnosis SAD/PD/GAD; T1= baseline assessment; T2=MRI measurement; interval= time between T1 and T2.

a: CDA =18 MDD+GAD, 17 MDD+PD, 9 MDD+PD+GAD, 8 MDD+GAD, 14 MDD+SAD+GAD, 8 MDD+PD+SAD, 8 MDD+PD+SAD+GAD; b: ANX=18 PD, 2 PD+GAD, 25 SAD, 3 SAD+GAD, 12 PD+SAD, 5 PD+SAD+GAD.

Variable	MDD (n=65)		CDA a (N=82)		ANX b (N=64)		HC (N=63)	
	N	%	N	%	N	%	N	%
male gender	24	36.9	28	34.2	18	28.1	24	38.1
scan site	17/23/25	26.2/35.4/38.4	26/31/25	31.7/37.8/30.5	21/20/23	32.8/31.3/35.9	24/27/12	38.1/42.9/19.0
right handed	59	90.8	76	92.7	60	93.8	58	92.1
SSRI user	16	24.6	34	41.5	19	29.7	0	0
recurrent MDD	39	60.0	46	56.1	-	-	-	-
MADRS category	22/23/20	33.8/35.4/30.8	8/32/42	9.8/39.0/51.2	34/19/11	53.1/29.7/17.2	63/0/0	100/0/0
1 yr diagn MDD	65	100	82	100	5	7.8	0	0
lifetime MDD	65	100	82	100	36	56.3	0	0
lifetime ANX	20	30.8	82	100	64	100	0	0
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
age	37.08	10.44	36.93	10.65	35.49	9.05	40.05	9.51
education	12.67	2.91	11.62	3.13	13.11	3.21	14.25	2.75
MADRS	13.43	9.10	20.21	9.33	10.48	8.62	1.10	1.86
BAI	8.97	8.19	17.91	9.41	13.22	9.51	2.05	2.49
onset MDD	25.38	10.35	24.21	11.53	-	-	-	-
onset ANX	-	-	18.22	11.03	14.48	10.42	-	-
	range		range		range		range	
MADRS	0 - 39		0 - 49		0 - 35		0 - 7	
BAI	0 - 50		0 - 47		0 - 42		0 - 10	

TABLE 2: DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF THE REMITTED, MILD, AND MODERATE/SEVERE MDD AND CDA SUBGROUPS

MADRS= Montgomery Asberg Depressive Rating Scale; BAI: Beck Anxiety Inventory; IDS= Inventory of Depressive Symptomatology; rem=MADRS scores indicative of a remitted depressive state (0-8); mild=MADRS scores indicative of a mild depressive state (9-18); modsev=MADRS scores indicative of a moderate to severe depressive state(>18); T1= baseline assessment; T2=MRI measurement; interval= time between T1 and T2. * = significant at $p<.05$, paired T-test.

Variable		MDD_rem (n=22)		MDD_mild (n=23)		MDD_modsev (n=20)	
		N	%	N	%	N	%
male gender		7	31.8	10	43.5	7	35.0
SSRI user		5	22.7	5	21.7	6	30.0
		Mean	SD	Mean	SD	Mean	SD
age	years	35.86	10.90	38.22	10.91	36.15	10.35
IDS T1	total score	25.10	11.15	26.39	7.64	34.06	1.84
IDS T2	total score	9.00	5.67	20.87	6.43	30.89	8.33
MADRS T2	total score	3.86	2.40	12.83	2.64	24.65	5.04
BAI T1	total score	10.48	7.71	11.83	7.11	14.05	12.13
BAI T2	total score	3.95	2.67	9.09	5.70	14.89	11.02
interval	days	64.62	28.5	60.52	36.22	74.44	54.36
		CDA_rem (n=8)		CDA_mild (n=32)		CDA_modsev (n=42)	
		N	%	N	%	N	%
male gender		1	12.5	9	28.1	17	40.5
SSRI user		3	37.5	16	50.0	15	35.7
		Mean	SD	Mean	SD	Mean	SD
age	years	36.12	6.64	37.42	12.28	36.45	10.12
IDS T1	total score	21.38	9.61	31.61	8.98	35.93	12.71
IDS T2	total score	11.25	5.95	24.29	7.93	36.15	9.52
MADRS T2	total score	5.38	3.02	14.10	2.52	27.55	6.11
BAI T1	total score	10.62	7.54	20.6	7.83	17.78	9.36
BAI T2	total score	7.25	5.04	18.07	6.47	20.75	9.76
interval	days	23.38	127.14	63.81	25.47	61.66	39.6

revealed that only the currently remitted and mildly depressed subgroups, but not the moderate/severe subgroups, showed this decrease in symptom severity (see Table 2).

