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Brain correlates of impaired goal management in bipolar mania

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Abstract

Background. Although executive impairment has been reported in mania, its brain functional correlates have been relatively little studied. This study examined goal management, believed to be more closely related to executive impairment in daily life than other executive tasks, using a novel functional magnetic resonance imaging (fMRI) paradigm in patients in this illness phase.

Methods. Twenty-one currently manic patients with bipolar disorder and 30 matched healthy controls were scanned while performing the Computerized Multiple Elements Test (CMET). This requires participants to sequentially play four simple games, with transition between games being made either voluntarily (executive condition) or automatically (control condition).

Results. CMET performance was impaired in the manic patients compared to the healthy controls. Manic patients failed to increase activation in the lateral frontal, cingulate and inferior parietal cortex when the executive demands of the task increased, while this increase was observed in the healthy controls. Activity in these regions was associated with task performance.

Conclusions. Manic patients show evidence of impaired goal management, which is associated with a pattern of reduced medial and lateral frontal and parietal activity.

Original Article

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Introduction

Besides its core clinical feature of episodes of mania and depression, bipolar disorder is now recognized to be accompanied by cognitive impairment. In some cases, this persists into euthymia (Anderson, Haddad, & Scott, 2012), where it has been found to be associated with impaired daily life functioning (Wingo, Harvey, & Baldessarini, 2009). Neurocognitive impairment has been documented in bipolar disorder across different cognitive domains, but executive function and working memory seem to be particularly affected (Bourne et al., 2013), and executive impairment may even persist during clinical remission (Dickinson, Becerra, & Coombes, 2017).

Mania appears to be characterized by more marked cognitive deficits than euthymia (Bora, 2018), and may be a risk factor for subsequent development of cognitive impairment in the euthymic phase (Robinson & Ferrier, 2006). Regarding executive impairment specifically, Volkert et al. (2015) examined 35 depressed bipolar patients, 20 hypomanic or manic patients and 55 healthy controls on a neuropsychological test battery covering attention, working memory, verbal memory and executive functioning and found that depression was characterized particularly by psychomotor slowing, whereas manic patients showed severe deficits in executive functioning. Murphy et al. (2001) also found that manic patients showed more wide-ranging impairment than depressed patients (characterized by a milder impairment) and healthy controls on a gambling task thought to reflect ventrolateral and anterior cingulate cortex (ACC) functions.

An important open question is how far executive dysfunction contributes to the pattern of functional brain changes associated with bipolar disorder, and particularly manic episodes, which take the form of underactivity in prefrontal and some other cortical regions at rest and during task performance, coupled with overactivity in subcortical structures such as the amygdala and hippocampus (Green, Cahill, & Malhi, 2007; Kupferschmidt & Zakzanis, 2011; Strakowski et al., 2012). Chen, Suckling, Lennox, Ooi, and Bullmore (2011) meta-analyzed voxel-based functional magnetic resonance imaging (fMRI) studies with different cognitive and emotional components. In a subanalysis of 29 studies using purely cognitive tasks they found that, across all mood states, patients showed decreased activation in the inferior frontal gyrus, the lingual gyrus, and the putamen, while abnormal subcortical activation was much less prominent than in the subanalysis of 22 studies using emotional tasks. Functional imaging studies of manic patients using executive tasks specifically have supported the above finding of reduced activation in the inferior frontal gyrus during the performance of tasks requiring inhibition of prepotent responses, such as the go/no-go task (Altshuler et al., 2005; Elliott et al., 2004; Hummer et al., 2013; Mazzola-Pomietto, Kaladjian, Azorin, Anton, & Jeanningros, 2009; Strakowski et al., 2008), the Stroop task (Blumberg et al., 2003), or the Stop Signal task (Cerullo et al., 2009; Pavuluri, Passarotti, Harral, & Sweeney, 2010). Other regions involved in response inhibition, like the ACC, have also shown hypoactivation, but less consistently. On the contrary, two studies that used a working memory task, such as the *n*-back task (Pomarol-Clotet et al., 2012; Townsend, Bookheimer, Foland-Ross, Sugar, & Altshuler, 2010), found reduced activation in the dorsolateral prefrontal cortex (DLPFC) and the parietal cortex, across different mood states in one case (Townsend et al., 2010) and specifically linked to mania in the other (Pomarol-Clotet et al., 2012).

