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Research paper

Visual memory dysfunction as a neurocognitive endophenotype in bipolar disorder patients and their unaffected relatives. Evidence from a 5-year follow-up Valencia study.

Patricia Correa-Ghisays[a,b,c,d], Joan Vicent Sánchez-Ortí[b,d], Rosa Ayesa-Arriola[a,h,i], Esther Setién-Suero[a,h,i], Vicent Balanzá-Martínez[a,d,e], Gabriel Selva-Vera[a,c,d,e], Juan Carlos Ruiz-Ruiz[b], Joan Vila-Francés[g], Anabel Martinez-Aran[a,j], Juliana Vivas-Lalinde[f], Candela Conforte-Molina[b], Constanza San-Martín[d,k], Carlos Martínez-Pérez[b], Inmaculada Fuentes-Durá[b], Benedicto Crespo-Facorro[a,l], Rafael Tabarés-Seisdedos[a,c,d,e,*]

[a] Centro Investigación Biomédica en Red de Salud Mental, CIBERSAM, Madrid, Spain
[b] Faculty of Psychology, University of Valencia, Valencia, Spain
[c] INCLIVA Health Research Institute, Valencia, Spain
[d] TMAP Unidad de evaluación en autonomía personal, dependencia y trastornos mentales graves, Department of Medicine, University of Valencia, Valencia, Spain
[e] Teaching Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, Valencia, Spain
[f] Departament of Psychiatry, Mental Health Service, Manises, Valencia, Spain
[g] IDAL - Intelligent Data Analysis Laboratory, University of Valencia, Valencia, Spain
[h] University Hospital Marqués de Valdecilla. Department of Psychiatry, IDIVAL, Santander, Spain
[i] Department of Psychiatry, IDIVAL, School of Medicine, Marqués de Valdecilla University Hospital, University of Cantabria, Santander, Spain
[j] Bipolar Disorders Unit, Neurosciences Institute, Hospital Clínic de Barcelona, IDIBAPS, Universitat de Barcelona, Catalonia, Spain
[k] Departament of Physioterapiy, University of Valencia, Valencia, Spain
[l] Hospital Universitario Virgen del Rocio, Universidad de Sevilla, Spain

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ABSTRACT

Background: Scarce research has focused on Visual Memory (VM) deficits as a possible neurocognitive endophenotype of bipolar disorder (BD). The main aim of this longitudinal, family study with healthy controls was to explore whether VM dysfunction represents a neurocognitive endophenotype of BD.

Methods: Assessment of VM by Rey–Osterrieth Complex Figure Test (ROCF) was carried out on a sample of 317 subjects, including 140 patients with BD, 60 unaffected first-degree relatives (BD-Rel), and 117 genetically-unrelated healthy controls (HC), on three occasions over a 5-year period (T1, T2, and T3). BD-Rel group scores were analyzed only at T1 and T2.

Results: Performance of BD patients was significantly worse than the HC group ($p < 0.01$). Performance of BD-Rel was also significantly different from HC scores at T1 ($p < 0.01$) and T2 ($p = 0.05$), and showed an intermediate profile between the BD and HC groups. Only among BD patients, there were significant differences according to sex, with females performing worse than males ($p = 0.03$). Regarding other variables, education represented significant differences only in average scores of BD-Rel group ($p = 0.01$).

Limitations: Important attrition in BD-Rel group over time was detected, which precluded analysis at T3.

Conclusions: BD patients show significant deficits in VM that remain stable over time, even after controlling sociodemographic and clinical variables. Unaffected relatives also show stable deficits in VM. Accordingly, the deficit in VM could be considered a potential endophenotype of BD, which in turn may be useful as a predictor of the evolution of the disease. Further studies are needed to confirm these findings.

* Corresponding author at: Teaching Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, Blasco-Ibáñez 17, 46010 Valencia, Spain.
E-mail address: Rafael.Tabares@uv.es (R. Tabarés-Seisdedos).