Groups matched on gender, handedness, distribution of diagnosis over scan-center, and age (all $X^2 < 7.23$, $p > .3$; age: $H_3 = 6.36$, $p = .10$). SSRI use was not significantly different across patient groups ($X^2_2 = 5.06$, $p = 0.08$). Groups differed in years of education ($H_3 = 28.77$, $p < .001$), due to healthy controls being higher educated than MDD and comorbid depression-anxiety (HC>MDD: $U = 1361.5$; HC>CDA: $U = 1292$; all $p < .008$).

BEHAVIORAL RESULTS

Overall, no effect of diagnosis was observed on planning accuracy ($F_{7.77;699.66} = 1.29, p = .25$) and performance speed ($F_{4.99;449.26} = .35, p = .86$). During the task, patients with anxiety disorders reported higher levels of anxious arousal than healthy controls (ANX>HC: VAS: $U = 1457, z = -2.7, p < .008$; all other comparisons: All $z < -2.24$, all $p > .025$) (Table 3).

IMAGING RESULTS

Brain activation patterns reflecting increasing task load were highly consistent over groups (Figure 2), involving clusters in bilateral DLPFC, frontopolar regions, superior frontal regions, lateral parietal cortices, and precuneus (Table S-2, reported at $p_{\text{FWE_wholebrain}} < .05$).

A main effect of diagnostic group was observed in the left DLPFC (Figure 3-A): MDD subjects showed increased activation in the left DLPFC relative to HC ($[x = -39, y = 36, z = 30]$, BA 9/46, $Z = 3.59, p_{\text{FWE_SVC}} = .04$). CDA showed increased left DLPFC activation as compared to HC that approached significance ($[x = -39, y = 36, z = 30]$, BA 9/46, $Z = 2.69, p_{\text{uncorrected}} = .004$). No other group comparison revealed significant differences. Results were unaffected by regional brain volume differences.

Effects of SSRI's

We repeated our analysis over 205 SSRI-free participants. Groups were similar to the overall groups with respect to demographic and clinical characteristics. Exclusion of the SSRI using patients did not change behavioral and imaging results. In addition, we directly compared SSRI-using and SSRI-free subjects. Clinical characteristics were similar in SSRI-free and SSRI-using groups. No effect of SSRI use was found.

Effects of illness severity

¹ Only three CDA patients were remitted at time of scanning (see Table 2). Therefore, we left the remitted CDA group out of the severity analyses.

Within the MDD and comorbid depression-anxiety¹ group, depressive state (remitted, mild, and moderate/severe) was unrelated to gender, scan center, and SSRI use.

Within MDD patients, illness severity was trend-wise associated with response times ($F_{2,58} = 3.07, p = .054, \eta^2 = .1$). Explorative post hoc t-tests showed that the moderately to severely depressed MDD patients showed increased response times during execution of all trial types, except for step-5 trials as compared to remitted patients (Step 1-4: all $T_{38} > 2.12, p < .04$; Step 5: $T_{38} = 1.69, p = .1$). Within patients with comorbid depression-anxiety, no effect of illness severity on response times was observed ($F_{1,68} = .93, p = .34$). Also, no effect of depression severity was observed on planning accuracy (MDD: $F_{2,60} = 1.05, p = .36$; CDA: $F_{1,68} = .87, p = .37$).

A multivariate analysis of covariance (MANCOVA) with Beck Anxiety Inventory scores as fixed factor showed no effect of anxiety scores on performance and response times (all $F < 1.07, p > .32$). Adding Montgomery Åsberg Depression

TABLE 3: TASK PERFORMANCE

VAS=Visual Analogue Scale. Baseline: baseline trials of the ToL task. Step 1 thru 5: ToL trials with the minimum amount of steps to achieve the goal configuration ranging from 1 thru 5. Total: total proportion of correct trials.

