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Disrupted network switching in euthymic bipolar disorder: working memory and self-referential paradigms

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Abstract:	Background: Patients with bipolar disorder (BD) frequently suffer from neurocognitive deficits that can persist during periods of clinical stability. Specifically, impairments in executive functioning such as working memory and in self-processing have been identified as the main components of the neurocognitive profile observed in euthymic BD patients. The study of the neurobiological correlates of these state-independent alterations may be a prerequisite to develop reliable biomarkers in BD. Methods: A sample of 27 euthymic BD patients and 25 healthy participants (HC) completed working memory and self-referential functional Magnetic Resonance Imaging (fMRI) tasks. Activation maps obtained for each group and contrast images (i.e., 2-back>1-back/self>control) were used for comparisons between patients and HC. Results: Euthymic BD patients, in comparison to HC, showed a higher ventromedial prefrontal cortex activation during working memory, a result driven by the lack of deactivation in BD patients. In addition, euthymic BD patients displayed a greater dorsomedial and dorsolateral prefrontal cortex activation during self-reference processing. Limitations: Pharmacotherapy was described but not included as a confounder in our models. Sample size was modest. Conclusion: Our findings revealed a lack of deactivation in the anterior default mode network (aDMN) during a working memory task, a finding consistent with prior research in BD patients, but also a higher activation in frontal regions within the central executive network (CEN) during self-processing. These results suggest that an imbalance of neural network dynamics underlying external/internal oriented cognition (the CEN and the aDMN, respectively) may be one of the first reliable biomarkers in euthymic bipolar patients.

Suggested Reviewers:	Hillary Blumberg, PhD MD Professor of Psychiatric Neuroscience, Yale School of Medicine hilary.blumberg@yale.edu Research devoted to understanding the brain circuitry differences that underlie mood disorders, including bipolar disorder.
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Cover Letter

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Dr. Paolo Brambilla and Dr. Jair Soares
Editors-in-Chief
Journal of Affective Disorders

July 29th, 2022

Dear Editors,

Please find attached an original manuscript entitled *Disrupted network switching in euthymic bipolar disorder: working memory and self-referential paradigms*, submitted for exclusive consideration of publication as a research article in *Journal of Affective Disorders.* All the authors reviewed and approved the submission of this manuscript.

In this study we aimed to explore the neurobiological underpinnings of persistent cognitive impairments in patients with bipolar disorder in the absence of mood symptomatology. This study is of highlighted relevance as we describe how euthymic bipolar patients failed to deactivate the default mode network during working memory processes, and hyperactivated the central executive network during self-processing. It should be noted that this is the first study suggesting that euthymic bipolar patients showed an inefficient network switching while performing goal-oriented or introspective tasks. These results are relevant to the understanding of state-independent traits in bipolar disorder patients and could be considered as one of the first findings detecting stable diagnostic biomarkers.

Thank you in advance for the consideration of our manuscript. We look forward to hearing from you.

Yours sincerely,

Marta Cano, PhD

RESPONSE TO REVIEWER'S COMMENTS

We thank the Editor and the reviewer for giving us the opportunity to improve and resubmit our manuscript titled "*Disrupted network switching in euthymic bipolar disorder: working memory and self-referential paradigms*".

Note: Text highlighted in yellow corresponds to new text insertions.

Reviewer 1:

1. The authors should be consistent in the definition of "euthymic BD patients" or "euthymic patient with BD", since it changes across sections of the manuscript. Furthermore, the authors should be consistent also in the definition of the word "selfprocessing" or "self-processing".

R: We completely agree with the reviewer's suggestions and, consequently, we are now consistent in the definition of "*euthymic BD patients*" and "*self-processing*" across the manuscript.

Abstract:

1. The authors should define the acronym of healthy participants (HC) in order to be consistent with the definition of the BD patient's acronym.

R: As suggested, we have now defined the acronym of healthy participants (*HC*).

2. The authors should specify the "between-group comparison" by specifying BD and HC group.

R: We thank the reviewer for their suggestion. We have now specified "between-group comparison" as "comparisons between patients and HC".

Abstract; Methods section; Lines 11-12: *"…contrast images (i.e., 2-back>1-back / self>control) were used for comparisons between patients and HC."*

3. The authors could reformulate the sentence related to the limitations in the abstract: How the pharmacotherapy was not controlled? The authors did not control them as confounding factors? This should be specified with a short clear sentence in the Abstract.

R: We apologize for the confusing terminology. We were referring that pharmacotherapy load was not used as a confounder in our analyses.

Abstract; Limitations section; Line 17: *"Pharmacotherapy was described but not included as a confounder in our models."*

4. It is not explained the possible relationship that could exist between pre-specified networks and internal and external cognition, could the author add a sentence or rephrase this part in the Abstract in order to have a clearer conclusion matched with the result information?

R: We acknowledge that we did not contextualize the relationship between pre-specified networks and internal/external cognitive processes. Due to the space constraint required for the abstract, we have now tried to clarify this relationship in brackets.

Abstract; Conclusion section; Lines 23-24: *"…imbalance of neural network dynamics underlying external /internal oriented cognition (the CEN and the aDMN, respectively) may be…"*

Introduction:

1. In the first section in which authors reported that neurocognitive functioning is related to specific psychotropic medication, it is not clear how the alteration of specific neurocognitive functioning is partially explained by psychotropic medication: could the authors give an example of these medication and related neurocognitive alteration?

R: Although the relationship between specific psychotropic medications and neurocognitive functioning in BD patients is still not fully understood, lithium, benzodiazepines and anticholinergic medications appear to have an acute cognitive impact on these patients.

Introduction section; Page 1; Lines 7-8: "*...it is only partially explained by psychotropic medication such as lithium, benzodiazepines and anticholinergics (Beunders et al., 2021; Cullen et al., 2019; Xu et al., 2020).*"

References:

Cullen, Breda et al. 2019. "Understanding Cognitive Impairment in Mood Disorders: Mediation Analyses in the UK Biobank Cohort." *British Journal of Psychiatry* 215(5): 683–90.

Xu, Ni, Benjamin Huggon, and Kate E.A. Saunders. 2020. "Cognitive Impairment in Patients with Bipolar Disorder: Impact of Pharmacological Treatment." *CNS Drugs* 34(1): 29–46.

Beunders, Alexandra J.M. et al. 2021. "Cognitive Performance in Older-Age Bipolar Disorder: Investigating Psychiatric Characteristics, Cardiovascular Burden and Psychotropic Medication." *Acta Psychiatrica Scandinavica* 144(4): 392–406.

2. The authors should check English grammar, since in some points there are typos or grammatical error (i.e., "Magnetic resonance imaging (MRI) has proven" instead of has been proven; "And specifically" instead of Specifically)

R: We thank the reviewer for noting these grammatical errors. They have been now corrected.

Introduction section; Page 1; Line 12: *"... (MRI) has been proven useful to ..."*

Introduction section; Page 1; Line 22: *"Specifically, working memory..."*

3. In the section related to the evaluation of neurobiological correlates of trait-alteration, could the authors clarify how neurobiological correlates of trait-like alterations could foster the detection of stable biomarkers? Could the authors report some findings related to this concept?

R: The topic raised by the reviewer was thoroughly discussed by our group. Other medical specialties are already using MRI biomarkers in their clinical practice, which highlights the potential of MRI research for precision medicine. In this sense, an exhaustive characterization of MRI correlates of trait-like alterations in BD (that is, those present in each of the 3 cyclic phases of the disease) may inform us about potential stable biomarkers, which could guide clinical decisions regarding early diagnosis as well as foster novel therapeutic developments.

Introduction section; Page 1; Lines 19-20: "*it could also foster the detection of diagnostic biomarkers, a significant milestone in the journey towards precision psychiatry (Salagre and Vieta, 2021) which has already been achieved in other medical specialties such as neurology (Rotstein and Montalban, 2019) and oncology (Smits, 2021).*"

Discussion section; Page 9; Lines 225-227: *"These preliminary findings support the existence of state-independent traits in BD patients and underline potential stable diagnostic biomarkers to early clinical diagnosis and in developing novel neurocognitive circuit-based therapeutic approaches.*"

References:

Rotstein, D., Montalban, X., 2019. Reaching an evidence-based prognosis for personalized treatment of multiple sclerosis. Nat. Rev. Neurol. 15, 287–300. https://doi.org/10.1038/s41582-019-0170-8

Smits, M., 2021. MRI biomarkers in neuro-oncology. Nat. Rev. Neurol. 17, 486–500. https://doi.org/10.1038/s41582-021-00510-y

4. The section related to the activation/deactivation during working memory paradigm of HC and BD has resulted not completely clear. For example, in the sentence "Therefore, while previous research suggests either a lower activation of the CEN or an excessive engagement of the default mode network (DMN)" is not completely clear if the lower CEN activation is related to BD or HC subjects: I would suggest the authors to clearly specify which group is related to the specific region's activation/deactivation.

R: We apologize for the lack of clarity. We have now specified which group (BD patients or HC) is related to the specific region's activation/deactivation.

Introduction section; Page 2; Lines 36-38: *"…only a higher response in the ventromedial prefrontal cortex (vmPFC) was reported as a consistent finding in BD patients."*

Introduction section; Page 2; Line 38-40: *"…that BD patients are characterized by either a lower activation of the CEN or an excessive engagement of the default mode network (DMN),"*

5. In the end of introduction section, could the authors specify which sociodemographic variables were analyzed? (matched between HC and BD).

R: As suggested, we have now added that both groups were matched by age and gender.

Introduction section; Page 3; Lines 77-78: "…*both euthymic BD patients and HC matched by age and gender…"*

6. Could the authors add why the n-paradigm and self-referential tasks are well suited for representing neural correlated related to working memory and self-processing? Could the author add references related to the use of these paradigms to evaluate such functions?

R: We acknowledge that the fMRI paradigms were scarcely explained in the introduction. The n-back task has been the main working memory paradigm used in neuroimaging and non-neuroimaging research, becoming a well-validated and rather conservative choice to evaluate working memory. In contrast, the self-referential task is characterized by its novelty, although it was previously validated to engage the neurobiological correlates of self-processing in healthy controls by Davey et al., 2016.