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1. Introduction

Endophenotypes are observable characteristics that can be robustly and reliably measured and are thought to be strongly genetic in origin (Kosger et al., 2015). Some methods have been used to identify the endophenotypic profile associated with mental illnesses such as BD, including genetic, neuroimaging, physiological, and neurocognitive measures (Castañeda and Tirado, 2008; Glahn et al., 2014). Over time, testable criteria were developed to aid in the objective identification of endophenotypes, (Gottesman and Gould, 2003): 1) To be associated with the illness within a larger population cluster, that is, when patients and healthy controls from the same population are compared, significant differences are found between both groups. 2) Dysfunctions have to be independent of the patient's clinical state, not being related to the temporal oscillations of the disease, which can be verified using cross-sectional studies comparing euthymic and non-euthymic groups, or with follow-up designs. 3) To be heritable and co-segregate within families, to check this criterion it is necessary to design studies including control groups and groups or relatives. Additionally, an endophenotype should be reproducible in subsequent measurements (Vieta, 2014). Regarding the first criterion, numerous research articles, reviews, and meta-analysis, have found several neurocognitive deficits that can be identified as suitable candidates to be endophenotypes of BD: attention, memory in general and executive functions such as cognitive flexibility, working memory, verbal fluency or response inhibition (Castañeda and Tirado, 2008; Bora et al., 2009; Maekawa et al., 2013; Bourne et al., 2013: Glahn et al., 2014; Santos et al., 2014; Volkert et al., 2016b). With regard to the second criterion, to assess "clinical state-independence" in BD, several longitudinal studies comparing patients and healthy controls detected neurocognitive deficits mostly during periods of euthymia (Lee et al., 2014; Russo et al., 2014; Georgiades et al., 2016). In relation to the third criterion, despite few existing studies with relatives of patients with BD (BD-Rel), growing evidence indicates that several cognitive deficits are also present in unaffected relatives of patients with BD, (Bora et al., 2009; Arts et al., 2011; Balanzá-Martínez et al., 2008; Miskowiak et al., 2017). This suggests that some neurocognitive deficits may be considered endophenotype candidates for the disorder (Russo et al., 2014). These studies have shown that the cognitive performance of unaffected BD-Rel is between that of patients with BD and that of healthy controls, in cognitive functions such as processing speed, divided attention, verbal memory, set shifting and planning (Drysdale et al., 2013; Nehra et al., 2014; Volkert et al., 2016a; Tatay-Manteiga et al., 2018). To our knowledge, in the only prospective longitudinal study that includes a BD-Rel group, manual motor speed dysfunction may qualify as a neurocognitive endophenotype of BD (Correa-Ghisays et al., 2017).

Concerning to visual memory as a cognitive function, some other studies have shown that both, verbal memory and visual memory (VM) are impaired in patients with BD (Ha et al., 2012). Although there are other instruments to measure non-verbal memory or visual memory, the Rey–Osterrieth Complex Figure Test (ROCF) has proven to be a useful and recognized neuropsychological tool to evaluate visual memory (Shin et al., 2006). In these regards, we found that there are a few cross-sectional studies that measure VM with ROCF and simultaneously include unaffected first-degree BD-Rel identifying deficits in VM in BD patients and also in BD-Rel (Frantom et al., 2008; Kulkarni et al., 2010; Maziade et al., 2011; Tatay-Manteiga et al., 2018). Conversely, those who have not found deficits in visual functions among BD-Rel, do not measured VM or used tests other than the ROCF (Doyle et al., 2005; Nehra et al., 2014; Kim et al., 2015).

To our knowledge, our study is the first to include, at the same time, repeated measurements of VM over time and the comparison with unaffected first-degree BD-Rel (Miskowiak et al., 2017). Therefore, we think that the inclusion of the longitudinal and family components in the design may further advance our understanding of the endophenotypic nature of VM in BD.

The objective of the present 5-year, a follow-up study was to explore if VM dysfunction represents a neurocognitive endophenotype of BD. We hypothesize that BD patients, regardless of clinical status and medication, and their first-degree relatives will have a worse performance in VM tasks than healthy controls. These deficits would remain stable over time in both groups, pointing to VM dysfunction as a neurocognitive endophenotype of BD.

2. Methods

2.1. Study design

This study is part of larger, ongoing research on severe mental disorders carried out by the CIBERSAM-G24 / TMAP-UV in Valencia, Spain. In this follow-up study, neurocognitive, clinical and functional data of psychiatric patients, their unaffected first-degree relatives and genetically-unrelated healthy volunteers are simultaneously assessed three times over a 5-year period (Balanzá-Martínez et al., 2005; Tabarés-Seisdedos et al., 2008; Salazar-Fraile et al., 2009; Selva-Vera et al., 2010; Correa-Ghisays et al., 2017).

