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Differential failure to deactivate the default mode network in unipolar and bipolar depression

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Abstract

Objectives: Neuroimaging studies have revealed evidence of brain functional abnormalities in bipolar depressive disorder (BDD) and major depressive disorder (MDD). However, few studies to date have compared these two mood disorders directly.

Methods: Matched groups of 26 BDD type I patients, 26 MDD patients and 26 healthy controls underwent fMRI while performing the n-back working memory task. A whole-brain ANOVA was used to compare the three groups and clusters of significant difference were examined further using ROI analysis.

Results: The whole-brain ANOVA revealed a single cluster of significant difference in the medial frontal cortex. The BDD and MDD patients both showed failure to deactivate in this area compared to the controls. The BDD patients showed significantly

greater failure of de-activation than the MDD patients, which was not accounted for by differences in severity or chronicity of illness between them.

Conclusions: Failure of de-activation, considered to reflect default mode network dysfunction, is present to a greater extent in bipolar than unipolar depression. The study of this network may be useful in the search for brain markers that distinguish the two disorders.

Key words: bipolar disorder, major depressive disorder, depression, default mode network, functional magnetic resonance imaging.

Distinguishing bipolar depressive disorder (BDD) from major depressive disorder (MDD) in individuals who have not as yet experienced a clear episode of mania is an as yet unfulfilled goal of affective disorder research (1-4). Among other things, this might have implications for treatment. Thus, while long-term antidepressant treatment is recommended for prevention of relapse in MDD (5), its use in bipolar disorder has been associated with detrimental adverse effects such as induced hypomania and mania and rapid cycling (6-8).

Most research on this question to date has focused on the question of whether the two forms of depression are distinguishable clinically. Presence of delusions and psychomotor retardation have been found to be significantly more associated with BDD than MDD, and other features such as shorter episode length or worse response to depression treatment may also be discriminatory (9). However, it is doubtful that such quantitative differences could be useful in clinical practice (3, 10).

Another potential way to distinguish the two disorders is by brain imaging, particularly functional brain imaging. In a review of studies using emotional paradigms, which have revealed robust evidence of abnormality in affective disorders generally, Almeida and Phillips (1) found two studies that directly compared BDD and MDD patients. One (11) examined neural responses to negative and positive facial emotions in 15 BDD and 15 MDD patients and 15 healthy controls. No differences were seen between the two patient groups in responses to happy faces, but increased activation was seen in the left amygdala in response to fearful and especially sad expressions. Examination of functional connectivity between the amygdala and the

orbitofrontal/medial frontal cortex in these patients, however, only revealed evidence of difference between patients and healthy controls (12). In a study published after Almeida and Phillips (1)' review, Cerullo et al. (13) compared 25 BDD and 25 MDD patients as well as 25 healthy controls during performance of a modified form of the continuous performance task where some trials used pictures with both neutral and emotional distractors. Comparison of the emotional to the neutral images revealed a wide range of clusters of significant difference between the two groups, including the lingual gyrus, the cuneus and precuneus, the occipital cortex, the middle temporal gyrus, the posterior cingulate gyrus, parahippocampal cortex and parts of the frontal and parietal cortex; in some of these areas the MDD patients showed greater activation than the BDD patients and in other the the reverse was true.

A small number of studies have compared patients with BDD and MDD during the performance of cognitive tasks. Bertocci et al. (14) compared 18 BDD patients, 23 MDD patients and 16 healthy controls during performance of a version of the n-back task where the stimuli (letters) were flanked by emotional or neutral faces. During neutral trials, they found that the BDD patients showed greater activation than the MDD patients in a predetermined region of interest (ROI) the left mid-dorsal anterior cingulate cortex, but not in the dorsolateral prefrontal cortex (DLPFC) or a number of subcortical ROIs. Diler et al. (15) compared 12 adolescent BDD patients and 10 MDD patients during performance of the Go/NoGo task and found no activation differences between the two patient groups. In the study of Cerullo et al. (13), cited above, comparison of activations during the non-emotional trials revealed that the MDD patients showed greater activations than the BDD patients in regions including the left inferior parietal lobule, the left and right parahippocampal gyrus, the left cerebellum, the medial frontal gyrus and the left post central gyrus.