Introduction section; Pages 1-2; Lines 27-28: *"…research has made significant efforts to identify the neurobiological correlates of these working memory deficits, mainly using the n-back paradigm (Owen et al., 2005)."*

Introduction section; Page 3; Lines 78-80:*"…while performing a classical n-back working memory task (Owen et al., 2005) and a novel self-processing task previously validated in HC (Davey et al., 2016)."*

References:

Owen, Adrian M., Kathryn M. McMillan, Angela R. Laird, and Ed Bullmore. 2005. "N-Back Working Memory Paradigm: A Meta-Analysis of Normative Functional Neuroimaging Studies." *Human Brain Mapping* 25(1): 46–59.

Davey, Christopher G., Jesus Pujol, and Ben J. Harrison. 2016. "Mapping the Self in the Brain's Default Mode Network." *NeuroImage* 132(October): 390–97.

https://linkinghub.elsevier.com/retrieve/pii/S1053811916001294.

Methods:

1. The authors should report the mean and variance of age related to HC and euthymic BD patients also in the text.

R: According to the reviewer's suggestion, we have now reported the mean and variance of age related to each group also in the main text.

Methods section; Page 4; Line 38: *"…twenty-seven euthymic BD patients (mean age = 48 ± 9)…"*

Methods section; Page 4; Line 91: *"…included twenty-five HC of comparable age (mean age = 44 ± 8)…"*

Discussion:

1. When the authors write about "deactivation failure", is that equivalent to an hyperactivation of the specific region? This could be specified, since deactivation failure may confuse the reader in some points.

R: We agree with the reviewer that this result may be confusing and requires further explanation in our manuscript. Briefly, our result emerges from a BD>HC contrast, indicating that BD patients show a higher activation than HC in the vmPFC (that is, a hyperactivation). However, HC deactivated the same region during the task (as shown in Figure S1). Therefore, we can interpret that BD patients did not achieve the same level of deactivation as HC (that is, a lack of deactivation or deactivation failure). We have now highlighted that our results in HC suggest that BD patients show a lack of deactivation.

Results section; Page 8; Lines 200-202: "*…the vmPFC region observed in our between-group analysis completely matched with the brain deactivation pattern of HC during the 2-back condition, therefore supporting a lack of deactivation in euthymic BD patients.*"

Discussion section; Page 9; Lines 233-235: *"…medial regions of the DMN (i.e., vmPFC and PCC/precuneus) were deactivated during working memory conditions in HC."*

2. The authors should reformulate the sentence "These preliminary findings support the existence of state-independent traits in BD patients and underline stable diagnostic biomarkers", clarifying the importance of identifying stable neural underpinning of BD patients based on these findings

R: We appreciate the reviewer's contribution to the discussion.

Discussion section; Page 9; Line 225-227: *"These preliminary findings support the existence of state-independent traits in BD patients and underline potential stable diagnostic biomarkers to early clinical diagnosis and in developing novel neurocognitive circuit-based therapeutic approaches."*

3. The authors need to explain better the sentence "Therefore, our task induced the expected neural activation pattern and proved to be a valid paradigm to explore neurocognitive impairments in our euthymic BD sample" since it is not clear and represent a key step for the discussion. Particularly, authors could clarify the important role of the paradigm in inducing the expected neural activation in HC and BD. In addition, from this sentence it is not clear if the task induces the expected neural activation patterns in HC or BD subjects.

R: We thank the reviewer for their comments. We have now indicated that HC recruited brain regions within the CEN, which are crucial for working memory processes. It should be noted that our only objective is stating that the baseline activation maps used

for our between-group comparisons are in harmony with previous research evaluating the neuronal underpinnings of working memory processes.

Discussion section; Page 9; Lines 228-230: *"…HC recruited brain regions previously identified as the frontoparietal CEN nodes, which are crucial during working memory processes and involve brain regions such as…"*

Discussion section; Page 9; Lines 231-233: *"In light of the fact that the n-back task induced the expected neural activation pattern in HC, it has proved to be a valid paradigm to explore working memory impairments in our euthymic BD sample."*

4. The authors should clarify the sentence "These studies have highlighted that vmPFC deactivation failures may be characterized as stable traits, while dlPFC alterations tended to normalize when the patients reached euthymia" since it is not clear: how the dlPFC alteration tended to be normalize? In addition, the authors should specify " euthymic BD patients" in this sentence.

R: As suggested, we have now clarified the findings interpreting the vmPFC alterations as stable traits versus the dlFPC alterations as state-dependent abnormalities.

Discussion section; Page 10; Lines 249-252: *"…vmPFC deactivation failures may be characterized as stable traits, which are observed in both the affective phases of the disease (mania and depression) and during remission, while dlPFC alterations tended to be normalized (with activation levels similar to HC) when exploring euthymic BD patients."*

5. The authors should be consistent in the definition of the group "euthymic BD patients" since it appears also cited as "euthymic patients".

R: According to the reviewer's suggestion, we are now consistent in the definition of the group "*euthymic BD patients*".

References:

Beunders, A.J.M., Kemp, T., Korten, N.C.M., Oudega, M.L., Beekman, A.T.F., Kupka, R.W., Stek, M.L., Schouws, S.N.T.M., Dols, A., 2021. Cognitive performance in older-age bipolar disorder: Investigating psychiatric characteristics, cardiovascular burden and psychotropic medication. Acta Psychiatr. Scand. 144, 392–406. https://doi.org/10.1111/acps.13342

Cullen, B., Smith, D.J., Deary, I.J., Pell, J.P., Keyes, K.M., Evans, J.J., 2019. Understanding cognitive impairment in mood disorders: mediation analyses in the UK Biobank cohort. Br. J. Psychiatry 215, 683–690. https://doi.org/10.1192/bjp.2019.188

Davey, C.G., Pujol, J., Harrison, B.J., 2016. Mapping the self in the brain's default mode network. Neuroimage 132, 390–397. https://doi.org/10.1016/j.neuroimage.2016.02.022

Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E., 2005. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. Hum. Brain Mapp. 25, 46–59. https://doi.org/10.1002/hbm.20131

Rotstein, D., Montalban, X., 2019. Reaching an evidence-based prognosis for personalized treatment of multiple sclerosis. Nat. Rev. Neurol. 15, 287–300. https://doi.org/10.1038/s41582-019-0170-8

Salagre, E., Vieta, E., 2021. Precision psychiatry: Complex problems require complex solutions. Eur. Neuropsychopharmacol. 52, 94–95. https://doi.org/10.1016/j.euroneuro.2021.07.003

Smits, M., 2021. MRI biomarkers in neuro-oncology. Nat. Rev. Neurol. 17, 486–500. https://doi.org/10.1038/s41582-021-00510-y

Xu, N., Huggon, B., Saunders, K.E.A., 2020. Cognitive Impairment in Patients with Bipolar Disorder: Impact of Pharmacological Treatment. CNS Drugs 34, 29–46.

https://doi.org/10.1007/s40263-019-00688-2

Highlights

- Euthymic bipolar patients show state-independent neurobiological alterations
- Bipolar patients failed to deactivate the DMN during working memory processing
- Higher CEN activations during self-processing were detected in bipolar patients

Abstract

Background: Patients with bipolar disorder (BD) frequently suffer from neurocognitive deficits that can persist during periods of clinical stability. Specifically, impairments in executive functioning such as working memory and in self-processing have been identified as the main components of the neurocognitive profile observed in euthymic BD patients. The study of the neurobiological correlates of these state-independent alterations may be a prerequisite to develop reliable biomarkers in BD.

Methods: A sample of 27 euthymic BD patients and 25 healthy participants (HC) completed working memory and self-referential functional Magnetic Resonance Imaging (fMRI) tasks. Activation maps obtained for each group and contrast images (i.e., 2-back>1-back/self>control) were used for comparisons between patients and HC.

Results: Euthymic BD patients, in comparison to HC, showed a higher ventromedial prefrontal cortex activation during working memory, a result driven by the lack of deactivation in BD patients. In addition, euthymic BD patients displayed a greater dorsomedial and dorsolateral prefrontal cortex activation during self-reference processing.

Limitations: Pharmacotherapy was described but not included as a confounder in our models. Sample size was modest.

Conclusion: Our findings revealed a lack of deactivation in the anterior default mode network (aDMN) during a working memory task, a finding consistent with prior research in BD patients, but also a higher activation in frontal regions within the central executive network (CEN) during self-processing. These results suggest that an imbalance of neural network dynamics underlying external/internal oriented cognition (the CEN and the aDMN, respectively) may be one of the first reliable biomarkers in euthymic bipolar patients.

Keywords (MeSH): Bipolar Disorder; Functional Neuroimaging; Self Concept; Memory, Short-Term; Default Mode Network.

Title Page (with Author Details)

Disrupted network switching in euthymic bipolar disorder: working memory and self-referential paradigms

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Conflict of interest:

DP has received grants and served as consultant or advisor for Rovi, Angelini, Janssen, Lundbeck and Servier. EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Adamed, Angelini, Biogen, Boehringer-Ingelheim, Celon Pharma, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Janssen, Lundbeck, Merck, Novartis, Orion Corporation, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work. Other authors declare that they have no competing interests.

Contributors:

DPC: Data acquisition, curation and analysis, writing (Original Draft).

MC: Writing (Original Draft - Review - Editing), Supervision.

GNV: Data acquisition, Writing (Review - Editing).

MSB: Data acquisition, Writing (Review- Editing).

MVG: Data acquisition, Writing (Review - Editing).

BS: Data acquisition, Writing (Review- Editing).

LM: Data acquisition, Writing (Review - Editing).

CT: Data acquisition, Writing (Review - Editing).

AMA: Writing (Review - Editing), Conception and design of the study, Supervision, Project Administration, Funding acquisition.

BJH: Methodology, Writing (Review).

DP: Writing (Review - Editing), Supervision.

EV: Writing (Review - Editing), Supervision.

NC: Writing (Review - Editing), Conception and design of the study, Supervision, Project Administration, Funding acquisition.