A further, relatively recently recognized aspect of executive function is goal management. This refers to the ability to carry out tasks while simultaneously keeping in mind and dealing with ongoing competing demands (Cullen, Brennan, Manly, & Evans, 2016; Duncan, Emslie, Williams, Johnson, & Freer, 1996; Shallice & Burgess, 1991). Impairment leads to so-called goal neglect, defined by Duncan et al. (1996) as an active search for a path toward a behavioral goal being replaced by performance that seems passive, inert, stereotyped, or fragmented, and also prone to irrelevant or ill-judged intrusions. Goal neglect is commonly seen in patients with frontal lobe lesions (Duncan et al., 1996), and has been argued to capture better than classical executive tests the kind of problems that such patients show in real life (Burgess et al., 2006). It is typically measured by tasks such as the Six Elements Task (Wilson, Alderman, Burgess, Emslie, & Evans, 1996), where subjects have to carry out parts of different tasks in a 10-min time period in circumstances where it would be impossible to complete all of them in the allotted time. The subjects accordingly must keep in mind the overall goal of the task by periodically switching from task to task. However, although neuropsychological studies often include goal management measures when examining executive function, there are, to our knowledge, no imaging studies on goal management in bipolar disorder and particularly in manic episodes. The present study took advantage of a recently developed fMRI-adapted version of the Six Elements Task to examine this aspect of executive function in bipolar disorder, specifically in patients with mania where the evidence of executive impairment is greatest.

Methods

Participants

Thirty-six patients with a manic episode were recruited from four hospitals in the metropolitan area of Barcelona, Spain (Benito Menni CASM, Sant Boi de Llobregat; Hospital General de Granollers; Hospital Sant Rafael, Barcelona; Hospital Sagrat Cor, Martorell). All patients fulfilled DSM-V criteria for bipolar disorder, confirmed by clinical interview and review of case notes. Patients were excluded if: (a) they were aged <18 or >65 years, (b) had a history of brain trauma or neurological disease, (c) had shown alcohol/substance abuse within 12 months prior to participation, or (d) had any contraindication for MRI scanning. Severity of manic and depressive symptoms was scored using the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) and Hamilton Depression Rating Scale (HDRS-21) (Hamilton, 1960). To be included in the study, patients were required to score ⩾17 in the YMRS and ⩽8 in the HDRS-21. Clinical evaluation also included the Positive Scale from the Positive and Negative Syndrome Scale (PANSS) (Kay, Flszbein, & Opfer, 1987). Overall severity of illness was rated using the Global Assessment of Functioning Scale (GAF) (Endicott, Spitzer, Fleiss, & Cohen, 1976) and the Clinical Global Impression Scale (CGI) (Guy, 1976). Clinical assessment took place within 72 h before the scanning session. Pre-morbid intelligence quotient (IQ) was estimated using the Word Accentuation Test (Test de Acentuación de Palabras, TAP (Del Ser, Gonzalez-Montalvo, Martinez-Espinosa, Delgado-Villapalos, & Bermejo, 1997; Gomar et al., 2011), a word reading test requiring pronunciation of Spanish words whose accents have been removed).

Thirty healthy controls, selected to be matched to the patients for age, sex and estimated IQ, as estimated by the TAP, were recruited from non-medical staff working in the hospital, their relatives and acquaintances, plus independent sources in the community. They were questioned and excluded if they reported a personal or family history of mental illness and/or treatment with psychotropic medication. All participants were right-handed.

All participants gave written informed consent prior to participation. All the study procedures had been previously approved by the Research Ethics Committee FIDMAG Sisters Hospitallers (Comité de Ética de la Investigación de FIDMAG Hermanas Hospitalarias) and complied with its ethical standards on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Healthy controls received a gift-card as a compensation for their participation in the study.

