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Multivariate patterns of gray matter volume in thalamic nuclei are associated with positive schizotypy in healthy individuals

Pasquale Di Carlo[1,2], Giulio Pergola[1,2], Linda A. Antonucci[1,3], Aurora Bonvino[1,4], Marina Mancini[1], Tiziana Quarto[1], Antonio Rampino[1,5], Teresa Popolizio[4], Alessandro Bertolino[1,5] and Giuseppe Blasi[1,5]

[1]Group of Psychiatric Neuroscience, Department of Basic Medical Science, Neuroscience, and Sense Organs – University of Bari Aldo Moro, Bari, Italy; [2]Lieber Institute for Brain Development, Johns Hopkins Medical Campus – Baltimore, MD, USA; [3]Department of Psychiatry and Psychotherapy – Ludwig-Maximilians University, Munich, Germany; [4]IRCCS 'Casa Sollievo della Sofferenza', San Giovanni Rotondo, Italy and [5]Azienda Ospedaliero-Universitaria Consorziale Policlinico, Bari, Italy

Original Article

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Author for correspondence:
Giuseppe Blasi,
E-mail: giuseppe.blasi@uniba.it

Abstract

Background. Previous models suggest biological and behavioral continua among healthy individuals (HC), at-risk condition, and full-blown schizophrenia (SCZ). Part of these continua may be captured by schizotypy, which shares subclinical traits and biological phenotypes with SCZ, including thalamic structural abnormalities. In this regard, previous findings have suggested that multivariate volumetric patterns of individual thalamic nuclei discriminate HC from SCZ. These results were obtained using machine learning, which allows case–control classification at the single-subject level. However, machine learning accuracy is usually unsatisfactory possibly due to phenotype heterogeneity. Indeed, a source of misclassification may be related to thalamic structural characteristics of those HC with high schizotypy, which may resemble structural abnormalities of SCZ. We hypothesized that thalamic structural heterogeneity is related to schizotypy, such that high schizotypal burden would implicate misclassification of those HC whose thalamic patterns resemble SCZ abnormalities.

Methods. Following a previous report, we used Random Forests to predict diagnosis in a case–control sample (SCZ = 131, HC = 255) based on thalamic nuclei gray matter volumes estimates. Then, we investigated whether the likelihood to be classified as SCZ (π-SCZ) was associated with schizotypy in 174 HC, evaluated with the Schizotypal Personality Questionnaire.

Results. Prediction accuracy was 72.5%. Misclassified HC had higher positive schizotypy scores, which were correlated with π-SCZ. Results were specific to thalamic rather than whole-brain structural features.

Conclusions. These findings strengthen the relevance of thalamic structural abnormalities to SCZ and suggest that multivariate thalamic patterns are correlates of the continuum between schizotypy in HC and the full-blown disease.

Introduction

Previous models posit a biological and behavioral continuum between conditions at greater risk for schizophrenia (SCZ) and the full-blown disorder (Barrantes-Vidal *et al.*, 2015; Guloksuz and van Os, 2017). In this context, schizotypy refers to a set of temporally stable traits, continually distributed in the general population, that resemble, in attenuated forms, some of the symptoms of SCZ (Meehl, 1989; Tien, 1991; Johns and van Os, 2001; van Os *et al.*, 2009; Ettinger *et al.*, 2014). Previous studies revealed that schizotypal traits are more frequent in first-degree relatives of patients with SCZ when compared with the general population (Vollema and Postma, 2002; Vollema *et al.*, 2002), suggesting a link between schizotypy and familial risk for this brain disorder (Ericson *et al.*, 2011; Walter *et al.*, 2016). Other evidence suggests that schizotypy and SCZ share behavioral and biological correlates (Abi-Dargham *et al.*, 2004; Fanous *et al.*, 2007; Taurisano *et al.*, 2014). In fact, both patients with SCZ and healthy individuals with high schizotypy scores have deficits in sustained attention (Gooding *et al.*, 2006) and working memory (Kerns and Becker, 2008), as well as brain structural abnormalities when compared with healthy controls (HC) (Kuhn *et al.*, 2012). On this basis, schizotypy is widely recognized as a valuable construct for the investigation of biological correlates relevant to SCZ without the confounds and limitations related to disease state, such as pharmacological treatment, chronicity, and clinical symptoms (Barrantes-Vidal *et al.*, 2015).