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CERCA Programme, and the Departament de Salut de la Generalitat de Catalunya for the PERIS grant SLT006/17/00357. EV thanks the support of the European Union Horizon 2020 research and innovation program [EU.3.1.1. Understanding health, wellbeing, and disease: Grant No 754907 and EU.3.1.3. Treating and managing disease: Grant No 945151]. This research was also supported by CIBER -Consorcio Centro de Investigación Biomédica en Red- [CB07/09/0004/029], Instituto de Salud Carlos III, Spanish Ministry of Science and Innovation.

Role of the Funding Sources:

Funding sources had no role in the study design.

Introduction

Euthymic bipolar disorder (BD) patients usually experience neurocognitive impairments (Sanchez-Moreno et al., 2017; Yatham et al., 2018). This poor neurocognitive functioning which includes deficits in attention, executive function, memory, verbal learning (Bora et al., 2009; Bourne et al., 2013) and, more recently, meta-cognition (Torres et al., 2021), seems not to be attributed to residual mood disturbances, and it is only partially explained by psychotropic medication such as lithium, benzodiazepines and anticholinergics (Beunders et al., 2021; Cullen et al., 2019; Xu et al., 2020). In addition, these neurocognitive deficits appear to be also present in unaffected relatives of BD patients (Arts et al., 2008; Kjærstad et al., 2021). Due to the apparent state-independence of this neurocognitive profile (Cullen et al., 2016; Matsuo et al., 2021), it has recently emerged as a potential stable trait for BD (Pomarol-Clotet et al., 2015; Teixeira et al., 2019). Magnetic resonance imaging (MRI) has been proven useful to explore activation patterns linked to endophenotypes of mood disorders (Soares and Mann, 1997; Xi et al., 2021), although multiple sources and types of heterogeneity, especially in BD, poses an obstacle to define reliable biomarkers (Wolfers et al., 2018). In this sense, not only evaluating the neurobiological correlates of trait-like alterations may allow avoiding the confounding influence of affective symptomatology on neurocognitive performance, but it could also foster the detection of diagnostic biomarkers, a significant milestone in the journey towards precision psychiatry (Salagre and Vieta, 2021) which has already been achieved in other medical specialties such as neurology (Rotstein and Montalban, 2019) and oncology (Smits, 2021).

Previous research has consistently placed executive function as the primary axis of neurocognitive deficits in BD patients (Lima et al., 2018). Specifically, working memory alterations appear to be one of the most persistent neurocognitive symptoms in euthymic phases (Kurtz and Gerraty, 2009; Soraggi-Frez et al., 2017). Indeed, working memory performance has been shown to have a direct impact on BD patients' quality of life (Mackala et al., 2014) and overall functional recovery (Bearden et al., 2011; Burdick and Millett, 2021). Consequently, functional magnetic resonance imaging (fMRI) research has made significant efforts to identify the neurobiological correlates of

these working memory deficits, mainly using the n-back paradigm (Owen et al., 2005). A recent fMRI meta-analysis evaluating euthymic BD patients (Mencarelli et al., 2019; Riley and Constantinidis, 2016) found the dorsolateral prefrontal cortex (dlPFC), the inferior frontal gyrus, the posterior parietal cortex and the precuneus as the main nodes involved in the working memory performance of these patients (Saldarini et al., 2022). Interestingly, these brain regions are closely related to the activity pattern observed in healthy participants (HC) during working memory paradigms, and they have consistently showed reduced activity in BD patients (Mencarelli et al., 2019; Riley and Constantinidis, 2016). However, these central executive network (CEN) nodes were not found in all studies (Dell'osso et al., 2015), and only a higher response in the ventromedial prefrontal cortex (vmPFC) was reported as a consistent finding in BD patients. Therefore, while previous research suggests that BD patients are characterized by either a lower activation of the CEN or an excessive engagement of the default mode network (DMN), further studies are required to clarify the role of these brain regions in the working memory alterations observed in euthymic BD patients.

In addition, the neurobiological underpinnings of other neurocognitive domains such as self-processing have been largely unexplored in BD despite being a hot topic of research in both major depression (Lou et al., 2019) and schizophrenia (Potvin et al., 2019). The polarity of BD symptomatology, with a decreased self-focus and distractibility during mania and an increased self-focus and rumination during depressive phases (Alloy et al., 2009; Batmaz et al., 2021; Herold et al., 2017), suggests that brain circuits engaged during self-related tasks may be also involved in the neurocognitive profile of these patients even during euthymia (Favaretto et al., 2020). To the best of our knowledge, only three previous studies, including depressed (Zhang et al., 2015), manic (Herold et al., 2017) and euthymic bipolar participants with comorbidities (Apazoglou et al., 2019), have evaluated patients' neural response to tasks requiring self-referential processing. Specifically, Zhang et al., 2015 reported that depressed patients did not show any significant difference in the brain activation pattern during self-processing compared to HC. Notwithstanding, they detected a reduced activation of the posterior cingulate gyrus (PCC) and precuneus when participants were matching or rejecting positive or negative traits to a relative

or close friend. Herold et al., 2017 found that manic patients exhibited a reduced engagement of the medial prefrontal cortex (mPFC) during a task where participants were asked to consider whether a picture was related to them. Finally, Apazoglou et al., 2019 observed an exploratory result of higher activation in medial brain regions (vmPFC, dmPFC, subgenual anterior cingulate and PCC) as well as in the inferior parietal cortex in euthymic bipolar participants in a focus-switching task. Although inconsistent and scarce, these results pointed to an alteration within medial nodes of the DMN, brain regions involved in tasks requiring introspection and internal focus (Davey et al., 2016), and closely related to rumination symptoms (Zhou et al., 2020).

Working memory and self-processing alterations can be seen as complementary, both from psychological and neurobiological points of view. Psychologically, while working memory deficits reflect an alteration within executive functions intrinsically related to the processing of external stimuli, self-processing requires introspection and assessment of internal stimuli. This dualism is also observable in the circuitry underlying both functions, with working memory tasks engaging the CEN and deactivating the DMN (Murphy et al., 2020; Satterthwaite et al., 2013) while self-processing paradigms relying in the opposite pattern (Davey et al., 2016). Therefore, the exploration of these complementary functions in the same sample of euthymic bipolar patients can provide further insights into the neural network dynamics related to both inward and outward dimensions of persistent neurocognitive deficits.

In this study, we aim to evaluate the neural activation of euthymic BD patients while performing neurocognitive tasks. Specifically, we want to explore potential state-independent trait biomarkers that could ultimately assist clinical practice in processes of differential diagnosis and interepisodic diagnostic validation. To this end, both euthymic BD patients and HC matched by age and gender were evaluated inside an fMRI scanner while performing a classical n-back working memory task (Owen et al., 2005) and a novel self-processing task previously validated in HC (Davey et al., 2016).

Methods

Participants

We recruited twenty-seven euthymic BD patients (mean age = 48 ± 9) from the Mood Disorders Outpatient Unit of Parc Tauli University Hospital and the Bipolar Disorder and Depressive Unit of Hospital Clinic, Barcelona. Euthymic status was assessed by a senior psychiatrist with extensive experience in mood disorders. Each patient was assessed using the Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1960) and the Young Mania Rating Scale (YMRS; Young et al., 1978). None of the patients could exhibit manic symptomatology (YMRS<12, mean score = 1.59) and only subsyndromal depressive symptoms were allowed (HDRS-17<15, mean score = 6.15).

The comparison sample included twenty-five HC of comparable age (mean age = 44 ± 8) and sex distribution to euthymic BD patients, from the local community through word of mouth. In order to rule out the possibility of current or lifetime psychiatric disorders and the use of psychotropic medication, participants from the comparison group underwent a medical anamnesis and the Structured Clinical Interview for DSM-IV Axis I Disorders non-patient version (First and Gibbon, 2004).

For both groups, exclusion criteria included: (1) presence or history of severe medical, neurological, intellectual or psychiatric disorders (other than BD in patients) and (2) contraindication to fMRI scanning or abnormal MRI upon visual inspection. In patients, anxiety and eating disorders comorbidities was not considered an exclusion criterion provided that BD was the main diagnosis and the primary reason for seeking assistance before euthymia. Sociodemographic and clinical characteristics of the study samples are summarized in Table 1. For a better description of medication load, antipsychotic (Venkatasubramanian and Danivas, 2013), antidepressant (Hayasaka et al., 2015) and benzodiazepine (Ashton, 2002) doses were converted to their equivalent in chlorpromazine, fluoxetine and diazepam respectively.

The study protocol was approved by the Institutional Review Board of the Parc Tauli University Hospital and the Hospital Clinic of Barcelona and conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent to participate in the study.

Neurocognitive tasks

N-Back task

Three conditions of the n-back task (Kirchner, 1958) were applied: 0-back, 1-back and 2-back. In the 0-back condition, participants were asked to respond to the occurrence of each letter "X". In the 1-back condition, participants were asked to decide whether the letter on screen matched the last one. In the 2-back condition, participants were instructed to indicate if the letter appearing in the screen matched the second last one. Each condition was presented four times in blocks of 49 seconds (1 second per letter) and separated by 10 seconds of cross-fixation and 1 second of a white screen. 1-back and 2-back blocks were preceded by 15 seconds of instructions. The signal detection theory index of sensitivity (d' = accuracy) was computed to assess task performance, indicating the participants' ability to discriminate between target letters and distractors (Nevin, 1969). Additionally, reaction times were registered as a secondary performance index. The task was practiced before entering the scanner to ensure participants' fully understanding of its functioning.

Self-reference task

The task consisted of two experimental conditions: self-reference and non-self-referential attention (Davey et al., 2016). During the self-referential condition, participants were presented with several neutral trait adjectives and asked to respond via a button box whether or not the word described their personality. A different set of adjectives were presented during the non-self-referential condition, where the participants were asked to respond if the word contained 5 or more vowels. For both conditions, participants viewed 8 blocks of 6 words presented for 5 seconds. Each 30 seconds block was interspersed with a 10 second cross-fixation and preceded by 5 seconds of task instructions (self or control). Reaction times to each trial were collected. The

task was practiced before entering the scanner to ensure participants fully understanding of its functioning as well as the words' meaning.