2.2. Participants

This study assessed a sample of 317 adult participants, including 140 BD patients, 60 of their unaffected first-degree relatives (parents, siblings, and offspring; BD-Rel) and 117 genetically unrelated healthy volunteers with no personal and family psychiatric history or healthy control group (HC). BD and BD-Rel were recruited from Mental Health Units (MHU) at several towns in the province of Valencia (Spain) (Foios, Catarroja, Paterna, Sagunto and Gandía), the psychiatry outpatient clinic of the University Hospital Dr. Peset and the Day-Hospital Miguel Servet, in Valencia City. HC group came from the same geographical area of residence, and as far as possible were matched in sex, age and years of education. Experienced psychiatrists confirmed a diagnosis of BD patients according to the Diagnostic and Statistical Manual of Mental Disorders - DSM most up-to-date at the time from their inclusion in the study (American Psychiatric Association, 1996, 2000, 2014), also validating that all were clinically stable and provided the pertinent clinical history data. The following exclusion criteria were used for the three groups: any substance use disorder in the past six months or be under the influence of toxic substances upon evaluation; illiteracy and/or severe intellectual disability; suffering from head trauma, motor dysfunctions, neurological disorders, cognitive impairment deemed as dementia, established ad-hoc or previously diagnosed following current DSM criteria, treatment with electroconvulsive therapy (TEC) or any medical condition that might hinder the correct performance of the tests. For the HC and BD-Rel groups, an additional exclusion criterion was suffering from severe mental illness and, only for the HC group, a family history of severe mental disorder. All participants signed an informed consent form approved by the Ethics Committee of the University Clinical Hospital of Valencia.

2.3. Assessments

The assessments took place at three moments: The second time point (T2) took place 1–2 years after the first assessment (baseline or T1), whereas the third time point (T3), took place an average not less than five years after T1. Due to significant attrition in the BD-Rel group over time, their performance could be assessed only at T1 and T2.

2.3.1. Sociodemographic and clinical variables

Sociodemographic data were collected at each assessment (T1, T2, and T3): sex, age, educational years, living status and occupational status. For patients, several clinical data were collected: age of onset, family history of severe mental illness, psychopharmacological treatment (comparison of "on and off" patients, but doses were not taken

into account) and adherence to treatment. In order to register BD patients mood state over the study period, "euthymia" variable was included, which was obtained from scores on the Young Mania Rating Scale (YMRS) (Young et al., 1978; Colom et al., 2002) and the Hamilton Rating Scale for Depression (HRSD-17) (Hamilton, 1960; Ramos-Brieva and Cordero-Villafáfila, 1986). Scores were registered as "1" if psychometric criteria for euthymia were fulfilled (defined as a total YMRS score, less or equal than 6 and a total HRSD-17 scoreless or equal than 8) and "0" if a non-euthymic state was found (defined as higher scores in one or both scales).

2.3.2. Visual memory assessment

The Rey–Osterrieth Complex Figure Test (ROCF) Figure A (Rey, 1999) was used to measure VM as part of an extensive battery of tests used in the major original research mentioned above. Participants copied the figure and then were asked to draw the figure two minutes after the copy (fRey2) and again, 20 min after the copy (fRey20). The direct score at each moment represents the number of elements in the figure that the subject can remember and reproduce correctly of a total of 18 units. Each element is scored from 0 to 2, with 36 points being the maximum score. The initial copy of the figure is also scored, and participants with scores one standard deviation (3.45) below the mean (30.48) were excluded according to the original scoring parameters. Applied to 21 subjects (19 BD, 1 BD-Rel and 1 HC).

2.4. Statistical analysis

For the statistical analysis, we compared BD and BD-Rel groups direct scores with HC group scores. As the two VM variables (fRey2 and fRey20) were highly correlated ($R = 0.94$), we decided to use an overall score of ROCF test (fReyT), calculated as the mean of the scores in the two subtests, which represents the cognitive domain "Visual Memory".

VM showed a high inverse Pearson correlation with age ($R = -0.45$; $p < 0.001$), so the effect of age was controlled at three-time points, by adjusting the linear trend of the fReyT scores to zero using the least squares regression adjustment, taking HC scores at T1 as a reference. This adjustment corrects the time and learning effect simultaneously. Fig. 1 shows the fReyT scores of all study participants and the linear trend with age, indicating that VM performance decreases more with age in the BD group than in BD-Rel and HC ($p < 0.001$).

