

Putamen volume as a predictor of repetitive and restricted behaviors and interests related intensity in autism

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Research Article

Keywords: RRB, phenotype, cortico-striatal-thalamo-cortical loop

Posted Date: April 13th, 2023

DOI: <https://doi.org/10.21203/rs.3.rs-2799683/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background. Repetitive and restricted behaviors and interests (RRBI) are core symptoms of autism with a complex entity and are commonly categorized into 'motor-driven' and 'cognitively-driven'. RRBI symptomatology depends on the individual's clinical environment limiting the understanding of RRBI physiology, particularly their associated neuroanatomical structures. The complex RRBI heterogeneity needs to explore the whole RRBI spectrum by integrating the clinical context (autistic individuals, their relatives and typical developing (TD) individuals). We hypothesized that different RRBI dimensions would emerge by exploring the whole spectrum of RRBI, and that these dimensions are associated with neuroanatomical signatures - involving cortical & subcortical areas.

Method. A sample of 792 individuals composed of 267 autistic subjects, their 370 first-degree relatives and 155 TD individuals was enrolled in the study. We assessed the whole patterns of RRBI in each individual by using the Repetitive Behavior Scale-Revised and the Yale-Brown Obsessive Compulsive Scale. We estimated brain volumes using MRI scanner for a subsample of the subjects ($n=152$, 42 ASD, 89 relatives and 13 TD). We first investigated the dimensionality of RRBI by performing a principal component analysis on all items of these scales and included all the sampling population. We then explored the relationship between RRBI-derived factors with brain volumes using linear regression models.

Results. We identified 3 main factors (with 30.3% of the RRBI cumulative variance): Factor 1 (FA1, 12.7%) reflected mainly the 'motor-driven' RRBI symptoms; Factor 2 and 3 (respectively 8.8% and 7.9%) gathered mainly Y-BOCS related items and represented the 'cognitively-driven' RRBI symptoms. These three factors were significantly associated with the right/left putamen volumes but with opposite effects: FA1 was negatively associated with an increased volume of the right/left putamen conversely to FA2 & FA3 (all uncorrected $p<0.05$). FA1 was negatively associated with the left amygdala (uncorrected $p<0.05$), and FA2 was positively associated with the left parietal structure (uncorrected $p=0.001$).

Conclusion. Our results suggested 3 coherent RRBI dimensions involving the putamen commonly and other structures according to the RRBI dimension. The exploration of the putamen's integrative role in RSBI needs to be strengthened in further studies.

Introduction

Autism Spectrum Disorders (ASD) are complex conditions characterized by atypical social communication, as well as restricted or stereotyped behaviors and interests (RRBI) (DSM-5, APA), affecting 1–2% of individuals from the general population (Baio et al., 2018). One source of this complexity relies on the heterogeneity of symptoms depicted by autistic individuals, specifically when considering the RRBI. These symptoms could be dichotomized in 'motor-driven' symptoms gathering the stereotyped movements (e.g. head banging) and the repetitive behaviors, and in 'cognitively-driven' symptoms, including obsessive-compulsive like symptoms and cognitive inflexibility (Scahill et al., 2015, Lefebvre et al., 2021). The determinants of this differential expression remain largely unknown, although the individual's cognitive skills seem to be a major modulator of RRBI. Individuals with a comorbid intellectual deficiency predominantly display motor-related symptoms, whereas autistic individuals without such deficiency express more those which are cognitively driven (Dajani & Uddin, 2015). Other modulators affect the expressiveness of these symptoms, such as the individual's age (Evans et al., 2017) or the associated social communication skills themselves. Studies exploring the familial aggregation of RRBI in autism report that the repetitive/stereotyped behaviors are mainly observed in probands and the obsessive-like symptoms in their non-affected relatives, independently of their cognitive abilities (Hollander et al., 2003, Wilcox et al., 2003). The apparent dichotomy of the RRBI is also reinforced by the use of distinct screening tools, opposing those dedicated to the exploration of RRBI in the context of autism, such as the Repetitive Behaviors Scale-Revised (RBS-R, Lam et al., 2007) and those measuring them in individuals with obsessive-compulsive disorders with the Y-BOCS as a gold standard (Goldman et al, 1989). However, contrary to an approach divided into repetitive behaviors for some individuals and obsessive symptoms for others, some authors have developed new tools to consider the wide diversity of RRBI better and offer a unifying approach to these symptoms. Although preliminary and performed in the general population, one study showed a high intra-familial correlation of RRBI, whether the index case has associated autistic symptoms (Evans et al., 2017). These findings encourage researchers to reconsider the nosology of RRBI and to adopt a more dimensional approach than a categorical to these symptoms.