Imaging acquisition and preprocessing

Functional imaging data were acquired with a 3-T scanner (Philips Ingenia, Best, The Netherlands), equipped with a 32-channel head coil. Imaging parameters were as follows: matrix size = 240 x 240 pixels; number of slices = 46; slice thickness = 3.1 mm; pulse angle = 70°; field of view = 80 x 80 mm; echo time = 35 ms; repetition time = 1700 ms. For each participant, a 12 minute 30 seconds and a 12-minute functional sequences (corresponding to n-back and self-reference tasks respectively) were acquired generating 442 and 424 whole-brain echoplanar imaging volumes per sequence. The first four (additional) images from each run were discarded to allow the magnetization to reach equilibrium. We also acquired a high-resolution T1-weighted anatomical image for each subject with 240 slices (slice thickness = 0.75 mm; flip angle = 8°; field of view = 352 x 352 pixels, echo time = 4569 ms; repetition time = 9752 ms) to discard gross radiological alterations.

Imaging data were processed on a Microsoft Windows platform using MATLAB R2021a (The MathWorksInc, Natick, Mass) and Statistical Parametric Mapping (SPM12; The Welcome Department of Imaging Neuroscience, London, UK) (Ashburner et al., 2013). Slice timing correction was used to adjust for differences in time acquisition across slices. Motion correction consisted in the alignment of each subject time-series to its mean image using a least-squares minimization and a 6-parameter rigid body spatial transformation. The resulting functional sequences were corregistered to each participant's anatomical scan, previously normalized to the SPM's T1 template using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL). Normalization parameters used during structural normalization were also applied to the corregistered functional data. Finally, functional images were smoothed with an isotropic Gaussian kernel of 8 mm full-width at half-maximum (FWHM).

Statistical analysis

Behavioural data

We evaluated in-scanner tasks performance using accuracy and reaction time data during each condition. Specifically, we conducted two-sample t-tests in order to compare tasks performance between euthymic BD patients and HC.

Neuroimaging data

First-level contrast images during n-back and self-referential tasks were calculated for each participant. Specifically, working memory was assessed by contrasting the 1-back to the 0-back condition and moderate-high memory load was computed by contrasting the 2-back to the 1-back condition. In addition, self-referential processing was assessed by contrasting the self-reference to the non-self-referential attention condition (self versus control). Therefore, regressors modelled each condition of interest, as well as the fixation cross and the motion parameters (i.e., 3 translations and 3 rotations). The Blood Oxygenation Level Dependent (BOLD) signal was convolved with a canonical hemodynamic response function, and a 128-second high-pass filter was applied to remove low-frequency drifts.

Then, first-level contrast images for each participant were included in second-level (group) analyses. We initially estimated the within-group activity patterns using six whole-brain one-sample t-tests (one per group and contrast). Between-group differences were explored using three whole-brain two-sample t-tests (one per each contrast). Statistical significance was set at a cluster-level family-wise-error (FWE) corrected threshold of $p<0.05$ (voxel-level probability of $p<0.001$).

Results

N-Back task

Behavioural results

Task performance measures indicated that euthymic BD patients showed a lower signal detection (d') compared to HC in the 1-back ($p=0.001$) and 2-back ($p<0.001$) conditions, but not during 0-

back (p=0.119). Additionally, euthymic BD patients exhibited a higher average reaction time to all stimuli during the task (p<0.05).

Neuroimaging results

Within-group analyses revealed that during moderate-high memory load HC showed larger responses to 2-back compared to 1-back in the supramarginal gyrus, postcentral gyrus, superior parietal lobe, dlPFC, supplementary motor cortex, dmPFC, angular gyrus and cerebellum. Euthymic BD patients showed a similar activation pattern, although only the more posterior regions (superior parietal lobule, cerebellum and precuneus) were found to be significantly more activated to 2-back compared to 1-back (Figure 1 and Table 2). When exploring 2-back < 1-back, HC showed smaller responses to 2-back compared to 1-back within limbic regions (hippocampus and amygdala), and the vmPFC, anterior cingulate cortex, fusiform gyrus, temporal lobe (pole, inferior and middle gyri) and occipital pole.

Between-group comparisons indicated that euthymic BD patients showed a significantly higher activation in the vmPFC during moderate-high memory load in comparison to HC. In order to assess whether this between-group difference was driven by a failure of deactivation in the euthymic BD patients during the moderate-high load condition, we computed activation and deactivation maps to both 1-back and 2-back conditions in HC (see Figure S1). Interestingly, the vmPFC region observed in our between-group analysis completely matched with the brain deactivation pattern of HC during the 2-back condition, therefore supporting a lack of deactivation in euthymic BD patients.

Self-reference task

Behavioural results

Euthymic BD patients showed higher reaction times to both self-referential and non-self-referential attention conditions compared to HC (p<0.001).

Neuroimaging results

Self-referential processing, compared to the control condition, activated the main nodes of the DMN: the medial prefrontal cortex (i.e., dmPFC extending to vmPFC), angular gyrus, PCC and

precuneus in both groups. Additionally, other brain regions such as the middle and inferior temporal gyrus, left ventrolateral prefrontal cortex, supplementary motor cortex, thalamus, caudate and crus 1 and 2 of the cerebellum were also activated in both groups (Figure 2 and Table 3). In contrast, the superior parietal lobule, angular gyrus, supramarginal gyrus, precentral and postcentral gyri, dlPFC, right anterior insula, middle and superior occipital gyri and other regions of the cerebellum exhibited smaller brain activations during self-referential processing in both groups.

Between-group analyses revealed that euthymic BD patients showed a higher trend-level activation in the dmPFC extending to the dlPFC during self-referential processing in comparison to HC. Specifically, within-group maps displayed that euthymic BD patients activated a larger area of the dmPFC, and they did not reduce the activation of the dlPFC as HC did (Figure 2).

Discussion

Consistent with previous findings (Pomarol-Clotet et al., 2015), our euthymic BD patients showed a deactivation failure of the vmPFC during working memory processes. To our knowledge, this is the first study to suggest that euthymic bipolar patients may also show a dmPFC-dlPFC hyperactivation during self-processing. These preliminary findings support the existence of state-independent traits in BD patients and underline potential stable diagnostic biomarkers to early clinical diagnosis and in developing novel neurocognitive circuit-based therapeutic approaches.

During the n-back paradigm, HC recruited brain regions previously identified as the frontoparietal CEN nodes, which are crucial during working memory processes and involve brain regions such as the anterior insula, parietal lobules, dmPFC, dlPFC, and cerebellum (Kim, 2019; Yaple et al., 2021). In light of the fact that the n-back induced the expected neural activation pattern in HC, it has proved to be a valid paradigm to explore working memory impairments in our euthymic BD sample. Also consistent with prior knowledge of goal-directed paradigms (Murphy et al., 2020), medial regions of the DMN (i.e., vmPFC and PCC/precuneus) were deactivated during working memory conditions in HC. This so called “low firing mode” of the DMN has been shown to play a prominent role in achieving a good performance across attentional tasks (Anticevic et al., 2012;

Mayer et al., 2010; Petersen and Miskowiak, 2021). Indeed, recent neural network models have revealed a complex partial anticorrelation between the working memory network and the DMN (Murphy et al., 2020; Vatansever et al., 2017; Yuan et al., 2021). According to these models, the frontoparietal cortex (as part of the CEN) may be triggering a DMN or dorsal attention system deactivation depending on whether an external or internal focus is needed. Therefore, our findings support that a balanced CEN-DMN interaction may be needed for working memory processing. In this sense, a deactivation failure within the DMN can be seen as an abnormal and persistent activation in a network linked to rumination, self-reference and mind-wandering when goal-directed actions are required.

In addition, the fact that we only observed a DMN deactivation failure but not an abnormal dorsal prefrontal cortex activity pattern is also in agreement with prior evidence from longitudinal studies (Alonso-Lana et al., 2019; Pomarol-Clotet et al., 2015). These studies have highlighted that vmPFC deactivation failures may be characterized as stable traits, which are observed in both the affective phases of the disease (mania and depression) and during remission, while dlPFC alterations tended to be normalised (with activation levels similar to HC) when explored in euthymic BD patients. Altogether with our behavioural findings (i.e., lower signal detection and higher reaction time in euthymic BD patients), fMRI results suggest that a persistent DMN activation may be explaining the persistence of neurocognitive deficits observed in euthymic BD patients. However, previous evidence does not fully support this claim, as both an abnormal dorsal PFC activation and a DMN deactivation failure have been found to be linked to neurocognitive impairments in BD (Alonso-Lana et al., 2019; Ott et al., 2021) and across mood disorders (Miskowiak and Petersen, 2019; Petersen and Miskowiak, 2021). Notwithstanding, recent research aiming to explain this discrepancy has proposed a bell-shaped model where, depending on task load, BOLD response would reflect a lower cortical efficiency (low demand – hyperactivity) or a lower cognitive capacity (high load – hypoactivity) (Petersen and Miskowiak, 2021). In this sense, Petersen & Miskowiak model proposes that HC and mood disorders patients' activity patterns could intersect with moderate task loads. Since our findings emerged from a moderate-high memory load contrast (2-back > 1-back), this model may be explaining why we

observed a DMN deactivation failure, but we did not detect an alteration in the dlPFC activity pattern.

As expected, our self-reference paradigm evoked the activation of core DMN nodes, involving the mPFC, angular gyrus, PCC and precuneus, in HC (Davey et al., 2016). Moreover, the brain regions found to be less activated during the self-reference condition compared to the control condition matched to a large extent with those brain regions activated during the working memory task (i.e., dlPFC and parietal lobules). This finding further supports the idea that the fMRI paradigms used during this study reflect complementary network dynamic states linked to internally or externally directed cognition (Murphy et al., 2020). That said, our self-reference dlPFC hyperactivation finding may be based on the same framework as the working memory vmPFC deactivation failure. Indeed, a higher activation (or lack of deactivation) of a brain region within the CEN during an introspective task may be also signalling an imbalance between the inward-outward switching system.