Pathophysiological models point out the thalamus as a pivotal node in the pathophysiology of SCZ (Andreasen *et al.*, 1994; Peters *et al.*, 2016; Sherman, 2016). Consistently, several findings suggest that thalamic structural abnormality is a biological phenotype associated with both

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SCZ and schizotypy (Ettinger *et al.*, 2014; Pergola *et al.*, 2015). In particular, previous results indicate decreased thalamic volume in both conditions compared to HC (Byne *et al.*, 2001; Kuhn *et al.*, 2012; van Erp *et al.*, 2016). However, the thalamus encompasses numerous nuclei anatomically segregated and belonging to independent brain circuits (Jones, 2007). Accordingly, *post-mortem* studies show a decreased volume in specific nuclei in SCZ compared to HC (Byne *et al.*, 2002, 2009). In particular, findings appear consistent for the pulvinar, whereas evidence is mixed for the other thalamic nuclei (Pergola *et al.*, 2015; Dorph-Petersen and Lewis, 2017). Consistently with the *post-mortem* results, *in vivo* brain imaging findings suggest that specific thalamic nuclei contribute to thalamic volume shrinkage in SCZ (Cobia *et al.*, 2017; Pergola *et al.*, 2017). In fact, previous *in vivo* results in this brain disorder suggest a volume decrease in the pulvinar, as well as in anterior and mediodorsal nuclei (Pergola *et al.*, 2015, 2017). Overall, *post-mortem* and *in vivo* brain imaging results highlight the relevance of nuclei-specific thalamic structural abnormalities in SCZ. Factors possibly confounding the findings include the complex architecture of thalamic nuclei and the heterogeneity of this biological phenotype. For example, HC included in between-groups comparisons might be characterized by biological and sub-clinical features progressively closer to those of SCZ. This heterogeneity may have hindered the characterization of phenotypic expression of thalamic structural abnormalities between HC and SCZ. Indeed, schizotypy in the healthy population may be relevant in this context.

An approach to investigate complex biological phenotypes is machine learning. This method allows classification and inference at the individual level (Zarogianni *et al.*, 2013; Kambeitz *et al.*, 2015). Additionally, it is a valuable tool to predict the likelihood of the allocation of each and every individual in a diagnostic group based on given characteristics. Thus, it may contribute to the understanding of individual heterogeneity based on imaging features (Rozycki *et al.*, 2017). Machine learning has been already used to investigate the relationship between SCZ and imaging phenotypes (Nieuwenhuis *et al.*, 2012; Salvador *et al.*, 2017), including those considering thalamic nuclei (Anticevic *et al.*, 2014). In this regard, our previous study (Pergola *et al.*, 2017) found that the multivariate volumetric patterns of thalamic nuclei discriminated HC from both SCZ and non-affected siblings, suggesting that the structural configuration of thalamic nuclei is a valid intermediate phenotype for SCZ.

Indeed, the results of this study and several others based on neuroimaging data indicated that about 25% of the subjects were misclassified by machine learning algorithms (Nieuwenhuis *et al.*, 2012; Rozycki *et al.*, 2017; Salvador *et al.*, 2017; Schwarz *et al.*, 2019). It is possible that the thalamic structure of those HC matching some of the criteria to identify schizotypy may have contributed to the misclassification. In other words, it is possible that the higher the level of schizotypy in HC, the closer the multivariate thalamic volumetric pattern of HC to that of SCZ, the greater the likelihood of misclassification of HC as SCZ.

The aim of this study was to investigate whether schizotypy is related to the variability in multivariate volumetric patterns of thalamic nuclei, such that it contributes to the misclassification of HC as SCZ. With this aim, first we parceled out the thalamus in different nuclei subdivisions (Pergola *et al.*, 2017). Then, we trained a machine learning algorithm that discriminated HC from SCZ based on multivariate volumetric patterns of thalamic nuclei. Thus, we tested whether schizotypy contributes to misclassification of HC as SCZ. Furthermore, we explored whether the discrimination between these groups of individuals was specific for thalamic features. With this purpose, we used a neuroanatomical brain atlas encompassing the whole brain and verified whether schizotypy contributes to the misclassification of this algorithm. We hypothesized that HC with relatively high schizotypy scores may present thalamic patterns prone to misclassification as SCZ.

Methods

Participants

Demographics are reported in Table 1. We recruited 386 Caucasian individuals: 131 SCZ (DSM-IV-TR) selected among consecutive outpatients at the University Hospital of Bari, and 255 HC. The sample partially overlaps with that used in a previous work (Pergola *et al.*, 2017) [84/131 SCZ – ≈64%; 88/255 HC – ≈35%, online Supplementary Material (SM) section 1.1]. Exclusion criteria for all individuals were history of drug or alcohol abuse in the past year, non-psychiatric clinically relevant conditions, history of neurological diseases and head trauma with loss of consciousness. Absence of psychiatric illness in HC was established using the Structured Clinical Interview for DSM-IV (SCID). Family history of psychiatric disorders was an exclusion criterion for HC. At the time of scan acquisition, all patients were on stable treatment with first and/or second-generation antipsychotics since at least four weeks. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, revised in 2008. All participants gave their informed consent. All procedures were approved by the ethics committee at Bari University Hospital.