It also seems consistent with what the literature reports about the involvement of a similar pattern of brain structures in RRBI. Animal models suggest a critical role of the cortico-basal-ganglia-thalamo-cortical loop in the emergence and maintenance of RRBI (Casado-Sainz et al., 2022). Induced deletion of Shank3 (*SHANK3* being a major gene associated with autism) in inhibitory neurons of the striatum results in repetitive/stereotyped-like behaviors, and conversely, deletion of Shank3 in excitatory neurons of the prefrontal cortex results in excessive self-grooming behaviors considered as an equivalent of obsessive-compulsive symptoms (Bey et al., 2018). In humans, studies exploring RRBI in autistic individuals also report abnormalities in subcortical structures, specifically the striatum. For example, using T1-weighted anatomical images from the Autism Brain Imaging Data Exchange, Schuetze et al. (2016) reported that stereotyped behaviors were positively associated with increased bilateral globus pallidus surface area. Paralleling these findings, the ENIGMA-OCD working group observed larger thalamic volume affecting the lateral, pulvinar, and ventral regions in children with OCD (Weeland et al, 2022). However, another mega-analysis by the OCD Brain Imaging Consortium (OBIC), pointed more toward the ventrolateral and dorsomedial prefrontal in obsessive-compulsive behaviors in humans (Fouche et al, 2017).

Altogether, the literature presents a certain coherence between the results of clinical, genetic and brain imaging studies suggesting a commonality of the RRBI with a differential expression according to the individual phenotypic characteristics. To better understand the heterogeneity and familial patterns of RRBI in autism, as well as the structural brain abnormalities that underlie them, we performed this study exploring RRBI in a sample of 792 individuals gathering autistic patients ($n = 267$), their non-affected first-degree relatives ($n = 370$) and typically developing individuals from the general population (TD) ($n = 155$). To embrace the diversity of the whole pattern of RRBI, we explored each enrolled individual with the Repetitive Behavior Scale-Revised (RBS-R) (Lam & Aman, 2007) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989), both considered as gold standard questionnaires to explore repetitive/stereotyped behaviors and obsessive-compulsive symptoms in clinical populations. We then ran a factor analysis on all RRBI to apprehend further the distribution of these symptoms independently of the subject's status (affected, non-affected relatives, or typically developing participants). We finally

performed a multiple linear regression model on a subsample of 152 subjects to explore the relationship between these RRBI-related factors, and the cortical/subcortical brain volumes based on MRI. We hypothesized that two main factors would emerge from the factor analysis, mirroring the dichotomized model of RRBI (repetitive/stereotyped vs obsessive/compulsive symptoms), but displaying common and specific associations with brain structures of the cortico-striatal-thalamo-cortical loop.

Methods

Participants

A sample of 792 individuals composed of 267 autistic subjects, their 370 first-degree relatives and 155 individuals from the general population with typical development (TD) were enrolled in the study at the Child and Adolescent Psychiatry Department, Robert Debre Hospital, Paris (France). Their demographic and clinical characteristics are reported in Table 1. Participants' clinical assessment procedures followed previously described methods (Lefebvre et al., 2021). ASD diagnosis was based on DSM-IV-TR/5 criteria and made by summing the information from the Autism Diagnosis Interview-Revised (ADI-R), the Autism Diagnostic Observation Scale - second edition (ADOS-2), and clinical reports from experts in the field. Cognitive abilities were assessed using the Wechsler Intelligence Scales adapted to age or the Raven's Progressive Matrices (RPM) for those with poor (or lack) verbal abilities (Raven et al., 2003).

Concerning first-degree relatives and TD, the presence of autistic symptoms was assessed by using the Social Responsiveness Scale-II (SRS-II) (Constantino & Gruber, 2012). We also explored their Axis I psychiatric conditions (in accordance with DSM-IV-TR/5 criteria) using semi-standardized direct interviews, the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime version (K-SADS-PL) (Kaufman et al., 2000) for subjects below 18-year-old or the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) for adults. The cognitive abilities of first-degree relatives and TD were estimated with Raven's Progressive Matrices (RPM) (Raven et al., 2003). Those with low, mild or below intellectual disabilities were excluded (IQ < 70).

Exploration of RRBI

To explore the diversity of RRBI in all subjects in the study, we used the Repetitive Behavior Scale-Revised (RBS-R) (Lam & Aman, 2007) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989), both considered as gold standard questionnaires to explore repetitive/stereotyped behaviors and obsessive-compulsive symptoms, respectively. The use of these 2 scales simultaneously and whatever the clinical profile of individuals we investigated allowed the exploration of the wide span of RRBI. For the purpose of the study, we used a self-report version of the Y-BOCS designed by the Tourette Syndrome Association Genetic Consortium (January 1995) (Goldman et al., 1989). This instrument, based on the symptom checklist and ordinal scales of the Y-BOCS, was used as parental hetero-questionnaires for children and as self-questionnaires for adults. The concordance for expert clinicians' assessment of obsessive-compulsive symptom severity was excellent (Swerdlow et al, 1999).