CMET task

We used an adapted version of the CMET paradigm developed by Cullen et al. (2016) that we have validated in healthy individuals (Fuentes-Claramonte et al., 2021). In the task, subjects had to play four different simple games, which were displayed sequentially in pseudorandom order. The games were all similar and involved moving an interactive element on the screen to the left or to the right (with their left or right index fingers) to score points: in the first game (Car), the participant had to move a car to pick up fuel from the road; in the second (Catch), they had to move a tube to receive balloons that fell from the sky; in the third (Ball), they had to move a bar to keep a ball in movement and bouncing to the walls on the screen; in the last game (Brick), participants had to move a bar to use a ball to break

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bricks on the screen (Fig. 1). During each task block subjects were required to play these games and earn as many points as possible. The games were played in two conditions: in the control condition (automatic switching), the transition between games was automatically done by the computer (without intervention of the participant) and game duration was always the same, 12 s. All games were played once in each block, adding to a total block duration = 48 s. In the executive condition (voluntary switching), the transition between games was made voluntarily by button-press (right thumb) and subjects were instructed to divide their time equally between the four games, although no information about time played was available to them, or were they given instructions on which was the optimal strategy (i.e. playing 12 s per game). Thus, the executive condition required subjects to play the games to earn points but also to keep in mind that they needed to switch games regularly to be able to play all of them in each block. Four blocks of each condition were presented in alternating order (each one lasting 48 s), starting with the automatic condition to serve as a reference for switching time. Instructions on the condition of the subsequent block were presented for 3 s immediately before each block started. Between blocks, a fixation cross was presented for 9 s. Total task duration was 8 min and 10 s. Before scanning, participants underwent a practice session where they learned how to use the game controllers to play and switch games, but without any timing requirements. Although they were reminded that they should play each game for approximately the same time during the scanning session, they were free to practice for as long as they needed to get familiar with the games during the practice session. There were no automatic switches during the practice session.

Stimuli were presented via MRI-compatible goggles (VisuaStim, Resonance Technology), and participants performed the task with an MRI-compatible response system (ResponseGrips, NordicNeuroLab).

Behavioral measures

During task performance, the total number of voluntary switches and the number of voluntary switches per block were registered. Additionally, we used the deviation from the optimal playing time as a measure of accuracy. The optimal playing time in each game was 12 s in each voluntary switching block. The deviation from this optimal time was calculated as the total time (in s) exceeding 12 s per game played for each block (time underplaying and overplaying a game were complementary, so only overplaying was penalized to avoid counting time twice). The deviation from optimal playing time was the sum of these deviations across the four blocks in the task, giving a range from 0 (perfect execution, played 12 s for all games in all blocks) to 144 (worse execution, no voluntary switches performed).

MRI data acquisition

All subjects were scanned using the same 3T Philips Ingenia scanner (Philips Medical Systems, Best, The Netherlands) located at the Sant Joan de Déu Hospital in Barcelona (Spain). Functional data were acquired using a T2*-weighted echo-planar imaging (EPI) sequence with 245 volumes and the following acquisition parameters: TR = 2000 ms, TE = 30 ms, flip angle = 70°, in-plane resolution = 3.5 × 3.5 mm, FOV = 238 × 245 mm, slice thickness = 3.5 mm, inter-slice gap = 0.75 mm. Slices (32 per volume) were acquired with an interleaved order parallel to the AC–PC plane. A high-resolution anatomical volume was acquired using a Fast Field Echo (FFE) sequence for anatomical reference and inspection (TR = 9.90 ms; TE = 4.60 ms; flip angle = 8°; voxel size = 1 × 1 mm; slice thickness = 1 mm; slice number = 180; FOV = 240 mm).

