Abstract

The psychosocial functioning of individuals suffering from bipolar disorder (BD) has a significant impact on prognosis and quality of life. The aim of this study ~~important implications for prognosis and quality of life. Our aim~~ was to assess brain functional correlates of psychosocial functioning in BD individuals during the performance of a working memory task. Sixty-two subjects **(**31 euthymic BD individuals and 31 matched healthy controls) underwent structural and functional magnetic resonance imaging scanning while performing the 1- and 2-back versions of the n-back task (1-back and 2-back). ~~n-back task.~~ The Functional Assessment Short Test (FAST) and its subdomains were used to assess functioning. Whole brain analysis revealed only overall activation differences between BD patients and healthy controls, but the patients showed failure of de-activation in the medial frontal cortex. ~~Whole-brain voxel-based correlations with the FAST scores were examined in the patient group.~~ Six clusters of significant inverse correlation with the FAST scores were found in the dorsolateral prefrontal cortex, the superior parietal cortex, and temporo-occipital regions bilaterally, and in the left inferior frontal cortex. Cognitive and occupational functioning were the subdomains most significantly associated with brain activation in these clusters. The results suggest that poor psychosocial functioning in BD individuals is associated with hypoactivation in a range of cortical regions, including the fronto-parietal working memory network and inferior temporo-occipital regions.
~~Poor psychosocial functioning in BD individuals is associated with hypoactivation in a broad range of cortical regions, particularly in the fronto-parietal working memory network and inferior temporo-occipital regions.~~

Keywords: working memory; bipolar disorder; functioning; fMRI; FAST; n-back

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Figure 1

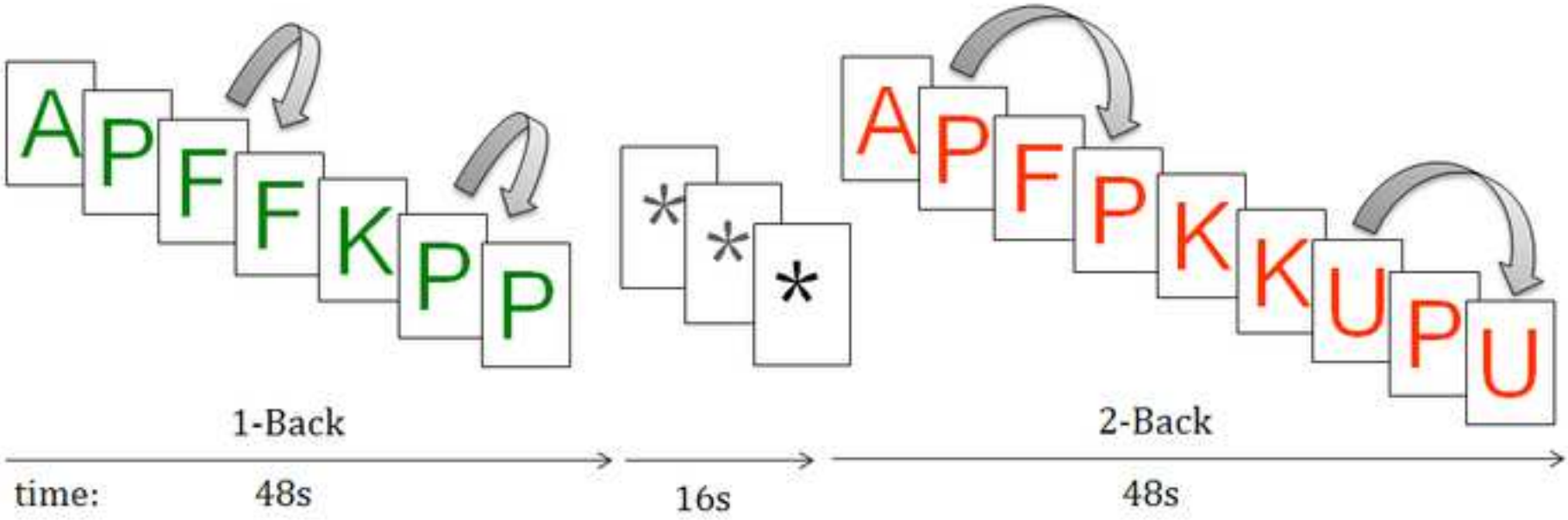

Figure 2

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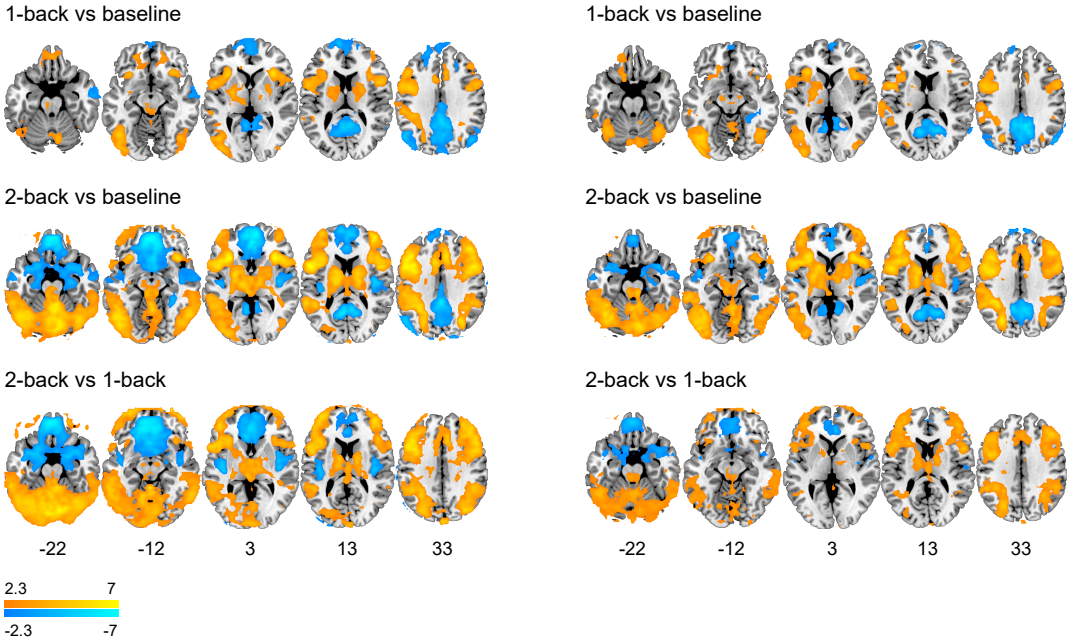

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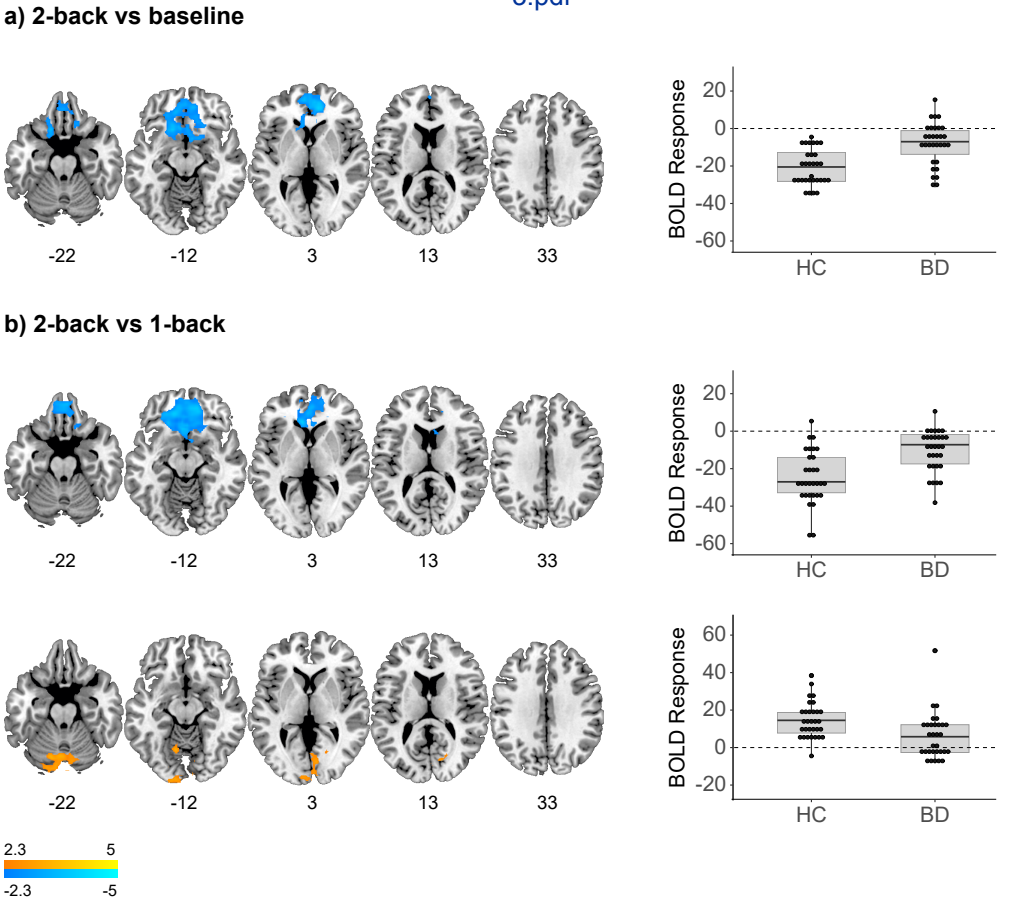