Brain volume estimations based on magnetic resonance imaging

MRI data were collected for a subsample of the subjects included in the study (n = 152), gathering 42 individuals with ASD, 89 first-degree relatives and 13 subjects from the general population. Acquisitions were performed using the following parameters: spoiled gradient recalled echo (SPGR), 1mm isotropic, repetition time (TR) = 25ms, echo time (TE) = 6ms, flip angle = 30°. For all participants, MRI data were collected using previously described parameters, with a 1.5 Tesla scanner using a T1-Weighted acquisition (Maruani et al., 2015). Raw DICOM images were converted to NIFTI format with dcm2niix (<https://github.com/rordenlab/dcm2niix>) and defaced with MRIdface (Bischoff et al., 2007). Cortical reconstruction and volumetric segmentation were performed with Freesurfer software version 6.0.0 (<http://surfer.nmr.mgh.harvard.edu/>) and visual control of the segmentation quality was done using the QCAPP (<https://github.com/neuroanatomy/QCApp>).

Statistical Analysis

The demographic and clinical characteristics of the three groups of participants (autistic individuals, their first degree relatives and TD) were compared using the Student's *t* test and the χ^2 test for continuous and discrete variables, respectively. To investigate the dimensions underlying RRBI variability, we performed a principal component analysis (PCA). We first standardized item-related scores from the RBS-R and the Y-BOCS. We then ran general linear models adjusted for age, sex, and age*sex interactions to generate residuals (Suppl. Tables 1 & 2). PCA with varimax rotation was then performed on the residual standardized RRBI values, including all the participants enrolled in the study regardless of their status. The number of factors was defined after visual exploration of the screen plot. To identify the items belonging to a specific factor, we observed which items had high loadings (> 0.20) for a specific factor but low loadings (< 0.10) for the others. PCA was performed using JMP Pro 16.0 (SAS Inc., Cary, NC).

To explore the interactions between RRBI-derived factors and brain volumes, we ran a similar analysis on brain volumes extracted from automatic segmentation of the grey and white matter structures. Each brain volume was standardized. We also used general linear models adjusted for age, sex, and age*sex interactions to generate structural brain volume residuals. The relationship between the RRBI-derived factors and standardized structural brain volume residuals was explored using linear regression methods. All tests were two-tailed. Type I error rate was controlled using the false discovery rate (FDR) method. Statistical analysis was performed using Python packages (Python Software Foundation. Python Language Reference, version 2.7). Brain map figures were generated using the ENIGMA toolbox (Larivière et al, 2021).

Ethics

The study was granted approval by the local Ethics Committee (ref: 2008-A00019-46) and registered in a public trial registry (NCT02628808). The study was carried out in accordance with Good Clinical Practice (ICH GCP) standards. Written informed consent was obtained from all participants. For patients who were unable to consent for themselves, a parent or legal guardian consented to the study on their behalf.

Results

Dimensionality of the RRBI symptoms

To explore the main dimensions underlying the diversity of RRBI reported in subjects enrolled in the study, we ran a principal component analysis. After visual inspection, we identified 3 main factors which accounted for 30.3% of the cumulative variance (Suppl. Table 3). Factor 1 (FA1, 12.7% of the variance) reflecting the 'motor-driven' RRBI or 'sensory motor behaviors / compulsions', with 43 items belonging to the RBS-R scale except one from the Y-BOCS. This item reflected the need to repeat routine activities - a frequent symptom reported in autistic patients, often associated with emotional dysregulation. In contrast, Factors 2 and 3 gathered mainly Y-BOCS-related items, reflecting the 'cognitively-driven' RRBI. Factor 2 encompassed 22 items, all from the Y-BOCS (FA2, 8.8% of the variance). FA2 gathered symmetry and ordering symptoms that may represent a 'rigidity/insistence on sameness' dimension. Factor 3 aggregated items associated with washing, checking, contamination and aggressive obsessive-compulsive symptoms (FA3, 7.9% of the variance). The subjects' scores showed a similar repartition depending on their conditions (autistic, related or TD) among the 3 factors (Suppl. Fig. 2).