Image preprocessing and analysis

Preprocessing and analysis were carried out with the FEAT module included in FSL 6.0 (FMRIB Software Library) software (Smith et al., 2004). The first 10 s (five volumes) of the sequence, corresponding to signal stabilization, were discarded. Preprocessing included motion correction (using the MCFLIRT algorithm), co-registration and normalization to a common stereotactic space (MNI, Montreal Neurological Institute template). For accurate registration, a two-step process was used. First, brain extraction was applied to the structural image, and the functional sequence was registered to it. Then the structural image was registered to the standard template. These two transformations were used to finally register the functional sequence to the standard space. Before group analyses, normalized 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 (GLM) were used to obtain activation maps in the two groups. At the first level, we defined a regressor for each condition: one for automatic switching blocks and one for voluntary switching blocks (fixation periods were not modeled and acted as implicit baseline). The contrast of interest was voluntary switching > automatic switching, to identify regions of increased sustained activation when playing the games with goal management demands. Additional contrasts were built to compare each condition against fixation. GLMs were fitted to generate individual activation maps for these contrasts and second level (group) analyses were performed within the FEAT module by means of mixed-effects GLMs (Beckmann, Jenkinson, & Smith, 2003). Statistical tests were carried out at $p < 0.05$, corrected at the cluster level using Gaussian random field methods. A threshold of $z > 2.6$ ($p < 0.005$) was used to define the initial set of clusters.

Given that a proportion of the patients achieved very few or no task switches during the voluntary switching blocks, and this could bias the comparison between conditions, we run a supplementary analysis with a different first-level design aimed to test brain activity in the voluntary blocks, relative to the rest of the task, controlling for the effect of playing the games and the transient signal changes associated with game switches (see online Supplementary information for details on this analysis and the results).

Results

From the 36 recruited manic bipolar patients, five did not complete the CMET task and eight were excluded because of excessive movement in the scanner, one due to an incidental MRI finding and one due to being left-handed. We compared 21 manic patients with 30 healthy controls. Demographic and clinical data for the patients and controls are shown in Table 1. The groups were not significantly different for age, sex and estimated premorbid IQ. Patients included in the study were on treatment with mood stabilizers ($n = 17$) (lithium alone or in combination $n = 13$, valproate alone or in combination $n = 5$, other mood

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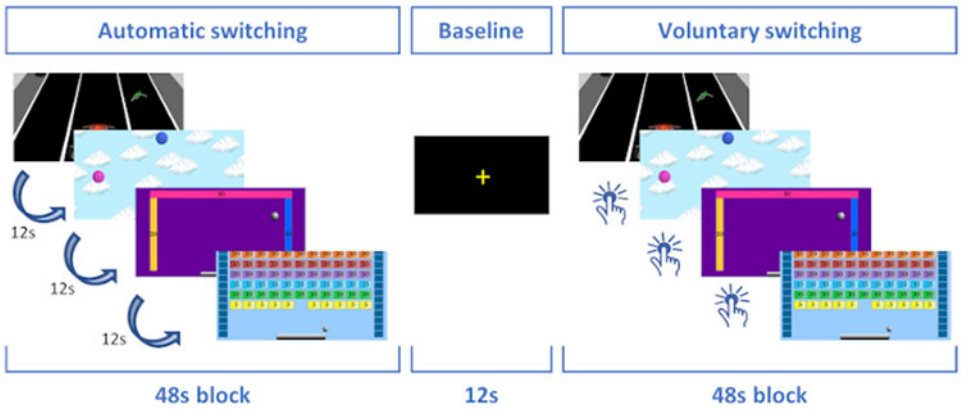

Fig. 1. CMET task. Participants sequentially played four games requiring left or right index button presses during each 48s block. In the automatic switching condition, the game changed every 12s without intervention of the participant. In the voluntary switching condition, the participant had to actively switch games by button press (right thumb), with the instruction to spend approximately the same amount of time playing each game. No time information was shown during either condition. A fixation cross was shown during baseline periods between blocks (12s).

