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Research paper

The genomics of visuospatial neurocognition in obsessive-compulsive disorder: A preliminary GWAS

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ABSTRACT

Background: The study of Obsessive-Compulsive Disorder (OCD) genomics has primarily been tackled by Genome-wide association studies (GWAS), which have encountered troubles in identifying replicable single nucleotide polymorphisms (SNPs). Endophenotypes have emerged as a promising avenue of study in trying to elucidate the genomic bases of complex traits such as OCD.
Methods: We analyzed the association of SNPs across the whole genome with the construction of visuospatial information and executive performance through four neurocognitive variables assessed by the Rey-Osterrieth Complex Figure Test (ROCFT) in a sample of 133 OCD probands. Analyses were performed at SNP- and gene-level.
Results: No SNP reached genome-wide significance, although there was one SNP almost reaching significant association with copy organization (rs60360940; $P = 9.98E-08$). Suggestive signals were found for the four variables at both SNP- ($P < 1E-05$) and gene-levels ($P < 1E-04$). Most of the suggestive signals pointed to genes and genomic regions previously associated with neurological function and neuropsychological traits.
Limitations: Our main limitations were the sample size, which was limited to identify associated signals at a genome-wide level, and the composition of the sample, more representative of rather severe OCD cases than a population-based OCD sample with a broad severity spectrum.
Conclusions: Our results suggest that studying neurocognitive variables in GWAS would be more informative on the genetic basis of OCD than the classical case/control GWAS, facilitating the genetic characterization of OCD and its different clinical profiles, the development of individualized treatment approaches, and the improvement of prognosis and treatment response.

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1. Introduction

Obsessive-Compulsive Disorder (OCD) is a severe neuropsychiatric disorder characterized by intrusive thoughts, images or impulses followed by repetitive and stereotypical motor or mental rituals carried out to avoid the discomfort caused by the obsessions (Barahona-Corrêa et al., 2015; Hollander et al., 2008). It is often a severely impairing disorder that affects 2–3 % of the population (Fineberg et al., 2012). The heterogeneity of this disorder has hampered the elucidation of specific biological substrates.

Of the different approaches that have been utilized, genome-wide association studies (GWAS) have emerged as the forerunner in attempts to understand the genetic underpinnings of neuropsychiatric disorders such as OCD. GWAS in clinical samples have proposed several OCD-related genes, such as *BTBD3* (rs6131295, $p = 3.84 \times 10–8$) (Stewart et al., 2013); *PTPRD* ($p = 4.13 \times 10–7$) (Mattheisen et al., 2015); *GRID2* (rs1030757, $p = 1 \times 10–6$); *KIT* (rs12504244, $p = 1.6 \times 10–6$); and *CASC8* (rs4733767 located 87.2 kb 5′ to *CASC8*, $p = 7.1 \times 10–7$) (Arnold et al., 2018). However, these studies have encountered difficulties in identifying replicable single nucleotide-polymorphisms (SNPs), partly due to the large heterogeneity that characterizes OCD. Efforts have been made to narrow the heterogeneity of phenotypes when studying the genomic basis of OCD and some studies suggest specific associations with OCD severity (Alemany-Navarro et al., 2020a) and OCD symptom dimensions (Alemany-Navarro et al., 2020b). Whole exome-sequencing (WES) studies have reported high burden of de novo damaging mutations (DNMs) in OCD trio analyses (Cappi et al., 2016, 2020; Halvorsen et al., 2021) and *CHD8* has been suggested as an OCD-risk gene through DNMs (Cappi et al., 2020; Halvorsen et al., 2021). In addition, variants with an elevated rate of rare damaging coding variation within highly loss-of-function—intolerant genes, such as *SLITRK5,* have been proposed as candidate OCD-risk genes (Halvorsen et al., 2021).

The study of sub-phenotypes or even transdiagnostic traits with reduced heterogeneity is needed in the biological characterization of psychiatric disorders (the Research Domain Criteria, RDoC; US National Institute of Mental Health, NIMH). Endophenotypes have a lower heterogeneity than the commonly studied nosological entities, and their function in linking genes and clinical symptoms (phenotypes) sheds light on the interactions between genes and environment in the development of complex disorders such as OCD (Braff, 2015; Need et al., 2009). In this sense, when studying the genomic basis of a disorder, the analysis of endophenotypes could yield great advantages in comparison to the classical case/control GWAS and also facilitate the identification of specific genetic associations.

Endophenotypes consist of neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological phenomena. These intermediate markers of brain dysfunction are located between clinical manifestations of the disease (phenotype) and the distal genotype. A trait is considered an endophenotype if it shares inheritable variations with a psychiatric disorder, if it is evident both during the active and inactive phases of the pathology, if it is co-transmitted within a family, and if it is evident in both affected family members from pathology and in healthy people (Bearden and Freimer, 2006; Gottesman and Gould, 2003; Roffman, 2019).

In the case of OCD, cognitive domains such as attention, executive function, processing speed, memory, visuospatial abilities, and working memory have been described as impaired among probands in multiple studies (Benzina et al., 2016; Segalàs et al., 2008; Shin et al., 2012; Snyder et al., 2015), and confirmed by a meta-analysis of 115 studies including 3452 adult OCD probands (Abramovitch et al., 2013). These cognitive dysfunctions have also been associated with clinical characteristics such as comorbid depression, disorder course and severity, and specific neuropsychological profiles have been described for different symptom dimensions (Abramovitch et al., 2019; Bragdon et al., 2018; Segalàs et al., 2008; Szabó et al., 2013; Valerius et al., 2008).

