

Neurogenetics of Dynamic Connectivity Patterns Associated With Obsessive-Compulsive Symptoms in Healthy Children

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ABSTRACT

BACKGROUND: Obsessive-compulsive symptoms (OCSs) during childhood predispose to obsessive-compulsive disorder and have been associated with changes in brain circuits altered in obsessive-compulsive disorder samples. OCSs may arise from disturbed glutamatergic neurotransmission, impairing cognitive oscillations and promoting overstable functional states.

METHODS: A total of 227 healthy children completed the Obsessive Compulsive Inventory–Child Version and underwent a resting-state functional magnetic resonance imaging examination. Genome-wide data were obtained from 149 of them. We used a graph theory–based approach and characterized associations between OCSs and dynamic functional connectivity (dFC). dFC evaluates fluctuations over time in FC between brain regions, which allows characterizing regions with stable connectivity patterns (attractors). We then compared the spatial similarity between OCS-dFC correlation maps and mappings of genetic expression across brain regions to identify genes potentially associated with connectivity changes. In post hoc analyses, we investigated which specific single nucleotide polymorphisms of these genes moderated the association between OCSs and patterns of dFC.

RESULTS: OCSs correlated with decreased attractor properties in the left ventral putamen and increased attractor properties in (pre)motor areas and the left hippocampus. At the specific symptom level, increased attractor properties in the right superior parietal cortex correlated with ordering symptoms. In the hippocampus, we identified two single nucleotide polymorphisms in glutamatergic neurotransmission genes (*GRM7*, *GNAQ*) that moderated the association between OCSs and attractor features.

CONCLUSIONS: We provide evidence that in healthy children, the association between dFC changes and OCSs may be mapped onto brain circuits predicted by prevailing neurobiological models of obsessive-compulsive disorder. Moreover, our findings support the involvement of glutamatergic neurotransmission in such brain network changes.

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Obsessive-compulsive disorder (OCD) is characterized by anxiety-inducing intrusive thoughts, images, or impulses (obsessions) and repetitive behaviors (compulsions). OCD has a lifetime prevalence of 1% to 3% and frequently follows a chronic course (1), imposing significant socioeconomic burdens (2). Its impact could be minimized with prevention and early treatment (3); thus, it is essential to characterize at-risk individuals from a dimensional perspective. Evidence suggests that subclinical obsessive-compulsive symptoms (OCSs) might herald OCD onset in a significant percentage of cases (4) and that the presence of such symptoms during childhood increases the probability to develop OCD in adulthood (5,6). Notably, neuroimaging studies have shown that clinical and subclinical OCSs share structural and functional underpinnings (7,8).

Prevailing neurobiological models of OCD indicate that alterations in cortico-striatal-thalamo-cortical (CSTC)

circuits account for a large percentage of variability in OCSs (9,10). These models are based in part on resting-state functional connectivity (FC) assessments, which, however, considered FC to be stationary (11–13). More recently, dynamic FC (dFC) has allowed a more realistic approximation to connectivity by considering the temporal dimension and, therefore, the fluctuations in the communication patterns between brain regions (14). Interestingly, dFC research has shown that functional streams repeatedly converge into specific brain nodes, named attractors (15). Such attractors are akin to hubs in static FC in the temporal dimension, which allows their description not only as brain nodes centralizing and redistributing information, but also as regions governing the brain temporal dynamics by causing functional streams of information to repeatedly converge into them (15–17). For instance, at rest, attractors have been identified in primary sensory cortices, pulling connectivity

from neighboring regions, as well as in regions of the default mode network, pulling connectivity from distant network nodes (15). The description of FC alterations in OCD patients in such terms could provide relevant information on the mechanisms underlying the emergence of OCSs, and although dFC captures connectivity fluctuations on a time scale of seconds, they may potentially be a novel way to characterize the fluctuating nature of OCSs as stemming from alterations in dynamic rather than static brain networks.

Computational studies hypothesize that changes in glutamatergic/GABAergic (gamma-aminobutyric acidergic) synaptic efficacy may contribute to psychiatric symptoms by altering the stability of brain attractor networks (i.e., the network of regions significantly connected to an attractor over time) (18,19). Network stability refers to the ability of attractors to pull and retain connectivity from other regions over time, thus impeding transitions between brain states. In OCD, increased glutamatergic neurotransmission may increase the firing rates of neurons and their synaptic efficacy, thus increasing the stability of attractor networks and promoting overstable states (18,19). In agreement with this, CSTC connectivity alterations in OCD have been described to be driven by an imbalance between the glutamatergic and GABAergic direct and indirect CSTC circuits (9), and studies have reported increased glutamatergic function/concentration in the striatum (20) and cerebrospinal fluid of patients with OCD (21,22). Likewise, genetic studies have unveiled significant associations between glutamate-related genes, OCD diagnosis (23,24), and treatment resistance (25). Treatment studies have also reported that elevated glutamate levels normalize after treatment (26), and that glutamate antagonists may be useful treatment coadjuvants (27). Notably, these effects might be also observed in other brain areas in association with distinct OCSs, accounting for the clinical heterogeneity of OCD and adding to the notion that different OCSs might arise from alterations in different areas (12,13,18,28).