Moreover, our self-reference dmPFC hyperactivation finding revealed that euthymic BD patients recruited a more extended region of the dmPFC, which may be interpreted as a lower cortical efficiency during self-reference processing. Previous research using the same self-processing paradigm have already highlighted that the dmPFC plays a relevant role moderating the posterior DMN functioning (Davey et al., 2016). This interaction may bring PCC self-representations into consciousness depending on the dmPFC interpretation of the task demands (Feng et al., 2018; Leech and Smallwood, 2019). By itself, the dmPFC has been closely related to abstract cognitive processes, including social cognition tasks (Zamani et al., 2022) as well as autobiographical abstract reasoning (D'Argembeau et al., 2014), self-relevant judgements and rumination (Denny et al., 2012; Zhou et al., 2020). Moreover, Apazoglou et al., (2019) also published exploratory results showing abnormal vmPFC and dmPFC hyperactivations during self-reference in euthymic bipolar patients. Therefore, our findings and previous exploratory research support the hypothesis that persistent alterations in the dmPFC during self-processing are characterizing bipolar patients during euthymia. Notwithstanding, the statistical significance level of these results require to be cautious in its interpretation.

Limitations:

There are some limitations that must be discussed. First, the vast majority of our patients, while euthymic, were treated with a significant load of pharmacotherapy that could be affecting our results. However, drug usage by means of dosage equivalents of chlorpromazine, fluoxetine and diazepam has been detailed in Table 1. Second, prior research suggests that certain cognitive biases should be expected towards negative self-reference associations in bipolar and unipolar depressive patients (Molz Adams et al., 2014). Therefore, a self-referential task including both negative and positive traits may be more effective in revealing neural alterations in self-processing. Notwithstanding, our design focusing only on neutral traits allows us to control for the effect of valence without needing to subdivide our sample, and therefore avoiding a loss of statistical power. Third, an n-back design with higher working memory load levels would be more optimal to assess the load-based models previously postulated (Petersen and Miskowiak, 2021). Nevertheless, we used a conservative and prevalent n-back model (Saldarini et al., 2022) to ensure a minimal patients' performance. Finally, while using a sample size similar to prior research evaluating BD, our sample size was still modest by current methodological standards (Szucs and Ioannidis, 2020).

Conclusions:

Our findings showed that euthymic bipolar patients failed to deactivate the anterior DMN during goal-oriented processing, and hyperactivated brain regions within the CEN during self-processing. Overall, our research suggests an inefficient segregation of brain dynamics coordinating internal and external processing in euthymic bipolar patients. Future research should use paradigms focused on inward-outward task-switching alterations in BD. In addition, further research is warranted to fully characterize state-independent traits in BD to be able to detect reliable biomarkers that could ultimately reduce the common misdiagnosis associated to bipolar disorder and to guide researchers and clinicians in the search of personalized treatments.

Table 1. Sociodemographic and clinical characteristics of the study samples

	Bipolars (n=27)	Controls (n=25)	Between-group differences †
Age, years: mean (±SD)	48.49 (9.19)	44.12 (7.98)	-1.82 (p = 0.073)
Sex, male: n (%)	13 (48%)	15 (60%)	0.73 (p = 0.392)
Bipolar diagnosis, Type I: n (%)	17 (63%)	-	-
Eating disorder: n	2	-	-
Kleptomania: n	1	-	-
YMRS: mean (±SD)	1.59 (±2.60)	0.96 (±1.70)	-1.01 (p = 0.315)
HRSD-17: mean (±SD)	6.15 (±2.76)	3 (±3.16)	-3.79 (p = <0.001)
WHO-5: mean (±SD)	10.31 (±3.87)	15.67 (±3.64)	5.02 (p = <0.001)
Age at onset, years: mean (±SD)	29.69 (±11.03)	-	-
Duration of illness, years: mean (±SD)	18.80 (±11.62)	-	-
Number of drugs: mean (±SD)	3.89 (±0.49)	-	-
Mood stabilizers / Anticonvulsants: n (%)	25 (93%)	-	-
Doses of psychotropic drugs (milligrams/day)			
Chlorpromazine equivalents	n=20 278 (±362)	-	-
Fluoxetine equivalents	n=16 45 (±19)	-	-
Diazepam equivalents	n=14 19 (±10)	-	-

YMRS = Young Mania Rating Scale; HRSD = Hamilton Depression Rating Scale; WHO-5 = World Health Organization Well-Being Index.

†Continuous variables analysed by t-tests; categorical variables analysed by X^2 test.

Table 2. Activity pattern during the moderate-high memory load contrast

Brain Regions	MNI Coordinates x	y	z	*k*	T-Value	p_{FWE}-Value
Healthy participants						
2-back > 1-back						
Right Supramarginal gyrus	42	-40	40	11071	6.66	< 0.001
Left Supramarginal gyrus						
Left/Right Superior parietal lobule						
Left/Right Angular gyrus						
Left/Right Postcentral gyrus						
Right Dorsolateral prefrontal cortex	28	15	51	6982	6.50	< 0.001
Left Dorsolateral prefrontal cortex	-28	12	54	5082	6.24	< 0.001
Left Cerebellum	-32	-60	-34	1779	6.24	< 0.001
Left/Right Supplementary motor Cortex	0	24	45	1211	5.68	0.003
Left/Right Dorsomedial prefrontal cortex						
2-back < 1-back						
Right Temporal pole	34	6	-36	2583	6.00	< 0.001
Right Inferior Temporal gyrus						
Right Middle Temporal gyrus						
Right Amygdala						
Right Hippocampus						
Left Temporal pole	-33	9	-39	789	4.81	0.020
Left Inferior Temporal gyrus						
Left Ventromedial prefrontal cortex	-10	50	-6	3527	5.90	< 0.001
Right Ventromedial prefrontal cortex						
Left/Right Anterior Cingulate cortex						
Right Occipital pole	21	-99	3	1121	5.83	0.004
Right Occipital Fusiform gyrus						
Left Occipital pole	-26	-99	-6	846	4.38	0.015
Left Occipital fusiform gyrus						
Left Hippocampus	-26	-10	-14	1774	5.23	< 0.001
Left Amygdala						
Left Putamen						
Bipolars > Controls (2-back > 1-back)						
Left Ventromedial prefrontal cortex	-12	51	-6	1167	4.66	0.003
Right Ventromedial prefrontal cortex						

pFWE = p value corrected for multiple comparisons by family-wise error.

Table 3. Activity pattern during the self-referential contrast

Brain regions	MNI Coordinates x	y	z	*k*	T-Value	p_{FWE}-Value
Healthy participants						
Self > Control						
Left Dorsomedial prefrontal cortex	-10	38	42	24193	12.53	< 0.001
Right Dorsomedial prefrontal cortex						
Left/Right Supplementary motor cortex						
Left/Right Ventromedial prefrontal cortex						
Left Orbital gyrus (posterior/lateral)	-36	32	-15	20844	10.07	< 0.001
Left Ventrolateral prefrontal cortex						
Left Angular gyrus	-50	-62	32	5071	10.61	< 0.001
Right Angular gyrus	56	-56	21	858	7.32	< 0.001
Left Posterior cingulate gyrus	-4	-46	26	6742	10.01	< 0.001
Right Posterior cingulate gyrus						
Left/Right Precuneus						
Right Middle temporal gyrus	60	-4	-22	4111	6.70	< 0.001
Left Middle temporal gyrus						
Right/Left Superior temporal gyrus						
Left Caudate	-12	18	14	1337	6.04	0.001
Right Caudate						
Left/Right Thalamus						
Right Cerebellum	26	-75	-39	10368	14.56	< 0.001
Left Cerebellum						
Right Cerebellum	3	-56	-50	1058	9.86	0.005
Self < Control						
Left Middle occipital gyrus	-32	-72	24	114662	12.89	< 0.001
Right Middle occipital gyurs						
Left/Right Superior occipital gyrus						
Left/Right Angular gyrus						
Left/Right Supramarginal gyrus						
Left/Right Superior parietal lobule						
Left/Right Postcentral gyrus						
Left/Right Precentral gyrus						
Right Anterior insula						
Left/Right Cerebrum						
Left Dorsolateral prefrontal cortex	-36	39	33	1520	7.22	0.001
Right Dorsolateral prefrontal cortex						
Left Orbital gyrus (anterior/medial)	-32	58	-16	633	6.59	0.043
Left Frontal pole						
Bipolars > Controls (Self > Control)						
Right Dorsomedial prefrontal cortex	21	48	23	598	4.80	0.053
Right Dorsolateral prefrontal cortex						

pFWE = p value corrected for multiple comparisons by family-wise error.

Figure 1. Brain regions showing larger (red) or smaller (blue) activation during the 2-back condition compared to 1-back in HC (top) and euthymic BD patients (bottom). Between-group findings (bipolars>controls) in the vmPFC are displayed in green.

Figure 2. Brain regions showing larger (red) or smaller (blue) activation during self-referential processing compared to the non-self-referential attention condition in HC (top) and euthymic BD patients (bottom). Between-group findings (bipolars>controls) in the dmPFC-dlPFC are displayed in yellow.

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Introduction

Euthymic bipolar disorder (BD) patients usually experience neurocognitive impairments (Sanchez-Moreno et al., 2017; Yatham et al., 2018). This poor neurocognitive functioning which includes deficits in attention, executive function, memory, verbal learning (Bora et al., 2009; Bourne et al., 2013) and, more recently, meta-cognition (Torres et al., 2021), seems not to be attributed to residual mood disturbances, and it is only partially explained by psychotropic medication such as lithium, benzodiazepines and anticholinergics (Beunders et al., 2021; Cullen et al., 2019; Xu et al., 2020). In addition, these neurocognitive deficits appear to be also present in unaffected relatives of BD patients (Arts et al., 2008; Kjærstad et al., 2021). Due to the apparent state-independence of this neurocognitive profile (Cullen et al., 2016; Matsuo et al., 2021), it has recently emerged as a potential stable trait for BD (Pomarol-Clotet et al., 2015; Teixeira et al., 2019). Magnetic resonance imaging (MRI) has been proven useful to explore activation patterns linked to endophenotypes of mood disorders (Soares and Mann, 1997; Xi et al., 2021), although multiple sources and types of heterogeneity, especially in BD, poses an obstacle to define reliable biomarkers (Wolfers et al., 2018). In this sense, not only evaluating the neurobiological correlates of trait-like alterations may allow avoiding the confounding influence of affective symptomatology on neurocognitive performance, but it could also foster the detection of diagnostic biomarkers, a significant milestone in the journey towards precision psychiatry (Salagre and Vieta, 2021) which has already been achieved in other medical specialties such as neurology (Rotstein and Montalban, 2019) and oncology (Smits, 2021).