We analyzed the variability of the fReyT values in each group by using a pairwise *t*-test. P-values were adjusted using Bonferroni

Table 1
Sociodemographic and clinical characteristics of the sample by groups at basal time of the study.

Characteristics		BD		BD-Rel		HC		Total	
		n	%	*n*	%	*n*	%	*n*	%
		140	44	60	19	117	37	317	100
Family relationship	Parents			6	10				
	Siblings			45	75				
	Children			9	15				
Sex	Male	57	41	20	33	46	39	123	38
	Female	83	59	40	67	71	61	194	62
Age	Min.	18		18		18		18	
	Mean	43		43		36		41	
	Max.	65		78		63		78	
Years of education	Min.	0		0		8		0	
	Mean	11		12		14		12,3	
	Max.	27		24		22		27	
Living Status	No	50	36	10	17	30	26	90	26
	Yes	90	64	50	83	87	74	227	74
Occupational status	No	102	73	16	27	18	15	136	38
	Yes	38	27	44	73	99	85	181	62
Young Mania Rating Scale (YMRS)	Min.	0		0		0		0	
	Mean	2		0		0		0	
	Max.	18		7		5		18	
Hamilton Rating Scale for Depression (HRSD-17)	Min.	0		0		0		0	
	Mean	4		1		1		2	
	Max.	21		23		10		23	
Euthymic state	No	27	19						
	Yes	113	81						
Antipsychotics	No	58	48						
	Yes	62	52						
Antidepressants	No	85	71						
	Yes	35	29						
Lithium	No	51	43						
	Yes	68	57						
Carbamazepine	No	99	84						
	Yes	19	16						
Benzodiazepines	No	53	45						
	Yes	66	55						

Abbreviations: BD: Patient with Bipolar Disorder; BD-Rel: Relative; HC: Healthy Control; *n*: group size; %: percentage.

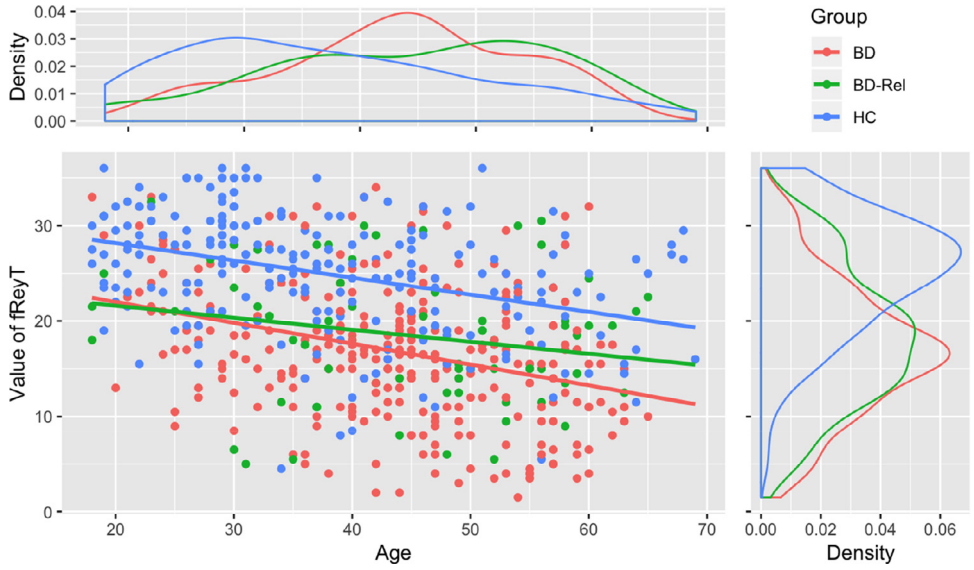

Fig. 1. Linear trend with age.
Abbreviations: BD: Patients with Bipolar Disorder. BD-Rel: Relative of patient. HC: Healthy control.

Table 2
Overall score of Rey–Osterrieth Complex Figure Test (ROCF) means by groups at three time points.

T1 (n = 317)			T2 (n = 193)			T3 (n = 90)	
BD (n = 140)	BD-Rel (n = 60)	HC (n = 117)	BD (n = 93)	BD-Rel (n = 10)	HC (n = 90)	BD (n = 65)	HC (n = 25)
24.9(6.3)	28.0(6.3)	31.5(5.8)	27.2(6.7)	29.2(9.3)	34.2(5.5)	27.1(6.6)	34.6(4.8)

Mean (Standard deviation).
Abbreviations: T1, T2 and T3: Three times of the study; BD: Patient with Bipolar Disorder; BD-Rel: Relative; HC: Healthy Control; n: group size.

correction ($p < 0.007$).