Here, we implemented a dFC approach to identify brain attractors associated with total and symptom-specific OCSs in a large sample of healthy children, free from the confounding effects of adult OCD samples, such as medication, chronicity, and comorbidities. Next, we explored the genetic signature of these attractors by meta-analyzing information from genetic databases (see [Supplemental Methods S1](#)) to identify genes that potentially underlie variations in dFC associated with OCSs. Capitalizing on the results from these analyses, we looked for potential polymorphisms within the genome-wide data of our sample moderating the association between imaging findings and OCSs. Stemming from the attractor hypothesis of OCD (18) and the prevailing neurobiological models of this disorder, we hypothesized that general and symptom-specific OCSs would be associated with variations in dFC (changes in the attractor profile) in CSTC regions, and that genes colocalizing with these imaging findings would be related to glutamatergic neurotransmission. Finally, we anticipated that expression-modifying single nucleotide polymorphisms (SNPs) in glutamatergic genes would moderate the association between CSTC attractors and OCSs. With this multidimensional perspective, we aim to provide an integrated view on the neurobiological determinants of the emergence of OCSs.

METHODS AND MATERIALS

Participants

This study included 227 healthy schoolchildren from the BREATHE (Brain Development and Air Pollution Ultrafine Particles in School Children) project (29). This project assessed the effect of pollution on neurodevelopment in 2897 children from 39 primary schools in the urban area of Barcelona, Spain. From those, 810 families were offered to participate in a neuroimaging substudy, and 491 were effectively contacted and 263 children completed the imaging protocol. Ten subjects were excluded based on image quality criteria ([Supplemental Methods S2](#)) and 1 subject was excluded because of incomplete psychometric data, resulting in 252 children.

During recruitment, pupils with special needs or with neurological, psychiatric, or other major medical conditions were excluded based on the reports of psychopedagogical offices. Teachers assessed attention-deficit/hyperactivity disorder (ADHD) symptoms with the ADHD Rating Scale-IV (30), and parents or legal guardians completed the Strengths and Difficulties Questionnaire (31).

Afterward, subjects underwent a clinical interview with a psychologist or psychiatrist who concluded that none met DSM-IV criteria for a psychiatric diagnosis. However, according to ADHD Rating Scale-IV data, 25 had subthreshold ADHD symptoms; thus, they were also excluded, leaving a final sample of 227 children. This sample was used in previous studies assessing brain correlates of OCSs (7,8).

OCSs were self-reported with the Obsessive Compulsive Inventory–Child Version (OCI-CV) (32), which assesses six symptom dimensions (doubt-checking, hoarding, neutralizing, obsessing, ordering, and washing) and provides a total OCS score by adding the dimensional subscores.

The study was approved by the ethical committees of IMIM-Parc de Salut Mar (No. 2010/41221/I), and the European Commission FP7-ERC-2010-AdG (No. ID268479). Written informed consent was obtained from all parents or legal guardians.

Imaging Data Acquisition and Preprocessing

Acquisition and preprocessing protocols are described in [Supplemental Methods S2](#) and [Figures S1 to S3](#).

Genotyping

Genotyping is detailed in [Supplemental Methods S3](#) and elsewhere (33). From the whole study sample, 149 children had both good-quality magnetic resonance imaging and genetic data. Hence, genetic analyses were performed in this subsample.

Data Analyses

Sociodemographic and Psychometric Data. Statistical analyses of sociodemographic and psychometric data were performed with SPSS version 23 (IBM Corp.).

OCS-Related Attractor Connectivity. Static FC approaches assess connectivity by averaging the entire blood oxygen level-dependent time series. However, brain dynamic changes occur at a shorter time scale. Here, we

implemented a graph theory-based dynamic stepwise FC (SFC) method (15) to characterize temporal information from FC in a nonstationary manner, which is achieved using a time moving window along the time series. First, we extracted the blood oxygen level-dependent time series within a whole-brain gray matter mask and applied a sliding window approach to split functional data into time windows of 30 seconds, with one lagged time point between them to achieve smooth transitions (15). Then, we computed Pearson's correlations across the time series of all voxels in each window to generate an FC (association) matrix per time window (Figure 1A), excluding negative correlations because of their ambiguity as indicators of topological patterns (34), and nonsignificant correlations ($p > .05$) likely attributable to noise (35). Afterward, we applied variance-stabilizing Fisher's transformations to the remaining coefficients before SFC analyses.

After these initial analyses, we computed, for each time window and using in-house scripts running on MATLAB R2020b (The MathWorks, Inc.), SFC values by calculating the connectivity steps from each voxel to the rest of brain voxels until seven steps were completed. The seven-step distance was selected based on previous path lengths research in FC

graphs (17). We obtained the weighted degree (or sum) of all the stepwise connections per voxel, which allowed us to identify voxels in which FC streams converge across multiple-step paths. Moreover, it has to be noted that dynamic changes occur at both local and distant levels (15). Because neighboring nodes engage in high connectivity strength, assessing total connectivity would highlight local connectivity while overshadowing distant patterns. Hence, for each voxel, SFC was estimated under two independent conditions: 1) considering direct (immediate) neighbor connections through triangle motifs (local connectivity; Equation S1 in the Supplement) and 2) considering connections outside the local neighborhood or triangle motifs (distant connectivity; Equation S2 in the Supplement) (Figure 1A).