In addition to activations, performance of a wide range of attention-demanding tasks is known to produce de-activations. The regions affected are similar across tasks and are collectively referred to as the default mode network; they include two midline regions, the medial prefrontal cortex (mPFC) and the posterior cingulate cortex/precuneus, and also the angular gyrus, the lateral temporal cortex, and the hippocampus (16, 17).

Default mode network dysfunction, including both failure of de-activation and changes in resting state connectivity, has been documented in a range of psychiatric and

neuropsychiatric disorders (for a review see Broyd et al. (18), and these include MDD (19-22) and bipolar disorder (23-29). To date, however, no studies have compared de-activation between these two mood disorders.

In this study we examined patterns of cognitive task activation and de-activation in patients with BDD and MDD and also healthy controls. The task used was the n-back task, which has been shown to produce patterns of abnormal activation in both groups of patients (14, 20, 21, 23, 24, 30-34). This task has also been found to produce robust performance related de-activations in healthy controls(35, 36).

METHODS

Participants

A sample of 26 BDD and 26 MDD patients were recruited from the acute units of Hospital Benito Menni CASM, the General Hospital of Granollers and the Hospital Clinic of Barcelona. The BDD patients met DSM-IV criteria for bipolar disorder type I and those with MDD met DSM-IV criteria for major depressive disorder, based on clinical interview and review of case notes. All patients were currently in a depressive episode and were scanned at a time when they had a 21-item Hamilton Depression Rating Scale (HDRS) score ≥ 17 .

Patients were excluded a) if they were left-handed; b) if they were younger than 18 or older than 65; c) if they had a history of brain trauma or neurological disease; d) if they had shown alcohol/substance abuse within 12 months prior to participation; and e) if they had undergone electroconvulsive therapy in the previous 12 months.

All patients were on drug treatment. The BDD patients were taking the following: mood stabilisers (n=23: lithium alone or in combination=15; valproate alone or in combination=6; lamotrigine=1), antidepressants (n=15) anxiolytics/ hypnotics (n=24) and/or antipsychotics (n=14: second generation=12; first generation=1; combination=1); data were missing for 2 patients. For the MDD group, the numbers were: antidepressants (n=23), anxiolytics/hypnotics (n=26) and/or antipsychotics (n=5: second generation=4; first generation=0; combination=1); mood stabilisers (n=1).

A group of 26 healthy controls were recruited via poster and web-based advertisement

in the hospital and local community, plus word of mouth requests. They met the same exclusion criteria as the patients, and they were also excluded if they reported a history of mental illness or treatment with psychotropic medication or had a first-degree relative with a psychiatric illness.

All three groups were matched on demographic variables including age, sex and premorbid IQ. This latter variable was estimated using the Word Accentuation Test (Test de Acentuación de Palabras, TAP) (37, 38) a pronunciation test that is conceptually similar to the National Adult Reading Test (NART) (39). Subjects have to pronounce low-frequency Spanish words whose accents have been removed.

The Clinical Research Ethics Committee of the Sisters Hospitallers (Comité de Investigación en Investigación Clínica de Hermanas Hospitalarias) approved the research protocol. All subjects included in the study gave written informed consent prior to participation.

Scanning procedure

All subjects underwent fMRI scanning while performing a sequential-letter version of the n-back task (40) in a 1.5 Tesla GE Signa scanner (General Electric Medical Systems, Milwaukee, Wis) located at the Sant Joan de Déu Hospital in Barcelona (Spain).

Two levels of memory load (1-back and 2-back) were presented in a blocked design manner. Each block consisted of 24 letters that were shown every 2 s (1 s on, 1 s off) and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within the blocks. Individuals had to indicate repetitions by pressing a button. Four 1-back and four 2-back blocks were presented in an interleaved way, and between them a baseline stimulus (an asterisk flashing with the same frequency as the letters) was presented for 16 s. To identify which task had to be performed, characters were shown in green in 1-back blocks and in red in the 2-back blocks. All participants first went through a training session outside the scanner.