Correlates between structural brain volumes and RRBI-related dimensions

We then explored the relationships between the RRBI-related dimensions and structural brain volume residuals using simple linear regressions (Figure 1, Table 2). FA1 was associated with increased left and right putamen volumes ($R^2=0.06$, $F=8.84$, regression coefficient=0.75, uncorrected $p<10^{-3}$, $r=0.24$; $R^2=0.04$, $F=5.48$, regression coefficient=0.58, uncorrected $p<10^{-3}$, $r=0.20$). An interaction between FA1 and the left amygdala volume was also observed ($R^2=0.03$, $F=4.18$, regression coefficient=0.03, uncorrected $p=0.04$, $r=0.17$). Our results were coherent with a recurrently reported brain volume increase of the amygdala in individuals with autism or anxiety disorders. However, the associations we reported did not survive adjustment for multiple comparisons (FA1 & left amygdala volume: corrected $p=0.41$; FA1 & left putamen volume: corrected $p=0.10$, FA1 & right putamen volume: corrected $p=0.30$) (Figure 1.A., Table 2).

FA2 was also associated with decreased left and right putamen volumes (respectively $R^2=0.06$, $F=8.06$, regression coefficient=-1.12, uncorrected $p<10^{-3}$, $r=-0.24$; $R^2=0.04$, $F=5.31$, regression coefficient=-0.89, uncorrected $p=0.02$, $r=-0.19$), and decreased left parietal volume ($R^2=0.001$, $F=0.16$, regression coefficient=-0.18, uncorrected $p<10^{-3}$, $r=-0.05$). Interestingly, decreased volume in the parietal lobe was associated in the literature with impairment in high-order cognitive processes, mainly executive dysfunctions. Despite the relevance of our findings, their significance did not survive after multiple comparisons correction (FA2 & left putamen volume: corrected $p=0.15$; FA2 & right putamen volume: corrected $p=0.33$; FA2 & left parietal volume: corrected $p=0.10$) (Figure 1.B. & Table 2). Similarly, FA3 was linked to decreased left and right putamen volumes ($R^2=0.04$, $F=6.20$, coefficient=-0.92, uncorrected $p=0.01$, $r=-0.21$; $R^2=0.32$, $F=4.60$, coefficient=-0.78, uncorrected $p=0.03$, $r=-0.18$). This association did not persist after correction for multiple comparisons (FA3 and left putamen volume: corrected $p=0.41$; FA3 and right putamen volume: corrected $p=0.44$) (Figure 1.C. & Table 2).

Discussion

The challenges in identifying biomarkers in neurodevelopmental disorders, particularly in autism, stem from the difficulties researchers have in considering the inter-individual phenotypic variability. It ranges from those with a developmental trajectory in the normal range (although carrying environmental and/or genetic vulnerability risk factors) to individuals with mild to severe impairment. The purpose of our study was, therefore, to account for this inter-individual variability by exploring the spectrum of RRBI assessed in a large population of individuals with autism, their unaffected first-degree relatives, and controls from the general population. Interestingly, our results underlined the potential implication of the putamen in the RRBI: an increase in the volume of the putamen was associated with 'low-order' symptoms (mainly stereotyped behaviors) and on the opposite, a decrease in the putamen volume with cognitively driven symptoms - (mainly obsessive-compulsive symptoms).

Dimensionality of the RRBI symptoms

The factor analysis revealed the multidimensionality of RRBI by identifying three dimensions: FA1 gathered the RBS-R-related items typically observed in autism (Jiujias, Kelley & Hall, 2017, Chaxiong, Dimian & Wolff, 2022); FA2 put together the items related to rigidity/insistence on sameness from the Y-BOCS, symptoms which were trait features of the individuals with autism but also those with obsessive-compulsive symptoms (Uljarevic et al., 2017; Zandt, Prior & Kyrios, 2007); and FA3 that included only Y-BOCS related items usually displayed by individuals with OCD (Delorme et al., 2006). Interestingly, FA2 put together the symmetry and ordering of obsessions/compulsions and the need to repeat things. These symptoms were described in the literature as settled clinical characteristics of autistic children with comorbid OCD (Ruzzano et al., 2015). Symmetry & ordering symptoms are frequently reported in the developmental subtype of OCD, which - beyond its juvenile onset - is characterized by an increased proportion of neurodevelopmental comorbidities, including Tourette's syndrome, ADHD, and autism, but also by significant impairment in executive functions (Darrow et al., 2017; Grassi et al., 2021; Bragdon et al., 2018). A few studies have highlighted the link between the intensity of symmetry/ordering symptoms and poor verbal working memory, visuospatial planning, inhibitory control, and cognitive flexibility abilities (Bragdon et al., 2018). Thus, among the characteristics shared by children with autism and OCD, executive dysfunction may play a critical role in these disorders (Boyd et al., 2009; Iversen & Lewis, 2021). Interestingly, unaffected first-degree parents of children with OCD or autism also showed executive impairments (Delorme et al., 2007; Seng et al., 2021; McLean et al., 2014). Overall, FA2 dimension we identified may be a testimony of the cumulative impact of executive impairment and the presence of RRBI. Finally, the FA3 dimension was driven by OCD-related symptoms since gathering the washing, checking, contamination, and aggressive symptoms (Ruzzano et al. 2015; Lamothe et al., 2022). This dimension was probably less related to autism but more a proxy of obsessive-compulsive symptoms (Lewin et al., 2011; McDougle et al., 1995).