We performed an ANCOVA of the fReyT at each-time point. The covariates included all the variables listed in Table 1 except the family relationship (only valid for BD-Rel), group and age, which was already controlled by the linear adjustment.

All the statistical analyses were performed in R language (version 3.3.1) [R Core Team, 2016].

3. Results

A summary of the sociodemographic and clinical characteristics of the participants can be found in Table 1. At T1, BD patients represented 44%, BD-Rel 19% and HC 37% of the total sample. Females accounted for 62% of the total sample. The mean age of the whole sample was 41 years, and the mean number of years of education was 12.3. According to YMRS and HRSD-17 scales, 80.7% of patients with BD were euthymic at T1. At T2, 193 participants were assessed: 93 BD, 10 BD-Rel and 90 HC; and at T3, 90 participants remained in the study: 65 BD and 25 HC. BD-Rel were excluded at this study time. fReyT mean scores for all groups at T1 and T2, and only for BD and HC groups at T3, are shown in Table 2. Overall, HC outperformed both BD and BD-Rel, and BD-Rel performed better than BD patients (Fig. 2).

Differences between BD patients an HC in fReyT were significant over the three assessments ($p < 0.001$). Differences between patients and BD-Rel in fReyT were significant only at T1 ($p = 0.002$), and not significant at T2 ($p = 0.60$). These differences remained unchanged when non-euthymic BD patients ($n = 31$) were excluded from analysis. Differences between BD-Rel and HC in fReyT were significant at T1 $p < 0.001$ and T2 approached the statistical significance ($p = 0.05$) (Table 3).

The analysis of the relationship between sociodemographic and clinical variables and fReyT at T1 (Table 4) showed significant differences only in the patients' group according to sex ($p = 0.03$), with worse performance among women. In the BD-Rel group, only years of education had a significant effect on VM performance ($p = 0.01$). At T2, BD-Rel group showed significant differences according to sex ($p = 0.03$), BD and HC groups presented significant differences according to years of education ($p < 0.01$ and $p = 0.03$).

Table 3
Differences by groups at three time points.

	T1		T2		T3	
Groups	T	p	T	p	t	p
BD < HC	−8.62	<0.001	−7.40	<0.001	−5.09	<0.001
BD < BD-Rel	−3.33	0.002	−0.94	0.60		
BD-Rel < HC	−3.56	<0.001	−2.33	0.05		

Abbreviations: T1, T2 and T3: Three times of the study; BD: Patients with Bipolar Disorder; BD-Rel: Relative of patient; HC: Healthy control.

A repeated-measures analysis was performed, but the result showed no significant differences on the VM evolution between groups, because the differences between subjects are more significant than the differences between periods for each individual.

4. Discussion

To the best of our knowledge, this is the first longitudinal study including three groups (patients with BD, BD-Rel, and HC), aimed to examine whether VM dysfunction may be considered an endophenotype of BD.

According to some of the criteria commonly used to determine neurocognitive endophenotypes (Gottesman and Gould, 2003; Hasler et al., 2006), our findings support that impaired VM, assessed with the ROCF test, meets the criteria to be considered as a useful