Variable		MDD		CDA		ANX		HC	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
VAS	total score	32.8	24.44	37.89	25.05	42.94	26.20	29.86	24.08
baseline	proportion correct	0.98	0.03	0.98	0.04	0.98	0.04	0.98	0.04
1 step	"	0.96	0.06	0.95	0.05	0.96	0.06	0.96	0.06
2 step	"	0.92	0.12	0.92	0.09	0.94	0.07	0.93	0.08
3 step	"	0.94	0.09	0.93	0.10	0.92	0.09	0.94	0.08
4 step	"	0.85	0.15	0.78	0.19	0.81	0.15	0.84	0.14
5 step	"	0.80	0.16	0.77	0.23	0.76	0.19	0.78	0.17
total	"	0.94	0.06	0.93	0.06	0.93	0.05	0.94	0.04
baseline	response time (s)	3.51	1.11	3.89	1.26	3.60	1.22	3.43	1.05
1 step	"	4.69	1.40	5.08	1.51	4.86	1.47	4.46	1.09
2 step	"	5.82	1.73	6.24	1.69	6.19	1.94	5.66	1.46
3 step	"	8.07	2.68	8.17	2.30	8.31	2.27	7.95	2.71
4 step	"	11.44	4.36	11.58	3.69	11.40	3.63	11.62	4.02
5 step	"	15.77	6.41	16.13	5.49	16.54	5.97	15.86	4.94

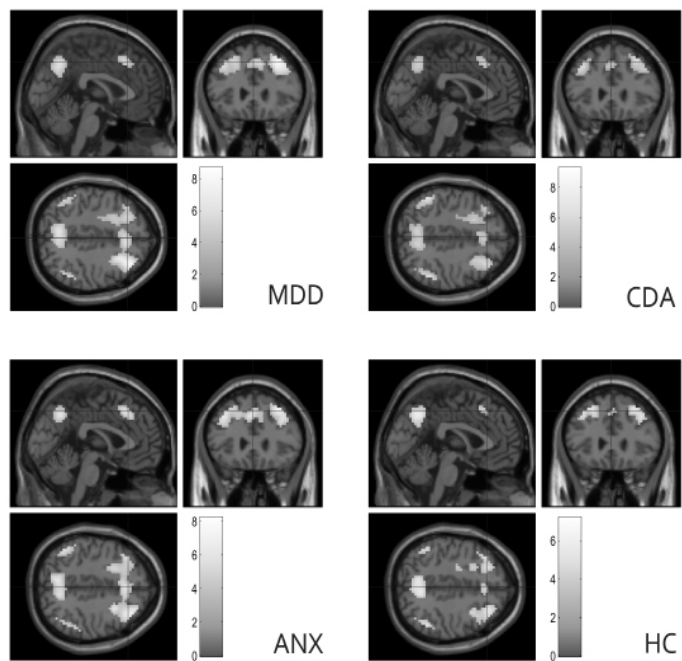
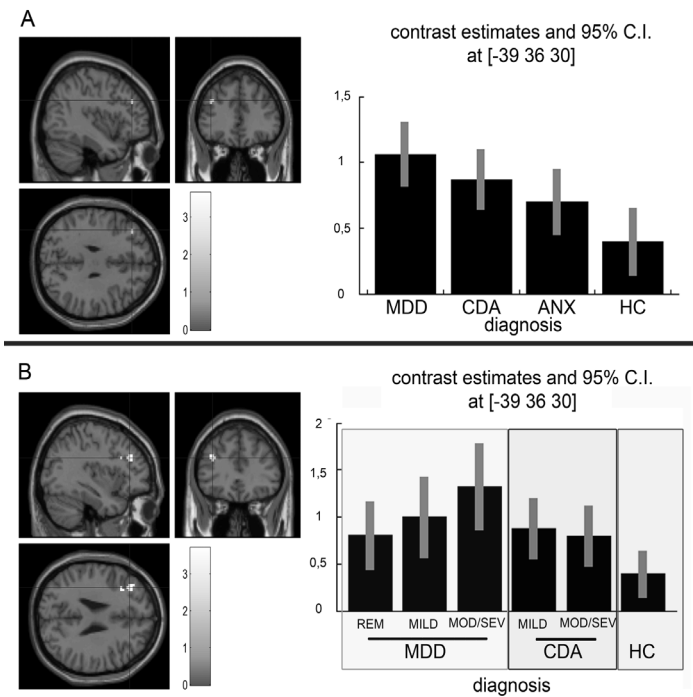