Correlation between structural brain volumes and RRBI-related dimensions

Our results were in line with publications stressing the critical role of the cortico-thalamic-striatal-cortical loop in RRBI. Our study revealed a central implication of the putamen across the 3 distinct dimensions we reported, as well as specific roles of subcortical and cortical structures per FA, which may shape the

diversity of symptoms, agglomerated on the dimensions. The positive association of the putamen and the left amygdala with FA1 was consistent with the role of the putamen in autonomic movements, described in complex motor stereotypies (Mahone et al., 2016) and in autism (Langhen et al., 2014, van Rooij et al., 2018, Mc Kinnon et al., 2019, Ferhat et al., 2023). Including the putamen, the basal ganglia play important roles in regulating repetitive behaviors (notably in autism) in association with the hippocampus, the hypothalamus, but also other neuroanatomical structures of the limbic system (including the amygdala) (Gandhi et al., 2021). Obviously, amygdala volume abnormalities were more usually related to anxiety, and more specifically to social anxiety in autism (Bellani et al., 2013, Gandhi et al., 2021, Jayakar et al., 2020).

In contrast to the positive association of the putamen volume with FA1, we observed a negative relationship with FA2 and FA3. Interestingly, our results replicated those of the ENIGMA-OCD consortium, which also reported a reduced putamen volume in OCD (Tang et al., 2016, Szeko et al., 2008). This reduced putamen volume may relate more to the compulsive component than the obsessive one in OCD (Bowen et al., 2021). FA2 was associated in addition to the decreased volume of the parietal cortex. Similar parietal abnormalities in cortical thickness, volume or surface area, may reflect the cortical dysmaturation in this area, frequently reported in children with OCD and autism (Boedhoe et al., 2018, Rus et al., 2017, Rooij et al., 2018). Interestingly, the parietal cortex is involved in social interactions, motor learning and repetitive behaviors in autism (Travers et al., 2014) but also participates in cognitive in/flexibility, which is coherent with the sameness nature of RRBI-related symptoms encompassed by FA2 (Gruner et al. 2017).

Limitations

The lack of power of the brain imaging part of our study did not allow us to explore the brain asymmetry structures associated with the dimensions we reported. We, however, observed a trend for a leftward asymmetry (based on p-value and coefficients $L > R$). A similar leftward brain asymmetry involving the putamen was previously reported in autism and OCD (Posterna et al., 2019; Rus et al., 2017, Kong et al., 2020; Boedhoe et al., 2017; Van den Heuvel et al., 2022). The role and impact of this brain asymmetry on the symptomatology of ASD and OCD remained unclear but may result from aberrant brain development trajectories.

When exploring the dimensions gathering the RRBI phenotypic variability, we did not include the effect of potential covariates, such as the whole pattern of comorbidities or the effect of executive dysfunctions, as mentioned above. For example, planning strategy impairments consistently reported in probands, and their first-degree relatives may specifically participate in FA2 (Bora, 2020).

Finally, one additional limitation may result from the wide range of ages of individuals enrolled in our study. This might have biased the volume estimates of the small brain structures, specifically subcortical structures such as the putamen or the amygdala, since it relied on a limited number of voxels (Herten et al., 2019; Lidauer et al., 2022; Schoemaker et al., 2016; Mulder et al., 2014). This effect may result from the opposite coefficient direction of the regression analysis we reported between FA1 and the neuroanatomical structures (positive regression), and between FA2 or FA3 (negative regression) and these. FA1 more reflected the autistic-related symptoms and thus was mainly based on symptoms displayed by probands with autism, younger than relatives and controls enrolled in our study

Conclusion

Our results stressed the pivotal role of the putamen in the determinism of RRBI. Variations in the putamen volume, in association with variations in cortical structures, influence the phenomenology of repetitive behaviors in individuals with autism, their relatives, and individuals from the control population. Exploration of the integrative role of the putamen needs to be strengthened in this specific context.

Abbreviations

ADI-R: Autism Diagnosis Interview-Revised

ADHD: Attention Deficit Hyperactivity Disorder

ADOS-2: Autism Diagnostic Observation Scale - second edition

ADOS-2 CSS: Autism diagnostic observation schedule -second edition - calibrated severity score.