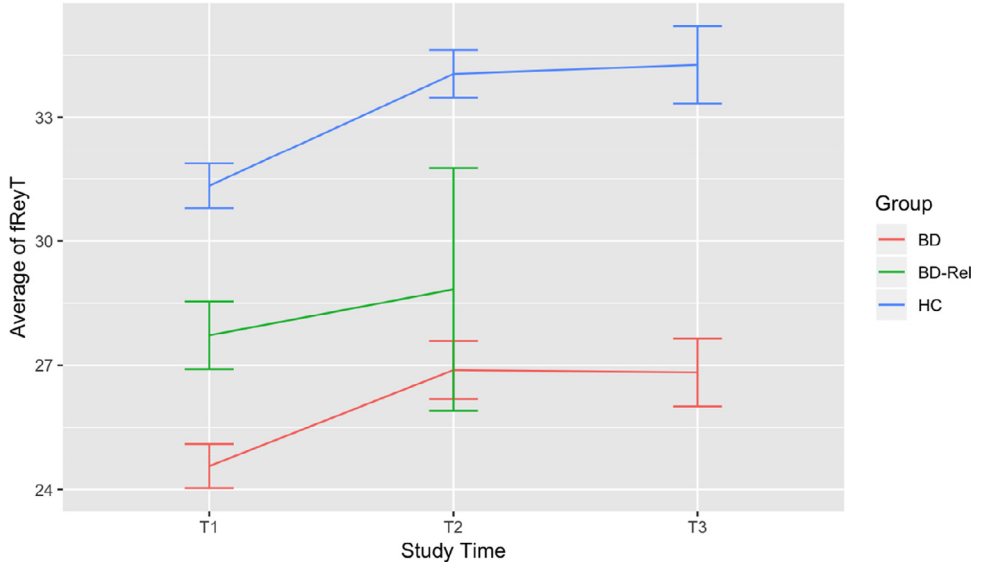

Fig. 2. Improvement of the three groups' fReyT scores at three time points.
Abbreviations: BD: Patients with Bipolar Disorder. BD-Rel: Relative of patient. HC: Healthy control.

Table 4
ANCOVA with independents variables at three time points.

	T1						T2						T3			
	BD		BD-Rel		HC		BD		BD-Rel		HC		BD		HC	
Variable	F	*p*	F	*p*	F	*p*	F	*P*	F	*p*	F	*p*	F	*p*	F	*p*
Sex	4.52	0.03	1.05	0.30	0.21	0.64	0.09	0.75	9.6	0.03	0.00	0.99	1.76	0.19	0.06	0.79
Years of education	2.48	0.12	6.35	0.01	1.40	0.23	9.03	<0.01	2.06	0.22	3.75	0.05	3.29	0.08	0.70	0.41
Status of coexistence	1.03	0.31	0.01	0.90	0.37	0.54	0.00	0.96	–	–	1.29	0.25	1.81	0.19	1.89	0.18
Occupational status	0.04	0.83	0.35	0.55	1.06	0.25	0.00	0.98	3.07	0.15	0.06	0.80	0.17	0.68	0.07	0.79
YMRS	2.08	0.15					2.71	0.12					0.21	0.64		
HRSD-17	0.03	0.85					0.29	0.59					0.00	0.98		
Euthymic state	1.05	0.30					0.14	0.70					0.11	0.73		
Antipsychotics	0.46	0.49					2.10	0.16					0.21	0.64		
Antidepressant	0.21	0.64					0.29	0.59					0.67	0.42		
Lithium	2.78	0.10					0.00	0.82					2.14	0.15		
Carbamazepine	0.44	0.50					2.04	0.17					2.91	0.10		
Benzodiazepines	0.00	0.92					0.68	0.42					0.05	0.81		

Abbreviations: BD: Patients with Bipolar Disorder; BD-Rel: Relative of patient; HC: Healthy control.

endophenotype of genetic vulnerability in BD patients for several reasons:

First, VM is associated with the disease within a population. We found significant differences in the performance of patients about the performance of HC after controlling sociodemographic variables. Concerning the presence of deficit associated upon diagnosis, patients with BD had several deficits, specifically on visual memory, working memory, attention, processing speed (Romero et al., 2016). Furthermore, another longitudinal study (Santos et al., 2014) concluded that patients with BD performed worse than control subjects in all assessed cognitive domains, including visual memory. Regarding this criteria, in a naturalistic longitudinal study (six weeks of treatment) compared patients with BD type I and II, and unipolar depression, in depressed mood, there is not difference between groups in the majority of functions evaluated. However, the patients with bipolar disorder II and patients with unipolar depression shows significant differences in their visual memory, indicating that this impairment is more characteristic of the bipolar disorders I and II than of the unipolar depression (Xu et al., 2012).

Second, in the present study, the clinical state independence supported by the longitudinal approach showed that BD patients' deficits were consistently stable at three measurements over 5 years, regardless of their clinical state. Moreover, these deficits remained after excluding non-euthymic patients from the analysis. Furthermore, Langenecker et al. (2010) compared HC with three bipolar patients' groups: euthymic, depressed and hypomanic/mixed. Controls outperformed euthymic and depressed patients on visual memory, among other cognitive functions. In the abovementioned study (Xu et al., 2012), depressed patients with either bipolar disorders type I and II or unipolar depression showed several cognitive dysfunctions, including visual memory. However, during clinical remission, cognitive performance improved, except for deficits in processing speed and visual memory, which represents a potential trait deficit in those domains. In a 6-month, double-blind trial with patients with bipolar depression, Toniolo et al. (2017) found that visual memory deficits remained stable over time. Other studies have also found that deficits in VM are independent of medication (Wilder-Willis et al., 2001; Lohr and Caligiuri, 2006), which concurs with present findings.