Subsequently, we computed the mean of these weighted degree maps, containing the connectivity convergences from each time window, to obtain a single local and distant SFC map per subject. In these final maps, increased SFC values represent voxels into which FC repeatedly converges across multiple-step paths and time windows, a proxy of attractors. An attractor may therefore be conceived of as a hub region within a multistep spatial network in which hubness remains largely unaltered across time windows.

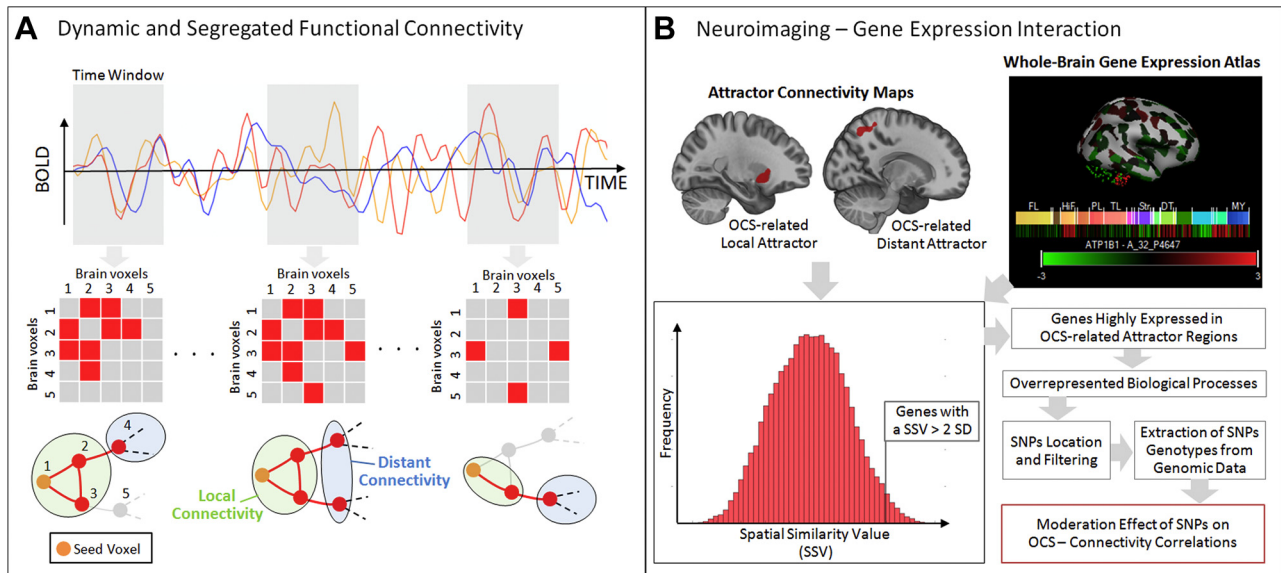


Figure 1. Neuroimaging-gene expression interaction analysis. **(A)** Dynamic functional connectivity was assessed through association matrices over time windows that represent distinct network configurations over time. Total connectivity was segregated into local and distant connectivity via triangle motifs; thus, the terms “local” and “distant” refer to network-based topology and not to Euclidean distances within the brain. Then, stepwise functional connectivity analyses were implemented to assess local and distant dynamic functional streams’ convergence at specific brain voxels. (Top) Representation of three association matrices at three time points. (Bottom) Representation of local and distant network configurations at three time points. **(B)** Connectivity segregation allowed to assess local and distant connectivity convergences targeting specific areas (attractors) and their relationship with OCSs. The resulting connectivity maps were combined with the gene expression AHBA to identify genes with expression levels spatially similar to OCS-related attractors. Then, we unselected genes enriched in biological processes and identified their expression quantitative trait loci (SNPs related to their expression) through brain (hippocampus and cortex) data of the GTEx project. Finally, we extracted the SNPs’ genotypes from the genome-wide data of our sample and assessed their moderation effect on the associations between OCSs and attractor connectivity. (Top left) Representation of brain regions with high local (left) or distant (right) connectivity convergences associated with symptoms. (Top right) brain representation of AHBA expression data for a selected representative gene (*ATP1B1*), generated with Brain Explorer 2 (Allen Institute for Brain Science). (Bottom left) Histogram representing the distribution of spatial similarity scores between dynamic connectivity maps and gene expression data from the AHBA. A statistical threshold of >2 SDs is shown. (Bottom right) Flowchart describing the workflow followed to identify and test the moderating effect of SNPs of genes expressed in OCS-related attractor regions on the associations between OCSs and attractor connectivity. AHBA, Allen Human Brain Atlas; BOLD, blood oxygen level-dependent; GTEx, Genotype-Tissue Expression; OCS, obsessive-compulsive symptoms; SNP, single nucleotide polymorphism.

Finally, we generated regression models with SPM12 (University College London, London, United Kingdom) to explore the associations between total or symptom-specific OCI-CV scores and local and distant SFC. Symptom-specific models included doubt-checking, hoarding, obsessing, and ordering scores as predictor variables, and neutralizing and washing scores as nuisance covariates because of lack of variance (mean < 1, median = 0). Likewise, age and sex were also included as nuisance variables. Results were independently evaluated within cortical and subcortical masks to maximize analysis sensitivity. Statistical significance was set at $p < .05$ (cluster-level, familywise error [FWE] corrected).