Table 1. Demographic and clinical data for the sample included in the analysis

	Mania	Control	Differences
Sex (M/F)	8/13	13/17	$\chi^2 = 0.01$, $p = 0.932$
Age	45.14 (12.44) Range: 18–61	39.87 (12.99) Range: 18–61	$t = 1.46$, $p = 0.150$
Estimated IQ	102.65 (9.33) Range: 77–112	103.23 (8.34) Range: 79–114	$t = 0.23$, $p = 0.82$
YMRS	22.57 (3.96) Range: 17–29		
HDRS	2.86 (3.55) Range: 0–8		
PANSS-P	17.33 (6.19) Range: 7–34		
CGI	4.48 (1.12) Range: 2–6		
GAF	55.76 (12.85) Range: 40–90		

Values are means (s.d.).

stabilizers $n = 1$) and with antidepressants ($n = 1$); 18 were taking antipsychotics (second generation $n = 16$, combination $n = 2$) with a chlorpromazine equivalent dose of 387.44 mg/d (s.d. = 137.78).

Behavioral performance

The relevant behavioral variables (number of voluntary switches and deviation from optimal playing time) were not normally distributed, so analyses were performed with non-parametric tests (Wilcoxon rank-sum test for group comparison and Spearman's *rho* for correlation). The mean total number of voluntary switches was significantly lower in the manic patients than in the healthy subjects (mania mean = 8.19, s.d. = 6.62, range = 0–24; control mean = 12.97, s.d. = 5.66, range = 0–32; $W = 449$, $p = 0.01$). A repeated measures analysis of variance (ANOVA) with one within-subjects factor (Game, with four levels, that coded the total time spent on each game) and one between-subjects factor (Group, with two levels, bipolar and control) revealed that no game was preferred over the others, since there were no differences in time spent on each game (no significant main effect of Game, $F = 1.293$, $p = 0.280$), nor a significant Game × Group interaction ($F = 1.014$, $p = 0.378$).

Deviation from optimal playing time (which reflects the difference between actual time spent playing each game and the gold standard of 12 s per block) was significantly larger in the manic patients compared to the healthy subjects (mania mean = 88.16s, s.d. = 39.29, range = 26.51–144; control mean = 37.14s, s.d. = 29.97, range = 8.38–144; $W = 81$, $p < 0.001$). Behavioral performance showed a learning effect, with deviation from optimal playing time becoming smaller as the task progressed in both groups (online Supplementary Fig. S1). This was confirmed by a linear mixed effects model with Block and Group as fixed effects and Subject as grouping factor (random effect), which showed a significant linear effect for Block and significant Group differences, but no Block×Group interaction (see online Supplementary Table S1 for the complete results).

In the patient group, scores in the YMRS showed a trend-level correlation with deviation from optimal playing time ($\rho = 0.42$, $p = 0.058$). We also explored the association between behavioral measures and scores in behavioral disorganization, with item P2 from the PANSS (conceptual disorganization) and item 7 from the YMRS (thought and language disorder), but no significant correlations were found.

Imaging results

Within-group activation maps

During the executive condition (voluntary switching) compared to the control condition (automatic switching), healthy subjects showed activation in the dorsolateral and inferior frontal cortex, the ACC extending to the pre-supplementary motor area (pre-SMA) and SMA, the frontal pole, and the inferior parietal cortex, all bilateral but more predominantly in the right hemisphere. Left-lateralized activity was observed in the pre/post-central gyrus. Significant signal increase was also observed in the posterior cingulate cortex (PCC) and precuneus, bilateral middle temporal cortex, basal ganglia, thalamus and cerebellum (Fig. 2a and Table 2). Manic patients did not show any activation increase in the executive condition, relative to control blocks.