Third, our results support that VM dysfunction is heritable and co-segregates within families as there were significant differences between BD-Rel and HC performance and these deficits remained stable over time. Moreover, although relatives outperformed patients at T1, these significant differences disappear at T2. Additionally, an intermediate pattern of performance in relatives was observed. In this regard, other studies have found VM deficits among BD-Rel (Frantom et al., 2008; Maziade et al., 2009; Kulkarni et al., 2010; Tatay-Manteiga et al., 2018). Conversely, other studies did not find significant differences between BD-Rel and HC although relatives' performance fell between that of controls and patients (Doyle et al., 2009; Nehra et al., 2014; Kim et al., 2015). However, VM was either not measured (Doyle et al., 2009: Copy Organization) or assessed with tests other than the ROCF, such as the Korean complex figure test (Kim et al., 2015) or Brief Visuospatial Memory Test-Revised (Nehra et al., 2014).

If confirmed, these results suggest that impaired VM represents an endophenotype of BD and thus should be the addressed by cognitive-enhancement and functional remediation efforts (Fuentes-Durá et al., 2012; Bonnin et al., 2016; Miskowiak et al., 2016; Van Rheenen et al., 2018).

The clinical relevance of the present research is to present VM dysfunction as a new BD neurocognitive endophenotype, that may be useful as a predictor of clinical evolution or to guide preventive or rehabilitative strategies.

4.1. Limitations

The analysis and comparisons of repeated measures should be viewed with caution, since substantial sample size attrition took place over the 5-year follow-up period, then weakening the reliability of longitudinal results, especially for relatives.

The VM functioning was evaluated with a single test: ROCF, which could hinder comparisons with other studies with different tests.

The relationship between neurocognitive performance and polypharmacy, comorbidities, social functioning and quality of life (Balanzá-Martínez et al., 2015; Dias et al., 2012; Sánchez-Moreno et al., 2018; Tatay-Manteiga et al., 2019) were not examined.

Although these factors are not considered as criteria for the identification of endophenotypes, the relationship between variables such as sex and years of education and VM performance of three groups over time has to be analyzed in studies with larger samples.

5. Conclusion

Significant differences in VM BD and BD-Rel performance compared with HC remain stable over time, even after sociodemographic variables confounder's adjustment (age, sex only for BD group, and years of education only for BD-Rel group).

Clinical variables, clinical status and pharmacological treatment do not seem to influence negatively on patients' performance on VM.

Therefore, the deficit in VM could be considered a potential endophenotype of BD.

However, to thoroughly explain VM dysfunction as an endophenotype of BD patients, it will require a further examination including others factors, larger samples, longer terms, more repeated measurements, and ideally with randomized clinical trials that consider

cognition such as a primary outcome (Martinez-Arán and Vieta, 2015).

Conflicts of interest

None.

CRediT authorship contribution statement

Patricia Correa-Ghisays: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Joan Vicent Sánchez-Ortí:** Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **Rosa Ayesa-Arriola:** Writing - review & editing. **Esther Setién-Suero:** Writing - review & editing. **Vicent Balanzá-Martínez:** Funding acquisition, Methodology, Project administration, Resources. **Gabriel Selva-Vera:** Writing - review & editing. **Juan Carlos Ruiz-Ruiz:** Writing - review & editing. **Joan Vila-Francés:** Formal analysis, Software, Validation, Writing - review & editing. **Anabel Martinez-Aran:** Writing - review & editing. **Juliana Vivas-Lalinde:** Investigation, Writing - review & editing. **Candela Conforte-Molina:** Data curation, Writing - review & editing. **Constanza San-Martín:** Writing - review & editing. **Carlos Martínez-Pérez:** Writing - review & editing. **Inmaculada Fuentes-Durá:** Writing - review & editing. **Benedicto Crespo-Facorro:** Writing - review & editing. **Rafael Tabarés-Seisdedos:** Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing - review & editing.

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