Genetic Signature of OCS-Related Attractors. As in previous publications (15,36), we used the Allen Human Brain Atlas (human.brain-map.org) (Supplemental Methods S1A) (37) to identify genes in which expression spatially overlapped with OCS-related SFC maps. Because gene expression differs between cortical and subcortical regions (38), we analyzed cortical and subcortical data separately. At the cortical level, Allen Human Brain Atlas transcriptional profiles, including 20,787 protein-coding genes, and OCS-related SFC maps were anatomically transformed to the 68 cortical regions of the Desikan-Killiany atlas (39,40). At the subcortical level, transcriptional profiles and SFC maps were transformed to the 16 subcortical regions from the FreeSurfer segmentation (41). Then, we calculated Pearson's correlations between the vectors of each gene's expression level, according to the Allen Human Brain Atlas, and the local and distant vectors of SFC at the cortical and subcortical levels. Finally, we built null hypothesis distributions comparing the cortical and subcortical transcriptome with our maps and identified genes surpassing a spatial correlation value of $r > 2$ SDs as the ones exhibiting a transcriptional profile spatially similar to OCS-related attractors (Figure 1B).

We next performed Gene Ontology–Biological Processes enrichment analyses (geneontology.org) (Supplemental Methods S1B) (42,43) for the genes highly expressed in OCS-related attractor regions to detect overrepresented biological processes. Statistical significance was determined with a Fisher's exact test ($p < .05$, false discovery rate [FDR] corrected) and a fold enrichment > 2 .

Following expert recommendations, we retrieved the SNPs of genes involved in overrepresented Gene Ontology–Biological Processes terms using the single-tissue expression quantitative trait loci viewer of the Genotype-Tissue Expression (GTEx) portal (gtexportal.org) (Supplemental Methods S1C) (44). SNPs were subsequently pruned based on linkage disequilibrium patterns from the CEU (Caucasian ancestry population) of the International Genome Sample Resource and the 1000 Genomes Project (<https://www.internationalgenome.org>), and following linkage cutoffs of $R^2 = 0.1$, and minor allele frequencies = 0.05 (ldlink.nci.nih.gov/?tab=snpclip) (Supplemental Methods S1D) (45).

Last, in post hoc analyses, genotypes for these SNPs were extracted from our genome-wide dataset using PLINK V1.9 (cog-genomics.org/plink/1.9) (46). Samples were grouped following a genetic dominant model (0 vs. 1 or 2 copies of the minor allele), and we evaluated the correlations between the eigenvalues of SFC peaks from the OCS-related attractor

Table 1. Sociodemographic and Psychometric Data

Sample Characteristics (N = 227)	Mean (SD), Range; n (%); or Mean (SD)	Median
Age, years	9.71 (0.86), 8–12.1	9.67
Sex		
Girls	118 (52%)	–
Boys	109 (48%)	–
Nonpsychiatric medication ^a	19 (8.4%)	–
School performance (0–5)	3.84 (0.98)	4
Mother's education (0–5)	4.56 (0.78)	5
OCI-CV Scores (N = 227)		
Doubt-checking	2.25 (1.52)	2
Hoarding	2.04 (1.26)	2
Neutralizing	0.38 (0.72)	0
Obsessing	1.59 (1.40)	1
Ordering	2.23 (1.60)	2
Washing	0.59 (0.82)	0
Total ^b	9.08 (4.08)	9

OCI-CV, Obsessive Compulsive Inventory–Child Version.

^aNonpsychiatric medication included acetaminophen, antihistamines, or antibiotics.

^bSeventy-five children (33% of our sample) had a total OCI-CV score ≥ 11 .

maps and the OCI-CV scores within each SNP subgroup with SPSS version 23 (Figure 1B). Statistical significance was corrected with Bonferroni procedures and contrasted between SNP subgroups using Fisher r -to- z transformations. These analyses allowed us to identify allelic variations moderating the relationship between OCSs and SFC values in our sample.

RESULTS

Sociodemographic and Psychometric Data

Table 1 shows sociodemographic and psychometric data of our sample. OCI-CV and Strengths and Difficulties Questionnaire scores were similar, and occasionally lower, than those of normative pediatric samples (Tables S1 and S2).

OCS-Related Attractor Connectivity

At the subcortical level, total OCI-CV score correlated negatively with local SFC values of a left ventral putamen cluster and positively with distant SFC values of a left hippocampus cluster (FWE-corrected $p < .05$). At the cortical level, total OCI-CV score correlated positively with distant SFC values of a left motor cortex–bilateral supplementary motor area (SMA) cluster (FWE-corrected $p < .05$) (Figure 2A, Table 2). Notably, SFC values of these clusters were significantly correlated between each other (positive correlation between hippocampal and motor-premotor clusters and negative correlations of these clusters with the putamen) (Table S3).

Symptom-specific analyses revealed a positive association between the ordering OCI-CV subscore and the distant SFC values of a right superior parietal cortex (SPC) cluster (FWE-corrected $p < .05$) (Figure 3A, Table 2).

We performed a 10-fold split half analysis to validate the above findings (Tables S4–S6). We found no significant differences in these analyses, which validated the imaging findings.