Some of the neurocognitive functions found to be impaired in OCD have been suggested as candidate endophenotypes of this disorder. In this sense, similar executive impairments in cognitive flexibility, motor inhibition, recall and organization of non-verbal information, planning, visuospatial working memory, and verbal fluency have been described in both OCD probands and their unaffected first-degree relatives (UFD) (Chamberlain et al., 2008, 2007; Rajender et al., 2011; Segalàs et al., 2010; Zartaloudi et al., 2019). In addition, a reduced activation of the lateral orbitofrontal, lateral prefrontal, and parietal cortices during reversal learning (Chamberlain et al., 2008); and an association between a reduced gray matter in orbitofrontal and inferior regions and motor inhibition deficits (Menzies et al., 2008) have been reported in OCD and UFD when compared to healthy controls, pointing to these neurobiological markers as candidate endophenotypes of OCD.

More concretely, deficits in non-verbal memory have been consistently reported in OCD. The Rey-Osterrieth Complex Figure Test (ROCFT; Osterrieth, 1994) is a neurocognitive tool used in the study of the organization of visuospatial information. Our group analyzed the performance of OCD patients, UFD, and healthy controls in verbal and non-verbal information processing and recall. While no impairments were observed regarding the verbal-memory tasks and the Rey-Osterrieth Complex Figure (ROCF) copy accuracy, OCD patients and UFD presented shared impairments in ROCF organization, and immediate and delayed recall (Segalàs et al., 2010). Different authors have reported deficits in the processing of non-verbal information and have pointed out the relevance of organizing the information in meaningful units during the encoding phase in order to facilitate later recall of such information. These deficits point to recall impairment as a possible consequence of deficiencies found in organizational strategies (Deckersbach et al., 2000; Penadés et al., 2005; Rampacher et al., 2010; Savage et al., 2000, 1999; Segalàs et al., 2008; Shin et al., 2004). However, the impairment observed in organizing information might be due to difficulty rather than inability to employ optimal organizational strategies (Deckersbach et al., 2000; Savage et al., 2000), as the impairments seem to decrease with both training and experience (Buhlmann et al., 2006).

To our knowledge, there are no studies which have examined the genomic basis of neurocognitive measures in OCD. The aim of this study is to carry out an exploratory analysis of the genetic basis of validated neurocognitive traits in OCD. Here, we analyze the genomic basis of construction, organization, short-, and long-term memory of visuospatial information, assessed by the ROCFT, in a sample of 133 OCD patients genotyped with the Infinium PsychArray by Illumina. We expected to find specific genomic signals for the different neurocognitive measures, especially for organizational strategy (copy organization), which would align with previous suggestions for its role as an OCD endophenotype.

2. Materials & methods

2.1. Subjects

One hundred thirty-three Caucasian Spanish OCD patients ($N = 133$; 67 women; mean age $= 38.02 \pm 10.98$) were recruited from the OCD clinic at Bellvitge Hospital, in Barcelona (Spain). Two different clinicians with extensive clinical experience diagnosed the patients according to the DSM-IV criteria for OCD diagnosis via the Structured Clinical Interview for DSM-IV Axis Disorders-Clinician Version (SCIDCV). Study participants were required to have an OCD diagnosis for at least one year, and patients with comorbid substance abuse/dependence (current or in the past six months), psychotic disorders, intellectual disability, severe organic or neurological pathology (except tic disorders), or autism spectrum disorders, were excluded from the study. Comorbid affective and anxiety disorders were not exclusion criteria, given the high prevalence of these comorbid conditions among OCD probands, as long as OCD was the primary diagnosis. Written consent was required

from all participants after having been fully informed about the study. The study was performed in accordance with the Helsinki Declaration of the World Medical Association and approved by the Ethical Committees of Bellvitge Hospital.

2.2. Clinical assessment

A structured interview was administered to patients during their first visit to our clinic to collect sociodemographic and clinical data, such as age of onset, family psychiatric history, including family history of OCD, depression, and Tourette's syndrome. The baseline severity of obsessive and compulsive symptoms was also assessed through the clinician-administered version of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989). Depressive symptoms were assessed with the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960).

2.3. Neuropsychological assessment

The Rey-Osterrieth Complex Figure test (ROCFT; Osterrieth, 1994) is a neuropsychological standardized measure that assesses visuo-spatial perception/construction and memory. During the test, the patient is first shown a geometric figure. The patient is instructed to copy the figure while being able to see the original one (copy condition), then instructed to redraw it immediately without being able to see the original (immediate recall) and then again 30 min later (delayed recall). The patient's accuracy is assessed during the copy, immediate and delayed recall conditions according to the system developed by Meyers and Meyers (Meyers J.E. and Meyers K.R., 1995), which analyzes the accuracy and placement of each of the 18 elements into which the figure is subdivided, scoring from 0 to 36. The organizational ability of the patient is assessed during the copy condition. To measure score for this variable, the figure is subdivided into 5 configural elements: the large rectangle, the diagonal cross, the vertical midline, the horizontal midline, and the vertex of the triangle on the right. The organization scoring ranges from 0 to 6, one point given (two points in the case of the rectangle) for each element when it is drawn as an unfragmented unit (Savage et al., 1999). By asking the patient to redraw the figure without being able to see the original one (immediate and delayed recall), the short- and long-term memory of the patient is assessed. During the 30-minute delay, distracting tests are administered to the patient.

2.4. Genotyping, quality control (QC), and imputation

One hundred thirty-three OCD patients were genotyped with the Infinium PsychArray-24 BeadChip from Illumina, which was developed in collaboration with the Psychiatric Genomics Consortium (PGC) and includes 50,000 variants that have been previously associated with different psychiatric disorders. Variant calling is detailed elsewhere (Alemany-Navarro et al., 2020a, 2020b).