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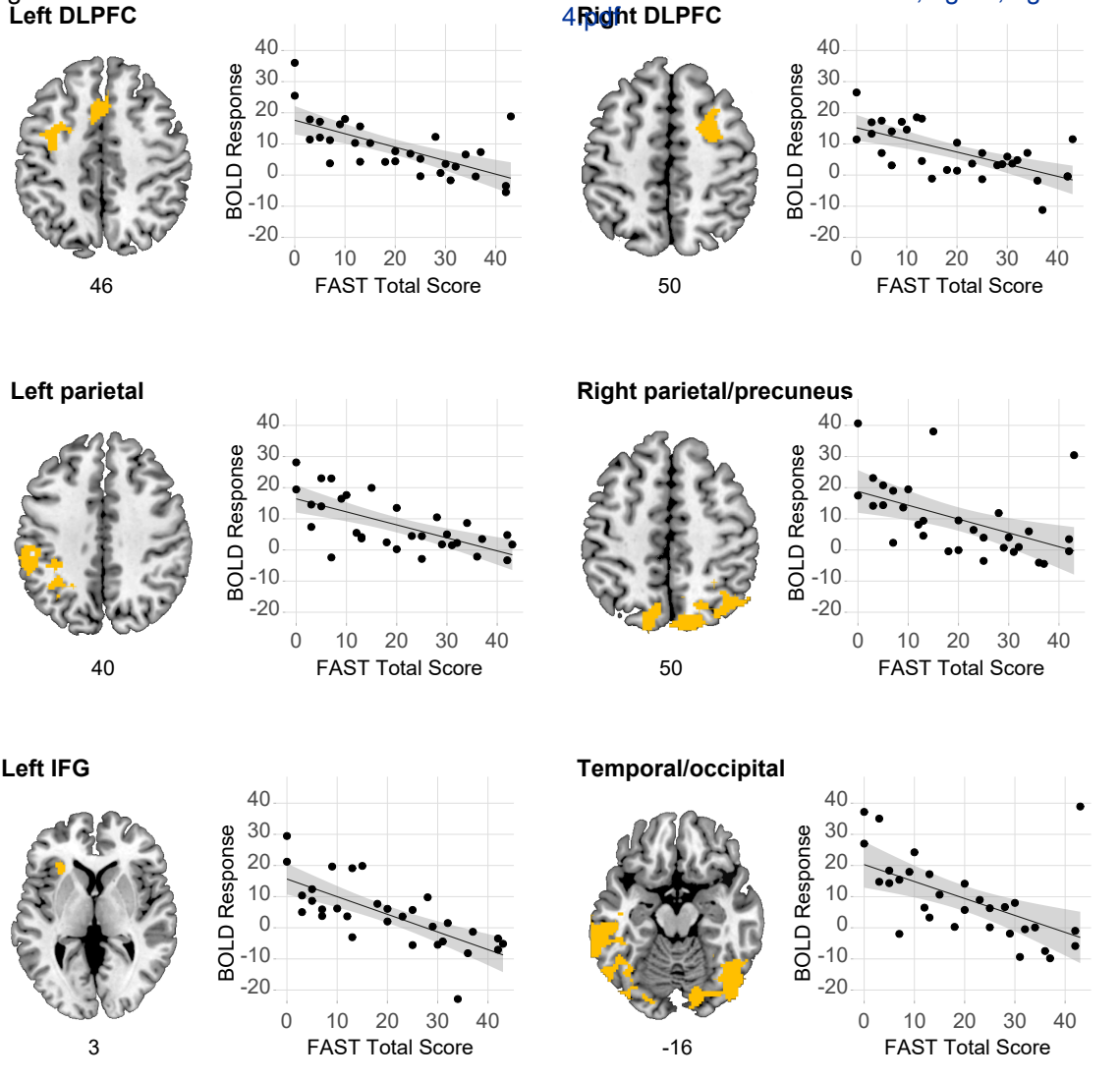

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions: NV and SA-L designed the study, managed the literature searches, undertook the statistical analysis, and wrote the first draft of the manuscript. EV, EP-C designed the study and supervised the realization of the study. SS, TM, JMG, CMB, LS, AR, ER-C helped in the recruitment of the patients and in the realization of the study procedures. PS-P and RS helped in the statistical analysis, revised the first draft and added critical comments to guide the redaction of the final manuscript. All the

authors revise the second draft of the article and provided critical comments to guide the redaction of the final manuscript. All authors approved the final manuscript.

Supporting Files

1. Introduction

Individuals suffering from bipolar disorder (BD) may experience persistent incapacity despite euthymia (Solé et al., 2018), and only one out of four reach~~es~~ both clinical remission and global functional recovery (Rosa et al., 2011). As a consequence, BD has significant~~is associated with severe disability, with important~~ implications for the patient's quality of life and for public health (Grande et al., 2016).

Predictors of long-term functioning have been widely studied and cognition has been found to be one of the most important factors that contributes to poor functional capacity in BD, even after controlling for potential clinical moderator variables and using different functional measurement methods (Baune and Malhi, 2015; Gitlin and Miklowitz, 2017).

Among the different approaches to measure psychosocial functioning, the clinician-rated Functional Assessment Short Test (FAST) ~~is one of the clinician-rated scales most commonly used and it~~ has been developed specifically to assess functioning in BD (Rosa et al., 2007) and is currently widely employed. Using this scale, functional deficits in BD ~~were~~ have been reported not only in the acute phases of the disease but also in euthymia (Léda-Rêgo et al., 2020; Rosa et al., 2010). These functional deficits have been found to be ~~and~~ associated with poor cognitive performance, particularly affecting ~~mainly predicted by~~ verbal memory and executive function ~~scores, along with other clinical and socio-demographical variables~~ (Bonnín et al., 2010; Mora et al., 2016, 2013)~~. Moreover, cognitive decline after a follow-up of 6 years in these cognitive domains correlated with poorer general, cognitive and occupational psychosocial functioning (Mora et al., 2013b), even in excellent lithium responders (Mora et al., 2016b).~~

It is ~~still~~ not known whether psychosocial functioning impairment in BD is related to the brain functional abnormalities observed in this disorder. Functional magnetic resonance imaging (fMRI) studies have found abnormal activation changes in fronto-limbic regions that might ~~explain~~ be relevant to the emotional dysregulation and cognitive symptoms present in the disorder (Phillips and Swartz, 2014). Another potential candidate here is the default mode network (DMN), which has also been found to show abnormality in ~~More recently,~~ BD in the shape of failure of de-activation during cognitive task performance in multiple studies ~~has been also characterized by a dysfunction in the default mode network (DMN)~~ (Alonso-Lana et al., 2019; Farruggia et al., 2020; Fernández-Corcuera et al., 2013; Pomarol-Clotet et al., 2015, 2012). The DMN is~~,~~ a set of brain regions including prominently two midline cortical areas, the medial frontal cortex and the posterior cingulate gyrus/precuneus, ~~strongly interconnected~~ that

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are active at rest but deactivate during attention-demanding tasks (Raichle, 2015). The DMN is implicated in self-directed cognitive operations such as autobiographical recall and planning the future (Buckner et al., 2008). Default mode network activity has been found to show a relationship to cognitive function in healthy subjects, in particular increased activity has been found to be associated with lapses in attention (Anticevic et al., 2012; Buckner et al., 2008).

O~~However, there is o~~nly one fMRI study to date appears to have~~, as far as we know, that has~~ examined the brain functional correlates of general functioning in BD (Yoshimura et al., 2014). In this study, which used a verbal fluency task in a sample of 10 euthymic BD type I participants and 10 healthy controls (HC), a significant positive correlation was found between Global Assessment of Functioning (GAF) scores and brain activation in the left anterior cingulate and lateral prefrontal cortex (Yoshimura et al., 2014). Besides the very small sample size, this study used the GAF scale, a well-known instrument that assesses a mix of functioning and clinical symptoms, and thus, it may be less sensitive to measure deficits in functioning (Akers et al., 2019). ~~Also, two other studies have examined brain structural correlates of psychosocial functioning using the GAF (Forcada et al., 2011) and FAST (Sartori et al., 2018). In the latter study, FAST scores in a sample of 35 euthymic BD individuals correlated with the left superior and rostral middle frontal cortex volumes, and with the right white matter and lateral ventricle volumes (Sartori et al., 2018).~~

~~Despite these previous findings, more studies are needed in order to ascertain the brain bases of the functional impairment in BD during euthymia. Thereby, t~~The aim of this study was to further examine the relationship between brain functional changes in BD and psychosocial functioning during euthymia. We examined brain activations and de-activations during performance of a working memory task, the n-back task, and measured psychosocial functioning using the FAST.

2. Methods

2.1. Participants

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~~The study enrolled 62 subjects.~~ The patient sample consisted of 31 currently euthymic adults meeting DSM-IV criteria for BD type I, recruited from two different hospitals in Barcelona (~~:~~ Benito Menni CASM and Hospital Clínic). BD patients were excluded if they were (a) younger than 18 or older than 65; (b) left-handed; (c) had a history of brain trauma or neurological disease, (d) had shown alcohol/substance abuse/dependency within 12 months prior to participation; or (e) had undergone electroconvulsive therapy in the previous 12 months. BD individuals were considered to be euthymic ~~if they did~~based on not ~~present~~ having had an episode~~s~~ of illness for at least three months before inclusion ~~and if they had~~plus having a total score on the Hamilton Rating Scale for Depression (HDRS-21) ≤8 and on the Young Mania Rating Scale (YMRS) ≤8 at the time of testing, in order to avoid the potentially confounding effects of subthreshold depressive and manic symptoms on cognitive function (Bonnín et al., 2012). ~~All BD individuals were taking medication at the time of the scanning, particularly all the BD individuals were treated with lithium or another mood stabilizer, 17 BD individuals were treated with atypical antipsychotics and 1 patient with a long-acting atypical formulation whilst 8 BD individuals were taking antidepressants.~~

The BD patients were additionally required to have an ~~Premorbid IQ~~ntelligence Quotient (IQ) ~~should be~~ in the normal ~~range (IQ≥85~~range. This was~~), as~~ estimated using the Word Accentuation Test (Test de Acentuación de Palabras, TAP) (Del Ser et al., 1997; Gomar et al., 2011), a pronunciation test that requires the pronunciation of low-frequency Spanish words whose accents ~~were~~ have been removed. This measure is conceptually similar to the English-language National Adult Reading Test (NART) (Nelson and Willison, 1991) and the Wide Ranging Achievement Test (WRAT) (Wilkinson and Robertson, 2017).