The behavioural measure used was the signal detection theory index of sensitivity, d' (41). Higher values of d' indicate better ability to discriminate between targets and

distractors. Subjects who had negative d' values in either or both of the 1-back and 2-back versions of the task, which suggests that they were not performing it, were a priori excluded from the study.

fMRI data acquisition and analysis

In each individual scanning session 266 volumes were acquired. A gradient echo echo-planar imaging (EPI) sequence depicting the blood oxygenation level-dependent (BOLD) contrast was used. Each volume contained 16 axial planes acquired with the following parameters: TR = 2000 ms, TE = 20 ms, flip angle = 70° , section thickness = 7 mm, section skip = 0.7 mm, in-plane resolution = 3x3 mm. The first 10 volumes were discarded to avoid T1 saturation effects.

fMRI image analyses were performed with the FEAT module, included in FSL software (42). At a first level, images were corrected for movement and eventually co-registered and normalised to a common stereotaxic space (Montreal Neurologic Institute template). Normalised images were spatially filtered with a Gaussian filter (FWHM = 5 mm). To minimize unwanted movement-related effects, individuals with an estimated maximum absolute movement > 3.0 mm or an average absolute movement > 0.3 mm were excluded from the study. General linear models were fitted to generate individual activation maps for the baseline versus 1-back and baseline versus 2-back contrasts for the three independent groups. Statistical tests of these contrasts were carried out at the cluster level with a family-wise corrected p-value of 0.05 using Gaussian random field methods. The default threshold of $z = 2.3$ was used to define the initial set of clusters.

Using the same fitted linear mixed-effects model, each patient subgroup was individually compared with the healthy controls. Subsequently, ANOVA was used to compare all three groups. Clusters of significant difference among the groups that were identified in this last whole-brain analysis were then used as regions-of-interest (ROIs) in order to examine the relative levels of activation/de-activation for each group in each cluster identified.

RESULTS

Demographic and clinical data for the patients and healthy controls are shown in **Table1**. The groups were well matched for age, sex and estimated premorbid IQ. The

MDD patients had higher scores on the HDRS than the BDD patients; also the BDD patients had a longer duration of illness, an earlier onset, a higher rate of history of psychotic symptoms and a larger number of previous depressive episodes than the MDD patients. There were no differences in functioning as assessed by Global Assessment of Functioning (GAF) between the two groups.

[Table 1 around here]

Performance on the n-back test

There were significant differences in performance among the groups on the 1-back ($F=4.91$, $p=0.01$) and the 2-back ($F=11.02$, $p<0.001$) versions of the task. Post-hoc testing (Tukey HSD) indicated that the BDD patients performed significantly worse than the healthy controls on the 1-back task (mean d' 3.48 ± 1.33 vs. 4.39 ± 0.84 , $p=0.008$) and that the MDD patients showed trend-level poorer performance than the healthy controls (mean d' 3.76 ± 0.97 vs. 4.39 ± 0.84 , $p=0.09$). No significant differences were found between the two patient groups (MDD mean d' 3.48 ± 1.33 vs. BDD mean d' 3.76 ± 0.97 , $p=0.61$)

On the 2-back task, the MDD patients performed significantly worse than the healthy controls (mean d' 2.26 ± 0.88 vs. 3.15 ± 0.98 , $p=0.002$), as did the BDD patients (mean d' 2.03 ± 0.85 , $p<0.001$). Again, there were no significant differences between the two patient groups (MDD mean d' 2.26 ± 0.88 vs. BDD mean d' 2.03 ± 0.85 ; $p=0.62$).

fMRI findings

Mean activations and de-activations in the three groups

Mean activations and de-activations for the healthy controls and the two patient groups are shown in **Figure 1 and Table 2**.

In the 2-back vs. baseline, healthy controls showed a pattern of bilateral DLPFC activations along with clusters in the anterior insula, both precentral gyri, the supplementary motor areas, the cerebellum, the thalamus, the basal ganglia, and parts of the superior parietal cortex. They also showed de-activations in the mPFC, the parahippocampus and adjacent cortical regions, and the primary visual areas extending

to the cuneus and precuneus. In the 1-back vs. baseline, activations followed a broadly similar pattern but the clusters were less extensive and no activations were seen in cerebellum and in the basal ganglia. De-activations were also present, particularly in cuneus/precuneus region .

Activations and de-activations in the MDD and BDD patients followed a broadly similar pattern to that seen in the healthy controls. However, the clusters were noticeably less extensive, particularly with respect to the mPFC de-activation cluster.