Previous research has consistently placed executive function as the primary axis of neurocognitive deficits in BD patients (Lima et al., 2018). Specifically, working memory alterations appear to be one of the most persistent neurocognitive symptoms in euthymic phases (Kurtz and Gerraty, 2009; Soraggi-Frez et al., 2017). Indeed, working memory performance has been shown to have a direct impact on BD patients' quality of life (Mackala et al., 2014) and overall functional recovery (Bearden et al., 2011; Burdick and Millett, 2021). Consequently, functional magnetic resonance imaging (fMRI) research has made significant efforts to identify the neurobiological correlates of

these working memory deficits, mainly using the n-back paradigm (Owen et al., 2005). A recent fMRI meta-analysis evaluating euthymic BD patients (Mencarelli et al., 2019; Riley and Constantinidis, 2016) found the dorsolateral prefrontal cortex (dlPFC), the inferior frontal gyrus, the posterior parietal cortex and the precuneus as the main nodes involved in the working memory performance of these patients (Saldarini et al., 2022). Interestingly, these brain regions are closely related to the activity pattern observed in healthy participants (HC) during working memory paradigms, and they have consistently showed reduced activity in BD patients (Mencarelli et al., 2019; Riley and Constantinidis, 2016). However, these central executive network (CEN) nodes were not found in all studies (Dell'osso et al., 2015), and only a higher response in the ventromedial prefrontal cortex (vmPFC) was reported as a consistent finding in BD patients. Therefore, while previous research suggests that BD patients are characterized by either a lower activation of the CEN or an excessive engagement of the default mode network (DMN), further studies are required to clarify the role of these brain regions in the working memory alterations observed in euthymic BD patients.

In addition, the neurobiological underpinnings of other neurocognitive domains such as self-processing have been largely unexplored in BD despite being a hot topic of research in both major depression (Lou et al., 2019) and schizophrenia (Potvin et al., 2019). The polarity of BD symptomatology, with a decreased self-focus and distractibility during mania and an increased self-focus and rumination during depressive phases (Alloy et al., 2009; Batmaz et al., 2021; Herold et al., 2017), suggests that brain circuits engaged during self-related tasks may be also involved in the neurocognitive profile of these patients even during euthymia (Favaretto et al., 2020). To the best of our knowledge, only three previous studies, including depressed (Zhang et al., 2015), manic (Herold et al., 2017) and euthymic bipolar participants with comorbidities (Apazoglou et al., 2019), have evaluated patients' neural response to tasks requiring self-referential processing. Specifically, Zhang et al., 2015 reported that depressed patients did not show any significant difference in the brain activation pattern during self-processing compared to HC. Notwithstanding, they detected a reduced activation of the posterior cingulate gyrus (PCC) and precuneus when participants were matching or rejecting positive or negative traits to a relative

or close friend. Herold et al., 2017 found that manic patients exhibited a reduced engagement of the medial prefrontal cortex (mPFC) during a task where participants were asked to consider whether a picture was related to them. Finally, Apazoglou et al., 2019 observed an exploratory result of higher activation in medial brain regions (vmPFC, dmPFC, subgenual anterior cingulate and PCC) as well as in the inferior parietal cortex in euthymic bipolar participants in a focus-switching task. Although inconsistent and scarce, these results pointed to an alteration within medial nodes of the DMN, brain regions involved in tasks requiring introspection and internal focus (Davey et al., 2016), and closely related to rumination symptoms (Zhou et al., 2020).

Working memory and self-processing alterations can be seen as complementary, both from psychological and neurobiological points of view. Psychologically, while working memory deficits reflect an alteration within executive functions intrinsically related to the processing of external stimuli, self-processing requires introspection and assessment of internal stimuli. This dualism is also observable in the circuitry underlying both functions, with working memory tasks engaging the CEN and deactivating the DMN (Murphy et al., 2020; Satterthwaite et al., 2013) while self-processing paradigms relying in the opposite pattern (Davey et al., 2016). Therefore, the exploration of these complementary functions in the same sample of euthymic bipolar patients can provide further insights into the neural network dynamics related to both inward and outward dimensions of persistent neurocognitive deficits.

In this study, we aim to evaluate the neural activation of euthymic BD patients while performing neurocognitive tasks. Specifically, we want to explore potential state-independent trait biomarkers that could ultimately assist clinical practice in processes of differential diagnosis and interepisodic diagnostic validation. To this end, both euthymic BD patients and HC matched by age and gender were evaluated inside an fMRI scanner while performing a classical n-back working memory task (Owen et al., 2005) and a novel self-processing task previously validated in HC (Davey et al., 2016).

Methods

Participants

We recruited twenty-seven euthymic BD patients (mean age = 48 ± 9) from the Mood Disorders Outpatient Unit of Parc Tauli University Hospital and the Bipolar Disorder and Depressive Unit of Hospital Clinic, Barcelona. Euthymic status was assessed by a senior psychiatrist with extensive experience in mood disorders. Each patient was assessed using the Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1960) and the Young Mania Rating Scale (YMRS; Young et al., 1978). None of the patients could exhibit manic symptomatology (YMRS<12, mean score = 1.59) and only subsyndromal depressive symptoms were allowed (HDRS-17<15, mean score = 6.15).

The comparison sample included twenty-five HC of comparable age (mean age = 44 ± 8) and sex distribution to euthymic BD patients, from the local community through word of mouth. In order to rule out the possibility of current or lifetime psychiatric disorders and the use of psychotropic medication, participants from the comparison group underwent a medical anamnesis and the Structured Clinical Interview for DSM-IV Axis I Disorders non-patient version (First and Gibbon, 2004).

For both groups, exclusion criteria included: (1) presence or history of severe medical, neurological, intellectual or psychiatric disorders (other than BD in patients) and (2) contraindication to fMRI scanning or abnormal MRI upon visual inspection. In patients, anxiety and eating disorders comorbidities was not considered an exclusion criterion provided that BD was the main diagnosis and the primary reason for seeking assistance before euthymia. Sociodemographic and clinical characteristics of the study samples are summarized in Table 1. For a better description of medication load, antipsychotic (Venkatasubramanian and Danivas, 2013), antidepressant (Hayasaka et al., 2015) and benzodiazepine (Ashton, 2002) doses were converted to their equivalent in chlorpromazine, fluoxetine and diazepam respectively.

The study protocol was approved by the Institutional Review Board of the Parc Tauli University Hospital and the Hospital Clinic of Barcelona and conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent to participate in the study.

Neurocognitive tasks

N-Back task

Three conditions of the n-back task (Kirchner, 1958) were applied: 0-back, 1-back and 2-back. In the 0-back condition, participants were asked to respond to the occurrence of each letter "X". In the 1-back condition, participants were asked to decide whether the letter on screen matched the last one. In the 2-back condition, participants were instructed to indicate if the letter appearing in the screen matched the second last one. Each condition was presented four times in blocks of 49 seconds (1 second per letter) and separated by 10 seconds of cross-fixation and 1 second of a white screen. 1-back and 2-back blocks were preceded by 15 seconds of instructions. The signal detection theory index of sensitivity (d' = accuracy) was computed to assess task performance, indicating the participants' ability to discriminate between target letters and distractors (Nevin, 1969). Additionally, reaction times were registered as a secondary performance index. The task was practiced before entering the scanner to ensure participants' fully understanding of its functioning.

Self-reference task

The task consisted of two experimental conditions: self-reference and non-self-referential attention (Davey et al., 2016). During the self-referential condition, participants were presented with several neutral trait adjectives and asked to respond via a button box whether or not the word described their personality. A different set of adjectives were presented during the non-self-referential condition, where the participants were asked to respond if the word contained 5 or more vowels. For both conditions, participants viewed 8 blocks of 6 words presented for 5 seconds. Each 30 seconds block was interspersed with a 10 second cross-fixation and preceded by 5 seconds of task instructions (self or control). Reaction times to each trial were collected. The

task was practiced before entering the scanner to ensure participants fully understanding of its functioning as well as the words' meaning.

Imaging acquisition and preprocessing

Functional imaging data were acquired with a 3-T scanner (Philips Ingenia, Best, The Netherlands), equipped with a 32-channel head coil. Imaging parameters were as follows: matrix size = 240 x 240 pixels; number of slices = 46; slice thickness = 3.1 mm; pulse angle = 70˚; field of view = 80 x 80 mm; echo time = 35 ms; repetition time = 1700 ms. For each participant, a 12 minute 30 seconds and a 12-minute functional sequences (corresponding to n-back and self-reference tasks respectively) were acquired generating 442 and 424 whole-brain echoplanar imaging volumes per sequence. The first four (additional) images from each run were discarded to allow the magnetization to reach equilibrium. We also acquired a high-resolution T1-weighted anatomical image for each subject with 240 slices (slice thickness = 0.75 mm; flip angle = 8˚; field of view = 352 x 352 pixels, echo time = 4569 ms; repetition time = 9752 ms) to discard gross radiological alterations.

Imaging data were processed on a Microsoft Windows platform using MATLAB R2021a (The MathWorksInc, Natick, Mass) and Statistical Parametric Mapping (SPM12; The Welcome Department of Imaging Neuroscience, London, UK) (Ashburner et al., 2013). Slice timing correction was used to adjust for differences in time acquisition across slices. Motion correction consisted in the alignment of each subject time-series to its mean image using a least-squares minimization and a 6-parameter rigid body spatial transformation. The resulting functional sequences were corregistered to each participant's anatomical scan, previously normalized to the SPM's T1 template using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL). Normalization parameters used during structural normalization were also applied to the corregistered functional data. Finally, functional images were smoothed with an isotropic Gaussian kernel of 8 mm full-width at half-maximum (FWHM).