All the BD individuals were taking medication at the time of the scanning: all were taking lithium or another mood stabilizer; 18 were taking atypical antipsychotics and 8 were taking antidepressants.

The healthy controls (

HC, ~~(~~n = 31) ~~were included to determine if areas of correlation in BD individuals where within those activated/deactivated by HC during the task. The 31 HC~~ were selected to be matched to the BD individuals for age, sex (as determined by the subjects' gender as reported in the interview) and TAP-estimated IQ, and they met the same exclusion criteria. HC were also excluded if they reported a history of mental illness or treatment with psychotropic medication, and/or had a first-degree relative with a

psychiatric illness. Healthy controls underwent structured psychiatric interview (SCID-I-II (First et al., 2002, 1997)) to exclude current or past psychiatric disorders.

The Clinical Research Ethics Committee of the Sisters Hospitallers approved the research protocol. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All subjects included in the study gave written informed consent prior to participation.

2.2. Psychosocial functioning assessment

Psychosocial functioning in the BD individuals was assessed by means of the FAST, an interviewer-administered instrument developed by the Bipolar and Depressive Disorders Program of the Hospital Clínic in Barcelona ~~(Spain)~~ to assess functional impairment in BD (Rosa et al., 2007), ~~even~~ including ~~in the early stages of disease~~first episode patients (Amoretti et al., 2021). High internal consistency, ~~high~~ validity and ~~strong~~ test-retest reliability ~~were reported for the FAST~~have been found for the test (Rosa et al., 2007). ~~The FAST assessment refers to the last~~ Ratings of functioning refer to the preceding 15 days and the scale comprises 24 items, which are divided in 6 specific areas of functioning: 1) a~~A~~utonomy; 2) o~~O~~ccupational functioning; 3) c~~C~~ognitive functioning; 4) f~~F~~inancial issues; 5) i~~I~~nterpersonal relationships; and 6) l~~L~~eisure t~~T~~ime. Items can be rated using a 4-point scale, from 0=no difficulty to 3=severe difficulty. The global score is calculated by summing the scores of each item, ~~ranging~~ and ranges from 0 to 72, ~~resulting in a measure of disability where~~ with higher scores ~~refer to~~indicating more ~~serious difficulties~~impairment: ~~. In BD,~~ scores from 0 to 11 indicate no impairment; from 12 to 20, ~~represent~~indicate ~~the category of~~ mild impairment; ~~moderate impairment comprises scores~~ from 21 to 40, moderate impairment; and ~~scores~~ above 40 ~~reflect~~ indicate severe functional impairment (Bonnín et al., 2018).

2.3. Scanning procedure

All subjects underwent functional MRI scanning in a single session using a 1.5 Tesla GE Signa scanner (General Electric Medical Systems, Milwaukee, Wis) located at the Sant Joan de Déu Hospital in Barcelona (Spain). Participants performed a sequential letter version of the n-back task (Gevins and

Cutillo, 1993) in the scanner, a ~~which was~~ widely employed ~~as a measure of~~ working memory test for use in fMRI ~~and~~ which produces robust activations and deactivations in healthy subjects (Mencarelli et al., 2019; Owen et al., 2005). Two levels of memory load (1-back and 2-back) were presented in a blocked design manner (Figure 1). In the 1-back task participants had to detect when one letter was repeated twice consecutively, whereas in the 2-back task there was one letter between the model and the goal letter. Each block consisted of 24 letters shown every 2 seconds (1 second on, 1 second off) and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within the blocks. Four 1-back and four 2-back blocks were presented in an interleaved way, and between them an asterisk flashing with the same frequency as the letters, representing a baseline stimulus, was presented for 16 seconds. Accordingly, the total number of stimuli in the 1-back and 2-back trials were 24 for four 1-back or 2-back blocks (making a total of 192 stimuli).

Participants~~, which first underwent a training session outside of the scanner,~~ had to indicate repetitions by pressing a button in the scanner. In order to identify which task had to be performed, characters were shown in green in 1-back blocks and in red in 2-back locks~~.~~. All participants first underwent a training session outside the scanner.

- Please insert Figure 1 here -

The behavioural measure used was the signal detection theory index of sensitivity (d') (Green and Swets, 1966). Higher values of d' indicate better ability to discriminate between targets and distractors. Subjects who had negative d' values ~~in the perf~~for performance in either or both of the 1-back and 2-back versions of the task, suggesting that they were not performing it, were a priori excluded from the study. Two subjects (both patients) obtained a positive d-prime and were excluded.

In each scanning session, 266 volumes were acquired. A gradient 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: repetition time (TR)=2000 ms, echo time (TE)=20 ms, flip angle=70°, section thickness=7 mm, section skip=0.7 mm, in-plane resolution=3 × 3 mm. The first 10 volumes were discarded to avoid T1 saturation effects. In addition, a high resolution structural T1-weighted MRI data were acquired for anatomical reference and inspection with the following

acquisition parameters: matrix size 512x512; 180 contiguous axial slices; slice thickness of 1 mm, no slice gap; voxel resolution 0.47x0.47x1 mm3; echo time (TE) = 3.93 ms, repetition time (TR) = 2000 ms and inversion time (TI) = 710 ms; flip angle 15°.

2.4. Analysis of task-related fMRI activations and de-activations

~~I~~Preprocessing and ~~maging~~ analyses were performed with the FEAT module, included in FSL software (version 4.1 for Linux) (Smith et al., 2004).

Pre-processing with FSL-FEAT included: a) motion correction (Jenkinson et al., 2002); b) non-brain removal (Smith, 2002); c) isotropic 5mm-FWHM Gaussian smoothing; d) high-pass temporal filtering; e) time series statistical analysis with local autocorrelation correction (Woolrich et al., 2001); and f) registration to the MNI 152 standard space (Jenkinson et al., 2002; Jenkinson and Smith, 2001). Individuals with an estimated maximum absolute movement > 3.0 mm or an average absolute movement > 0.3 mm were excluded from the study to minimize unwanted movement-related effects.

Analysis followed a block design. General linear models (GLM) were fitted to generate individual activation maps for the 1-back vs. baseline, 2-back vs. baseline and 2-back vs. 1-back comparison. To further reduce the potential effect of movement, movement parameters were included as nuisance covariates in the fitting of individual linear models.

Differences in fMRI activation maps between BD individuals and HC and the association between FAST scores and brain activation were generated within the FEAT module, using mixed effects GLM models (Beckmann et al., 2006). FEAT uses Gaussian random field theory to properly account for the spatially distributed patterns when performing statistical tests. The analyses were carried out with the FLAME stage 1 with a default threshold of z=2.3 to define the initial set of clusters and a family-wise corrected p value < 0.05. To ~~study~~ examine the ~~association~~ relationship between functioning and brain activation during the n-back task, whole-brain regression analyses were performed, including sex, age and TAP-estimated IQ as covariates, since these factors would be expected to independently influence fMRI findings. The analyses were again carried out with a default threshold of z=2.3 and a family-wise corrected p value < 0.05.

~~In order to explore the associations with the six FAST subdomains, the significant clusters obtained in the above analysis were defined as regions of interest (ROIs) and mean parameter estimates for activation were extracted. Regression analyses between the extracted parameters estimates of the ROIs and the six FAST subdomains, controlling for sex, age and estimated IQ score, were conducted. All p-values were two-tailed and statistical significance was set at $p<0.05$. Bonferroni correction for multiple comparisons was applied. Statistical tests were carried out with the Statistical Package for Social Sciences (SPSS, v. 23 for Windows).Similarly, the possible association between the mean parameter estimates for activation of the ROI and subsyndromal symptoms (HDRS-21 and YMRS scores) was evaluated.~~Demographic and clinical variables were compared between HC and the BD individuals. Normality of continuous variables was evaluated and parametric (t-test) or non-parametric tests (Mann-Whitney) were applied as appropriate.

3. Results

3.1. Demographic and clinical data

Demographic characteristics and clinical data for the BD individuals and healthy controls are shown in Table 1. The two groups were matched for sex, age and TAP-estimated IQ. Mean FAST total score in the patients was 19.90, indicating mild impairment according to Bonnín et al. (Bonnín et al., 2018). A breakdown of the FAST total scores revealed that, according to the thresholds of severity defined by Bonnín et al. (Bonnín et al., 2018), 10 BD individuals showed no impairment in functioning (scores between 0 and 11), 7 BD individuals showed mild impairment (scores between 12 and 20), 11 BD individuals showed moderate impairment (scored between 21 and 40), and 3 BD individuals reported severe impairment (scores > 40).

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3.2. Behavioural results

~~Individuals suffering from BD~~The BD patients performed more poorly than the HC on the 1-back (d'=3.91 ± 0.96 versus 4.57 ± 0.57, t=3.287, p=0.002) and on the 2-back (d'=2.81 ± 0.76 versus 3.67 ± 0.77, t=4.466, p<0.001) versions of the task. To examine the possible association between behavioural performance and FAST total scores in BD individuals, a multiple regression analysis was carried out, controlling for sex, age and estimated IQ scores. Task performance was significantly inversely associated with the FAST total score on both the 1-back (t=-2.575, p=0.016) and the 2-back (t=-3.228, p=0.003) versions of the task. The overall model for the 2-back task performance was significant (1-back: $F_{[4,26]}$=2.562, adjusted R^2=0.17, p=0.062; 2-back: $F_{[4,26]}$=3.615, adjusted R^2=0.26, p=0.018).