[**Figure 1** around here]

Between-group differences

The 2-back vs. baseline contrast revealed that, compared to the healthy controls, the MDD patients showed significantly reduced activation in a single cluster located in the cerebellum extending to superior occipital regions and a failure to deactivate in the mPFC (see **Figure 2** and **Table 2**). No differences were found in the 1-back vs baseline condition.

The BDD patients showed significantly reduced activation compared to the healthy controls in clusters in the left DLPFC and the right cerebellum and they also showed failure of de-activation in the mPFC (see **Figure 2** and **Table 2**). In the 1-back vs baseline, bipolar patients showed less deactivation in dorsomedial prefrontal cortex and cuneus/precuneus

[**Figure 2** around here]

Whole brain ANOVA including all three groups resulted in one cluster of significant difference in the 2-back vs. baseline condition. This was located in the mPFC (see **Figure 3** and **Table 2**). No differences were found in the 1-back vs. baseline condition.

[**Figure 3** around here]

Box plots for de-activations within an ROI based on this cluster are shown in **Figure 3**. All three groups showed de-activation, with the levels in the MDD and BDD being

significantly greater than in the healthy controls. There was also a significant difference between the MDD and BDD patients, with the latter showing the lowest levels of deactivation (i.e. the most pronounced failure of deactivation).

Relationship with demographic and clinical characteristics

To examine the possible association between the degree of mPFC abnormality and these factors, a multiple regression analysis was carried out on the combined sample of patients. Specifically, the mean individual BOLD response in the mPFC cluster was considered as the dependent variable and the following variables were taken as independent (predictor) variables: group (MDD or BDD), age, illness duration, illness onset, HDRS, MADRS and number of depressive episodes. Since history of psychotic symptoms was almost completely restricted to the bipolar group, its effect could not be tested. The overall model was not significant ($R^2=0.19$, $F_{[7,41]}=1.42$, $p=0.22$) and the only significant individual predictor was the group variable ($\beta=-2.65$, $p=0.01$).

Relationship with drug treatment

We also examined mean activations in the mPFC cluster in relation to antipsychotic and antidepressant treatment in the combined sample of patients. No significant difference between those taking antipsychotics ($N=19$, 14 BDD and 5 MDD) and those not taking these drugs ($n=31$, 10 BDD and 21 MDD), (-5.66 ± 18.89 vs. -10.58 ± 23.05 ; $t=0.78$, $p=0.44$) or between those taking antidepressants ($n=38$, 15 BDD and 23 MDD) and not taking antidepressants ($n=12$, 9 BDD and 3 MDD) (-10.01 ± 20.04 vs. -4.60 ± 26.15 ; $t=-0.76$, $p=0.45$). Mood stabilizers could not be examined as 23 of the 26 BDD patients were taking these drugs in contrast to only 1 of the MDD patients, ie this treatment modality was a proxy for group membership

DISCUSSION

This study found that, while both BDD and MDD patients showed activation and deactivation differences from healthy controls, only the latter finding distinguished the two patient groups. In particular, failure of de-activation in the mPFC was present to a significantly greater degree in the BDD patients. This difference did not appear to be attributable to differences in severity or chronicity of illness between the two groups, or to those aspects of treatment status that could be examined.

Comparing both patient groups individually with the healthy controls revealed evidence of reduced activation, although these changes were considerably more extensive in the BDD than in the MDD patients. Specifically, the BDD patients showed reduced activation in the DLPFC, similar to previous findings by ourselves (23) in a larger (and overlapping) sample of patients and healthy controls, and to findings in two other studies using the n-back task (32, 34). In contrast, the comparison between the MDD patients and the healthy controls revealed only reduced cerebellar activation. One possible explanation for the failure to find evidence of DLPFC changes in the MDD patients might be in terms of lack of power – reduced activation in this frontal region was found in another, larger study by our group using the n-back task (20).

Alternatively, it could be that DLPFC hypoactivation is not a robust finding in MDD. In support of this latter interpretation Wang et al. (43), meta-analyzed 11 voxel based fMRI studies of MDD patients that used working memory tasks, and found reduced activation in the insula, precentral gyrus and precuneus, but not in the DLPFC or other frontal regions. Instead there was increased activation in the left inferior and middle frontal gyrus and the left precentral gyrus.