QC procedures were performed on the raw data with Plink 2.0 (Purcell et al., 2007). Biallelic autosomal variants with a minor allele frequency (MAF) >1 % (MAF > 0.01) were selected. Variants that did not present Hardy-Weinberg Equilibrium (HWE; $P < 1E-04$) or a call rate >98 % were removed. Individual samples with a call rate lower than 98 % were excluded. Relatedness and principal component analyses (PCA) were performed for independent SNPs (not in linkage disequilibrium, LD). Individual samples with a pi-hat value >0.2 at the identity by descent (IBD) analyses were excluded, as well as those that deviated by >5 standard deviations (S·D) from the mean in the first two components of the PCA analyses.

Phasing and imputation were carried out using Eagle v2.4 and Minimac4 through the Michigan Imputation Server Pipeline (Das et al., 2016) for autosomal chromosomes. The reference panel used was HRC r1.1 2016 (GRCh37/hg19). After imputation, variants with a MAF > 0.01, HWE < 1E-06, and a call rate > 98 % were kept.

2.5. Statistical analyses

Correlation analyses were performed for each pair of variables assessed as dependent variables in the regression models. SNP-level association analyses were performed for the four measures assessed by the ROCFT. GenABEL library for R (Aulchenko et al., 2007) was used for immediate recall, delayed recall and copy accuracy using a linear regression model via *mlreg* function. A rank-based inverse normal transformation (INT) (Pain et al., 2018) was applied to copy accuracy before the analysis in order to satisfy the normality assumption. Given the ordinal nature of the copy organization variable, SNP-level analysis for this variable was performed by applying a proportional odds logistic mixed model, "POLMM" method, using GRAB library for R (Bi et al., 2021). A log-additive model was assumed in the regressions (genotype scores as 0, 1, or 2). We included age, sex, age of OCD onset, and depression and obsessive-compulsive severity (HDRS (Hamilton, 1960) and Y-BOCS (Goodman et al., 1989)) as covariates in the regressions.

Gene-based analyses were performed with MAGMA v1.10 (de Leeuw et al., 2015) on the GWAS results of the four variables, selecting an annotation window of 5 kb around the genes, and the default gene analysis model (*snp-wise = mean*).

3. Results

3.1. Subjects, genotyping, and QC

After QC procedures, a final sample of 127 subjects (64 women; mean age = 37.83 ± 11.06) for immediate recall, delayed recall and copy accuracy, and 113 individuals (58 women; mean age = 37.73 ± 10.78) for copy organization; and 258,689 biallelic autosomal SNPs (MAF > 0.01) were kept for imputation. Table 1 summarizes clinical and sociodemographic data from the sample.

3.2. Imputation

Imputed markers with an imputation quality >0.6 (r2 > 0.6) were selected (n = 8,848,854 autosomal markers), from which 2,661,707 passed QC and had a MAF > 0.01.

Table 1
Sociodemographic and clinical characteristics of the final sample ($N = 127$).

Age, years	37.83 ± 11.06 (17–70)
Male/Female	63/64 (50.0/50.0)
Age at onset of OCD	21.22 ± 9.44 (4–45)
Y-BOCS score	
Global	25.57 ± 5.61 (10–38)
Obsessions	12.89 ± 2.81 (5–19)
Compulsions	12.69 ± 3.00 (5–20)
Baseline HDRS score	11.06 ± 5.31 (1–25)
Current comorbidity	
No comorbidity	80 (62.99)
Mood disorder	25 (19.69)
Tics	14 (11.02)
Eating disorders	8 (6.30)
Presence of dimensions	
Aggressive/checking	89 (70.08)
Symmetry/ordering	56 (44.09)
Contamination/cleaning	65 (51.18)
Hoarding	29 (22.83)
Sexual/religious	34 (26.77)
Family psychiatric history	
No psychiatric diagnosis	50 (39.37)
OCD	32 (25.20)
Mood disorder	37 (29.13)
Tics/Tourette Syndrome	9 (7.09)

Data are mean ± SD (range) or number of subjects (percentage). *OCD,* obsessive compulsive disorder; *Y-BOCS*, Yale-Brown Obsessive Compulsive Scale; *HDRS*, Hamilton Depression Rating Scale.

3.3. SNP-level analyses

Correlation analyses reported each pair of variables to be correlated (Supplementary Table 1, Table S1). However, except for the correlation between immediate and delayed recall, correlation coefficients were moderate or low. We decided to perform independent GWAS for each variable to facilitate the integration of our results with those of other studies, and to enable future replication of our results and meta-analyses by other authors who may not have information for all of the cognitive variables assessed here. In addition, this approach will help identify connections between the genetic backgrounds of these variables, thus find convergence in the results regarding overlaps of the cognitive information (Pearson/Spearman correlation tests) and genetic information (GWAS of each variable). Analyses at the variant-level with the