FIGURE 2:
MAIN EFFECTS OF
INCREASING TASK
LOAD

Activation maps of the main effect of increasing task load within the four diagnostic groups (MDD: n=65; CDA: n=82; ANX: n=64; HC: n=63). Activations are displayed at $p < .001$, uncorrected.

**FIGURE 3:
BETWEEN-GROUP
COMPARISONS**

A) Left: Increased DLPFC activation as compared to HC. Right: Parameter estimates and 95% confidence intervals showing increased activation of the left DLPFC in MDD as compared HC, and trendwise in CDA; B) Left: Areas showing increased DLPFC activation in the moderately/severely depressed MDD patients as compared to HC. Right: Parameter estimates and 95% confidence intervals showing increased activation of the left DLPFC is specific for moderately/severely depressed MDD patients. Group difference is displayed at $p<.001$, uncorrected. Rem=remitted depressed patients; mild= mildly depressed patients; mod/ sev=moderately/severely depressed patients



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Rating Scale scores as a covariate or omitting the SSRI users from the analysis did not affect these results.

Imaging correlates of depression severity

The increased left dorsolateral PFC activation relative to healthy controls was found to be specific for the moderately and severely depressed MDD patients: MNI coordinates: [x=-36 y=33 z=27], BA 46/9, $Z=3.62$, $p_{svc}=.04$ [see Figure3-B]. No differences in left dorsolateral PFC activation were observed between the mild and remitted MDD subgroups and healthy controls. Within comorbid depression-anxiety patients, no effect of depression severity on dorsolateral PFC activation was observed. Omission of the SSRI-users from the analysis did not affect these results. Adding Beck Anxiety Inventory scores to the models did not change the effects of depressive state on activation patterns.

Imaging correlates of anxiety severity

No effect of anxiety severity was observed on task related activity in MDD, CDA and ANX.

In the present study, we used a parametric visuospatial planning task (Tower of London) to investigate the neurophysiological correlates of increased planning load in a large sample of outpatients with MDD, MDD with comorbid anxiety disorders, and anxiety disorders only, compared with healthy controls. Anxiety disorders included in this study were panic disorder, social anxiety disorder, and generalized anxiety disorder. To our knowledge, this is the first functional neuroimaging study that was able to test for effects comorbidity of depression and anxiety, depressive state, and medication use on visuospatial planning and its neural correlates. Also, to our knowledge, this is the first functional neuroimaging study to investigate the neural correlates of executive function (i.e., planning) in PD and SAD, two highly prevalent anxiety disorders.

Taken together, our results indicate that depression with or without anxiety disorders is not associated with gross trait visuospatial planning impairments, but with subtle state abnormalities. Increased DLPFC activation coupled with subtle decreases in response speed during task execution was observed in MDD patients with moderate/severe depression only. MDD patients with mild or (newly) remitted depression showed similar performance and DLPFC activation as HC. This observation is in line with 18FDG-PET findings of Holthoff and colleagues (2004), who reported that remission was accompanied by dorsolateral and dorsomedial PFC (and cingulate) metabolism as compared with the active depressed state, although no direct comparison with healthy controls was made. Furthermore, we observed that in MDD with comorbid anxiety disorders increased left DLPFC activation occurred subthreshold, independent of illness severity. In PD and SAD, normal performance and no planning related activation differences were observed, nor did we find significant correlations of anxiety severity in anxiety disorder patients with or without comorbid depression. Results were unrelated to variations in regional gray matter volume. Finally, no overall effects of SSRI-use were observed, consistent with reports in bipolar patients (Goswami et al., 2009).