Demographics, neuropsychological, and clinical assessment

Participants were evaluated for handedness with the Edinburgh Handedness Inventory (Oldfield, 1971) and for socio-economic status (SES) (Hollingshead, 1975). The SES considers the occupational status and the educational level of both parents. The Schizotypal Personality Questionnaire (SPQ) (Raine, 1991) was administered to HC. The SPQ is a 74-item validated self-report questionnaire with a 'yes/no' response format for the assessment of Schizotypal Personality. We used a three-factor model including positive, negative, and disorganized factors (Vollema and Hoijtink, 2000). Non-complete questionnaires were excluded. One hundred and seventy-four HC with complete SPQ evaluation were used for the association analyses between SPQ scores and machine learning outcomes. Demographics and SPQ scores of this sample are reported in Table 1 and eTable 1. To investigate homogeneity between levels of schizotypy in our cohort with those of larger populations, SPQ scores in our sample were compared with those of a previous study including healthy individuals (Fonseca-Pedrero *et al.*, 2018). SM 1.2 and eTable 1 report statistics on this comparison.

Imaging data acquisition and preprocessing

Structural magnetic resonance imaging data were acquired with a General Electric (Milwaukee, WI, USA) 3 Tesla whole-body scanner using a standard quadrature head coil. We used a whole-brain T1 inversion recovery fast spoiled gradient recalled sequence with the following parameters: TR = 26 ms/TE = 3 ms/NEX = 1; flip angle 6°; bandwidth 31.25; field of view 250 mm; matrix size 256 × 256; 124 contiguous 1.3 mm thickness axial slices; voxel

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Table 1. Demographics of the sample used in this study

		HC	SCZ	HC *v.* SCZ	*p* value	HC_{SPQ}
Gender	M/F	118/137	93/38	$\chi^2 = 20.4$	<0.001	75/99
Age in years	Mean (s.d.) range	26.5 (6.7) 18–63	32.9 (9.0) 16–58	$\|t\| = 7.2$	<0.001	25.6 (6.7) 18–63
SES		40.8 (16.1)	29.3 (15.4)	$\|t\| = 6.8$	<0.001	42.0 (15.6)
Handedness		0.69 (0.5)	0.73 (0.4)	$\|t\| = 0.8$	0.4	0.68 (0.5)
SPQ		–	–	–	–	10.6 (8.0)
SPQ Positive		–	–	–	–	4.6 (4.5)
SPQ Negative		–	–	–	–	6.7 (5.4)
SPQ Disorganized		–	–	–	–	3.3 (3.5)

HC, healthy controls; SCZ, patients with schizophrenia; M, male; F, female; s.d., standard deviation; SES, socio-economic status; SPQ, Schizotypal Personality Questionnaire.

size = 0.9 × 0.9 × 1.3 mm; acquisition time 6′08″. Images included in the study were free of neurological abnormalities (assessed by TP, a board-certified neuro-radiologist), acquisition, and segmentation artifacts (SM 1.3). Data were pre-processed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Gray matter and white matter images were normalized using DARTEL and re-sampled to 1.1 mm^3 isotropic voxels, in order to soften potential issues related to non-isotropic acquisition of images (Mechelli *et al.*, 2005).

Brain features extraction for machine learning multivariate analyses

We performed two different regions of interest (ROIs) analyses using two sets of brain features. The first set encompassed the thalamus, taking into account its subdivision in different nuclei. The second set encompassed the entire brain and was used as a negative control to suggest specificity of the results for multivariate volumetric patterns of thalamic nuclei. These two sets of brain features were obtained as follows:

(1) **Thalamic Subdivisions (ThSub).** We used an already published procedure (Pergola *et al.*, 2017) based on the 'Thalamus atlas' (Krauth *et al.*, 2010; Jakab *et al.*, 2012) to obtain gray matter volume estimates (GMV) of the whole thalamus and seven thalamic nuclei bilaterally (anterior/midline nuclei; mediodorsal thalamic nucleus; intralaminar nuclei; ventrolateral nucleus; ventral anterior region; geniculate nuclei; pulvinar; see SM 1.4).
(2) **Automated Anatomic Labeling (AAL).** We used GMV estimates of 106 ROIs available in the Automated Anatomical Labeling atlas (Tzourio-Mazoyer *et al.*, 2002). We excluded thalamic ROIs to have a spatially independent control set.

GMV estimates of each ROI were marginalized for gender, linear as well as quadratic terms of age, and total brain GMV estimate. Linear model residuals of each ROI were used as features in the following multivariate classification analyses.

Machine learning multivariate classification

We separately used each set of brain features to classify participants – HC *v.* SCZ – taking advantage of a machine learning approach. We used Random Forests (Breiman, 2001) to train two independent classifiers based on the ThSub and AAL brain features. We used the *caret* R package v.6.0–77 (Kuhn, 2008) to implement a nested-designed supervised model (SM 1.5). All the analyses were performed with R 3.4.1. We used a nested-designed framework to separate train and test sets, to cross-validate the train set, and to estimate accuracy in the test set. Critically, the test set is independent of the train set since subjects have not been used to build the classifier rules (Bzdok and Meyer-Lindenberg, 2018). To further control sampling bias, we computed model performance as the average test set accuracy and its standard deviation over re-samplings of the train set (permutations = 1000). Furthermore, we also computed sensitivity, specificity, positive, and negative predictive values. Moreover, we computed feature importance in discriminating HC *v.* SCZ (SM 1.5). To assess the statistical significance of the classification performance of both classifiers, we permuted diagnostic labels of each classifier to generate the correspondent random null distribution of classification accuracy (permutations = 1000). We defined the empirical *p* value as the number of times the accuracies in the null distribution are greater than the average accuracy of the true classifier, divided by the number of permutations. Moreover, to quantify the magnitude of the difference between the true accuracy distribution and its null distribution, we computed the Cohen's *d* confidence interval 95% (CI_{95}).