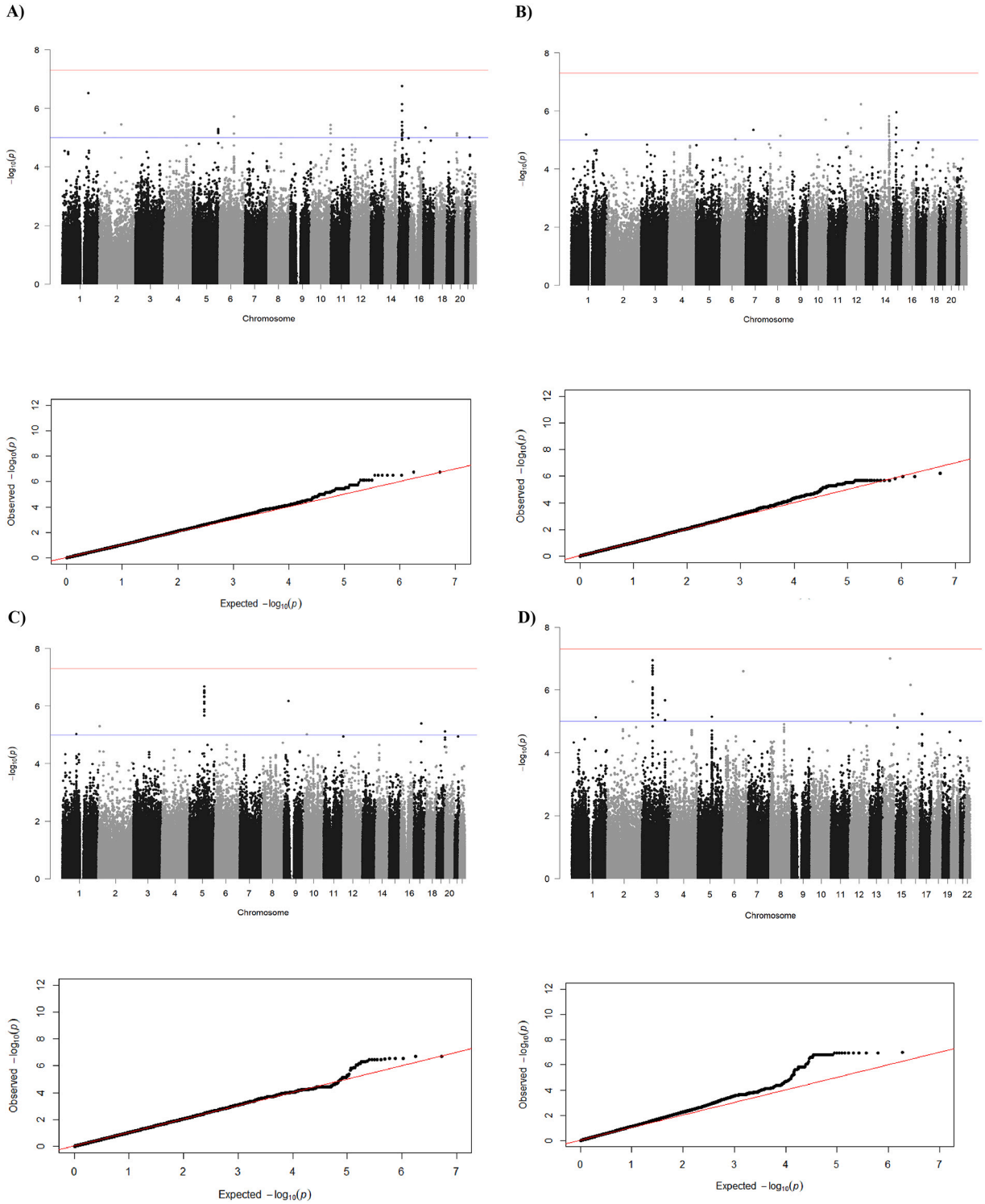

Fig. 1. Manhattan and Q-Q plots of the GWAS on the A) immediate recall, B) delayed recall, C) copy accuracy, and D) copy organization variables. The blue line on the Manhattan plots indicates the threshold for suggestive association ($P < 1E\text{-}05$). The red line indicates genome-wide association ($P = 5E\text{-}08$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

immediate recall, delayed recall, copy accuracy, and copy organization variables reported suggestive associations ($P < 1E-05$) for 75, 86, 35, and 73 SNPs, respectively. No SNP reached genome-wide association ($P = 5E-08$). Manhattan and Q-Q plots are shown in Fig. 1. We carried out LD analyses to identify index SNPs for each block of correlated markers (r2 > 0.5) using the *clump* function from Plink. Table 2 shows results for index SNPs with $P < 1E-06$ with each of the four variables. Although we did not consider correction for the four GWAS performed given the correlation between the four variables (Table S1) assessed as dependent variables, we present results that pass the stricter *P*-threshold (taking into account that four GWAS were performed) for suggestive association ($P < 2.5E-06$) in bold in Table 2. While no SNP reached genome-wide significance for any variable, there was one SNP in chromosome 14 which nearly reached genome-wide association with copy organization (rs60360940; $P = 9.98E-08$). Two common signals with $P < 1E-05$ were found for immediate and delayed recall, both in chromosome 15: rs16959426 ($P = 1.73E-07$ and $P = 6.73E-06$ for immediate and delayed recall, respectively) and rs335507 ($P = 6.71E-06$ for immediate and $P = 1.10E-06$ for delayed recall).

Regional association plots for the immediate recall top signals in chromosome 15, and the copy organization top markers in chromosome 3 were constructed (Figs. 2 and 3) with LocusZoom software, based on 1000 genome CEU population data (hg19/1000Genomes Mar 2012 EUR) (Pruim et al., 2010). Fig. 2 shows a genomic region that includes *SEMA6D,* which codes for a semaphorin domain (Sema domain), and is involved in nervous system development (Alto and Terman, 2017; Leslie et al., 2011). Fig. 3 represents a region including *PDZRN3* (PDZ Domain Containing Ring Finger 3), which codes for an ubiquitin ligase that is involved in vascular morphogenesis and cell differentiation during embryogenesis and the postnatal period (Sewduth et al., 2014).

3.4. Gene-based analysis

Results which passed the standard threshold for suggestive signals (*P*

Table 2
Results of the SNP-level analyses on immediate and delayed recall for suggestively associated index SNPs.