Statistical analysis

Behavioural data

We evaluated in-scanner tasks performance using accuracy and reaction time data during each condition. Specifically, we conducted two-sample t-tests in order to compare tasks performance between euthymic BD patients and HC.

Neuroimaging data

First-level contrast images during n-back and self-referential tasks were calculated for each participant. Specifically, working memory was assessed by contrasting the 1-back to the 0-back condition and moderate-high memory load was computed by contrasting the 2-back to the 1-back condition. In addition, self-referential processing was assessed by contrasting the self-reference to the non-self-referential attention condition (self versus control). Therefore, regressors modelled each condition of interest, as well as the fixation cross and the motion parameters (i.e., 3 translations and 3 rotations). The Blood Oxygenation Level Dependent (BOLD) signal was convolved with a canonical hemodynamic response function, and a 128-second high-pass filter was applied to remove low-frequency drifts.

Then, first-level contrast images for each participant were included in second-level (group) analyses. We initially estimated the within-group activity patterns using six whole-brain one-sample t-tests (one per group and contrast). Between-group differences were explored using three whole-brain two-sample t-tests (one per each contrast). Statistical significance was set at a cluster-level family-wise-error (FWE) corrected threshold of $p<0.05$ (voxel-level probability of $p<0.001$).

Results

N-Back task

Behavioural results

Task performance measures indicated that euthymic BD patients showed a lower signal detection (d') compared to HC in the 1-back ($p=0.001$) and 2-back ($p<0.001$) conditions, but not during 0-

back (p=0.119). Additionally, euthymic BD patients exhibited a higher average reaction time to all stimuli during the task ($p<0.05$).

Neuroimaging results

Within-group analyses revealed that during moderate-high memory load HC showed larger responses to 2-back compared to 1-back in the supramarginal gyrus, postcentral gyrus, superior parietal lobe, dlPFC, supplementary motor cortex, dmPFC, angular gyrus and cerebellum. Euthymic BD patients showed a similar activation pattern, although only the more posterior regions (superior parietal lobule, cerebellum and precuneus) were found to be significantly more activated to 2-back compared to 1-back (Figure 1 and Table 2). When exploring 2-back < 1-back, HC showed smaller responses to 2-back compared to 1-back within limbic regions (hippocampus and amygdala), and the vmPFC, anterior cingulate cortex, fusiform gyrus, temporal lobe (pole, inferior and middle gyri) and occipital pole.

Between-group comparisons indicated that euthymic BD patients showed a significantly higher activation in the vmPFC during moderate-high memory load in comparison to HC. In order to assess whether this between-group difference was driven by a failure of deactivation in the euthymic BD patients during the moderate-high load condition, we computed activation and deactivation maps to both 1-back and 2-back conditions in HC (see Figure S1). Interestingly, the vmPFC region observed in our between-group analysis completely matched with the brain deactivation pattern of HC during the 2-back condition, therefore supporting a lack of deactivation in euthymic BD patients.

Self-reference task

Behavioural results

Euthymic BD patients showed higher reaction times to both self-referential and non-self-referential attention conditions compared to HC ($p<0.001$).

Neuroimaging results

Self-referential processing, compared to the control condition, activated the main nodes of the DMN: the medial prefrontal cortex (i.e., dmPFC extending to vmPFC), angular gyrus, PCC and

precuneus in both groups. Additionally, other brain regions such as the middle and inferior temporal gyrus, left ventrolateral prefrontal cortex, supplementary motor cortex, thalamus, caudate and crus 1 and 2 of the cerebellum were also activated in both groups (Figure 2 and Table 3). In contrast, the superior parietal lobule, angular gyrus, supramarginal gyrus, precentral and postcentral gyri, dlPFC, right anterior insula, middle and superior occipital gyri and other regions of the cerebellum exhibited smaller brain activations during self-referential processing in both groups.

Between-group analyses revealed that euthymic BD patients showed a higher trend-level activation in the dmPFC extending to the dlPFC during self-referential processing in comparison to HC. Specifically, within-group maps displayed that euthymic BD patients activated a larger area of the dmPFC, and they did not reduce the activation of the dlPFC as HC did (Figure 2).

Discussion

Consistent with previous findings (Pomarol-Clotet et al., 2015), our euthymic BD patients showed a deactivation failure of the vmPFC during working memory processes. To our knowledge, this is the first study to suggest that euthymic bipolar patients may also show a dmPFC-dlPFC hyperactivation during self-processing. These preliminary findings support the existence of state-independent traits in BD patients and underline potential stable diagnostic biomarkers to early clinical diagnosis and in developing novel neurocognitive circuit-based therapeutic approaches.

During the n-back paradigm, HC recruited brain regions previously identified as the frontoparietal CEN nodes, which are crucial during working memory processes and involve brain regions such as the anterior insula, parietal lobules, dmPFC, dlPFC, and cerebellum (Kim, 2019; Yaple et al., 2021). In light of the fact that the n-back induced the expected neural activation pattern in HC, it has proved to be a valid paradigm to explore working memory impairments in our euthymic BD sample. Also consistent with prior knowledge of goal-directed paradigms (Murphy et al., 2020), medial regions of the DMN (i.e., vmPFC and PCC/precuneus) were deactivated during working memory conditions in HC. This so called “low firing mode” of the DMN has been shown to play a prominent role in achieving a good performance across attentional tasks (Anticevic et al., 2012;

Mayer et al., 2010; Petersen and Miskowiak, 2021). Indeed, recent neural network models have revealed a complex partial anticorrelation between the working memory network and the DMN (Murphy et al., 2020; Vatansever et al., 2017; Yuan et al., 2021). According to these models, the frontoparietal cortex (as part of the CEN) may be triggering a DMN or dorsal attention system deactivation depending on whether an external or internal focus is needed. Therefore, our findings support that a balanced CEN-DMN interaction may be needed for working memory processing. In this sense, a deactivation failure within the DMN can be seen as an abnormal and persistent activation in a network linked to rumination, self-reference and mind-wandering when goal-directed actions are required.

In addition, the fact that we only observed a DMN deactivation failure but not an abnormal dorsal prefrontal cortex activity pattern is also in agreement with prior evidence from longitudinal studies (Alonso-Lana et al., 2019; Pomarol-Clotet et al., 2015). These studies have highlighted that vmPFC deactivation failures may be characterized as stable traits, which are observed in both the affective phases of the disease (mania and depression) and during remission, while dlPFC alterations tended to be normalised (with activation levels similar to HC) when explored in euthymic BD patients. Altogether with our behavioural findings (i.e., lower signal detection and higher reaction time in euthymic BD patients), fMRI results suggest that a persistent DMN activation may be explaining the persistence of neurocognitive deficits observed in euthymic BD patients. However, previous evidence does not fully support this claim, as both an abnormal dorsal PFC activation and a DMN deactivation failure have been found to be linked to neurocognitive impairments in BD (Alonso-Lana et al., 2019; Ott et al., 2021) and across mood disorders (Miskowiak and Petersen, 2019; Petersen and Miskowiak, 2021). Notwithstanding, recent research aiming to explain this discrepancy has proposed a bell-shaped model where, depending on task load, BOLD response would reflect a lower cortical efficiency (low demand – hyperactivity) or a lower cognitive capacity (high load – hypoactivity) (Petersen and Miskowiak, 2021). In this sense, Petersen & Miskowiak model proposes that HC and mood disorders patients' activity patterns could intersect with moderate task loads. Since our findings emerged from a moderate-high memory load contrast (2-back > 1-back), this model may be explaining why we

observed a DMN deactivation failure, but we did not detect an alteration in the dlPFC activity pattern.

As expected, our self-reference paradigm evoked the activation of core DMN nodes, involving the mPFC, angular gyrus, PCC and precuneus, in HC (Davey et al., 2016). Moreover, the brain regions found to be less activated during the self-reference condition compared to the control condition matched to a large extent with those brain regions activated during the working memory task (i.e., dlPFC and parietal lobules). This finding further supports the idea that the fMRI paradigms used during this study reflect complementary network dynamic states linked to internally or externally directed cognition (Murphy et al., 2020). That said, our self-reference dlPFC hyperactivation finding may be based on the same framework as the working memory vmPFC deactivation failure. Indeed, a higher activation (or lack of deactivation) of a brain region within the CEN during an introspective task may be also signalling an imbalance between the inward-outward switching system.

Moreover, our self-reference dmPFC hyperactivation finding revealed that euthymic BD patients recruited a more extended region of the dmPFC, which may be interpreted as a lower cortical efficiency during self-reference processing. Previous research using the same self-processing paradigm have already highlighted that the dmPFC plays a relevant role moderating the posterior DMN functioning (Davey et al., 2016). This interaction may bring PCC self-representations into consciousness depending on the dmPFC interpretation of the task demands (Feng et al., 2018; Leech and Smallwood, 2019). By itself, the dmPFC has been closely related to abstract cognitive processes, including social cognition tasks (Zamani et al., 2022) as well as autobiographical abstract reasoning (D'Argembeau et al., 2014), self-relevant judgements and rumination (Denny et al., 2012; Zhou et al., 2020). Moreover, Apazoglou et al., (2019) also published exploratory results showing abnormal vmPFC and dmPFC hyperactivations during self-reference in euthymic bipolar patients. Therefore, our findings and previous exploratory research support the hypothesis that persistent alterations in the dmPFC during self-processing are characterizing bipolar patients during euthymia. Notwithstanding, the statistical significance level of these results require to be cautious in its interpretation.