To obtain an index of the likelihood of a subject to be classified as SCZ, we defined the global classification score (π-SCZ) for each subject as the average of Random Forests classification scores (SM 1.5). Note that classification scores were computed in the test set at each re-sampling, thus providing an unbiased prediction estimate. π-SCZ ranges between 0 and 1 and is an index of the likelihood to be classified as SCZ (0 = highest likelihood to be classified as HC; 1 = highest likelihood to be classified as SCZ). When $\pi\text{-SCZ} \geqslant 0.5$, the subject was classified as SCZ, otherwise was classified as HC.

Importantly, the homogeneity of the feature set is a necessary assumption to consider π-SCZ dependent on the phenotype under investigation. On this basis, in the present study, we did not consider premorbid intelligence as a feature of interest in our primary analysis, as we did in a previous investigation (Pergola *et al.*, 2017). We adopted this approach because it would have generated a different set of classification rules accounting for premorbid intelligence–thalamic interactions. Thus, π-SCZ would have been dependent on a multivariate space not specifically related to thalamic patterns only. However, we included premorbid intelligence in a supplementary analysis to control for its effect on classification (SM 1.6).

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Following analyses were based on the association between HC misclassification and schizotypy. In particular, we aimed to investigate whether differences in the performance of ThSub- *v.* AAL-based algorithms might have driven the association between HC misclassification and schizotypy. With this purpose, we checked whether the two algorithms outperformed each other in terms of specificity (χ^2-test), considering both the whole sample and those with complete SPQ evaluation. Then, we explored the overlap between predictions of the two classifiers that we quantified as the percentage of subjects attributed to the same class. In this way, despite of almost equivalent classification performances, different algorithms may correctly classify divergent groups of subjects, which may have specific phenotypic attributes. Furthermore, we investigated the algorithm performance stability running additional analyses including only HC with SPQ and adopting a dimensionality reduction technique for the AAL dataset (SM 1.6). Finally, we sought to replicate previous findings (Pergola *et al.*, 2017) including univariate *t* tests between individual thalamic nuclei GMV and diagnosis (SM 1.7).

Relevance of schizotypy to misclassification and classification scores

We investigated how schizotypy affected the HC *v.* SCZ classification outcome based on the multivariate structural patterns of thalamic nuclei. With this aim, we assessed the association of levels of schizotypy with the likelihood to be classified as SCZ (π-SCZ). As we specified above, π-SCZ closer to 1 indicated greater probability for an SCZ-like pattern, while π-SCZ close to 0 indicated greater probability for an HC-like pattern. Thus, we considered true negatives (TN, i.e. HC classified as such) the HC with a π-SCZ < 0.5, and false positives (FP, i.e. HC erroneously classified as SCZ) the HC with a π-SCZ $\geqslant 0.5$. Then, we performed an analysis of covariance (ANCOVA) with FP/TN as the independent variable. SPQ total scores and SPQ factor scores were used as the dependent variables in separate models, with age, gender, handedness, and SES as covariates. Furthermore, we explored the association of π-SCZ with SPQ scores performing multiple regressions with the same covariates.

To test the specificity of the findings for multivariate structural patterns of thalamic nuclei compared to whole-brain features, we repeated all these analyses using the classification outcome based on AAL. Results were Bonferroni corrected considering the four SPQ and the two machine learning analyses ($n = 2 \times 4 = 8$, $\alpha = 0.00625$). Effect sizes are reported as partial-r^2. To further support the relevance of multivariate patterns, we checked whether SPQ scores are individually correlated with thalamic nuclei GMV (SM 1.7).

Relevance of demographics to misclassification and classification scores

We verified whether misclassification and classification scores were associated with demographics to investigate other plausible sources of misattribution (SM 1.8).

Results

Machine learning multivariate classification

Table 2 reports machine learning performance statistics. The ThSub algorithm based on the thalamic features yielded an accuracy of 72.5% (empirical p value < 0.001, Cohen's d CI_{95} 2.34–2.57; Fig. 1*a*). The AAL algorithm based on whole-brain features yielded an accuracy of 67.6% (empirical p value $= 0.018$, Cohen's d CI_{95} 1.44–1.64; Fig. 1*b*). Despite almost equivalent prediction accuracies, the overlap among classifiers prediction at the single-subject level was 61.1%. Bilateral mediodorsal and anterior-midline nuclei showed both high multivariate feature relevance (empirical p value < 0.0001) and association with diagnosis (corrected p value < 0.05; eTable 2). Performance remained stable through sensitivity analyses (eTable 3). Notably, specificity values did not differ ($\chi^2 = 0.3$, p value $= 0.57$).