Both the BDD and the MDD patients in our study showed failure of de-activation compared to the healthy controls. This is again in agreement with previous studies from our group using the n-back task (20, 23, 24). Other studies using a range of cognitive and emotional tasks have also found failure of de-activation affecting in MDD patients, which affected particularly the mPFC (19, 21, 22). Bertocci et al. (14) also found de-activation changes in their study examining groups of BDD and MDD patients: the unipolar patients showed failure of de-activation in in the left and right midcingulate region compared to healthy controls, and there were similar changes in this region in the bipolar patients on the right.

The key finding of the present study was that medial frontal failure of de-activation was greater in the BDD than the MDD patients. One possible explanation for this finding could be in terms of illness factors, i.e. the fact that the BDD patients showed a longer duration of illness and a larger number of previous depressive episodes, something that is a common finding in studies comparing the two disorders (3, 44, 45). However, neither of these clinical variables emerged as significant predictors of mPFC activity in the regression analysis. Nor did severity of depressive symptoms as measured by the

HDRS appear to be a significant predictive factor. Finally, drug treatment did not seem to be an important influence on the findings, although this could only be examined for antipsychotics and antidepressants.

Another potential explanation for the greater failure of de-activation in patients with BDD could be the more frequent history of psychotic symptoms in these patients in our sample. We could not test this possibility in our study historical psychotic symptoms were in 17 patients of the BDD group but only one of the MDD group, and so was effectively a surrogate for group membership. Several studies have found that presence of psychotic symptoms in major affective disorder influences brain functional changes (for a review see Busatto (46)) although it should be noted that the three fMRI studies included in this review only considered activation changes. We also failed find any evidence for an association between the presence of psychotic symptoms and failure to de-activate in the mPFC in our previous study of BDD patients (23).

Assuming these two explanations can be discounted, greater failure of de-activation in BDD than MDD patients presumably reflects a higher level of underlying default mode network dysfunction in the former disorder than in the latter. Why this might be so is unclear. Based mainly on studies that have found activation rather than de-activation in its two midline ‘hubs’ in the mPFC and the posterior cingulate cortex/precuneus, the function of the default mode network has been linked to cognitive activities such as thinking about the past, planning for the future, performing theory of mind tasks and making self vs other judgments (16, 47). However, the mPFC, in particular, may also have a role in functions that might be more relevant to mood disorders. Thus, Price and Drevets (48) have noted that this area, together with the medial orbitofrontal cortex, has anatomical connections with the amygdala, the rostral part of the insula, the hypothalamus and the periaqueductal gray substance, as well as other cortical and subcortical areas, such as the striatum and thalamus. They argue that data from animals suggest that this extended system is involved in forebrain modulation of visceral function in response to sensory or emotive stimuli. Phillips and Swartz (49) have made a closely similar proposal. Greater alteration of the mPFC in BDD than MDD patients might therefore reflect greater dysregulation in this system.

In conclusion, this study finds evidence of greater failure to deactivate the mPFC in BDD compared to MDD, despite the fact that these two presentations of affective illness show no qualitative clinical differences. This brain functional change may therefore be useful in the search for brain markers to distinguish the two disorders in their early stages. Some limitations need to be acknowledged. Sample sizes, though in the range of those typically used in functional imaging studies of major affective disorder, were relatively small, and it is possible that use of larger samples would have resulted in activation as well as de-activation differences between BDD and MDD patients. Also, the need to match the patient groups for age may have resulted in the BDD and/or the MDD group being demographically atypical, because these two types of patients have different mean ages of onset. As always in studies of patients with MDD, it is impossible to exclude the possibility that some patients diagnosed will develop manic or hypomanic episodes at in the future. The examination of the potential influence of medication on our findings was limited. However, Phillips et al. (50) reviewed the potential effects in functional neuroimaging studies in BD, and found no changes or even a normalizing effect of antipsychotics and lithium; findings were similar in another recent review (51).

AUTHOR DISCLOSURE

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Conflict of interest

All authors declare that they have no conflicts of interest.