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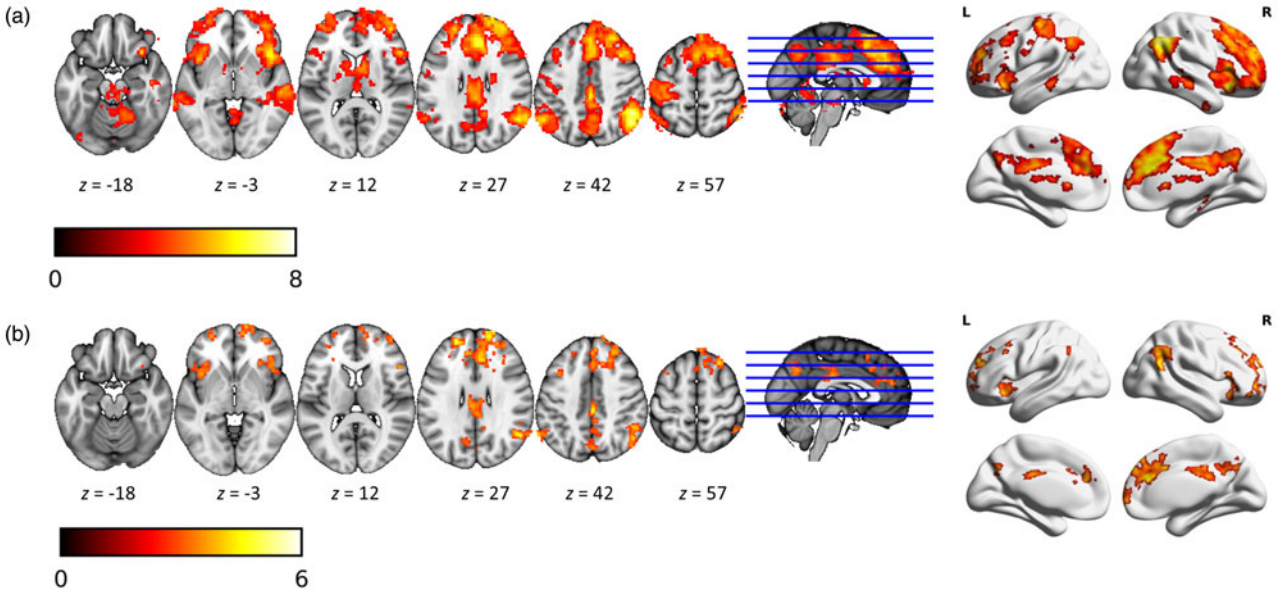

Fig. 2. Brain activation maps for the executive > control contrast for the control group (a). The mania group did not show any significant activation in this contrast. (b) Regions of significant differences between groups in this contrast, indicating that while controls increased fronto-parietal and cingulo-opercular activity in response to increased executive demands, patients failed to do so. Images are displayed in neurological convention (right is right). Color bars depict *z* values.

However, they did show activation in similar regions during the executive condition relative to baseline (see online Supplementary Figure 2).

Between-group comparison

The manic patients showed significantly less activation than the controls in the frontal cortex, including the bilateral DLPFC, inferior frontal cortex, ACC and SMA, and anterior frontal cortex, in the executive > control contrast. Significant differences were also observed in the bilateral inferior parietal cortex and PCC/precuneus (Fig. 2b and Table 2). No regions showed greater activation in the mania group relative to the control group.

To further characterize this hypoactivation in terms of its association with executive impairment, we extracted the beta values (parameter estimates) from the clusters of significant differences for each subject (eight regions: a cluster comprising the ACC and right DLPFC, the left DLPFC, right and left inferior frontal cortex, right and left inferior parietal cortex, the left orbitofrontal cortex and the PCC), and examined correlations between these and the deviation from optimal playing time as an index of behavioral performance (given that variables were not normally distributed, we used Spearman's *rho*). Results are shown in Table 3 and illustrated in online Supplementary Figure 3. Activity in these regions was associated with task performance in the whole sample (negative correlations indicate that increased activity is associated to reduced deviation times), although the correlations seem to be mainly driven by the mania group and were not significant in the control group. Clinical severity of manic symptoms, measured with the YMRS, was not associated with brain activity.

Since the behavioral performance indices showed two outliers in deviation from optimal playing time in the control group (their performance was more than 2 S.D.s distal from the group mean), we repeated the analyses excluding these two subjects. Results remained essentially identical when these two subjects were excluded.

Discussion

The CMET task showed that mania is characterized by hypo-activation in well-known executive networks, including the fronto-parietal and cingulo-opercular regions that have been previously associated with task control and goal management (Berkman, Falk, & Lieberman, 2012; Dosenbach et al., 2006; Lopez-Garcia et al., 2016), accompanied by impairment in behavioral performance. Although manic patients displayed some activation of the executive networks, they failed to increase the activity of these regions in response to the increases in the executive demands of the task.