SNP	CHR	BP	RefA	AltA	MAF	N	B (S.E.)	P	VARIANT (GENE, BP)
a) Immediate recall									
rs7533272	1	175038348	G	A	0.44	127	3.93 (0.77)	3.02E-07	Intronic (TNN)
rs67014083	2	147644851	A	G	0.10	127	4.94 (1.07)	3.53E-06	Intergenic (PABPC1P2, 296 293; ACVR2A, 957 235)
rs3115238	2	34952517	G	A	0.27	127	3.64 (0.81)	6.79E-06	Intronic (LOC105374458)
rs13165241	5	171656546	T	C	0.10	127	5.6 (1.23)	5.11E-06	Intronic (UBTD2)
rs6938549	6	96711264	G	A	0.22	126	4.31 (0.91)	1.90E-06	Intergenic (FUT9, 47 776; UFL1, 258 418)
rs74643201	10	132879484	C	T	0.10	127	−5.59 (1.21)	3.69E-06	Intergenic (MIR378C, 118 553; TCERG1L, 11 170)
rs16959426*	15	47706262	A	T	0.20	126	4.58 (0.88)	1.73E-07	Intronic (SEMA6D)
rs74561350	15	47925959	C	T	0.21	127	4.36 (0.90)	1.20E-06	Intronic (SEMA6D)
rs335507*	15	53363263	G	T	0.16	126	−4.5 (1.00)	6.71E-06	Intergenic (ONECUT1, 280 730; LINC02490, 45 299)
rs8068028	17	14686627	A	G	0.04	127	9.15 (2.00)	4.58E-06	Intergenic (HS3ST3B1, 433 906; LOC101928475, 231 495)
rs2294248	20	7999642	G	A	0.32	127	−3.44 (0.77	7.19E-06	Intronic (TMX4)
rs62215908	21	43940640	T	C	0.05	125	7.68 (1.74)	9.82E-06	Intronic (SLC37A1)
b) Delayed recall									
rs10881479	1	104357400	C	A	0.31	126	3.76 (0.83)	6.42E-06	Intergenic (AMY1C, 56 086; LOC100129138, 258 245)
rs12203277	6	96705021	T	A	0.22	126	4.11 (0.93)	9.34E-06	Intergenic (FUT9, 41 533, UFL1 264 661)
rs6974056	7	52952144	T	G	0.24	126	4.06 (0.88)	4.50E-06	Intergenic (LOC107986794, 1 491 191; POM121L12, 151 182)
s111370684	8	85176513	T	C	0.07	127	−5.82 (1.30)	7.21E-06	Intronic (RALYL)
rs181500	10	119181871	T	G	0.44	126	3.44 (0.72)	2.01E-06	Regulatory region variant (PDZD8, 46 920; EMX2OS, 61 933)
rs10849488	12	6654050	A	G	0.23	127	3.92 (0.86)	5.80E-06	Non coding transcript exon variant (IFFO1)
rs1542256	12	98178796	A	G	0.28	126	3.92 (0.78)	5.83E-07	Regulatory region variant (PAFAH1B2P2, 28 501; MIR4495, 154 038)
rs57593039	14	88453546	C	T	0.08	127	6.34 (1.32)	1.53E-06	Intronic (GALC)
rs16959426*	15	47706262	A	T	0.20	126	4.11 (0.91)	6.37E-06	Intronic (SEMA6D)
rs335507*	15	53363263	G	T	0.16	126	−4.88 (1.00)	1.10E-06	Intergenic (ONECUT1, 280 730; LINC02490, 45 299)
c) Copy accuracy									
rs148865837	1	95763744	C	A	0.04	125	−1.17 (0.26)	9.48E-06	intergenic (RWDD3, 50 963; LINC01760, 12 740)
rs2011516	2	10120605	A	G	0.22	127	−0.68 (0.15)	4.93E-06	intronic (GRHL1)
rs7704455	5	104208609	G	T	0.29	126	0.62 (0.12)	2.05E-07	intergenic (NUDT12, 1 310 119; RAB9BP1, 226 566)
rs117850073	9	30575155	C	T	0.02	125	1.84 (0.37)	6.65E-07	intergenic (LINC01242, 166,703; LINC01243, 796,454)
rs4606374	10	19402519	T	C	0.26	125	0.61 (0.14)	9.54E-06	intronic (MALRD1)
rs2541240	17	53042872	G	A	0.31	127	0.60 (0.13)	4.04E-06	intronic (COX11)
rs77295560	19	57845465	G	A	0.07	127	0.90 (0.20)	7.56E-06	intergenic (ZNF543, 3 327; ZNF304, 17 174)
d) Copy organization									
rs857643	1	168831532	T	A	0.35	113	−1.32 (0.30)	7.45E-06	intergenic (LINC00626, 69 406; LINC00970, 41 611)
rs6433545	2	176432399	T	C	0.39	113	−1.43 (0.29)	5.48E-07	intergenic (ATP5MC3, 385 961; LNPK, 356 211)
rs2036893	3	73706022	G	A	0.46	113	1.32 (0.27)	8.44E-07	intergenic (PDZRN3-AS1, 28 972; LINC02005, 152 373)
rs56018103	3	73718030	T	C	0.22	113	1.76 (0.34)	1.13E-07	intergenic (PDZRN3-AS1, 40 980; LINC02005, 140 365)
rs2272022	3	112063850	C	A	0.37	113	−1.42 (0.32)	6.13E-06	exonic (CD200)
rs7639623	3	158964973	C	A	0.29	113	−1.48 (0.32)	2.15E-06	intronic (IQCJ, IQCJ-SCHIP1)
rs10045935	5	99302219	C	T	0.37	113	−1.40 (0.32)	7.11E-06	intergenic (LINC02113, 388 561; LOC100133050, 412 990)
rs2473520	6	139431060	G	T	0.18	113	1.91 (0.38)	2.55E-07	intergenic (ABRACL, 66 621; HECA, 25 157)
rs60360940	14	70750659	G	A	0.20	113	1.87 (0.36)	9.98E-08	intergenic (ADAM21P1, 36 141; SYNJ2BP-COX16, 41 139)
rs9453	14	100808845	A	G	0.19	113	1.61 (0.37)	6.16E-06	exonic (WARS1)
rs2560406	16	24102562	T	G	0.51	113	1.52 (0.31)	6.88E-07	intronic (PRKCB)
rs12945873	17	14463990	G	A	0.45	113	1.43 (0.32)	5.78E-06	intergenic (HS3ST3B1, 211 269; LOC101928475, 454 132)

SNP, single nucleotide polymorphism; *N*, sample size; *B (S.E.)*, Beta value (standard error); *CHR*, chromosome; *BP*, base pairs; *RefA,* reference allele; *AltA,* alternative allele; *SNPs among the top index signals shared by both immediate and delayed recall regression analyses. Regression model adjusted for age, sex, age at onset, and depression and obsessive-compulsive severity levels (HADS, Y-BOCS).