Misclassification and classification scores are related to positive schizotypy

Decomposing the performance of the ThSub classifier, we found that 42 out of 174 HC were misattributed to SCZ diagnosis (FP, specificity = 75.9%). ANCOVA indicated that FP scored higher for the total SPQ score ($F_{1,169} = 4.4$, p value $= 0.037$) compared to TN. Analysis of the three SPQ subscales indicated greater scores in FP for the positive schizotypy subscale ($F_{1,169} = 9.5$, corrected p value $= 0.019$, partial-$r^2 = 0.053$; Table 3; Fig. 2*a*) but not for the negative (p value $= 0.073$) and disorganized subscales (p value $= 0.46$). Furthermore, there was a positive association between π-SCZ and positive schizotypy ($t_{169} = 2.9$, corrected p value $= 0.038$, partial-$r^2 = 0.046$; Table 3; Fig. 2*b*). This association was not significant for total SPQ, negative, and disorganized factors (p values > 0.1).

All these analyses were not significant when using AAL (specificity = 82.2%) as the classifier of interest. In particular, FP were not associated with higher SPQ scores when compared with TN, nor π-SCZ was associated with SPQ scores (p values > 0.05; Table 3). Again, specificity values did not differ among classifiers ($\chi^2 = 1.7$, p value $= 0.19$), suggesting that the results are not dependent on algorithm performance. Moreover, SPQ scores were not associated with individual thalamic nuclei GMV (p values > 0.1).

Misclassification and classification scores are not associated with demographics

FP and TN did not differ in terms of sex, age, SES, and handedness when using the ThSub classifier (p values > 0.1; Table 3). FP had higher right-hand scores compared to TN when using the AAL classifier (p value $= 0.0013$). π-SCZ was not associated with demographics (p values > 0.05; Table 3).

Discussion

In the present study, we found that multivariate structural patterns of thalamic nuclei allow discrimination between healthy subjects and patients with SCZ. Furthermore, we found that high positive schizotypy confers to HC proneness to misclassification as SCZ based on such thalamic features. Overall, these findings suggest the relevance of multivariate structural thalamic patterns as a biological phenotype of SCZ. Furthermore, they suggest that an increase in the levels of schizotypy in HC implicates greater similarity between their thalamic structural patterns and those of SCZ. This biological configuration may result in misattribution of HC to the clinical population by a machine learning algorithm.

These findings are consistent with the previous reports describing thalamic structural abnormalities in HC with high

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Table 2. Machine learning classification performances

	Accuracy %	Sensitivity %	Specificity % Mean (s.d.)	NPV%	PPV%	Empirical *p* value	Cohen's *d* CI_{95}
ThSub	72.5 (3.6)	59.1 (7.3)	79.4 (4.9)	79.2 (3.6)	59.9 (6.0)	<0.001	2.34–2.57
AAL	67.6 (3.7)	39.7 (8.4)	81.8 (6.1)	72.6 (2.5)	53.6 (7.9)	0.018	1.44–1.64

Table reports statistics of the classification performance (HC *v.* SCZ) obtained by the Thalamic Subdivisions (ThSub) and the Automated Anatomic Labeling (AAL) Random Forests classifiers. CI_{95}, 95% confidence interval; NPV, negative predictive value; PPV, positive predictive value; s.d., standard deviation.

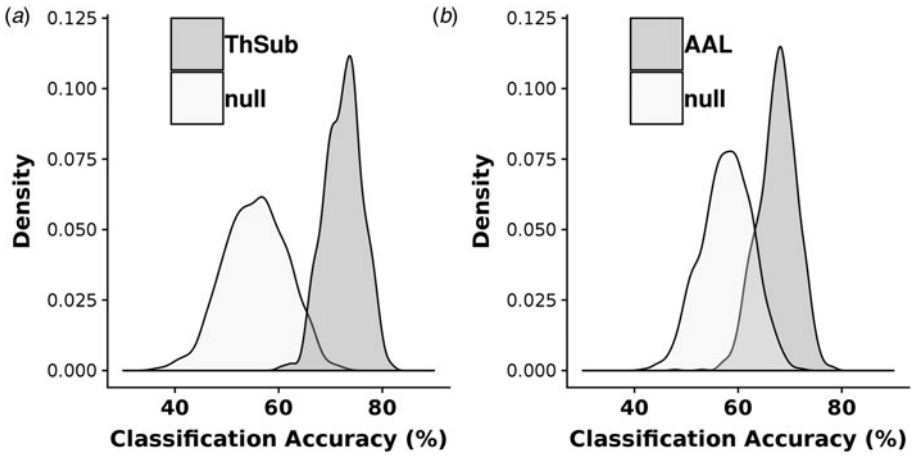

Fig. 1. Density plots of Random Forests classification accuracies. Density curves compare classification accuracy (*x*-axis) distribution over 1000 re-sampling between (*a*) the Thalamic Subdivisions features (ThSub) or (*b*) the Automated Anatomic Labeling whole-brain features (ALL) with the respective null distribution obtained through permutation of diagnostic labels.