3.3. fMRI findings

Within-group activations and de-activations

~~Mean~~ Clusters of activations in HC (Figure 2) in the 1-back versus baseline contrast ~~included bilateral activations~~were seen bilaterally in the dorsolateral prefrontal cortex (DLPFC), precentral cortex, supplementary motor area, inferior frontal cortex and insula, basal ganglia, parts of the temporal, parietal, occipital cortex, cerebellum and the left thalamus. In the 2-back versus baseline and in the 2-back versus 1-back contrasts, activations followed a broadly similar pattern to the 1-back versus baseline contrast, but the clusters were more extensive, the basal ganglia were more activated and activations were also seen bilaterally in the thalamus.

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The ~~control group~~HC ~~also~~ also showed areas of deactivation: these ~~that~~ were ~~mainly~~ seen bilaterally in the medial prefrontal cortex and posterior cingulate/precuneus in the 1-back versus baseline and more markedly ~~but particularly~~ in the 2-back versus baseline contrast. In the 2-back versus 1-back contrast, only the medial frontal cortex showed task-related deactivations.

In the BD ~~individuals~~patients, patterns of activation~~s~~ and de-activation~~s~~ were similar to those of the HC, although activations were less extensive and with smaller activations in the cerebellum and inferior middle occipital cortex. ~~Mainly~~ D~~d~~e-activations were ~~noticeably smaller~~also less extensive than in the

HC, particularly in the medial prefrontal cortex in the 2-back versus baseline and in the 2-back versus 1-back contrasts.

Between group differences

In the 1-back versus baseline and 2-back versus baseline contrast, there were no significant activation or de-activation differences between the HC and BD individuals. In the 2-back versus baseline contrast, the patients showed a significant failure to de-activate in a cluster ~~(cluster 1)~~ encompassing bilaterally the medial frontal cortex, the anterior cingulate cortex and the left caudate (peak MNI coordinates x=-8, y=44, z=-28; cluster size=3895 voxels; Z=4.1; p<0.001) (Figure 3). ~~No cluster of significant different activation between HC and BD individuals was found.~~

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In the 2-back versus 1-back contrast, the BD ~~individuals~~ patients ~~presented~~ showed a similar cluster ~~(cluster 1)~~ of significant failure of deactivation (peak in BA 11; peak MNI coordinates x=-14, y=40, z=-10; cluster size=4633 voxels; z score=4.17; p<0.001). They ~~, and~~ also showed a cluster of significantly reduced activation in ~~in a cluster (cluster 2) that included bilaterally~~ the cerebellum and ~~the~~ occipital region bilaterally~~s~~ (peak MNI coordinates x=-16, y=-74, z=-26; cluster size=2087 voxels; z score =3.65; p<0.001) (Figure 3).

Analysis of correlation with FAST total scores in the patient group

No significant clusters were seen in the 1-back versus baseline and 2-back versus baseline contrasts. However, in the 2-back versus 1-back contrast, six clusters of significant negative correlation were found (Figure 4). There were no clusters of significant positive correlation.

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~~In order to explore the associations with the six FAST subdomains, the significant clusters obtained in the above analysis were defined as regions of interest (ROIs) and mean parameter estimates for activation were extracted. Regression analyses between the extracted parameters estimates of the ROIs and the six~~

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~~FAST subdomains, controlling for sex, age and estimated IQ score, were conducted. All p-values were two-tailed and statistical significance was set at p<0.05. Bonferroni correction for multiple comparisons was applied. Statistical tests were carried out with the Statistical Package for Social Sciences (SPSS, v. 23 for Windows).~~

~~Similarly, the possible association between the mean parameter estimates for activation of the ROI and subsyndromal symptoms (HDRS-21 and YMRS scores) was evaluated.~~

~~The first significant~~One cluster ~~(left DLPFC)~~ included the left DLPFC, the left precentral cortex and the middle cingulate and supplementary motor area bilaterally (peak in BA 6; ~~AAL atlas region: left precentral cortex;~~ MNI coordinates x=-34, y=-8, z=48; cluster size=1285 voxels; Z=3.74; p<0.001).

~~The~~A second cluster ~~(right DLPFC)~~ was similar to the first cluster, but on the right ~~side~~, and encompasse~~d~~s the right DLPFC and the right superior frontal cortex (peak near BA 8; ~~AAL atlas region: right frontal middle cortex;~~ MNI coordinates x=22, y=2, z=48; cluster size=584 voxels; Z=3.75; p=0.0149).

The third cluster ~~(left parietal)~~ encompassed mainly the left inferior parietal cortex, extending from the supramarginal and angular gyrus to the superior parietal cortex (peak in BA 40; ~~AAL atlas region: left inferior parietal;~~ MNI coordinates x=-36, y=-52, z=46; cluster size=1512 voxels; Z=3.88; p<0.001).

The fourth cluster ~~(right parietal and precuneus)~~ included mainly the bilateral superior parietal cortex extending to the right angular gyrus, along with calcarine, cuneus, and precuneus bilaterally (peak in BA 7; ~~AAL atlas region: right superior parietal;~~ MNI coordinates x=20, y=-76, z=52; cluster size=1937 voxels; Z=4.52; p<0.001).

The fifth cluster ~~(left inferior frontal gyrus - IFG),~~ was located in the left ~~IFG~~inferior frontal gyrus, extending to the anterior insula and the superior temporal pole (peak in BA 38; ~~AAL atlas region: left superior temporal pole;~~ MNI coordinates x=-44, y=24, z=-22; cluster size=549 voxels; Z=3.77; p=0.0211).

The sixth cluster ~~(temporal and occipital),~~ encompassed inferior temporal and occipital regions bilaterally and the cerebellum, extending to the middle temporal cortex in the left hemisphere (peak in BA 21; AAL

atlas region: left middle temporal; MNI coordinates x=-68, y=-34, z=-8; cluster size=5552 voxels; Z=4.9; p<0.001).

~~In the evaluation of the possible association between the six clusters of significant negative correlation and subsyndromal symptoms (Supplementary Table 1), an inverse significant association only existed between the right DLPFC and subsyndromal depressive symptoms.~~

Analysis of correlation with FAST subdomains

In order to further explore the associations with ~~the six~~ FAST subdomains, the significant clusters obtained in the above analysis were defined as regions of interest (ROIs) and mean parameter estimates for activation were extracted. Regression analyses between the extracted parameters estimates of the ROIs and the six FAST subdomains, controlling for sex, age and estimated IQ score, were conducted. All p-values were two-tailed ~~and statistical significance was set at p<0.05.~~ and Bonferroni correction for multiple comparisons was applied. ~~Statistical tests were carried out with the Statistical Package for Social Sciences (SPSS, v. 23 for Windows).~~ Associations between the mean parameter estimates for activation of the ROI and subsyndromal symptoms (HDRS-21 and YMRS scores) were examined in the same way.

~~To examine the association between mean activation in each of the significant clusters with FAST subdomains scores, multiple regression analyses were carried out including sex, age and estimated IQ as covariates~~The findings are reported in detail in ~~(~~ Supplementary Table ~~2~~1. Briefly, the subdomain c~~Significant models were found for cognitive and occupational functioning. C~~ognitive functioning was significantly inversely associated with four out of six ROIs (left DLPFC: β=-0.615, p < 0.001; right DLPFC: β=-0.677, p < 0.001; left IFG: β=-0.6571, p < 0.001; temporal and occipital: β=-0.630, p < 0.001). Occupational functioning was also significantly inversely associated with two ROIs, the right DLPFC (β=-0.665, p < 0.001) and the left IFC (β=-0.700, p < 0.001).

~~In the evaluation of the possible association between the six clusters of significant negative correlation and~~ With respect to subsyndromal symptoms (Supplementary Table ~~Table 1~~2), a significant inverse correlation was found for ~~a inverse significant association only existed between the right DLPFC and~~ subsyndromal depressive symptoms with the right DLPFC cluster.

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4. Discussion

~~In the present study, we found that psychosocial~~ This study found that functioning in euthymic BD individuals, as measured using the FAST, ~~is~~ was ~~correlated~~ associated with reduced ~~brain~~ activation~~s~~ in a broa~~a~~d range of cortical regions during a working memory task. These regions included the~~Higher scores in the FAST scale, indicating poorer psychosocial functioning, were correlated with less activation in both~~ right and left DLFPC, left IFG and superior parietal and temporo-occipital regions bilaterally, among other areas. These clusters of significant correlation were, however, only seen in the 2-back versus 1-back contrast ~~associated with increased cognitive load and broadly encompassed the regions engaged by either HC or BD individuals during the task.~~

The regions found to be inversely correlated with functioning were broadly within the regions activated by both the HC and BD patients during the task, and were mainly located in the fronto-parietal and temporal cortex. They accordingly can be considered to be located in the so-called working memory network, related to attentional control and monitoring strategies (Owen et al., 2005). It has also been suggested that these regions form part of an extended multiple demands network that underlies performance of a range of different cognitive tasks that have in common executive control (Camilleri et al., 2018). In this respect it is interesting that we also identified a negative significant correlation between behavioural performance of BD individuals in the 2-back task (d-prime scores) with FAST total scores, meaning that worse behavioural performance in the task correlated with worse psychosocial functioning (higher FAST total scores). Thus, functioning was inversely correlated with both behavioural performance of the 2-back task and brain activation in the same 2-back contrast.~~In this respect it is interesting that we also identified a significant correlation between a behavioural measure of working memory performance ' of BD individuals in the 2-back vs baseline conditionand FAST total scores.~~

W~~Furthermore, w~~e found that the negative correlations between brain activations and FAST total scores were mainly driven by two subdomains of the scale, cognitive functioning and occupational functioning. ~~The~~ FAST ~~subdomain~~ cognitive functioning ~~, which measures cognitive performance from a non-neuropsychological perspective, and is therefore considered more subjective than a cognitive battery,~~ was significantly associated with brain activation in four out of six clusters, ~~particularly~~involving ~~with~~ the bilateral DLPFC, the left IFG and the temporal and occipital cortex. ~~The subdomain~~FAST occupational dysfunction was associated with reduced activation levels in two clusters ~~s, mainly~~ in the right DLPFC

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and the left IFG ~~cluster~~. Interestingly, in BD, occupational and cognitive functioning have been found to be the most affected subdomains, with a prevalence of 65.6% and 49.2%, respectively, along with an overall functional impairment prevalence of 58.6% in one study (Léda-Rêgo et al., 2020). Additionally, work disability and cognition are closely related and reduced performance on working memory has emerged as an important factor for predicting occupational functioning over time (Bonnín et al., 2010).