Genetic Signature of OCS-Related Attractors

At the subcortical level, the total symptom-related local attractor map, encompassing the putamen cluster, colocalized with the expression levels of 61 genes (Table S7) not enriched for any biological process (FDR-corrected $p_s > .05$). The total symptom-related distant attractor map, comprising the hippocampus cluster, colocalized with the expression levels of 583 genes (Table S7), 232 of which contributed to 64 biological processes (FDR-corrected $p_s < .05$), including glutamate-related pathways and synaptic vesicle regulation (Table S8). According to GTEx data for the hippocampus, 37 of the 232 genes presented a total of 788 expression quantitative trait loci (SNPs that regulate gene expression) in the hippocampus. Linkage disequilibrium pruning reduced these SNPs to 19, 18 of which were available in our sample. The correlation between the total OCI-CV score and distant SFC values of the left hippocampus was only significant in children with one or two

copies of the minor allele C in SNPs rs7613638 of the *GRM7* gene and rs11145747 of the *GNAQ* gene (Bonferroni-corrected $p_s < .0027$) (Figure 2B).

At the cortical level, the total symptom-related distant attractor map, encompassing the motor cortex-SMA cluster, colocalized with the expression levels of 237 genes (Table S7) not engaged in overrepresented biological processes (FDR-corrected $p_s > .05$). The ordering symptom-related distant attractor map, comprising the SPC cluster, colocalized with the expression levels of 457 genes (Table S7), 81 of which were enriched for nine biological processes (FDR-corrected $p_s < .05$), including nervous impulse transmission and synaptic signaling (Table S9). According to GTEx cortical data, 26 of the 81 genes had 1275 expression quantitative trait loci, which, after linkage disequilibrium pruning, were reduced to 35. We retrieved the genotypes of these 35 SNPs and found that the correlation between the ordering OCI-CV and distant SFC values of the right SPC was only significant in children with 1 or 2 copies of the minor allele T in the SNP rs2143290 of the *ATP1B1* gene and 0 copies of the minor allele C in the SNP rs6490097 of the *TESC* gene (Bonferroni-corrected $p_s < .0014$) (Figure 3B).