schizotypy scores (Byne *et al.*, 2001; Takahashi *et al.*, 2008; Kuhn *et al.*, 2012), first-degree relatives (Byne *et al.*, 2009; Okada *et al.*, 2016; Pergola *et al.*, 2017), and SCZ compared to HC (Glahn *et al.*, 2008; Fornito *et al.*, 2009; van Erp *et al.*, 2016). Furthermore, they are consistent with the evidence of anomalies in thalamo-cortical circuitry in SCZ (Lynall *et al.*, 2010; van den Heuvel *et al.*, 2010; Salomon *et al.*, 2011; Anticevic *et al.*, 2014; Woodward *et al.*, 2016) and in individuals at familial risk for this disorder (Anticevic *et al.*, 2015; Antonucci *et al.*, 2016). Moreover, they are in line with the psychosis dimensional model, which posits a continuous phenotypic variation in the general population with patients laying at the extreme of the phenotypic distribution (Claridge, 1997; Ettinger *et al.*, 2015; Lenzenweger, 2015). Within this framework, they suggest that multivariate thalamic structural patterns are biological correlates of a continuum between schizotypy and SCZ.

Interestingly, we found that the thalamic-based misclassification is specifically related to the cognitive-perceptual (i.e. positive) domain of schizotypy. This relationship is consistent with the models involving thalamic nuclei in salience (Gilbert and Sigman, 2007; Peters *et al.*, 2016) and in the regulation of high-order cognitive functioning (Sherman, 2016). In SCZ, abnormalities of the structure of the thalamus (Andreasen *et al.*, 1994) may implicate abnormal integration of perceptual inputs and sensory gating, which may result in positive symptoms (Pynn and DeSouza, 2013; Vukadinovic, 2014), and in cognitive anomalies related to the disruption of thalamo-cortical reciprocal connections (Gilbert and Sigman, 2007; Bolkan *et al.*, 2017; Schmitt *et al.*, 2017). In this perspective, a possible speculation on our findings is that a thalamic volumetric configuration related to schizotypy may contribute to cognitive-perceptual sub-clinical phenomena lying in a continuum with symptoms of full-blown SCZ. Future brain imaging studies might investigate this topic from a longitudinal perspective (Ferguson and Gao, 2014).

Interestingly, we did not find the association between schizotypy and misclassification based on whole-brain features. Moreover, we found that the individuals correctly discriminated by ThSub only partially overlap with those correctly discriminated by AAL classifier. These results suggest that there is no relationship between multivariate whole-brain features and schizotypy. Indeed, this construct appears more specifically related to the thalamic structural patterns.

The HC/SCZ classification accuracy of the present study was comparable with those found in other reports using neuroimaging brain features only (Nieuwenhuis *et al.*, 2012; Anticevic *et al.*, 2014; Rozycki *et al.*, 2017; Salvador *et al.*, 2017), confirming the potential role of the thalamus as a disease biomarker (Anticevic *et al.*, 2014; Pratt *et al.*, 2018). Differently, other approaches (Nieuwenhuis *et al.*, 2017; Dwyer *et al.*, 2018) model simultaneously neuroanatomical and behavioral data to predict diagnosis or SCZ development in cohorts of individuals at high risk (Zarogianni *et al.*, 2017). However, while the latter approaches point to improve prediction accuracy by adding more layers of information, here we investigated possible sources of misclassification associated with inter-individual phenotypic heterogeneity of thalamic nuclei. Indeed, prediction accuracy of multivariate predictive models remains steadily between 70% and 80% in the psychiatric field (Nieuwenhuis *et al.*, 2017; Rozycki *et al.*, 2017; Salvador *et al.*, 2017; Schwarz *et al.*, 2019). The reasons behind this boundary merit further investigation. In this regard, we excluded that the demographical variables collected in this study were a source of misclassification, confounding machine learning outcome.

A limitation of this study is that it is based on the dimensional model of schizotypy in continuum with SCZ (Ettinger *et al.*,

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Table 3. Association of classifiers outcome with SPQ scores and demographics in healthy controls

Machine learning analyses False positive/true negative Specificity %		ThSub 42/132 75.9		AAL 31/143 82.2	
		Test statistic	*p* value	Test statistic	*p* value
Misclassification ANCOVA (*F*-value)	SPQ	4.4	0.037*	1.1	0.286
	Positive	9.5	**0.0024****	0.1	0.935
	Negative	3.2	0.073	3.2	0.075
	Disorganized	0.5	0.460	0.7	0.397
χ^2-test (χ^2)	Sex	0.3	0.566	1.3	0.252
t-test (*t*-value)	Age	−0.3	0.798	−0.1	0.969
	Hollingshead	−1.2	0.222	−1.2	0.238
	Edinburgh	0.1	0.952	3.3	0.0013
Classification probability Multiple regression (*t*-value)	SPQ	1.6	0.121	1.1	0.296
	Positive	2.9	**0.0048****	0.6	0.866
	Negative	1.1	0.264	1.9	0.060
	Disorganized	0.1	0.908	0.8	0.784
t-test (*t*-value)	Sex ($m > f$)	<0.1	0.997	1.1	0.269
Linear regression (*t*-value)	Age	−0.3	0.753	−1.6	0.105
	Hollingshead	−0.5	0.624	−1.5	0.146
	Edinburgh	−0.7	0.472	1.2	0.203