Limitations:

There are some limitations that must be discussed. First, the vast majority of our patients, while euthymic, were treated with a significant load of pharmacotherapy that could be affecting our results. However, drug usage by means of dosage equivalents of chlorpromazine, fluoxetine and diazepam has been detailed in Table 1. Second, prior research suggests that certain cognitive biases should be expected towards negative self-reference associations in bipolar and unipolar depressive patients (Molz Adams et al., 2014). Therefore, a self-referential task including both negative and positive traits may be more effective in revealing neural alterations in self-processing. Notwithstanding, our design focusing only on neutral traits allows us to control for the effect of valence without needing to subdivide our sample, and therefore avoiding a loss of statistical power. Third, an n-back design with higher working memory load levels would be more optimal to assess the load-based models previously postulated (Petersen and Miskowiak, 2021). Nevertheless, we used a conservative and prevalent n-back model (Saldarini et al., 2022) to ensure a minimal patients' performance. Finally, while using a sample size similar to prior research evaluating BD, our sample size was still modest by current methodological standards (Szucs and Ioannidis, 2020).

Conclusions:

Our findings showed that euthymic bipolar patients failed to deactivate the anterior DMN during goal-oriented processing, and hyperactivated brain regions within the CEN during self-processing. Overall, our research suggests an inefficient segregation of brain dynamics coordinating internal and external processing in euthymic bipolar patients. Future research should use paradigms focused on inward-outward task-switching alterations in BD. In addition, further research is warranted to fully characterize state-independent traits in BD to be able to detect reliable biomarkers that could ultimately reduce the common misdiagnosis associated to bipolar disorder and to guide researchers and clinicians in the search of personalized treatments.

Table 1. Sociodemographic and clinical characteristics of the study samples

	Bipolars (n=27)	Controls (n=25)	Between-group differences †
Age, years: mean (±SD)	48.49 (9.19)	44.12 (7.98)	-1.82 (p = 0.073)
Sex, male: n (%)	13 (48%)	15 (60%)	0.73 (p = 0.392)
Bipolar diagnosis, Type I: n (%)	17 (63%)	-	-
Eating disorder: n	2	-	-
Kleptomania: n	1	-	-
YMRS: mean (±SD)	1.59 (±2.60)	0.96 (±1.70)	-1.01 (p = 0.315)
HRSD-17: mean (±SD)	6.15 (±2.76)	3 (±3.16)	-3.79 (p = <0.001)
WHO-5: mean (±SD)	10.31 (±3.87)	15.67 (±3.64)	5.02 (p = <0.001)
Age at onset, years: mean (±SD)	29.69 (±11.03)	-	-
Duration of illness, years: mean (±SD)	18.80 (±11.62)	-	-
Number of drugs: mean (±SD)	3.89 (±0.49)	-	-
Mood stabilizers / Anticonvulsants: n (%)	25 (93%)	-	-
Doses of psychotropic drugs (milligrams/day)			
Chlorpromazine equivalents	n=20 278 (±362)	-	-
Fluoxetine equivalents	n=16 45 (±19)	-	-
Diazepam equivalents	n=14 19 (±10)	-	-

YMRS = Young Mania Rating Scale; HRSD = Hamilton Depression Rating Scale; WHO-5 = World Health Organization Well-Being Index.

†Continuous variables analysed by t-tests; categorical variables analysed by X^2 test.

Table 2. Activity pattern during the moderate-high memory load contrast

Brain Regions	MNI Coordinates x	y	z	*k*	T-Value	p_{FWE}-Value
Healthy participants						
2-back > 1-back						
Right Supramarginal gyrus	42	-40	40	11071	6.66	< 0.001
Left Supramarginal gyrus						
Left/Right Superior parietal lobule						
Left/Right Angular gyrus						
Left/Right Postcentral gyrus						
Right Dorsolateral prefrontal cortex	28	15	51	6982	6.50	< 0.001
Left Dorsolateral prefrontal cortex	-28	12	54	5082	6.24	< 0.001
Left Cerebellum	-32	-60	-34	1779	6.24	< 0.001
Left/Right Supplementary motor Cortex	0	24	45	1211	5.68	0.003
Left/Right Dorsomedial prefrontal cortex						
2-back < 1-back						
Right Temporal pole	34	6	-36	2583	6.00	< 0.001
Right Inferior Temporal gyrus						
Right Middle Temporal gyrus						
Right Amygdala						
Right Hippocampus						
Left Temporal pole	-33	9	-39	789	4.81	0.020
Left Inferior Temporal gyrus						
Left Ventromedial prefrontal cortex	-10	50	-6	3527	5.90	< 0.001
Right Ventromedial prefrontal cortex						
Left/Right Anterior Cingulate cortex						
Right Occipital pole	21	-99	3	1121	5.83	0.004
Right Occipital Fusiform gyrus						
Left Occipital pole	-26	-99	-6	846	4.38	0.015
Left Occipital fusiform gyrus						
Left Hippocampus	-26	-10	-14	1774	5.23	< 0.001
Left Amygdala						
Left Putamen						
Bipolars > Controls (2-back > 1-back)						
Left Ventromedial prefrontal cortex	-12	51	-6	1167	4.66	0.003
Right Ventromedial prefrontal cortex						

pFWE = p value corrected for multiple comparisons by family-wise error.

Table 3. Activity pattern during the self-referential contrast

Brain regions	MNI Coordinates x	y	z	*k*	T-Value	p_{FWE}-Value
Healthy participants						
Self > Control						
Left Dorsomedial prefrontal cortex	-10	38	42	24193	12.53	< 0.001
Right Dorsomedial prefrontal cortex						
Left/Right Supplementary motor cortex						
Left/Right Ventromedial prefrontal cortex						
Left Orbital gyrus (posterior/lateral)	-36	32	-15	20844	10.07	< 0.001
Left Ventrolateral prefrontal cortex						
Left Angular gyrus	-50	-62	32	5071	10.61	< 0.001
Right Angular gyrus	56	-56	21	858	7.32	< 0.001
Left Posterior cingulate gyrus	-4	-46	26	6742	10.01	< 0.001
Right Posterior cingulate gyrus						
Left/Right Precuneus						
Right Middle temporal gyrus	60	-4	-22	4111	6.70	< 0.001
Left Middle temporal gyrus						
Right/Left Superior temporal gyrus						
Left Caudate	-12	18	14	1337	6.04	0.001
Right Caudate						
Left/Right Thalamus						
Right Cerebellum	26	-75	-39	10368	14.56	< 0.001
Left Cerebellum						
Right Cerebellum	3	-56	-50	1058	9.86	0.005
Self < Control						
Left Middle occipital gyrus	-32	-72	24	114662	12.89	< 0.001
Right Middle occipital gyurs						
Left/Right Superior occipital gyrus						
Left/Right Angular gyrus						
Left/Right Supramarginal gyrus						
Left/Right Superior parietal lobule						
Left/Right Postcentral gyrus						
Left/Right Precentral gyrus						
Right Anterior insula						
Left/Right Cerebrum						
Left Dorsolateral prefrontal cortex	-36	39	33	1520	7.22	0.001
Right Dorsolateral prefrontal cortex						
Left Orbital gyrus (anterior/medial)	-32	58	-16	633	6.59	0.043
Left Frontal pole						
Bipolars > Controls (Self > Control)						
Right Dorsomedial prefrontal cortex	21	48	23	598	4.80	0.053
Right Dorsolateral prefrontal cortex						

pFWE = p value corrected for multiple comparisons by family-wise error.

Figure 1. Brain regions showing larger (red) or smaller (blue) activation during the 2-back condition compared to 1-back in HC (top) and euthymic BD patients (bottom). Between-group findings (bipolars>controls) in the vmPFC are displayed in green.

Figure 2. Brain regions showing larger (red) or smaller (blue) activation during self-referential processing compared to the non-self-referential attention condition in HC (top) and euthymic BD patients (bottom). Between-group findings (bipolars>controls) in the dmPFC-dlPFC are displayed in yellow.

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Figure 1

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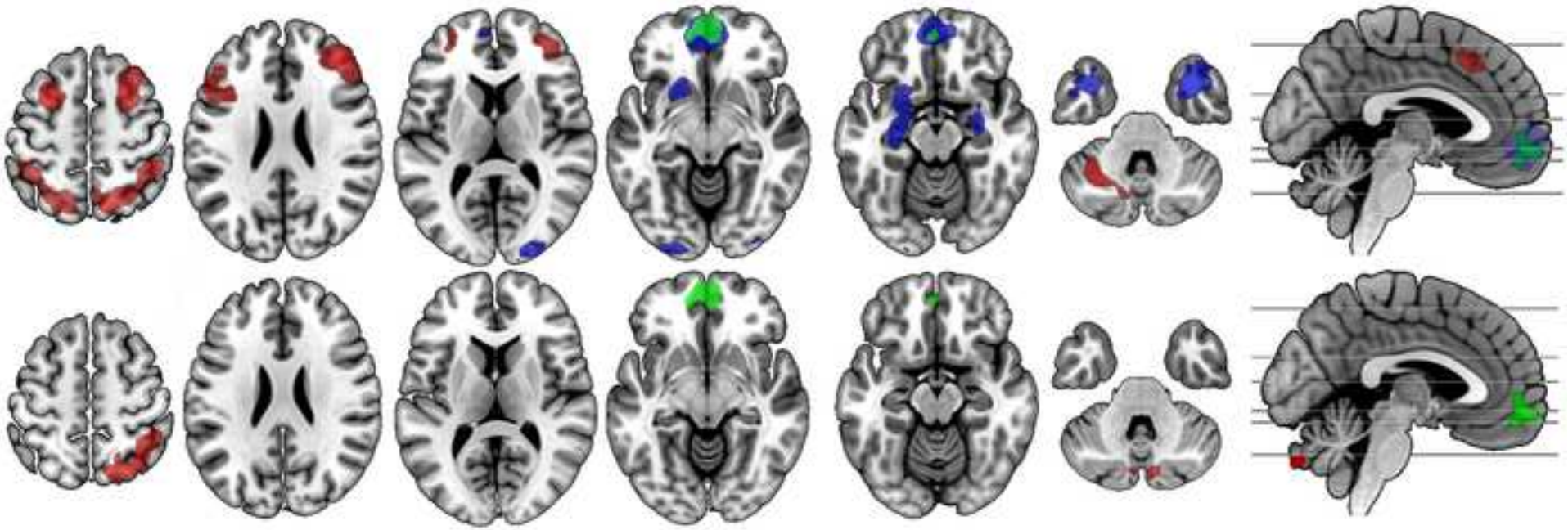

Figure 2

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