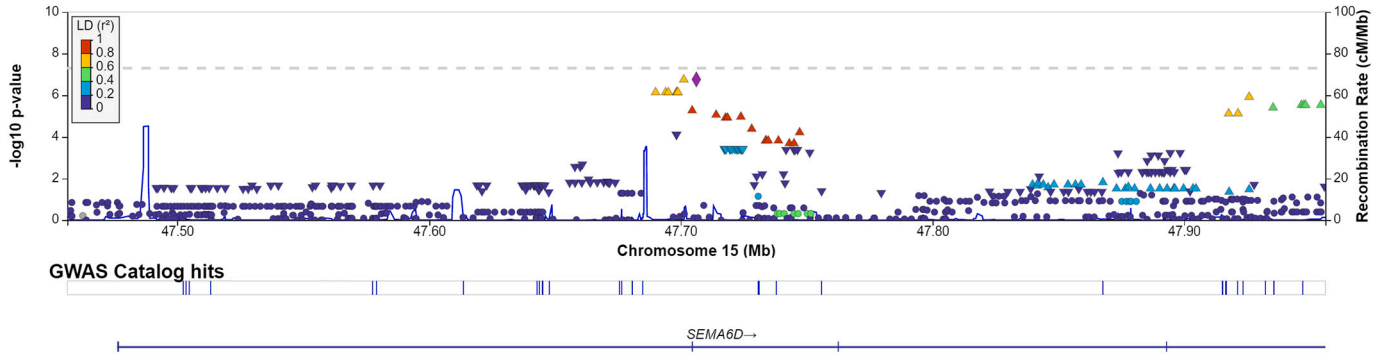

Fig. 2. Regional association plot with linkage disequilibrium (LD) information for immediate recall. Multiple suggestive signals ($P < 1E-05$) in LD were located in the depicted genomic region in chromosome 15. The purple rhombus is the SNP with the lowest *P*-value in the region (Reference SNP). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

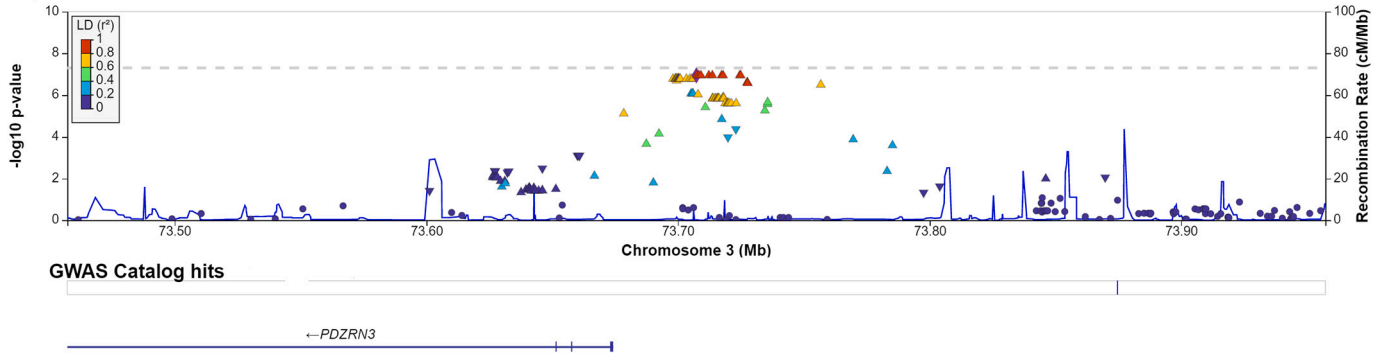

Fig. 3. Regional association plot with linkage disequilibrium (LD) information for copy organization. Multiple suggestive signals ($P < 1E-05$) in LD were located in the depicted genomic region in chromosome 3. The purple rhombus is the SNP with the lowest *P*-value in the region (Reference SNP). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

< 1E.04) found in the gene-based analysis can be seen in Table 3. No genes reached genome-wide significance ($P < 5E-06$). SNPs that passed the stricter *P*-threshold for suggestive associations ($P < 2.5E-05$), corrected to take into account that four GWAS were performed, are presented in bold.