On the other hand, we did not find that failure of de-activation in the medial frontal cortex, the main area of difference between BD patients and HC found in this study, was associated with functioning as measured using the FAST. Medial frontal failure of de-activation is now a relatively robust finding in BD, having been documented ~~These regions, mainly located in the fronto-parietal and temporal cortex, are commonly activated during fMRI working memory paradigms such as the n-back task and were related to attentional control and monitoring strategies (Owen et al., 2005). It has also been suggested that they are engaged as a non-specific general cognitive activation network that underlies different cognitive tasks (Camilleri et al., 2018). However, these clusters of significant correlation did not match the brain regions where significant differences were found between euthymic BD individuals and HC. In comparison to HC, BD individuals presented a failure to deactivate the medial frontal cortex during the performance of the 2-back versus baseline and 2-back versus 1-back contrasts, along with a small cluster of reduced activation in the cerebellum and inferior occipital cortex in the latter contrast. This failure to de-activate the medial frontal cortex has been previously reported in BD~~in patients individuals regardless of affective state ~~and also in their healthy siblings, acting as a trait marker of this disorder~~ (Alonso-Lana et al., 2019; Fernández-Corcuera et al., 2013; Pomarol-Clotet et al., 2015, 2012). Other studies have reported similar changes in deactivation but in the posterior cingulate cortex/precuneus (Allin et al., 2010; Costafreda et al., 2011). Despite the fact that, as noted in the Introduction, the DMN is considered to be involved in cognitive function – specifically, attentional lapses (Anticevic et al., 2012; Buckner et al., 2008) – our findings do not provide support for a role in impaired functioning (including cognitive functioning) in patients with BD, as measured by the FAST. A previous study comparing cognitively preserved and impaired euthymic BD individuals, likewise found that cognitive impairment was associated with a reduced activation in the right DLPFC but not with the failure of de-activation in the medial frontal cortex (Alonso-Lana et al., 2016).

~~In the present study, this persistent DMN dysfunction does not seem to be related to psychosocial functioning in BD, at least in a direct manner. Conversely, we found significant correlations with brain regions that mainly belong to the "working memory network". This finding also supports the results of previous studies identifying a strong influence between neuropsychological performance and functional difficulties in individuals with BD. Impairment in cognition, particularly in executive function and verbal memory, has been seen to be strongly related to the psychosocial functioning of BD individuals assessed by means of the FAST, not only cross sectionally but also in longitudinal studies (Bonnín et al., 2010; Léda Rêgo et al., 2020; Mora et al., 2013; Rosa et al., 2010; Solé et al., 2018). Indeed, every complex every-day life activity requires the temporal availability of a certain amount of cognitive information that can be manipulated in order to allow individuals to interact with any life context (Gruszka and Nęcka, 2017). Thus, working memory capacity might be associated with different functional outcomes. In addition, we also identified a significant correlation between the behavioural performance of BD individuals and FAST total scores in the 2-back task, although this measure can only be considered as a proxy of working memory performance. Similarly, in a previous study comparing cognitively preserved and impaired euthymic BD individuals, cognitive impairment was associated with a reduced activation of the right DLPFC but not with the DMN dysfunction that was presented to a similar degree in both groups (Alonso-Lana et al., 2016a). Moreover, psychosocial functioning in BD is also influenced by the severity of other clinical features such as episode recurrence, residual clinical symptomatology, and illness progression and so it seems to be present in a heterogeneous way in different mood-states or subgroups of patients rather than be a stable trait (Samalin et al., 2017; Solé et al., 2018).~~

Our results ~~also partially match~~show some similarities to those reported in the only previous study ~~correlating~~ examining fMRI correlates of functioning in BD~~and fMRI activation~~. During a verbal fluency task, Yoshimura et al. (Yoshimura et al., 2014) found a significant inverse correlation between ~~the~~ GAF ~~global~~ score and ~~the~~ activation in two small clusters in the left anterior cingulate cortex and left lateral prefrontal cortex in 10 euthymic BD individuals. The areas identified in our study were larger and affected other areas as well, but it is possible ~~These areas of correlation again did not match the regions where significant differences were found between euthymic BD individuals and HC.~~ that, ~~our significant brain activations related to psychosocial functioning also affected other brain areas and were located bilaterally. These~~these differences reflect~~could~~ the ~~the differences in brain activations elicited by the distinct~~different tasks used and ~~tasks employed but also by t~~he smaller sample size ~~(10 BD individuals,~~

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10 HC) and the use of the GAF scale in the Yoshimura et al's, study. Another potential factor might be that the GAF scale is not , which is not as specific to psychosocial functioning as the FAST and also takes into account the level of current symptomatology. Indeed, in the present study, the psychosocial functioning has been assessed with the FAST scale, specifically aimed at assessing psychosocial functioning in BD individuals without taking in consideration severity of disease. Furthermore, the present findings rely on a bigger sample size.

Furthermore, we found that the correlation between brain activations and FAST total scores were mainly driven by two subdomains of the scale, cognitive and occupational functioning. The FAST subdomain *cognitive functioning*, which measures cognitive performance from a non-neuropsychological perspective, and is therefore considered more subjective than a cognitive battery, was significantly associated with the brain activation of four out of six clusters, particularly with the bilateral DLPFC, the left IFG and the temporal and occipital cortex. The subdomain *occupational dysfunction* was associated with activation levels, mainly in the right DLPFC and the left IFG cluster. In BD, occupational and cognitive functioning have been found indeed to be the most affected subdomains, with a prevalence of 65.6% and 49.2%, respectively, along with an overall functional impairment prevalence of 58.6% (Léda-Rêgo et al., 2020). Moreover, work disability and cognition are closely related and reduced performance on working memory has emerged as an important factor for predicting occupational functioning over time(Bonnín et al., 2010).

to date that have edsFinally, a longitudinal design would better capture functional trajectories and associated changes in neuroimaging.

ThisAs one of is only two studies the first study assessing examining the association between fMRI brain activations during a working memory task and psychosocial functioning in BD, our findings need to be interpreted withtherefore findings should be taken with caution. Nevertheless, the emergence of the lateral prefrontal cortex of as implicated in impaired functioning in euthymic patients with the disorder is noteworthy. If confirmed, this finding Despite this, the present study pointed out specific brain areas that correlate with the functional status of BD individuals. This might possibly beprove useful for future clinical interventions aimed at enhancing the psychosocial and/or cognitive performance of BD individualspatients, for example by targeting this region for and improving their psychosocial functioning, such as functional remediation, particularly addressing cognition and occupation subdomains

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~~in order to obtain global clinical and functional recovery in BD. Ideally, one possible relevant consequence of the present study might be to support anatomical targets for experimental studies of Trtranscranial magnetic stimulation (TMS) as an intervention for functional outcome in BD.~~ ***~~Limitations.~~*** The present study has limitations. At 31, the sample size of BD patients was relatively small. ~~As well as the relatively small sample sizes, As for substance use, we asked both~~ Ppresence of ~~patients and controls about~~ alcohol/substance abuse was based on subjective report unconfirmed by ~~within 12 months prior to participation, that represented an exclusion criterion but we did not perform an alcohol/substance~~ urinary or blood testing. Furthermore, BD individuals were taking medications, which differed in dosage and type. However, previous evidence suggests that the confounding effect of medication on neuroimaging findings in BD is relatively limited (Hafeman et al., 2012). The~~Likewise,~~ BD individuals included in the present study only displayed on average mild/moderate impairment in functioning. ~~by means of specific tools such as the Structured Clinical Interview (SCID) or the Mini International Neuropsychiatric Interview (MINI).~~We did not assess functioning i~~I~~n the ~~control group~~HC; h~~, functioning was not assessed by means of the FAST. H~~owever, ~~psychosocial functioning in~~psychosocial functioning in HC is expected to be preserved, with scoring on the FAST being almost wholly in the 'no impairment' range (Rosa et al., 2007), with accordingly little possibility to identify correlation between functioning and brain activations~~brain:behavioural correlations, with little possibility to identify a correlation between functioning and brain activations. Likewise, BD individuals included in the present study only displayed average mild/moderate impairment in functioning. The present study should be considered as exploratory and needs replication. Future studies with bigger sample sizes in psychosocial functioning among BD individuals should be conducted in order to confirm these findings and to guide personalized psychiatric interventions. Furthermore, BD individuals were taking medications, which differed in dosage and type. However, previous evidence suggests that the confounding effect of medication on neuroimaging findings in BD is relatively limited (Hafeman et al., 2012). Moreover~~Finally, the present study was carried out with a 1.5 T scanner. A 3.0 T scanner would provide higher resolution images and higher sensitivity for detecting changes in brain activation. However, signal-to-noise ratio was improved by reducing the number of slices and increasing the voxel volume, which is an efficient way of improving the signal strength in 1.5T scanners.