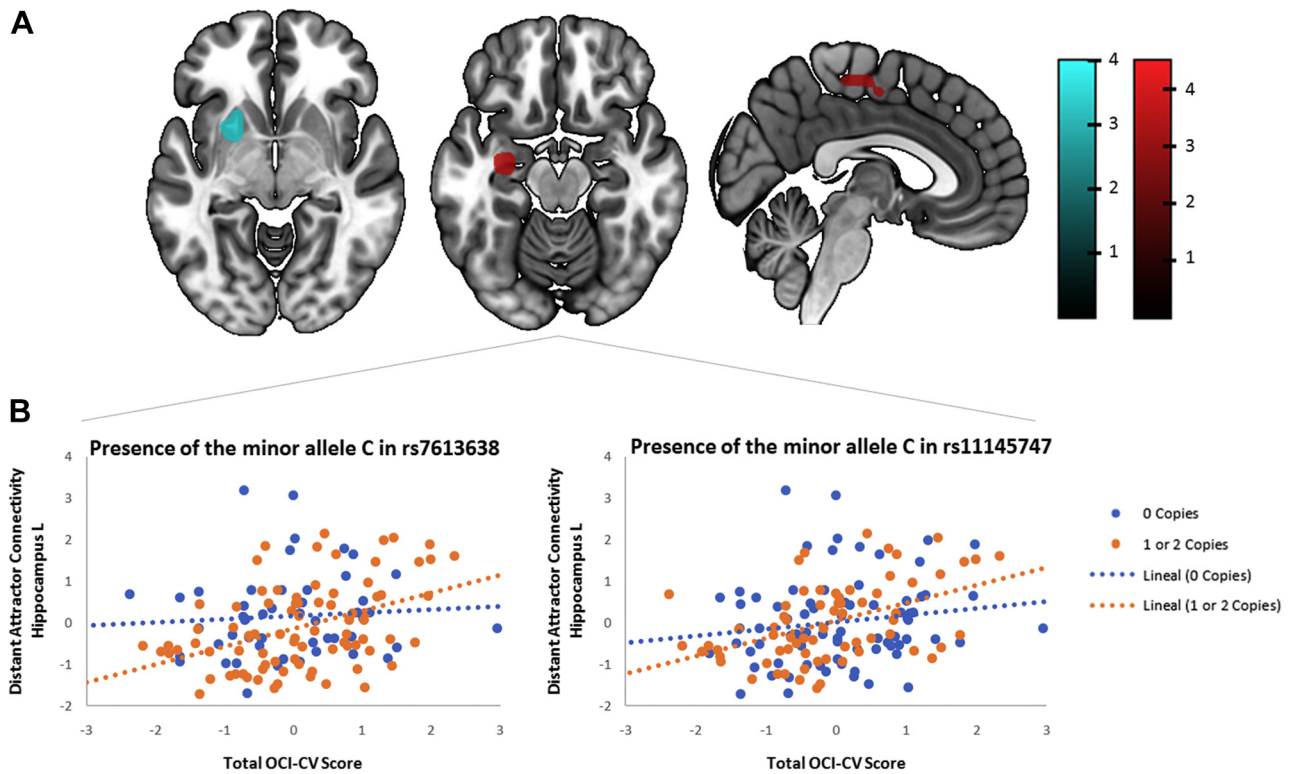


Figure 2. Neurogenetics of local/distant attractor connectivity associated with total obsessive-compulsive symptoms. **(A)** Associations between local/distant attractor connectivity and total obsessive-compulsive symptoms. The cyan color represents reduced local attractor connectivity associated with the total OCI-CV score. The red color represents increased distant attractor connectivity associated with the total OCI-CV score. Color bars indicate t values. Images are displayed in neurological convention. **(B)** Scatter plots of the moderator effect of the presence of the minor allele C in the SNPs rs7613638 of the *GRM7* gene (0 copies: $r = 0.074$; 1 or 2 copies: $r = 0.43$, $z = 2.11$, $p = .035$) and rs11145747 of the *GNAQ* gene (0 copies: $r = 0.153$; 1 or 2 copies: $r = 0.459$, $z = 2.00$, $p = .045$) on the correlation between the total OCI-CV score and the distant attractor connectivity of the left hippocampus. L, left; OCI-CV, Obsessive Compulsive Inventory–Child Version; SNP, single nucleotide polymorphism.

Table 2. Associations Between Local/Distant Attractor Connectivity and Obsessive-Compulsive Symptoms

Mask	Attractor	Contrast	Brain Region	x, y, z ^a	t	df	p-FWE	CS, Voxels
Total OCI-CV								
Subcortical	Local	Negative	Ventral putamen L	-22, 10, -8	3.50	223	.036	6
	Distant	Positive	Hippocampus L	-28, -8, -20	4.25	223	.004	13
Cortical	Distant	Positive	Motor cortex L-SMA R/L	-10, -32, 64	4.02	223	.002	25
Ordering OCI-CV								
Cortical	Distant	Positive	Superior parietal R	15, -56, 58	4.19	218	.022	14

CS, cluster size; L, left; OCI-CV, Obsessive Compulsive Inventory–Child Version; p-FWE, familywise error corrected p value at the cluster level; R, right; SMA, supplementary motor area.

^aAnatomic coordinates (x, y, z) are given in Montreal Neurological Institute space. The voxel size is 6 × 6 × 6 mm.

All interactions were submitted to formal moderation analyses via linear regression models in SPSS. We assessed the significance of the interaction term (with the allelic information) over and above the significance of the model without the interaction term. As displayed in Tables S10 to S13, the interaction term was significant for all the above findings except for the presence of the minor allele of rs11145747, which moderated the correlation between total symptoms and hippocampal connectivity at a trend level ($p = .109$).

DISCUSSION

We identified four brain nodes of functional convergence (attractors) associated with OCSs in healthy children. Changes

in three nodes, located within the CSTC circuitry and in adjacent limbic structures, were related to overall symptom severity, while changes in the SPC node were uniquely associated with ordering symptoms. In two of these nodes, we identified genetic variants potentially underpinning the relationship between OCSs and dynamic brain activity fluctuations. Concurring with our hypotheses, the genetic variants identified in one of these nodes were related to glutamatergic neurotransmission.

Overall OCS severity was positively related to distant attractor properties of the left motor cortex–bilateral SMA and the left hippocampus. These are, therefore, areas of convergence of long-range functional streams originating at different