4. Discussion

The present study explores preliminary findings on the genomic basis of four neurocognitive standardized measures assessed by the ROCFT: a benchmark test for the neuropsychological assessment of psychiatric and neurological patients regarding visuospatial perception and memory. We analyzed common variation by its association with copy

Table 3
Results of the gene-level analyses for suggestively associated genes.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P
IMMEDIATE RECALL								
TNN	1	175031994	175122202	205	10	127	39.384	4.10E-05
UBTD2	5	171631648	171715795	30	6	126	42.918	8.86E-06
IFFO1	12	6643694	6670249	11	2	125	39.753	3.51E-05
UQCRFS1	19	29693167	29709136	6	3	126	37.816	7.79E-05
DELAYED RECALL								
UBTD2	5	171631648	171715795	30	6	126	38.236	6.58E-05
IFFO1	12	6643694	6670249	11	2	125	42.821	9.26E-06
COPY ACCURACY								
MEGF10	5	126560206	126801914	509	9	127	37.232	9.84E-05
LOC101928208	7	29755114	29787218	13	2	126	37.716	8.11E-05
COPY ORGANIZATION								
IQCJ-SCHIP1	3	158782041	159620155	261	13	113	41.763	1.48E-05
SCHIP1	3	158986036	159620155	130	9	113	40.493	2.57E-05
CTXN3	5	126979713	126999322	2	1	113	37.923	7.46E-05
WARS1	14	100795125	100847680	4	1	113	41.466	1.69E-05

CHR, chromosome; *START* and *STOP* in base pairs. *NSNP*, number of single nucleotide polymorphisms; *N*, sample size; *ZSTAT*, Z statistic.

accuracy and organization, as well as immediate and delayed recall of a geometric figure via SNP-level and gene-based analyses. Our analyses found suggestive signals ($P < 1E-05$) for the four variables, immediate and delayed recall having some common signals. No SNPs reached genome-wide significance for any variable, although one SNP in chromosome 14 almost reached significant association with copy organization (rs60360940; $P = 9.98E-08$). Gene-based analyses showed suggestive signals for genes previously reported to be associated with neurological function and neuropsychological traits for immediate recall, copy accuracy and copy organization. No genes reached genome-wide association ($P < 5E-06$) for any variable.

The top SNP for immediate recall (rs16959426; chr 15; $P = 1.73E-07$) was also among the suggestive signals for delayed recall ($P = 6.73E-06$), as was expected considering the high correlation between immediate and delayed recall ($r = 0.927$, $P = 3.29E-46$; Table S1). This SNP was in LD with multiple other suggestively associated SNPs forming a single peak covering a genomic region which includes the gene *SEMA6D* (Semaphorin 6D) (Fig. 2). Another variant of *SEMA6D* was among the index SNPs (not in LD) suggestively associated with immediate recall (rs74561350, $P = 1.20E-06$). *SEMA6D* is involved in axon guidance, synapse formation, and dendrite development (Alto and Terman, 2017; Leslie et al., 2011). Different variants of this gene have been associated with reading skills (rs1817178), and suggestively associated with reading-related brain regions in children (Thomas et al., 2021). A second common suggestive signal for both immediate and delayed recall (rs335507, see Table 2) was also located in chromosome 15 and was ~132 kb away from an exonic region of *EEF1A1P22* (eukaryotic translation elongation factor 1 alpha 1 pseudogene 22); a gene associated with neurocognitive function, PHF-tau quantification in Alzheimer's disease, gut microbiota, metabolic rate in childhood obesity and other traits (Comuzzie et al., 2012; Ishida et al., 2020; LeBlanc et al., 2012; Wang et al., 2020). The described role of these genomic regions in neurocognition and their implication in our study regarding immediate and delayed recall through independent signals highlight them as relevant for further analysis in future studies, especially the *SEMA6D* gene.

The top SNP for delayed recall (rs1542256; chr12; $P = 5.83E-07$) was a variant located in a regulatory region nearby *PAFAH1B2P2* (28.5 kb); a gene associated with immediate logical memory recall and general cognitive function (Chung et al., 2018; Davies et al., 2018), and impaired cerebral cortex formation during fetal development (Sweeney et al., 2000). Multiple SNPs in chromosome 14 in LD were suggestively associated with delayed recall, covering a region encompassing *GALC*; a gene associated with Krabbe Disease, a severe neurological condition caused by a dysfunction of sphingolipid metabolism (Beecham et al., 2013; Patsopoulos et al., 2019); and *GPR65*; a gene associated with Parkinson's disease and other neurodegenerative diseases (Chang et al., 2017; Nalls et al., 2019; Sawcer et al., 2011; Smeland et al., 2021). The top signal for the copy accuracy SNP-level analysis was an intergenic variant (rs7704455; chr 5; $P = 2.05E-07$) located between *NUDT12*; a gene associated with unipolar depression and intelligence; and *RAB9BP1;* a gene associated with educational attainment and insomnia (Davies et al., 2018; Demange et al., 2021; Hek et al., 2013; Okbay et al., 2022; Watanabe et al., 2022). In the copy organization analysis, the top signal (rs60360940; chr 14; $P = 9.98E-08$) was an intergenic variant located between *ADAM21P1* pseudogene (36.14 kb) and *SYNJ2BP-COX16* readthrough (41.14 kb). This genomic region has been associated with cholesterol measurement and mitochondrial metabolism through different variants (Hoffmann et al., 2018; Sinnott-Armstrong et al., 2021). Interestingly, different OCD symptomatic dimensions are associated with various metabolic processes and mitochondrial function. Some examples are: sphingolipid metabolism (mentioned above), associated with the order dimension; peroxisomal lipid metabolism, associated with the aggressive dimension; and glucuronidation processes which are associated with hoarding symptoms (Alemany-Navarro et al., 2020b). In addition, we found four independent suggestive signals in chromosome 3 for copy organization. Two of them were located nearby *PDZRN3,* which has been associated with childhood-onset schizophrenia (Fig. 3) through de novo variants (Ambalavanan et al., 2016). This gene is located within a genomic region that is transcribed into a characterized long non-coding RNA: *PDZRN3-AS1* (*PDZRN3* Antisense RNA 1), which has been found in Type 2 Diabetes Mellitus. The two other independent suggestive signals in chromosome 3 were an exonic variant of *CD200*; a gene involved in innate and adaptive immune function; and an intronic variant of *IQCJ*; a gene that has been related to different psychiatric traits and disorders (such as attention deficit and hyperactivity disorder, antisocial behavior, substance abuse and smoking initiation) (Karlsson Linnér et al., 2021; Liu et al., 2019), as well as subcortical volume in healthy individuals (van der Meer et al., 2020).