Financial disclosures

None of the authors declare any financial disclosures related to this study.

Contributors

Drs. McKenna, Pomarol-Clotet, Rodríguez-Cano and Vieta were involved in the design of the study. Drs. Alonso-Lana, Goikolea, Paloma-Fernández, Rodríguez-Cano and Sarró participated in recruitment, clinical evaluation and data acquisition. Drs. Rodríguez-Cano and Sarró were principally responsible for data pooling and Drs. Alonso-Lana, Salvador undertook the statistical analysis. Drs Pomarol-Clotet, Rodríguez-Cano, Sarró, Alonso-Lana and Salvador were responsible for preparation of the final version of the manuscript. All authors contributed to and have approved the final manuscript.

Figure 1: Areas of significant activation (red- yellow) and deactivation (blue) from the 2-back vs. baseline contrast in the three groups of subjects.

HC: Healthy controls; MDD: Major Depressive Disorder; BDD: Bipolar Depressive Disorder. The right side of the image is right side of the brain. MNI coordinates for each one of the axial slices are shown in the last row. Colors depict scores from statistical z maps.

Figure 2: Brain clusters showing statistically significant differences in the 2-back v. baseline condition among the MDD and BDD groups compared with the healthy controls.

HC: Healthy controls; MDD: Major Depressive Disorder; BDD: Bipolar Depressive Disorder. The right side of the image is the right side of the brain. Colors depict scores from statistical z maps.

Figure 3: Cluster of significant difference found comparing the two patient groups and healthy controls.

Brain region in the mPFC cortex where significant difference was found comparing the two patient groups and healthy controls in the 2-back v. baseline contrast; Box plot based on mean activation values extracted from the significant cluster. ***: significant at $p < 0.001$; *.significant at $p < 0.05$ based on the posthoc Turkey's HSD test. The right

side of the image is the right side of the brain. HC: Healthy controls; MDD: Major Depressive Disorder; BDD: Bipolar Depressive Disorder.

Table 1. Demographic and clinical characteristics of the groups (N=78). Values are given as mean (standard deviation).

	MDD N=26	BDD N=26	HC N=26	<i>Statistics</i>
Age	46.50 (13.30)	45.58 (9.23)	46.77 (11.18)	F=0.23; p=0.79
Gender	10/16	10/16	10/16	$\chi^2=0.00$; p=1.00
TAP fsiq	99.42 (7.14)	101.16 (9.49) ^a	99.60 (9.96) ^a	H=1.60; p=0.45
Duration of illness (years)	10.50 (9.78)	18.35 (11.30)	-	t=-3.10; p=0.03
Illness onset (years)	36.00 (18.86)	27.23 (12.09)	-	t=2.53; p=0.01
HDRS	27.00 (4.51)	24.04 (4.60)	-	t=2.34; p=0.02
MADRS	33.71 (6.10) ^b	29.88 (5.62)	-	t=2.31; p=0.02
GAF	47.50 (6.24)	45.45 (11.77) ^c	-	Z=-0.01; p=0.99
History of psychotic symptoms (yes/no)	1/25	17/7 ^b	-	$\chi^2=24.31$; p<0.001
Number of depressive episodes	3.69 (3.77)	6.24 (3.68) ^a	-	Z=-2.76; p=0.006

MDD: Major Depressive Disorder; BDD: Bipolar Disorder in depressive phase; HC: Healthy controls; TAP: Word Accentuation Test (Test de Acentuación de Palabras); HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; GAF: Global Assessment of Functioning; F: one-way ANOVA test; χ^2 : Chi-square test; H: Kruskal-Wallis test; t: t-student test; Z: Mann-Whitney U tests. ^a one missing; ^b two missings; ^c four missings.

Table 2. Significant activations and deactivations in the 1-back vs. baseline and 2-back vs baseline conditions and between-group differences.