ASD: Autism Spectrum Disorder

DSM: Diagnostic and statistical manual of mental disorders

K-SADS-PL: Kiddie-Schedule for Affective Disorders and Schizophrenia for School - Age Children, Present and Lifetime version

FA: Factor Analysis

IQ: Intellectual quotient

OCD: Obsessive-Compulsive Disorder

MRI: Magnetic Resonance Imaging

PARIS: Paris Autism Research International Sibpair

RRBI: Repetitive and Restricted Behaviors and Interests

RPM: Raven's Progressive Matrices

TD: Typically developing

Declarations

ACKNOWLEDGMENTS

We gratefully acknowledge all individuals who participated in the study and the Clinical Investigation Center of the Robert Debre Hospital (Paris, France).

FUNDING

This study was part of a large genetic study sponsored by INSERM, and funded by the Institut Pasteur, INSERM, Fondation FondaMental, APHP, Fondation de France, Fondation à la Recherche Médicale, Roche Institute for Research and Translational Medicine, and Investissements d'Avenir program (ANR-11-IDEX-0004-02, ANR-10-COHO-10-01, ANR-12-SAMA-0014).

AUTHOR CONTRIBUTIONS

Contributions

AL, NT, AM, AB, DG, AA, ML, DU, CC, LM, MB, MA, ML, TB, RT, GD, CM, RD designed the study. AL, AP, AM, AB, ME, DG, AA, MA, RD collected the data. AL conducted the analyses. AL, NT, RT, CM and RD made substantial contributions to the interpretation of the data. AL, CM, and RD wrote the first and final draft of the manuscript. All author(s) read and approved the final manuscript.

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ETHICS DECLARATIONS

Ethics approval and consent to participate

All participants (where appropriate) and their parent/legal guardian provided written informed consent. The Paris Autism Research International Sibpair (PARIS) study sample was granted approval by the local Ethics Committee or "Comité de Protection des Personnes" on 2008 November 14th, authorised by the French authorities (ANSM B80738-70 on 2008, August 11th), and registered in a public trial registry (NCT02628808).

Consent for publication

Consent for publication was obtained from all participants prior to the study.

Competing interests

The authors have no competing interests to declare.

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Tables

Table 1. Clinical and demographic characteristics of the individuals enrolled in the study.

	ASD (N=267)	Relatives (N=370)	Controls (N=155)	R ²	F	p-value
Age	17.7 (12.9)	38.0 (17.2)	38.0 (14.9)	0.3	139.4	<0.001
Sex - Male ratio (% , n)	86%, 230	57%, 174	55%, 86	113.4*	-	<0.001
Full IQ	95.9 (24.4)	95.9 (1.4)	108.1 (1.9)	0.2	44.1	<0.001
NVIQ	95.6 (23.2)	113.3 (14.7)	100.2 (19.8)	0.1	32.0	<0.001
SRS T-score	72.2 (12.6)	46.0 (8.5)	44.4 (7.8)	0.6	556.6	<0.001
ADI - A	16.4 (9.5)	-	-	-	-	-
ADI - B	11.5 (7.8)	-	-	-	-	-
ADI - C	4.9 (3.5)	-	-	-	-	-
ADI - D	2.6 (1.7)	-	-	-	-	-
ADOS-CSS	4.6 (2.1)	-	-	-	-	-
ASD: autistic individuals; NVIQ: Non-verbal IQ; ADI-A: ADI-Social interaction domain score; ADI-B: ADI-Communication domain score; ADI-C: Stereotypes & restricted interests domain score; ADI-D: ADI-before 36 months symptoms score; ADOS-CSS: ADOS-Calibrated severity score; *Chi-squared value.						

Table 2. Linear regressions between the factors and each cortical, subcortical, cerebellar and callous structures.