Our finding of normal executive functioning related fronto-striatal activation in panic disorder and social anxiety disorder are consistent with those of Van den Heuvel and coworkers (2005b) during classical Stroop performance in panic disorder. In the present study we chose to capitalize on our sample size by incorporating all anxiety disorders within one group, which enabled us to identify their shared task-related activity patterns as compared with the comorbid group, in which MDD was often accompanied by more than one anxiety disorder. Taken together, these findings suggest that, in contrast to obsessive compulsive disorder (van den Heuvel et al., 2005a), executive function in panic disorder, social anxiety disorder, and generalized anxiety disorder is not abnormal.

Similar to Fitzgerald and coworkers (2007), we observed increased dorsolateral PFC activation during Tower of London performance in MDD, although in the contralateral hemisphere. The explanation for this lateralization difference

between the study of Fitzgerald and ours is unclear, but could result from a number of methodological issues, such as small sample size, the non-parametric task design, and the inclusion of error-trials in the study of Fitzgerald.

In the present study, task-related activity was assessed using a parametric load contrast, which is likely to be more specific for detecting task-related activity (Friston, Holmes, Poline, Price, & Frith, 1996). In addition, we could not replicate the findings of abnormal Tower of London performance coupled with decreased frontal-striatal activation as reported by Elliott and colleagues (1997). However, the sample size in this early PET study was small ($n=6$), and the use of psychotropic medication and presence of comorbid Axis-I disorders was not controlled for. Also, Elliott and coworkers (1997) included the functional maps of poorly performing subjects; consequently, the possibility that decreased prefrontal activation was due to non-engagement during task blocks cannot be ruled out. Finally, our results are not in line with the observations of Goethals and coworkers (2005), who observed slower Tower of London performance coupled with decreased prefrontal perfusion in nine medicated MDD patients relative to nine control subjects. However, these authors used a fixed-order dual-scan ^{99m}Tc -SPECT method difficult to compare with conventional PET- and fMRI paradigms.

This is the first study that explicitly investigated executive functioning in comorbid depression-anxiety disorder. Our clinical data appear to support the suggestion that patients with comorbid depression-anxiety differ from MDD patients in their clinical profile and course (Bruce et al., 2005; Kessler et al., 2005; Rush et al., 2005), as the comorbid depression-anxiety patients showed higher depression and anxiety symptom scores than MDD patients. Also, the number of remitted comorbid depression-anxiety patients did not increase between the NESDA baseline measurement (T₁) and the MRI measurement (T₂), whereas depression and anxiety severity decreased substantially between T₁ and T₂ in MDD patients; almost one-third of the MDD patients reached the remitted phase by the time of scanning (i.e. within two months on average). With respect to task performance, contrary to our expectations, CDA patients showed no executive deficits as measured with the Tower of London, but showed a trend of increased left DLPFC recruitment as a function of increased planning load. This discrepancy in findings may indicate that CDA is primarily characterized by anxiety related neuropathology (i.e. no planning deficits), as in most patients the anxiety disorder was the first to manifest. However, this suggestion should be further tested in future research. Nevertheless, our results indicate that with respect to neural correlates of visuospatial planning, the comorbid condition of depression and anxiety is not identical to the pattern observed in MDD, especially with regard to the effects of depression severity.

The present results of similar task performance (i.e., error rates) across groups appear to be at odds with a number of neuropsychological studies that showed executive deficits in MDD. Given that executive functions are implicated particularly in novel problem solving (Alvarez & Emory, 2006), the

Tower of London arguably has adequate face validity. In contrast, the construct validity and specificity of executive tasks like the frequently used Wisconsin Card Sorting Test and verbal fluency tasks has been called into question (Alvarez & Emory, 2006; Carpenter, Just, & Reichle, 2000). Interestingly, whereas previous Tower of London imaging studies (Elliott et al., 1997; Fitzgerald et al., 2007; Goethals et al., 2005) have reported abnormal performance in MDD, neuropsychological studies have shown mixed results: two studies reported impaired performance in middle-aged MDD subjects (Elliott et al., 1996; Naismith et al., 2003), but studies in younger subjects failed to demonstrate impaired Tower of London performance in MDD (Naismith, Longley, Scott, & Hickie, 2007; Porter, Gallagher, Thompson, & Young, 2003; Purcell, Maruff, Kyrios, & Pantelis, 1997). Behavioral results from the present study are therefore in agreement with these latter neuropsychological studies and may indicate that cognitive functioning is relatively unaffected in the outpatient population (Castaneda et al., 2008; Castaneda et al., 2010; Gladsjo et al., 1998; van Wingen et al., 2009).