Reduced prefrontal activation has been a regular finding in inhibition and working memory fMRI studies in mania. The meta-analysis of Hajek, Alda, Hajek, and Ivanoff (2013) included 10 studies of response inhibition (147 bipolar patients in manic state and 151 healthy subjects) and reported, similar to our results, diminished activity within the frontal lobes including the right inferior frontal cortex, and in the left medial frontal cortex extending into the ACC. Both the inferior frontal cortex and the ACC are central nodes of the cingulo-opercular network, that also includes portions of the anterior prefrontal cortex (frontal poles) and is involved in task control and the maintenance of task sets (Nelson et al., 2010). The right inferior frontal cortex has been strongly associated with response inhibition (Aron, Robbins, & Poldrack, 2004, 2014), although its role seems to extend to other executive tasks (Chatham et al., 2012; Erika-Florence, Leech, & Hampshire, 2014; Swick & Chatham, 2014) and current views ascribe it to a more general task-control function (Menon & Uddin, 2010). In this aspect our results are consistent with previous reports of reduced inferior frontal and ACC activation in manic patients during executive control (Altshuler et al., 2005; Blumberg et al., 2003; Elliott et al., 2004), even in first episodes (Strakowski et al., 2008). Moreover, hypo-activation in the mania group was also evident in fronto-parietal regions (DLPFC and inferior parietal cortex), also involved in cognitive

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Table 2. Regions of significant activation increase in the executive > control contrast

Region	MNI coordinates			Z	Cluster size	p
	x	y	z			
Control group						
ACC	4	34	26	7.13	24 295	<0.001
Inferior frontal cortex/anterior insula	34	22	−12	6.78		
SMA	2	18	48	6.71		
DLPFC	28	52	18	6.44		
Cerebellum	−36	−66	−38	5.67	6217	<0.001
Inferior parietal cortex	−54	−58	42	5.72	4312	<0.001
Precentral gyrus	−38	−20	64	5.68		
Angular gyrus/inferior frontal cortex	50	−58	40	7.29	3153	<0.001
Caudate/putamen	0	16	6	5.08	2128	<0.001
Anterior insula/inferior frontal cortex	−36	22	−10	5.64	1292	<0.001
Middle temporal cortex	−58	−32	−10	4.55	498	<0.001
Control > Mania						
Superior frontal cortex	−22	54	30	5.33	4620	<0.001
Anterior frontal cortex/DLPFC	22	64	28	5.21		
ACC	12	26	38	5.14		
PCC	2	−30	40	4.99	1326	<0.001
Precuneus	10	−66	36	3.77		
Angular gyrus/inferior parietal cortex	52	−60	26	4.92	913	<0.001
Inferior frontal cortex/anterior insula	34	22	−12	4.09	687	<0.001
Inferior frontal cortex/anterior insula	−36	20	−10	4.43	426	<0.001
Orbitofrontal cortex	−28	58	−2	3.75	249	0.006
Inferior parietal cortex	−60	−62	40	5.21	239	0.008
DLPFC	−34	16	60	4.19	193	0.028

ACC, anterior cingulate cortex; DLPFC, Dorsolateral prefrontal cortex; SMA, Supplementary Motor Area.

Table 3. Spearman correlations between activation increase in the executive > control contrast and behavioral performance in the whole sample and in healthy subjects and mania patients separately

	Whole sample		Healthy controls		Mania	
	ρ	p	ρ	p	ρ	p
DLPFC/ACC (R)	−0.615	<0.001	−0.034	0.858	−0.727	<0.001
DLPFC (L)	−0.490	<0.001	0.026	0.983	−0.551	0.009
Inferior frontal (R)	−0.607	<0.001	−0.287	0.124	−0.462	0.035
Inferior frontal (L)	−0.419	0.002	0.083	0.661	−0.308	0.175
Inferior parietal (R)	−0.531	<0.001	−0.080	0.673	−0.501	0.021
Inferior parietal (L)	−0.218	0.125	0.359	0.052	0.036	0.878
Orbitofrontal (L)	−0.351	0.011	0.108	0.570	−0.322	0.154
PCC (B)	−0.549	<0.001	−0.291	0.119	−0.399	0.073

R, Right; L, Left; B, Both.

control (Lopez-Garcia et al., 2016) and with a proposed role in the dynamic adjustments of behavior in response to environmental cues (Dosenbach et al., 2006).