Region (AAL Atlas)	BA	Voxels	P value	Z score	MNI x,y,z
HC					
1-back > baseline					
Precuneus Left	6	8612	1.69e-13	5.89	-54,-2,48
Parietal Inferior Left	40	3131	1.97e-06	5.94	-38,-44,44
Precentral Right	6	2838	5.72e-06	5.26	36,-2,50
Occipital Inferior Left	19	1797	0.000366	5.48	-42,-72,-12
Parietal Inferior Right	40	852	0.0348	4.9	34,-50,42
Baseline > 1-back					
Precuneus Right	-	16827	1.32e-21	7.04	4,-78,50
Frontal Superior Medial Left	10	4908	5.38e-09	6.44	-4,68,26
Occipital Middle Left	19	1818	0.000334	5.86	-42,-76,36
Temporal Middle Left	21	825	0.0403	4.41	-62,-12,-18
2-back > Baseline					
Supplementary Motor Area Left	-	71142	0	8.15	2,16,48
Baseline > 2-back					
Rectus Left	11	18442	8.72e-23	7.81	-2,50,-14
Precuneus Right	30	6237	1.34e-10	6.85	6,-52,18
Occipital Superior Right	-	866	0.0341	6.36	18,-92,36

MDD						
1-back > baseline						
	Supplementary Motor Area Left	-	10842	6.9e-16	6.4	0,6,56
	Parietal Inferior Left	7	2069	0.000116	4.98	-32,-58,54
	Occipital Inferior Left	19	1976	0.000171	5.05	-50,-74,-10
	Angular Right	7	1264	0.00419	4.71	36,-58,50
Baseline > 1-back						
	Precuneus Right	-	16788	1.43e-21	6.84	4,-78,50
	Frontal Superior Medial Left	10	1910	0.000225	5.25	-8,64,32
	Angular Left	39	930	0.0229	4.24	-44,-70,30
	Occipital Middle Right	39	829	0.0395	4.66	44,-80,28
2-back > Baseline						
	Supplementary Motor Area Right	32	24911	4.83e-28	7.03	4,18,48
	Parietal Inferior Left	40	18744	4.82e-23	6.34	-30,-48,42
	Parietal Inferior Right	40	3816	2.38e-07	6.51	46,-50,48
Baseline > 2-back						
	Precuneus Right	30	10913	8.52e-16	6.45	6,-56,18
	Frontal Medial Orbital Left	11	5670	6.84e-10	5.5	-2,52,-10
BDD						
1-back > baseline						
	Parietal Inferior Left	40	13986	5.4e-19	5.32	-42,-44,44
	Frontal Middle Right	46	2996	3.22e-06	4.14	38,34,24
	Parietal Superior Right	7	1043	0.0126	3.78	34,-58,54
Baseline > 1-back						
	Precuneus Right	7	4473	2.11e-08	4.43	6,-66,60
2-back > Baseline						
	Parietal Inferior Left	40	37314	5.47e-37	7.21	-40,-46,42
	Parietal Inferior Right	40	4047	1.19e-07	5.93	34,-50,42
Baseline > 2-back						
	Cingulum Posterior Right	23	3562	5.36e-07	5.21	6,-50,30
MDD vs. HC						
MDD > HC						
1- back vs baseline	-					
2-back vs. baseline	Rectus Left	11	1221	0.00186	3.8	0,48,-18
HC > MDD						
1-back vs baseline	-					
2-back vs baseline	Occipital Superior Left	17	1668	0.000174	4.05	-16,-86,8
BDD vs. HC						
BDD > HC						
1- back vs baseline	Frontal Superior Medial Right	10	1302	0.00118	4.86	4,68,32
	Calcarine Left	18	1148	0.00279	3.89	-4,-68,20
2-back vs baseline	Rectus Left	11	8070	1.15e-14	5.65	-2,50,-16
HC > BDD						
1-back vs baseline	-					

2-back vs baseline	Cerebellum Right		1475	0.00047	4.12	22,-66,-38
	Frontal Inferior Operculum Left	48	1074	0.00429	3.55	-40,12,18

ANOVA

1-back vs baseline	-					
2-back vs baseline	Rectus Left	11	3689	2.66e-08	5.21	-2,50,-16

AAL: Automated Anatomical Labeling, BA: Brodmann Area; MNI: Montreal Neurological Institute

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HC

MDD

BDD

z=-19

z=-3

z=6

z=28

z=46

z=56

bdi_12517_f1.tif

MDD VS HC

BDD VS HC

z= -19

z=-3

z=6

z=28

z=46

z=56

bdi_12517_f2.tif

bdi_12517_f3.tif

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