Facteur 1						Facteur 2					Facteur 3				
	F	R²	Coef	p	FDR	F	R²	Coef	p	FDR	F	R²	Coef	p	F
Cortical structures															
Left frontal	0.09	0.001	0.12	0.75	0.91	0.003	0.0001	0.03	0.99	0.99	0.04	0.0001	-0.10	0.85	0.99
Right frontal	0.23	0.002	0.17	0.63	0.90	0.05	0.0001	-0.12	0.82	0.99	0.17	0.001	-0.21	0.68	0.99
Left occipital	0.52	0.004	0.16	0.47	0.90	0.0003	0.0001	-0.01	0.99	0.99	0.49	0.003	-0.23	0.49	0.99
Right occipital	0.94	0.007	0.22	0.33	0.90	0.51	0.004	0.26	0.48	0.87	0.03	0.0001	-0.05	0.87	0.99
Left parietal	0.29	0.002	0.16	0.59	0.90	0.16	0.001	-0.18	0.001	0.10	0.95	0.007	-0.43	0.33	0.99
Right parietal	1.37	0.01	0.34	0.24	0.90	0.98	0.007	-0.45	0.32	0.86	2.66	0.02	-0.69	0.11	0.99
Left temporal	1.02	0.007	0.28	0.31	0.90	0.08	0.001	0.12	0.78	0.99	0.01	0.0001	-0.04	0.93	0.99
Right temporal	0.64	0.005	0.21	0.42	0.90	0.06	0.0001	-0.09	0.83	0.99	0.09	0.001	-0.12	0.76	0.99
Subcortical structures															
Left accumbens	0.25	0.002	-0.09	0.62	0.90	0.54	0.004	0.21	0.46	0.87	0.23	0.002	0.13	0.64	0.99
Right accumbens	0.32	0.002	0.11	0.57	0.90	0.58	0.004	-0.22	0.45	0.87	0.63	0.005	-0.22	0.43	0.99
Left amygdala	4.18	0.030	0.41	0.04	0.41	1.89	0.01	-0.44	0.17	0.75	0.80	0.006	-0.27	0.37	0.99
Right amygdala	0.10	0.001	-0.06	0.76	0.91	0.02	0.0001	-0.04	0.89	0.75	0.002	0.0001	-0.01	0.97	0.99
Left caudate	0.38	0.003	0.13	0.54	0.90	3.39	0.02	-0.61	0.07	0.66	2.94	0.02	-0.53	0.89	0.99
Right caudate	0.64	0.43	0.16	0.43	0.90	2.25	0.02	-0.48	0.14	0.75	2.65	0.02	-0.48	0.11	0.99
Left hippocampus	0.02	0.0001	-0.03	0.89	0.92	0.08	0.001	0.09	0.78	0.98	0.51	0.004	0.23	0.47	0.99
Right hippocampus	0.35	0.002	0.12	0.55	0.90	1.48	0.01	-0.39	0.23	0.78	0.07	0.001	-0.08	0.79	0.99
Left pallidum	0.21	0.002	0.13	0.64	0.90	1.04	0.008	-0.43	0.31	0.86	0.25	0.002	-0.19	0.62	0.99
Right pallidum	0.17	0.001	-0.10	0.68	0.90	0.003	0.0001	-0.02	0.96	0.99	0.004	0.0001	0.02	0.95	0.99
Left putamen	8.84	0.06	0.75	0.003	0.10	8.06	0.06	-1.12	0.005	0.15	6.20	0.04	-0.92	0.01	0.99
Right putamen	5.48	0.04	0.58	0.02	0.30	5.31	0.04	-0.89	0.02	0.33	4.60	0.32	-0.78	0.03	0.99
Left thalamus	0.04	0.0001	0.05	0.84	0.92	0.08	0.001	-0.11	0.78	0.99	0.005	0.0001	-0.03	0.94	0.99
Right thalamus	0.20	0.001	0.11	0.65	0.90	0.58	0.004	-0.29	0.45	0.86	0.12	0.001	-0.12	0.73	0.99
Cerebellum															
Left Cerebellum	0.01	0.01	0.27	0.19	0.90	1.38	0.01	-0.37	0.24	0.78	1.03	0.007	-0.29	0.31	0.99
Right Cerebellum	1.33	0.01	0.24	0.25	0.90	0.83	0.006	-0.30	0.36	0.87	0.66	0.005	-0.24	0.42	0.99
Corpus Callosum															
Anterior corpus callosum	1.57	0.001	-0.004	0.19	0.98	0.01	0.0001	0.02	0.93	0.99	0.13	0.001	-0.09	0.72	0.99
Mid anterior corpus callosum	0.02	0.001	-0.02	0.89	0.92	0.04	0.0001	0.05	0.84	0.99	0.09	0.001	-0.07	0.77	0.99
Central corpus	0.33	0.001	0.56	0.56	0.90	0.30	0.002	0.14	0.59	0.99	0.12	0.001	0.08	0.73	0.99

callosum															
Midposterior corpus callosum	0.57	0.004	0.14	0.45	0.90	2.39	0.02	-0.43	0.13	0.75	2.98	0.02	-0.44	0.08	C
Posterior corpus callosum	0.02	0.001	0.03	0.89	0.92	1.81	0.01	-0.46	0.18	0.75	2.89	0.02	-0.54	0.09	C

F-value, R-squared, linear regression-derived coefficients (Coef), standard errors (SE) and p-value from the linear regressions were reported; FDR: False Discovery Rate was calculated to correct for multiple testing. In bold, non-corrected p-value<0.05.