Table reports test statistics and uncorrected *p* values: *p value < 0.05; **p values surviving multiple comparisons threshold ($\alpha = 0.00625$) in bold font.
ThSub, Thalamic Subdivisions; AAL, Automated Anatomic Labeling; SPQ, Schizotypal Personality Questionnaire.

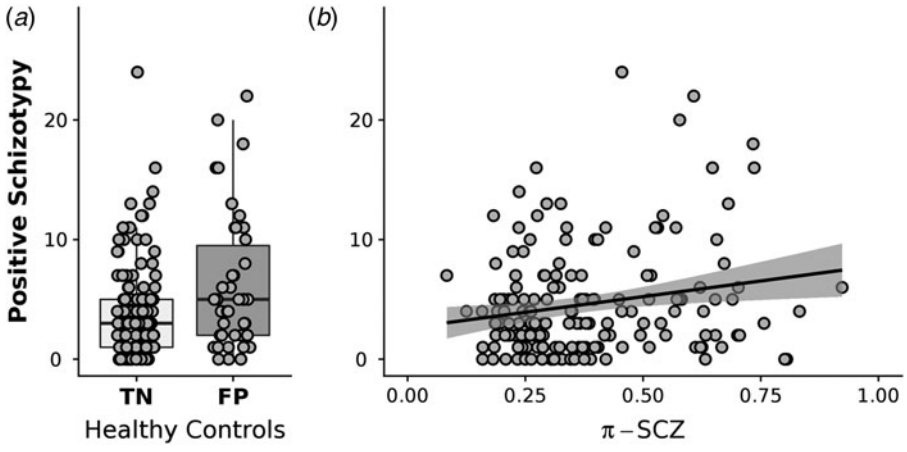

Fig. 2. Relevance of positive schizotypy for healthy controls classification. (*a*) Boxplot showing that false positives (FP, healthy controls misclassified to SCZ diagnosis) have higher positive schizotypy scores than true negatives (TN, healthy controls correctly classified). (*b*) Scatterplot showing the relationship between the likelihood to be classified as SCZ (π-SCZ) based on multivariate volumetric patterns of thalamic nuclei and positive schizotypy scores. Shaded area indicates 95% confidence interval.

2015). However, the alternative categorical model (Meehl, 1989; Lenzenweger, 2015) should be considered for future investigations. Moreover, SPQ scores in our sample are lower when compared with other healthy populations (Fonseca-Pedrero *et al.*, 2018) and show reduced variability (SM 1.2 and eTable 1). This is particularly true for the disorganized factor: thus, the non-significant association may reflect a floor effect. Another limitation is that HC and SCZ were not homogeneous for age, gender, and SES. We considered the effects of age and gender on GMV estimates and did not find any association of SES with classification outcomes. Indeed, a full match of these variables between groups would have dramatically decreased the sample size. A further limitation is that machine learning algorithms could be theoretically confounded by a large number of individual attributes that have not been collected in this study. Future machine learning studies should assess further sources of misclassification and whether risk- or resilience-related structural variations for psychosis may be present in the brain. Finally, intra-diagnostic variability merits further investigation. Here, we did not collect SPQ for SCZ. Although schizotypy construct may be valid also in patients, literature is mixed on this topic (Brosey and Woodward, 2015; Cicero *et al.*, 2019).

In conclusion, the findings of the present study suggest that the multivariate signatures of thalamic nuclei structure relate to positive

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schizotypy in healthy individuals and strengthen the role of the thalamus in cognitive-perceptual disturbances related to SCZ. Future studies are needed to fully investigate the potential of this topic and further disentangle how structural thalamic abnormalities are key for the pathophysiology of this brain disorder.

Author ORCIDs. Pasquale Di Carlo, 0000-0002-5150-5274; Giulio Pergola, 0000-0002-9193-1841; Linda A. Antonucci, 0000-0002-7919-7402; Aurora Bonvino, 0000-0001-8772-5992; Marina Mancini, 0000-0003-4175-8769; Antonio Rampino, 0000-0002-9654-3266; Teresa Popolizio, 0000-0002-9364-9663; Giuseppe Blasi, 0000-0003-0878-1131.