Imaging results of the present study are partially in agreement with previous imaging studies in MDD using other executive tasks such as the Stroop task, working memory tasks (n-back and delayed match to sample) and verbal fluency tasks, although these tasks may be characterized as tasks of selective attention and behavioural inhibition as well. Most (Matsuo et al., 2007; Wagner et al., 2006; Walter, Vasic, Hose, Spitzer, & Wolf, 2007), but not all (Videbech et al., 2004) neuroimaging studies using working memory or Stroop tasks reported similar task performance in patients and controls. Increased (dorsal) lateral PFC (Matsuo et al., 2007; Wagner et al., 2006; Walter et al., 2007), frontopolar (Matsuo et al., 2007) and ACC (Wagner et al., 2006) activation has been reported during n-back and Stroop performance in MDD, although not consistently (Siegle et al., 2007). In contrast, two studies using a verbal fluency paradigm in MDD reported impaired performance coupled with increased (Okada, Okamoto, Morinobu, Yamawaki, & Yokota, 2003) or normal dorsolateral PFC activation (Videbech et al., 2003). However, verbal fluency tasks rely heavily on intact semantic memory, and therefore verbal fluency impairment may be reflective of a more generalized impairment than executive dysfunction (Henry & Crawford, 2005).

The present study has a number of strengths. We recruited a large and representative outpatient sample, which allowed us to compare several clinical groups to our healthy controls, and to investigate the effects of psychotropic drug use (SSRIs) and symptom severity within each clinical group. All patients were extensively screened, according to the NESDA protocol (Penninx et al., 2008). Moreover, our control subjects were also recruited through NESDA, were similarly screened and scan-naïve. Therefore, familiarity with researchers and/or experimental procedures could be ruled out as a potential confound. Furthermore, we used an event-related design, to decrease expectancy effects and to allow post hoc selection of correct trials; in addition, we excluded

participants that performed insufficiently, to minimize the risk of non-compliance as a confounder.

Several potential limitations should also be noted. First, since the epidemiological NESDA cohort was recruited through general practitioners and outpatient clinics, we may not have been fully able to capture the most severe end of the depressive spectrum. Second, MDD and comorbid depression-anxiety patients differed slightly from healthy controls in years of education, although neither performance nor task-associated brain activity was significantly correlated with education level (data not shown). Third, since we employed only one executive task, care needs to be taken when generalizing our results outside the executive function domains of planning (Kafer & Hunter, 1997; Unterrainer & Owen, 2006), problem solving (Unterrainer & Owen, 2006), and inhibition (Culbertson & Zillmer, 1998). Fourth, although similar 3-tesla systems were used at each site in this multi-center study, variability in image acquisition may have occurred due to minor differences in hardware (receiver coil), imaging parameters, and timing of software upgrades; also, scanning sessions were scheduled at different hours (between 8 am and 8 pm) across participating centers, but no systematic scanning time x diagnosis bias occurred.

Our findings of relatively increased prefrontal activation associated with task load in currently depressed patients are in agreement with previous studies in MDD and could be interpreted as reflecting less efficient recruitment of neural resources when faced with increasing task demands in MDD, a suggestion that is in line with neurocircuitry models of depression (i.e. Drevets et al., 2008; Mayberg, 1997; Clark, Chamberlain, Shakian, 2009). We also found that increased dorsolateral PFC recruitment in MDD is present only in the moderate to severe depressive state, but not in mildly depressed and remitted states, which suggests high resilience of the brain executive network and does not indicate permanent frontal damage. Also, since the increased recruitment of planning resources occurred in the context of normal planning accuracy, we need to be careful in interpreting our findings as supportive of the notion of executive dysfunction in MDD outpatients. Finally, our results of increased dorsolateral PFC activation in severe MDD, but not in severe comorbid depression-anxiety seem to indicate subtle differences in neurophysiological profiles in MDD patients with or without comorbid anxiety disorders. Therefore, we may conclude that prefrontal hyperactivation during high planning demands is not a trait characteristic, but a state characteristic of MDD, occurring independent of SSRI use; however, executive dysfunction is not a feature of anxiety disorders (i.e., panic disorder, social anxiety disorder, generalized anxiety disorder), supporting the current distinction between anxiety disorders and depression.