As one of only two studies to date that have examined associations between brain activations functioning in BD, our findings need to be interpreted with caution. Nevertheless, the emergence of the lateral

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prefrontal cortex of as implicated in impaired functioning in euthymic patients with the disorder is noteworthy. If confirmed, this finding might possibly prove useful for future interventions aimed at enhancing the psychosocial and/or cognitive performance of BD patients. Ideally, one possible relevant consequence of the present study might be to support anatomical targets for experimental studies of TMS as an intervention for functional outcome in BD.

~~This is the first study assessing the association between fMRI brain activations during a working memory task and psychosocial functioning in BD, therefore findings should be taken with caution. Despite this, the present study pointed out specific brain areas that correlate with the functional status of BD individuals. This might be useful for clinical intervention aimed at enhancing the cognitive performance of BD individuals and improving their psychosocial functioning, such as functional remediation, particularly addressing cognition and occupation subdomains in order to obtain global clinical and functional recovery in BD. Ideally, one possible relevant consequence of the present study might be to support anatomical targets for experimental studies of Transcranial magnetic stimulation (TMS) as an intervention for functional outcome in BD. As a consequence, the development of early interventions for BD aimed at improving functioning might contribute to reduce the burden and disability associated with BD and, hence, to increase quality of life.~~

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Table 1 Demographic and clinical data

Variable	BD Individuals (n=31)	Healthy Controls (n=31)	T value[b]	p-value
Sex: male/female	11 (35.5%) / 20 (64.5%)	11 (35.5%) / 20 (64.5%)		
Age (years)	45.54 (9.4)	44.84 (9.4)	-0.293	0.770
Estimated IQ (TAP)	106.61 (6.53)	106.35 (6.50)	- 0.156	0.877
FAST *total score*	19.90 (13.4)			
FAST *autonomy*[a]	2 (3) Range: 0 - 6			
FAST *occupational functioning*[a]	6 (13) Range: 0 - 15			
FAST *cognitive functioning*[a]	3 (7) Range: 0 – 13			
FAST *financial issues*[a]	0 (1) Range: 0 - 4			
FAST *interpersonal relationships*[a]	3 (5) Range: 0 - 8			
FAST *leisure time*[a]	2 (2) Range: 0 - 5			
HDRS-21[a]	2 (3) Range: 0 - 7			
YMRS[†]	1 (2) Range: 0 - 6			

Abbreviations: BD=bipolar disorder; F=females; **FAST**=Functioning Assessment Short Test; **HDRS-21**=Hamilton Rating Scale for Depression; **IQ**=intellectual quotient; **M**=males; **SD**=standard deviation; **TAP**=Test de Acentuación de Palabras - Word Accentuation Test; **YMRS**=Young Mania Rating Scale.
Notes: Values are means and standard deviations.
[a] Variable is not normally distributed. Values are medians and inter-quartile ranges (IQR).
[b] Comparisons were performed with two-sample t-tests. All t-values with a degree of freedom = 62

Figure legends

Figure 1. Sequential-letter version of the n-back task with two levels of memory load, 1-back (green) and 2-back (red).

Figure 2. Activation map for (a) healthy controls and (b) bipolar disorder individuals in the 1-back versus baseline, 2-back versus baseline and 2-back versus 1-back contrast. Colour bars indicate z scores; red to yellow colours indicate significant activation and blue to cyan colours indicate regions with significant deactivation. Numbers refer to Montreal Neurological Institute (MNI) z coordinates of the slice shown. The right side of the image is the right side of the brain.

Figure 3. Between group comparison in the (a) 2-back versus baseline and in the (b) 2-back versus 1 back contrasts. Color bars indicate z scores; red to yellow colours indicate areas hypo-activated by the bipolar disorder individuals and blue to cyan colours indicate failure to de-activate in the patient group. Boxplots of mean activations and de-activations for BD individuals and controls. Numbers refer to Montreal Neurological Institute (MNI) z coordinates of the slice shown. The right side of the image is the right side of the brain.

Figure 4. FAST correlations. Areas of significant negative correlation between the FAST total score and brain activity in the 2-back versus 1-back contrast. Box-plots of correlation between the FAST total score and the 6 clusters of brain activity in the 2-back versus 1-back contrast.

1. Introduction

Individuals suffering from bipolar disorder (BD) may experience persistent incapacity despite euthymia (Solé et al., 2018), and only one out of four reach both clinical remission and global functional recovery (Rosa et al., 2011). As a consequence, BD has significant implications for the patient's quality of life and for public health (Grande et al., 2016). Predictors of long-term functioning have been widely studied and cognition has been found to be one of the most important factors that contributes to poor functional capacity in BD, even after controlling for potential clinical moderator variables and using different functional measurement methods (Baune and Malhi, 2015; Gitlin and Miklowitz, 2017).

Among the different approaches to measure psychosocial functioning, the clinician-rated Functional Assessment Short Test (FAST) has been developed specifically to assess functioning in BD (Rosa et al., 2007) and is currently widely employed. Using this scale, functional deficits in BD have been reported not only in the acute phases of the disease but also in euthymia (Léda-Rêgo et al., 2020; Rosa et al., 2010). These functional deficits have been found to be associated with poor cognitive performance, particularly affecting verbal memory and executive function (Bonnín et al., 2010; Mora et al., 2016, 2013).

It is not known whether psychosocial functioning impairment in BD is related to the brain functional abnormalities observed in this disorder. Functional magnetic resonance imaging (fMRI) studies have found abnormal activation changes in fronto-limbic regions that might be relevant to the emotional dysregulation and cognitive symptoms present in the disorder (Phillips and Swartz, 2014). Another potential candidate here is the default mode network (DMN), which has also been found to show abnormality in BD in the shape of failure of de-activation during cognitive task performance in multiple studies (Alonso-Lana et al., 2019; Farruggia et al., 2020; Fernández-Corcuera et al., 2013; Pomarol-Clotet et al., 2015, 2012). The DMN is a set of brain regions including prominently two midline cortical areas, the medial frontal cortex and the posterior cingulate gyrus/precuneus, that are active at rest but deactivate during attention-demanding tasks (Raichle, 2015). The DMN is implicated in self-directed cognitive operations such as autobiographical recall and planning the future (Buckner et al., 2008). Default mode network activity has been found to show a relationship to cognitive function in healthy subjects, in particular increased activity has been found to be associated with lapses in attention (Anticevic et al., 2012; Buckner et al., 2008).

Only one fMRI study to date appears to have examined the brain functional correlates of general functioning in BD (Yoshimura et al., 2014). In this study, which used a verbal fluency task in a sample of 10 euthymic BD type I participants and 10 healthy controls (HC), a significant positive correlation was found between Global Assessment of Functioning (GAF) scores and brain activation in the left anterior cingulate and lateral prefrontal cortex (Yoshimura et al., 2014). Besides the very small sample size, this study used the GAF scale, a well-known instrument that assesses a mix of functioning and clinical symptoms, and thus, it may be less sensitive to measure deficits in functioning (Akers et al., 2019).

The aim of this study was to further examine the relationship between brain functional changes in BD and psychosocial functioning during euthymia. We examined brain activations and de-activations during performance of a working memory task, the n-back task, and measured psychosocial functioning using the FAST.

2. Methods

2.1. Participants

The patient sample consisted of 31 currently euthymic adults meeting DSM-IV criteria for BD type I, recruited from two different hospitals in Barcelona (Benito Menni CASM and Hospital Clínic). BD patients were excluded if they were (a) younger than 18 or older than 65; (b) left-handed; (c) had a history of brain trauma or neurological disease, (d) had shown alcohol/substance abuse/dependency within 12 months prior to participation; or (e) had undergone electroconvulsive therapy in the previous 12 months. BD individuals were considered to be euthymic based on not having had an episode of illness for at least three months before inclusion plus having a total score on the Hamilton Rating Scale for Depression (HDRS-21) $\leq$8 and on the Young Mania Rating Scale (YMRS) $\leq$8 at the time of testing, in order to avoid the potentially confounding effects of subthreshold depressive and manic symptoms on cognitive function (Bonnín et al., 2012).

The BD patients were additionally required to have an IQ in the normal range. This was estimated using the Word Accentuation Test (Test de Acentuación de Palabras, TAP) (Del Ser et al., 1997; Gomar et al.,

2011), a pronunciation test that requires the pronunciation of low-frequency Spanish words whose accents have been removed. This measure is conceptually similar to the English-language National Adult Reading Test (NART) (Nelson and Willison, 1991) and the Wide Ranging Achievement Test (WRAT) (Wilkinson and Robertson, 2017).

All the BD individuals were taking medication at the time of the scanning: all were taking lithium or another mood stabilizer; 18 were taking atypical antipsychotics and 8 were taking antidepressants.

The healthy controls (HC, n = 31) were selected to be matched to the BD individuals for age, sex (as determined by the subjects' gender as reported in the interview) and TAP-estimated IQ, and they met the same exclusion criteria. HC were also excluded if they reported a history of mental illness or treatment with psychotropic medication, and/or had a first-degree relative with a psychiatric illness. Healthy controls underwent structured psychiatric interview (SCID-I-II (First et al., 2002, 1997)) to exclude current or past psychiatric disorders.

The Clinical Research Ethics Committee of the Sisters Hospitallers approved the research protocol. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All subjects included in the study gave written informed consent prior to participation.

2.2. Psychosocial functioning assessment

Psychosocial functioning in the BD individuals was assessed by means of the FAST, an interviewer-administered instrument developed by the Bipolar and Depressive Disorders Program of the Hospital Clínic in Barcelona to assess functional impairment in BD (Rosa et al., 2007), including first episode patients (Amoretti et al., 2021). High internal consistency, validity and test-retest reliability have been found for the test (Rosa et al., 2007). Ratings of functioning refer to the preceding 15 days and the scale comprises 24 items, which are divided in 6 specific areas of functioning: 1) autonomy; 2) occupational functioning; 3) cognitive functioning; 4) financial issues; 5) interpersonal relationships; and 6) leisure time. Items can be rated using a 4-point scale, from 0=no difficulty to 3=severe difficulty. The global score is calculated by summing the scores of each item, and ranges from 0 to 72, with higher scores

indicating more impairment: scores from 0 to 11 indicate no impairment; from 12 to 20, indicate mild impairment; from 21 to 40, moderate impairment; and above 40 indicate severe functional impairment (Bonnín et al., 2018).