The coordinated activity of fronto-parietal and cingulo-opercular networks is proposed to regulate the implementation of top-down control (Dosenbach, Fair, Cohen,

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Schlaggar, & Petersen, 2008), which is also supported by our current results that link regions from these two networks to goal management in healthy individuals (see also Fuentes-Claramonte et al., 2021). Moreover, the DLPFC and the ACC have also been involved in voluntary task selection in task-switching contexts in healthy individuals (Orr & Banich, 2014; Wisniewski, Reverberi, Tusche, & Haynes, 2015). Following on this, the brain functional alterations that we have observed in manic patients have been found in the context of impaired performance in the CMET task. Moreover, the regions showing reduced activation in the manic patients were linked to task performance. Thus, the findings of hypoactivation of executive control areas during a goal management task provide a plausible mechanism for poor regulation in daily life goal-directed behavior in manic patients.

An open question remains as to whether the reported alterations in task performance and brain activity during executive function are specific to manic episodes or a trait marker of bipolar disorder. Although some studies have found fronto-parietal hypoactivation across all three phases of bipolar disorder (see Townsend et al., 2010), others have found reduced fronto-parietal activity during mania and depression, but not in euthymia (Pomarol-Clotet et al., 2015). Consistent with the latter, Alonso-Lana et al. (2019) recently showed that DLPFC and parietal hypoactivation during a working memory task normalized after recovery from mania in a longitudinal study, and inferior frontal gyrus function during response inhibition has also shown improvement after treatment with lamotrigine (Pavuluri et al., 2010). Neuropsychological studies have also shown severe executive impairment in manic patients that seemed to recover after remission (Volkert et al., 2015). An important next step of this research will be to reassess the patients after remission of the manic episode, which will help to understand if the observed behavioral and brain functional alterations are state- or trait-related. Furthermore, examination of drug-free patients would also be desirable, since all participants in our study were under pharmacological treatment, a common limitation of many studies of affective disorders.

We might also consider hypoactivation in task-control regions to be characteristic not only of manic episodes but, more generally, of mood episodes or other conditions characterized by executive impairment, since it has also been found in schizophrenia (Alústiza, Radua, Pla, Martin, & Ortuño, 2017; Landin-Romero et al., 2015; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Poppe et al., 2016), bipolar depression (Penfold, Vizueta, Townsend, Bookheimer, & Altshuler, 2015; Pomarol-Clotet et al., 2015), and to a lesser extent also unipolar depression (Kikuchi et al., 2012; Miller, Hamilton, Sacchet, & Gotlib, 2015). Moreover, even within bipolar patients in the euthymic phase, those with executive impairment (as measured by neuropsychological tests) have shown hypoactivation in the lateral prefrontal cortex during a working memory task, compared with cognitively preserved patients with similar clinical status (Alonso-Lana et al., 2016). This is also supported by the fact that, although patients with greater clinical severity tended to show greater executive impairment at the behavioral level, no association with symptom severity was apparent with brain activity in our data. Although this should be taken with caution given that these correlations were run in a relatively small sample, it is not implausible to consider that the observed hypoactivation reflects a disturbance that is shared across different disorders and that may ultimately be associated with impaired regulation of thought and behavior in mania and other conditions (McTeague, Goodkind, & Etkin, 2016).

Conclusions

To our knowledge, this is the first study to address goal management in bipolar disorder during a manic episode. Our results replicate, using a novel and more ecologically valid experimental paradigm, previous findings of hypoactivation in task-control brain areas during executive function. Moreover, we can link this hypoactivation to impaired behavioral performance during the executive task, thus providing a possible mechanism that may (probably in conjunction with others) disturb the ability of the individual to regulate their own behavior.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721002452

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Ethical standards. 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.

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