Figures

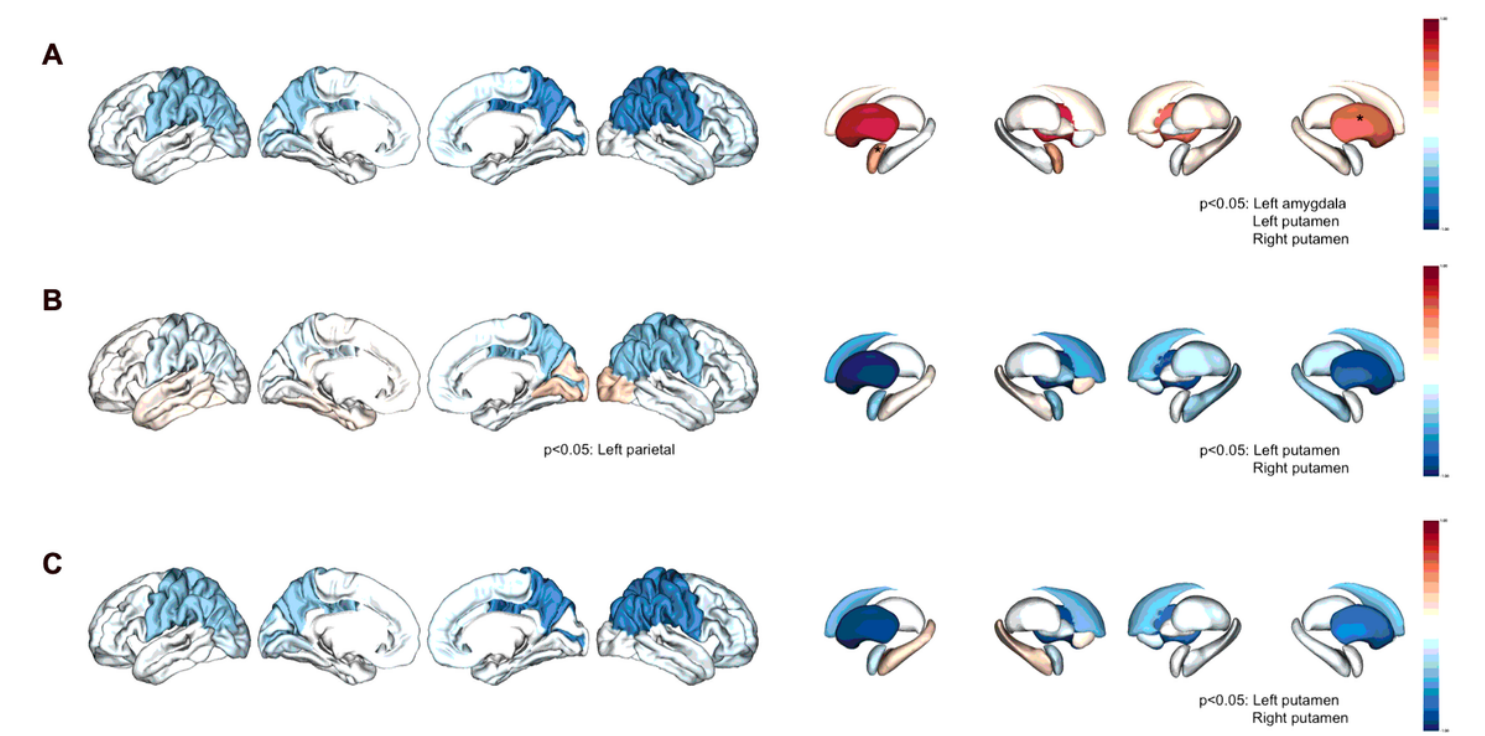


Figure 1

Brain map of linear regression-derived coefficients regarding the relationship between repetitive and restricted behaviors and interests-related factors and neuroanatomic structures.

A- Representation of the linear regression-derived coefficient obtained for each cortical volume (at left) and subcortical volume (at right) considering Factor 1. Extreme values of the linear regression-derived coefficients are represented in blue (<-1)) and in red (>+1). P-values <0.05 before FDR correction were obtained for the left amygdala, left putamen and right putamen volumes; **B-** Representation of the linear regression-derived coefficient obtained for each cortical volume (at left) and subcortical volume (at right) considering Factor 2. Extreme values of the linear regression-derived coefficients are represented in blue (<-1)) and in red (>+1). P-values <0.05 before FDR correction were obtained for the left parietal, left putamen and right putamen volumes; **C-** Representation of the linear regression-derived coefficient obtained for each cortical volume (at left) and each subcortical volume (at right) considering Factor 3. Extreme values of the linear regression-derived coefficients are represented in blue (<-1)) and in red (>+1). P-values <0.05 before FDR correction were obtained for the left amygdala, left putamen and right putamen volumes.

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