In conclusion, future longitudinal studies need to investigate the hypothesis that prefrontal over-recruitment during planning performance normalizes after recovery from depression in MDD without comorbid anxiety. Also, whereas the present results indicate that within the context of a neutral task executive

functions in MDD and anxiety disorders are not grossly abnormal, future research should investigate whether executive functions are compromised when processing emotional stimuli, to further elucidate the role of executive functions in controlling emotions in these disorders.

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COMPARISON OF THE CURRENT SAMPLE TO THE NESDA MAIN-SAMPLE

Groups were highly representative of the main NESDA sample with respect to diagnosis distribution, sex distribution, depression severity and anxiety severity at the time of baseline measurement. Out of the 2981 included in the main sample, 1961 matched our diagnostic inclusion criteria and were aged between 18 and 57. Of these 1961, 19 % (66% female) fulfilled the criteria for our MDD group, 33 % (66% female) for CDA, 21% (70 % female) for ANX and 28% (67 % female) for the HC group. Finally, the total group of subjects in the MRI study consisted of 24 % (63% female) MDD, 30 % (66% female) CDA, 23 % (72% female) ANX and 23 % (62% female) HC. Although the sub sample of participants included in the MRI study were highly representative of the main sample at the time of baseline interview, at the time of scanning diagnostic groups showed lower depressive scores than at the time of baseline measurements (paired sample non-parametric test; MDD: $z = -5.0$; CDA: $z = -4.1$; ANX: $z = -3.7$; all $p < .001$, see table S2), but showed equivalent anxiety scores (mean # days between baseline measurement and MRI = 65 ± 45). Overall, patients groups included in the MRI study were on average two years younger. The sub sample of healthy controls were slightly older (+ 2.8) and higher educated (+ 1.4 years) than the HC in the main sample.

Variable		MDD (n=65)		CDA (n=82)		ANX (n=64)	
		Mean	SD	Mean	SD	Mean	SD
IDS T1	total score	28.18	9.67	32.8	11.81	22.55	1.66
IDS T2	total score	19.76	11.03	29.06	11.83	18.67	10.70
BAI T1	total score	12.05	9.05	18.13	9.00	14.16	8.02
BAI T2	total score	9.13	8.27	18.33	9.06	13.60	9.50
interval	days	65.95	39.95	58.66	51.12	68.11	31.18

**TABLE S-1:
ILLNESS SEVERITY
AT T1 AND T2 WITHIN
PATIENT GROUPS**

IDS= Inventory of Depressive Symptomatology; BAI= Beck's Anxiety Inventory; T1=time of baseline assessment; T2=time of MRI measurement; interval = time between T1 and T2.

Lobe	region	MNI coordinate			Z value
		x	y	z	
TABLE S-2: MAIN EFFECTS OF INCREASING TASK LOAD OVER ALL SUBJECT (N=274)					
Main effects for the contrast 'increasing task load' are reported at $p<.05$, FWE-corrected. BA= Brodmann Area; side=hemisphere; L=left; R=right.					
<i>Frontal</i>					
Left	superior frontal	-21	12	54	>8
	middle frontal	-36	30	39	7.07
	middle frontal	-36	54	12	5.82
Right	superior frontal	27	12	54	>8
	middle frontal	33	24	48	>8
	medial frontal	3	24	45	6.54
<i>Parietal</i>					
Left	precuneus (BA 7)	-6	-63	42	7.70
	inferior parietal	-51	-51	42	7.24
	inferior parietal	-54	-42	42	6.58
Right	precuneus (BA 7)	9	-63	48	6.95
	precuneus (BA 7)	9	-60	57	6.89
	inferior parietal	51	-45	42	7.21
	inferior parietal	48	-54	42	6.79
<i>Occipital</i>					
Left	angular gyrus (BA	-42	-72	36	5.70
Right	angular gyrus (BA	42	-72	33	6.72