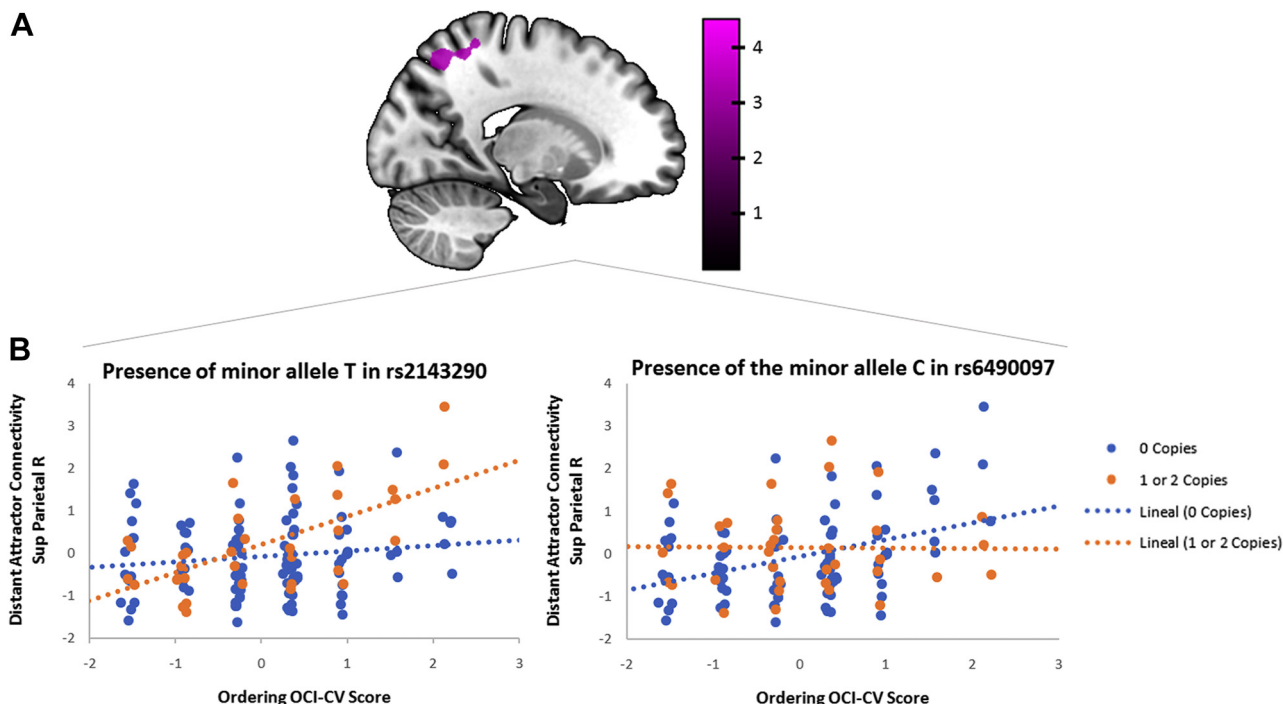


Figure 3. Neurogenetics of distant attractor connectivity associated with ordering obsessive-compulsive symptoms. (A) Association between distant attractor connectivity and ordering obsessive-compulsive symptoms. The violet color represents increased distant attractor connectivity associated with the ordering OCI-CV score. Color bars indicate t values. Images are displayed in neurological convention. (B) Scatter plots of the moderator effect of the presence of the minor allele T in the SNP rs2143290 of the *ATP1B1* gene (0 copies: $r = 0.136$; 1 or 2 copies: $r = 0.644$, $z = 3.08$, $p = .002$) and the presence of the minor allele C in the SNP rs6490097 of the *TESC* gene (0 copies: $r = 0.406$; 1 or 2 copies: $r = -0.01$, $z = 2.15$, $p = .032$) on the correlation between the ordering OCI-CV score and the distant attractor connectivity of the right superior parietal cortex. OCI-CV, Obsessive Compulsive Inventory–Child Version; R, right; SNP, single nucleotide polymorphism; Sup, superior.

locations throughout the brain. These pulling properties are sustained over time, preventing flexible dynamics of information interchange across brain circuits as a function of increasing symptom severity. As part of the sensorimotor CSTC loop, the motor-premotor cortices receive inputs from subcortical motor regions (47), mediating motor control and stimulus response-based habitual behaviors (9). Reverberating subcortical inputs to the SMA may alter FC within the sensorimotor loop, impairing the ability to disengage from ongoing behaviors and stereotyped motor patterns. Consistent with habit-based dominance theories in OCD, such alterations may facilitate the emergence of compulsions (48). This may concur with recent findings reporting that children with compulsive phenotypes showed structural alterations in the motor cortex and increased FC between the sensorimotor and the default mode networks, suggesting that motor/premotor regions may be strongly connected to distant cortical regions (49). Likewise, these results comply with the well-established efficacy of low-frequency repetitive transcranial magnetic stimulation targeting the SMA on improving OCSs (50), which may be explained by its inhibitory effects on SMA hyperconnectivity. Further studies are warranted to better understand FC alterations in the SMA, even at subclinical stages, especially considering its important role on compulsivity (51) and habit-based behaviors (48).

Conversely, the hippocampus is a brain hub connected to multiple cortical regions, important for different processes including mnemonic, emotional, and spatial functions, as well as for dealing with approach-avoidance conflicts (52,53). Most of these functions could be related to OCS pathophysiology; thus, it is difficult to link our findings to a specific psychological process. Speculatively, they may be related to studies reporting memory biases favoring threat-related stimuli (54) and avoidance tendencies (55) in OCD. Regardless, this finding concurs with research reporting increased FC between the hippocampus and distant regions in OCD (56).

We found that mechanisms leading to increased hippocampal SFC values in children with more OCSs were potentially related to glutamatergic neurotransmission. Two SNPs in the *GRM7* and *GNAQ* genes increased the likelihood of observing such increased SFC. *GRM7* encodes the metabotropic glutamate receptor mGluR7, and its polymorphisms have been associated with psychiatric and neurodevelopmental conditions (57,58), and with fear extinction in preclinical models (59). mGluR7 modulates hippocampal excitatory transmission by decreasing NMDA receptor activity (60). Hence, altered *GRM7* expression in the hippocampus could increase glutamatergic activity in this region, increasing its SFC and hampering cognitive fluctuations in favor of over-stable functional states. *GNAQ*, in turn, encodes the $G_{\alpha q}$ protein, which activates intracellular pathways in response to the activation of receptors such as mGluR5, which regulates hippocampal NMDA receptor activity (61). Altered *GNAQ* expression has been observed in schizophrenia (62), whereas $G_{\alpha q}$ knockdown and knockout results in diminished spatial memory, enhanced behavioral responses to psychostimulants (63), and impaired mGluR-dependent long-term depression in the hippocampus (64). Hence, impaired *GNAQ* expression may alter glutamate-dependent synaptic plasticity and cognitive fluctuation. Importantly, the effect of this last SNP only trended

toward significance in a formal moderation analysis. Therefore, caution is warranted to interpret this finding.