The presence of neurological genes among the top signals for the four variables in the SNP-level analysis and some of those being present among the suggestive signals in gene-based analysis results is worthy of note. This is the case for *IQCJ/IQCJ-SCHIP1* ($P = 1.48E-05$) and *WARS1* ($P = 1.69E-05$), which are suggestively associated with copy organization through the SNP and gene-level analyses. *WARS1* (Tryptophanyl-TRNA Synthetase 1) plays a role in linking tryptophan to tRNA, and is involved in neurodevelopment; neurite degeneration in motor neurons in distal hereditary motor neuropathy; the regulation of ERK expression (thought to be a fundamental element of striatal motor functions); and neurocognitive dysfunction in older human immunodeficiency virus (HIV) patients (Djurovic et al., 2010; Maffezzini et al., 2019; Mak et al., 2017; Marshall et al., 2008; Tsai et al., 2017; Wang et al., 2019). The above-mentioned *IQCJ* gene forms part of a characterized genomic region that also encompasses the neighbor *SCHIP1* gene, leading to a single readthrough transcript (*IQCJ-SCHIP1*). This transcript is involved in axon initial segment and nodes of Ranvier maintenance, which is essential for keeping optimal neuronal polarity (Papandréou et al., 2015). A third gene found to be involved in copy organization through the gene-based analysis is *CTXN3*, which has been associated with schizophrenia status and its interaction with prefrontal dorsolateral activation during a functional magnetic resonance imaging protocol of digit recall; and metabolism of amyloid precursor protein, involved in Alzheimer's disease pathogenesis (Chouraki et al., 2014; Panichareon et al., 2012; Potkin et al., 2009; Šerý et al., 2015). Gene-based analysis for the other variables also showed genes with a described neurological role, such as *TNN* and *UQCRFS1* (immediate recall, Table 3), that have been shown to be involved in educational attainment (Okbay et al., 2022), and PHF (paired helical filaments)-tau measurement in AD through epistatic processes (Wang et al., 2020), respectively; and *MEGF10* (Copy accuracy, Table 3), which mediates amyloid-beta peptide uptake in the brain and has been associated with schizophrenia and antipsychotic response (Chen et al., 2009, 2008; Singh et al., 2010; Yu et al., 2018).

Despite the observed significance in the correlation tests performed for each pair of cognitive variables, only immediate and delayed recall had a high correlation coefficient. This may explain why specific loci and genes were found to be associated with each cognitive variable, and that the greatest overlaps were obtained for immediate and delayed recall. In addition, the correlation of different cognitive measures may not necessarily translate into genetic overlaps when accounting for common variation. The enrichment of associated loci in intergenic and intronic regions aligns with the greater presence of noncoding transcription within the brain in comparison to other tissues, and the prevalence of these types of variants in GWAS of neuropsychiatric disorders (Gandal et al., 2018; Stranger et al., 2011). Further research on the genomic basis of neurocognitive performance in OCD needs the application of other approaches, such as next-generation sequencing, in order to elucidate the involvement of different kinds of genetic variation in neurocognitive traits, and, especially visuospatial perception, among OCD probands.

4.1. Limitations

It is important to account for the absence of a control group in the present study, and the limited sample size, which likely hindered the finding of significant associations, despite the usual belief that greater clinical homogeneity given by the study of traits underlying nosological entities instead of case/control status groups may facilitate the finding of genetic signals (Iacono et al., 2017). In line with this, despite our sample size limitations, we found signals quite close to the genome-wide significance threshold that point to genes with described neurological roles, which should drive the development of further studies on the genomic basis of neurocognition in OCD. Importantly, controlling for depression and OCD severity in the study design might have hindered significance at the genome-wide level, considering the great genetic pleiotropy among neuropsychiatric traits. However, we decided to look for specific genetic basis of the neuropsychological variables assessed in this study in order to better investigate their possible role as endophenotypic signatures of OCD. Despite the possible relevance of adding variables such as years of education or intelligence quotient as covariates in analyses of neuropsychological traits, we did not have this information for the entire sample. Future studies should account for the possible role of these variables in the genetic associations with the assessed cognitive variables.

5. Conclusions

Our preliminary results show that studying neurocognitive variables in GWAS with OCD patients might be more informative about the genetic basis of OCD than the classical case/control GWAS. Furthermore, the low comorbidity of our OCD sample when compared to the comorbidity rates usually reported in the literature, increases the validity of our results, as the use of patients with "pure" OCD can be considered ideal for neuropsychological studies. The conjunction of different approaches in analyzing the genetic underpinnings of candidates for OCD endophenotypes would shed light onto the biomolecular mechanisms underlying this disorder; their dynamic nature, an important factor to consider in probands' treatment and prognosis; and their tissue-specificity, whose relevance lies in the growing evidence for the involvement of different biological systems in OCD. Further trans-diagnostic and trans-dimensional research on the genomic basis of neurocognitive traits is necessary to genetically characterize OCD and its different clinical profiles completely.

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Conflict of interest

The authors declare that they have no conflict of interest.

Data availability

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

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Ethics approval and patient consent

Written consent was required from all participants after having been fully informed about the study. The study was performed in accordance with the Helsinki Declaration of the World Medical Association and approved by the Ethical Committees of Bellvitge Hospital.

CRediT authorship contribution statement

The authors confirm contribution to the paper as follows: **study conception and design**: MA, MT, CS, MF, PA, AC; **data collection**: CS, ER, PA, JMM, SB, MA, VS; **analysis and interpretation of results**: MA, SD, RC, MT; **draft manuscript preparation**: MA, MT, AL, SD, RC, CS. All authors reviewed the results and approved the final version of the manuscript.

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