2.3. Scanning procedure

All subjects underwent functional MRI scanning in a single session using a 1.5 Tesla GE Signa scanner (General Electric Medical Systems, Milwaukee, Wis) located at the Sant Joan de Déu Hospital in Barcelona (Spain). Participants performed a sequential letter version of the n-back task (Gevins and Cutillo, 1993) in the scanner, a widely employed working memory test for use in fMRI which produces robust activations and deactivations in healthy subjects (Mencarelli et al., 2019; Owen et al., 2005). Two levels of memory load (1-back and 2-back) were presented in a blocked design manner (Figure 1). In the 1-back task participants had to detect when one letter was repeated twice consecutively, whereas in the 2-back task there was one letter between the model and the goal letter. Each block consisted of 24 letters shown every 2 seconds (1 second on, 1 second off) and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within the blocks. Four 1-back and four 2-back blocks were presented in an interleaved way, and between them an asterisk flashing with the same frequency as the letters, representing a baseline stimulus, was presented for 16 seconds. Accordingly, the total number of stimuli in the 1-back and 2-back trials were 24 for four 1-back or 2-back blocks (making a total of 192 stimuli).

Participants had to indicate repetitions by pressing a button in the scanner. In order to identify which task had to be performed, characters were shown in green in 1-back blocks and in red in 2-back locks. All participants first underwent a training session outside the scanner.

- Please insert Figure 1 here -

The behavioural measure used was the signal detection theory index of sensitivity (d') (Green and Swets, 1966). Higher values of d' indicate better ability to discriminate between targets and distractors. Subjects who had negative d' values for performance in either or both of the 1-back and 2-back versions of the task, suggesting that they were not performing it, were a priori excluded from the study. Two subjects (both patients) obtained a positive d-prime and were excluded.

In each scanning session, 266 volumes were acquired. A gradient 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: repetition time (TR)=2000 ms, echo time (TE)=20 ms, flip angle=70°, section thickness=7 mm, section skip=0.7 mm, in-plane resolution=3 × 3 mm. The first 10 volumes were discarded to avoid T1 saturation effects. In addition, a high resolution structural T1-weighted MRI data were acquired for anatomical reference and inspection with the following acquisition parameters: matrix size 512x512; 180 contiguous axial slices; slice thickness of 1 mm, no slice gap; voxel resolution 0.47x0.47x1 mm3; echo time (TE) = 3.93 ms, repetition time (TR) = 2000 ms and inversion time (TI) = 710 ms; flip angle 15°.

2.4. Analysis of task−related fMRI activations and de-activations

Preprocessing and analyses were performed with the FEAT module, included in FSL software (version 4.1 for Linux) (Smith et al., 2004). Pre-processing with FSL-FEAT included: a) motion correction (Jenkinson et al., 2002); b) non-brain removal (Smith, 2002); c) isotropic 5mm-FWHM Gaussian smoothing; d) high-pass temporal filtering; e) time series statistical analysis with local autocorrelation correction (Woolrich et al., 2001); and f) registration to the MNI 152 standard space (Jenkinson et al., 2002; Jenkinson and Smith, 2001). Individuals with an estimated maximum absolute movement > 3.0 mm or an average absolute movement > 0.3 mm were excluded from the study to minimize unwanted movement-related effects.

Analysis followed a block design. General linear models (GLM) were fitted to generate individual activation maps for the 1-back vs. baseline, 2-back vs. baseline and 2-back vs. 1-back comparison. To further reduce the potential effect of movement, movement parameters were included as nuisance covariates in the fitting of individual linear models.

Differences in fMRI activation maps between BD individuals and HC and the association between FAST scores and brain activation were generated within the FEAT module, using mixed effects GLM models (Beckmann et al., 2006). FEAT uses Gaussian random field theory to properly account for the spatially distributed patterns when performing statistical tests. The analyses were carried out with the FLAME stage 1 with a default threshold of z=2.3 to define the initial set of clusters and a family-wise corrected p

value < 0.05. To examine the relationship between functioning and brain activation during the n-back task, whole-brain regression analyses were performed, including sex, age and TAP-estimated IQ as covariates, since these factors would be expected to independently influence fMRI findings. The analyses were again carried out with a default threshold of z=2.3 and a family-wise corrected p value < 0.05.

3. Results

3.1. Demographic and clinical data

Demographic characteristics and clinical data for the BD individuals and healthy controls are shown in Table 1. The two groups were matched for sex, age and TAP-estimated IQ. Mean FAST total score in the patients was 19.90, indicating mild impairment according to Bonnín et al. (Bonnín et al., 2018). A breakdown of the FAST total scores revealed that, according to the thresholds of severity defined by Bonnín et al. (Bonnín et al., 2018), 10 BD individuals showed no impairment in functioning (scores between 0 and 11), 7 BD individuals showed mild impairment (scores between 12 and 20), 11 BD individuals showed moderate impairment (scored between 21 and 40), and 3 BD individuals reported severe impairment (scores > 40).

- Please insert Table 1 here –

3.2. Behavioural results

The BD patients performed more poorly than the HC on the 1-back (d'=3.91 ± 0.96 versus 4.57 ± 0.57, t=3.287, p=0.002) and on the 2-back (d'=2.81 ± 0.76 versus 3.67 ± 0.77, t=4.466, p<0.001) versions of the task. To examine the possible association between behavioural performance and FAST total scores in BD individuals, a multiple regression analysis was carried out, controlling for sex, age and estimated IQ scores. Task performance was significantly inversely associated with the FAST total score on both the 1-back (t=-2.575, p=0.016) and the 2-back (t=-3.228, p=0.003) versions of the task. The overall model for the 2-back task performance was significant (1-back: $F_{[4,26]}$=2.562, adjusted R^2=0.17, p=0.062; 2-back: $F_{[4,26]}$=3.615, adjusted R^2=0.26, p=0.018).

3.3. fMRI findings

Within-group activations and de-activations

Clusters of activations in HC (Figure 2) in the 1-back versus baseline contrast were seen bilaterally in the dorsolateral prefrontal cortex (DLPFC), precentral cortex, supplementary motor area, inferior frontal cortex and insula, basal ganglia, parts of the temporal, parietal, occipital cortex, cerebellum and the left thalamus. In the 2-back versus baseline and in the 2-back versus 1-back contrasts, activations followed a broadly similar pattern to the 1-back versus baseline contrast, but the clusters were more extensive, the basal ganglia were more activated and activations were also seen bilaterally in the thalamus.

- Please insert Figure 2 here –

The HC also showed areas of deactivation: these were seen bilaterally in the medial prefrontal cortex and posterior cingulate/precuneus in the 1-back versus baseline and more markedly in the 2-back versus baseline contrast. In the 2-back versus 1-back contrast, only the medial frontal cortex showed task-related deactivations.

In the BD patients, patterns of activation and de-activation were similar to those of the HC, although activations were less extensive and with smaller activations in the cerebellum and inferior middle occipital cortex. De-activations were also less extensive than in the HC, particularly in the medial prefrontal cortex in the 2-back versus baseline and in the 2-back versus 1-back contrasts.

Between group differences

In the 1-back versus baseline and 2-back versus baseline contrast, there were no significant activation or de-activation differences between the HC and BD individuals. In the 2-back versus baseline contrast, the patients showed a significant failure to de-activate in a cluster encompassing bilaterally the medial frontal cortex, the anterior cingulate cortex and the left caudate (peak MNI coordinates x=-8, y=44, z=-28; cluster size=3895 voxels; $Z=4.1$; $p<0.001$) (Figure 3).

- Please insert Figure 3 here –

In the 2-back versus 1-back contrast, the BD patients showed a similar cluster of significant failure of deactivation (peak in BA 11; peak MNI coordinates x=-14, y=40, z=-10; cluster size=4633 voxels; z score=4.17; p<0.001). They also showed a cluster of significantly reduced activation in the cerebellum and occipital region bilaterally (peak MNI coordinates x=-16, y=-74, z=-26; cluster size=2087 voxels; z score =3.65; p<0.001) (Figure 3).

Analysis of correlation with FAST total scores in the patient group

No significant clusters were seen in the 1-back versus baseline and 2-back versus baseline contrasts. However, in the 2-back versus 1-back contrast, six clusters of significant negative correlation were found (Figure 4). There were no clusters of significant positive correlation.

- Please insert Figure 4 here –

One cluster included the left DLPFC, the left precentral cortex and the middle cingulate and supplementary motor area bilaterally (peak in BA 6; MNI coordinates x=-34, y=-8, z=48; cluster size=1285 voxels; Z=3.74; p<0.001). A second cluster was similar to the first cluster, but on the right, and encompassed the right DLPFC and the right superior frontal cortex (peak near BA 8; MNI coordinates x=22, y=2, z=48; cluster size=584 voxels; Z=3.75; p=0.0149). The third cluster encompassed mainly the left inferior parietal cortex, extending from the supramarginal and angular gyrus to the superior parietal cortex (peak in BA 40; MNI coordinates x=-36, y=-52, z=46; cluster size=1512 voxels; Z=3.88; p<0.001). The fourth cluster included mainly the bilateral superior parietal cortex extending to the right angular gyrus, along with calcarine, cuneus, and precuneus bilaterally (peak in BA 7; MNI coordinates x=20, y=-76, z=52; cluster size=1937 voxels; Z=4.52; p<0.001). The fifth cluster was located in the left inferior frontal gyrus, extending to the anterior insula and the superior temporal pole (peak in BA 38; MNI coordinates x=-44, y=24, z=-22; cluster size=549 voxels; Z=3.77; p=0.0211). The sixth cluster encompassed inferior temporal and occipital regions bilaterally and the cerebellum, extending to the middle temporal cortex in the left hemisphere (peak in BA 21; AAL atlas region: left middle temporal; MNI coordinates x=-68, y=-34, z=-8; cluster size=5552 voxels; Z=4.9; p<0.001).