Local SFC values of the left ventral putamen decreased with increasing OCSs; that is, the ventral putamen received fewer inputs from neighboring regions, and these were less stable in individuals with more symptoms. This region is a subcortical relay station of the ventral cognitive CSTC circuit, which mediates response inhibition and cognitive emotion control (9). Youths and adults with OCD show reduced FC within this loop (11,65), and in adults, compulsivity has been associated with diminished resting-state activity within this area (66). Indeed, in this same sample, static, nonsegregated FC estimates were also negatively associated with total OCSs (8). Here, this association was limited to local connections, adding to the notion that nonsegregated assessments emphasize local FC (15). Connectivity alterations in this region may result in decreased information exchange across different CSTC loops, whose fiber tracts are progressively compressed within the same striatal nuclei (67). In this regard, recent research with large youth samples provides an anatomical basis for such decreased connectivity, as compulsivity has been associated with reduced myelin-related growth in the left ventral striatum (68) and OCSs with decreased fractional anisotropy in the superior corticostriatal tract (49,69).

Our last set of findings involved ordering symptoms and distant SPC SFC values. Ordering symptoms are among the most prevalent in healthy children (70), and in OCD they are closely linked to compulsivity (71) and have been related to alterations in sensorimotor regions, including the parietal cortex (72,73). The SPC is a multimodal hub that integrates information from distributed cortical regions (16), contributing to somatosensory, visuospatial, and attentional processes (74). Alterations in the flexible functioning of SPC may account for previous findings reporting that symmetry/ordering symptoms were more strongly related to sensorimotor, attention, and visuospatial impairments than to obsessive/checking symptoms (75,76). Additionally, we identified two SNPs in the *ATP1B1* and *TESC* genes that acted as a risk and a protective factor, respectively, in the association between ordering and SPC connectivity values. These genes have not been previously linked to ordering or OCD, although their expression is altered in bipolar disorder and schizophrenia (77,78). *ATP1B1* encodes the $\beta 1$ subunit of the sodium/potassium ATPase, which generates electrochemical gradients that drive glutamate uptake, regulating electrical excitability (79). Therefore, impaired *ATP1B1* expression in the SPC could alter neuronal excitability, increasing its SFC and predisposing to ordering symptoms. *TESC*, in turn, encodes tescalcin, a calcium-binding protein that regulates cellular pH by controlling NHE-1 activity. Reduced NHE-1 prevents NMDA receptor-induced excitotoxicity (80); thus, changes in *TESC* expression in the SPC may protect against glutamatergic neurotransmission increases and system over-stability.

This study has noteworthy limitations. Because this is a correlational study, we cannot infer causality from our findings, which should be interpreted accordingly. Likewise, we lacked a matched group of OCD patients, which prevented determining whether our findings replicate in clinical samples. Longitudinal studies are warranted to ascertain whether our results are

predictive of OCD development or solely linked to subclinical OCSs. This, combined with the novelty of the methodological approach and the lack of a detailed neurocognitive assessment of participants, has made the discussion of our findings somewhat speculative in parts. There are also limitations in image acquisition and preprocessing. These include using a 1.5T magnet and resampling data to a low spatial resolution, which may have resulted in lower spatial resolution. Moreover, we opted for a 6-minute sequence to prevent excessive movement, although longer acquisition times may provide more stable imaging results, and we did not directly supervise whether children kept the eyes closed throughout the acquisition, which may have added variability to our data. Additionally, genetic analyses were conducted in the same study sample. In this regard, the SNPs of our genetic analyses were selected according to GTEx anatomical labeling, as opposed to a cluster-based selection. Therefore, we did not include SNPs located in the fringe of our imaging cluster, where noisy components leading to overfitting and circularity issues are typically found (81). Indeed, of the 18 SNPs selected, significant findings were only observed in glutamatergic genes, as predicted by our hypotheses. Finally, it remains to be clearly established how genetic variations and changes in synaptic and neural functioning are mechanistically related to network-level fluctuations and the obsessive-compulsive phenotype.

In conclusion, this is the first study combining multisource neurobiological information to assess the relationship between subclinical OCSs with dynamic SFC and its putative genetic signature. Our findings support the attractor hypothesis (18) and indicate that even at subclinical stages, total OCSs are linked not only to CSTC alterations, which is congruent with neurobiological models of OCD (9,82), but also to alterations beyond the CSTC, which concurs with evidence involving areas outside these circuits in the development of OCSs (82,83). Likewise, ordering OCSs were associated with SPC alterations, supporting the notion that some FC features may be symptom specific (12,13,28). We also identified SNPs that moderated the risk for OCS-related attractors. Attractors were linked to glutamatergic neurotransmission, albeit we identified other biological processes that may be involved in the development of ordering-related attractors. Further research is warranted to characterize the link between these pathways and attractor emergence. Taken together, we have identified putative biomarkers of risk for developing OCD and potential therapeutic targets for interventions aimed at restoring the excitation/inhibition imbalance allegedly underlying obsessive-compulsive symptoms.

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This study has been conducted with data from the population-based cohort BREATHE, which is described in Sunyer *et al.* (29). Subsamples of this cohort have been used in previous studies, with different goals: assessing the influence of traffic pollution exposure on brain functional connectivity and the effects of airborne copper exposure on motor performance and functional neuroanatomy of the basal ganglia (84,85), as well as the brain structural and static functional correlates of obsessive-compulsive symptoms (7,8). This work is part of the doctoral thesis of Maria Suñol, which is published online at <http://hdl.handle.net/2445/174698>.

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