Analysis of correlation with FAST subdomains

In order to further explore the associations with FAST subdomains, the significant clusters obtained in the above analysis were defined as regions of interest (ROIs) and mean parameter estimates for activation

were extracted. Regression analyses between the extracted parameters estimates of the ROIs and the six FAST subdomains, controlling for sex, age and estimated IQ score, were conducted. All p-values were two-tailed and Bonferroni correction for multiple comparisons was applied. Associations between the mean parameter estimates for activation of the ROI and subsyndromal symptoms (HDRS-21 and YMRS scores) were examined in the same way.

The findings are reported in detail in Supplementary Table 1. Briefly, the subdomain cognitive functioning was significantly inversely associated with four out of six ROIs (left DLPFC: β=-0.615, $p < 0.001$; right DLPFC: β=-0.677, $p < 0.001$; left IFG: β=-0.6571, $p < 0.001$; temporal and occipital: β=-0.630, $p < 0.001$). Occupational functioning was also significantly inversely associated with two ROIs, the right DLPFC (β=-0.665, $p < 0.001$) and the left IFC (β=-0.700, $p < 0.001$).

With respect to subsyndromal symptoms (Supplementary Table 2), a significant inverse correlation was found for subsyndromal depressive symptoms with the right DLPFC cluster.

4. Discussion

This study found that functioning in euthymic BD individuals, as measured using the FAST, was associated with reduced activation in a broad range of cortical regions during a working memory task. These regions included the right and left DLFPC, left IFG and superior parietal and temporo-occipital regions bilaterally, among other areas. These clusters of significant correlation were, however, only seen in the 2-back versus 1-back contrast

The regions found to be inversely correlated with functioning were broadly within the regions activated by both the HC and BD patients during the task, and were mainly located in the fronto-parietal and temporal cortex. They accordingly can be considered to be located in the so-called working memory network, related to attentional control and monitoring strategies (Owen et al., 2005). It has also been suggested that these regions form part of an extended multiple demands network that underlies performance of a range of different cognitive tasks that have in common executive control (Camilleri et al., 2018). In this respect it is interesting that we also identified a negative significant correlation between behavioural performance of BD individuals in the 2-back task (d-prime scores) with FAST total scores,

meaning that worse behavioural performance in the task correlated with worse psychosocial functioning (higher FAST total scores). Thus, functioning was inversely correlated with both behavioural performance of the 2-back task and brain activation in the same 2-back contrast.

We found that the negative correlations between brain activations and FAST total scores were mainly driven by two subdomains of the scale, cognitive functioning and occupational functioning. FAST cognitive functioning was significantly associated with brain activation in four out of six clusters, involving the bilateral DLPFC, the left IFG and the temporal and occipital cortex. FAST occupational dysfunction was associated with reduced activation levels in two clusters in the right DLPFC and the left IFG. Interestingly, in BD, occupational and cognitive functioning have been found to be the most affected subdomains, with a prevalence of 65.6% and 49.2%, respectively, along with an overall functional impairment prevalence of 58.6% in one study (Léda-Rêgo et al., 2020). Additionally, work disability and cognition are closely related and reduced performance on working memory has emerged as an important factor for predicting occupational functioning over time (Bonnín et al., 2010).

On the other hand, we did not find that failure of de-activation in the medial frontal cortex, the main area of difference between BD patients and HC found in this study, was associated with functioning as measured using the FAST. Medial frontal failure of de-activation is now a relatively robust finding in BD, having been documented in patients individuals regardless of affective state (Alonso-Lana et al., 2019; Fernández-Corcuera et al., 2013; Pomarol-Clotet et al., 2015, 2012). Other studies have reported similar changes in deactivation but in the posterior cingulate cortex/precuneus (Allin et al., 2010; Costafreda et al., 2011). Despite the fact that, as noted in the Introduction, the DMN is considered to be involved in cognitive function – specifically, attentional lapses (Anticevic et al., 2012; Buckner et al., 2008) – our findings do not provide support for a role in impaired functioning (including cognitive functioning) in patients with BD, as measured by the FAST. A previous study comparing cognitively preserved and impaired euthymic BD individuals, likewise found that cognitive impairment was associated with a reduced activation in the right DLPFC but not with the failure of de-activation in the medial frontal cortex (Alonso-Lana et al., 2016).

Our results show some similarities to those reported in the only previous study examining fMRI correlates of functioning in BD. During a verbal fluency task, Yoshimura et al. (Yoshimura et al., 2014) found a significant inverse correlation between GAF score and activation in two small clusters in the left

anterior cingulate cortex and left lateral prefrontal cortex in 10 euthymic BD individuals. The areas identified in our study were larger and affected other areas as well, but it is possible that these differences reflect the different tasks used and the smaller sample size in Yoshimura et al's study. Another potential factor might be that the GAF scale is not specific to psychosocial functioning as the FAST and also takes into account the level of current symptomatology.

The present study has limitations. At 31, the sample size of BD patients was relatively small. Presence of alcohol/substance abuse was based on subjective report unconfirmed by urinary or blood testing. Furthermore, BD individuals were taking medications, which differed in dosage and type. However, previous evidence suggests that the confounding effect of medication on neuroimaging findings in BD is relatively limited (Hafeman et al., 2012). The BD individuals included in the present study only displayed on average mild/moderate impairment in functioning. We did not assess functioning in the HC; however, psychosocial functioning in HC is expected to be preserved, with scoring on the FAST being almost wholly in the 'no impairment' range (Rosa et al., 2007), with accordingly little possibility to identify correlation between functioning and brain activations. Finally, the present study was carried out with a 1.5 T scanner. A 3.0 T scanner would provide higher resolution images and higher sensitivity for detecting changes in brain activation. However, signal-to-noise ratio was improved by reducing the number of slices and increasing the voxel volume, which is an efficient way of improving the signal strength in 1.5T scanners.

As one of only two studies to date that have examined associations between brain activations functioning in BD, our findings need to be interpreted with caution. Nevertheless, the emergence of the lateral prefrontal cortex of as implicated in impaired functioning in euthymic patients with the disorder is noteworthy. If confirmed, this finding might possibly prove useful for future interventions aimed at enhancing the psychosocial and/or cognitive performance of BD patients. Ideally, one possible relevant consequence of the present study might be to support anatomical targets for experimental studies of TMS as an intervention for functional outcome in BD.

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Table 1 Demographic and clinical data

Variable	BD Individuals (n=31)	Healthy Controls (n=31)	T value[b]	p-value
Sex: male/female	11 (35.5%) / 20 (64.5%)	11 (35.5%) / 20 (64.5%)		
Age (years)	45.54 (9.4)	44.84 (9.4)	-0.293	0.770
Estimated IQ (TAP)	106.61 (6.53)	106.35 (6.50)	- 0.156	0.877
FAST *total score*	19.90 (13.4)			
FAST *autonomy*[a]	2 (3) Range: 0 - 6			
FAST *occupational functioning*[a]	6 (13) Range: 0 - 15			
FAST *cognitive functioning*[a]	3 (7) Range: 0 – 13			
FAST *financial issues*[a]	0 (1) Range: 0 - 4			
FAST *interpersonal relationships*[a]	3 (5) Range: 0 - 8			
FAST *leisure time*[a]	2 (2) Range: 0 - 5			
HDRS-21[a]	2 (3) Range: 0 - 7			
YMRS[†]	1 (2) Range: 0 - 6			

Abbreviations: BD=bipolar disorder; F=females; **FAST**=Functioning Assessment Short Test; **HDRS-21**=Hamilton Rating Scale for Depression; **IQ**=intellectual quotient; **M**=males; **SD**=standard deviation; **TAP**=Test de Acentuación de Palabras - Word Accentuation Test; **YMRS**=Young Mania Rating Scale.
Notes: Values are means and standard deviations.
[a] Variable is not normally distributed. Values are medians and inter-quartile ranges (IQR).
[b] Comparisons were performed with two-sample t-tests. All t-values with a degree of freedom = 62

Figure legends

Figure 1. Sequential-letter version of the n-back task with two levels of memory load, 1-back (green) and 2-back (red).

Figure 2. Activation map for (a) healthy controls and (b) bipolar disorder individuals in the 1-back versus baseline, 2-back versus baseline and 2-back versus 1-back contrast. Colour bars indicate z scores; red to yellow colours indicate significant activation and blue to cyan colours indicate regions with significant deactivation. Numbers refer to Montreal Neurological Institute (MNI) z coordinates of the slice shown. The right side of the image is the right side of the brain.

Figure 3. Between group comparison in the (a) 2-back versus baseline and in the (b) 2-back versus 1 back contrasts. Color bars indicate z scores; red to yellow colours indicate areas hypo-activated by the bipolar disorder individuals and blue to cyan colours indicate failure to de-activate in the patient group. Boxplots of mean activations and de-activations for BD individuals and controls. Numbers refer to Montreal Neurological Institute (MNI) z coordinates of the slice shown. The right side of the image is the right side of the brain.

Figure 4. FAST correlations. Areas of significant negative correlation between the FAST total score and brain activity in the 2-back versus 1-back contrast. Box-plots of correlation between the FAST total score and the 6 clusters of brain activity in the 2-back versus 1-back contrast.

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The relationship between cognition and functioning in Bipolar Disorder: An investigation using functional imaging during working memory performance

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