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References

Abi-Dargham A, Kegeles LS, Zea-Ponce Y, Mawlawi O, Martinez D, Mitropoulou V, O'Flynn K, Koenigsberg HW, Van Heertum R, Cooper T, Laruelle M and Siever LJ (2004) Striatal amphetamine-induced dopamine release in patients with schizotypal personality disorder studied with single photon emission computed tomography and [123I]iodobenzamide. *Biological Psychiatry* **55**, 1001–1006.

Andreasen NC, Arndt S, Swayze V, Cizadlo II T, Flaum M, O'Leary D, Ehrhardt JC and Yuh WT (1994) Thalamic abnormalities in schizophrenia visualized through magnetic resonance image averaging. *Science* **266**, 294–298.

Anticevic A, Cole MW, Repovs G, Murray JD, Brumbaugh MS, Winkler AM, Savic A, Krystal JH, Pearlson GD and Glahn DC (2014) Characterizing thalamo-cortical disturbances in schizophrenia and bipolar illness. *Cerebral Cortex* **24**, 3116–3130.

Anticevic A, Haut K, Murray JD, Repovs G, Yang GJ, Diehl C, McEwen SC, Bearden CE, Addington J, Goodyear B, Cadenhead KS, Mirzakhanian H, Cornblatt BA, Olvet D, Mathalon DH, McGlashan TH, Perkins DO, Belger A, Seidman LJ, Tsuang MT, van Erp TG, Walker EF, Hamann S, Woods SW, Qiu M and Cannon TD (2015) Association of thalamic dysconnectivity and conversion to psychosis in youth and young adults at elevated clinical risk. *JAMA Psychiatry* **72**, 882–891.

Antonucci LA, Taurisano P, Fazio L, Gelao B, Romano R, Quarto T, Porcelli A, Mancini M, Di Giorgio A, Caforio G, Pergola G, Popolizio T, Bertolino A and Blasi G (2016) Association of familial risk for schizophrenia with thalamic and medial prefrontal functional connectivity during attentional control. *Schizophrenia Research* **173**, 23–29.

Barrantes-Vidal N, Grant P and Kwapil TR (2015) The role of schizotypy in the study of the etiology of schizophrenia spectrum disorders. *Schizophrenia Bulletin* **41** (Suppl. 2), S408–S416.

Bolkan SS, Stujenske JM, Parnaudeau S, Spellman TJ, Rauffenbart C, Abbas AI, Harris AZ, Gordon JA and Kellendonk C (2017) Thalamic projections sustain prefrontal activity during working memory maintenance. *Nature Neuroscience* **20**, 987–996.

Breiman L (2001) Random forests. *Machine Learning* **45**, 5–32.

Brosey E and Woodward ND (2015) Schizotypy and clinical symptoms, cognitive function, and quality of life in individuals with a psychotic disorder. *Schizophrenia Research* **166**, 92–97.

Byne W, Buchsbaum MS, Kemether E, Hazlett EA, Shinwari A, Mitropoulou V and Siever LJ (2001) Magnetic resonance imaging of the thalamic mediodorsal nucleus and pulvinar in schizophrenia and schizotypal personality disorder. *Archives Of General Psychiatry* **58**, 133–140.

Byne W, Buchsbaum MS, Mattiace LA, Hazlett EA, Kemether E, Elhakem SL, Purohit DP, Haroutunian V and Jones L (2002) Postmortem assessment of thalamic nuclear volumes in subjects with schizophrenia. *American Journal of Psychiatry* **159**, 59–65.

Byne W, Hazlett EA, Buchsbaum MS and Kemether E (2009) The thalamus and schizophrenia: current status of research. *Acta Neuropathologica* **117**, 347–368.

Bzdok D and Meyer-Lindenberg A (2018) Machine learning for precision psychiatry: opportunities and challenges. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* **3**, 223–230.

Cicero DC, Jonas KG, Li K, Perlman G and Kotov R (2019) Common taxonomy of traits and symptoms: linking schizophrenia symptoms, schizotypy, and normal personality. *Schizophrenia Bulletin* (published online ahead of print 9 February).

Claridge G (1997) Theoretical background and issues. In Claridge G (ed.), *Schizotypy: Implications for Illness and Health*. Oxford, UK: Oxford University Press, pp. 3–18.

Cobia DJ, Smith MJ, Salinas I, Ng C, Gado M, Csernansky JG and Wang L (2017) Progressive deterioration of thalamic nuclei relates to cortical network decline in schizophrenia. *Schizophrenia Research* **180**, 21–27.

Dorph-Petersen KA and Lewis DA (2017) Postmortem structural studies of the thalamus in schizophrenia. *Schizophrenia Research* **180**, 28–35.

Dwyer DB, Cabral C, Kambeitz-Ilankovic L, Sanfelici R, Kambeitz J, Calhoun V, Falkai P, Pantelis C, Meisenzahl E and Koutsouleris N (2018) Brain subtyping enhances the neuroanatomical discrimination of schizophrenia. *Schizophrenia Bulletin* **44**, 1060–1069.

Ericson M, Tuvblad C, Raine A, Young-Wolff K and Baker LA (2011) Heritability and longitudinal stability of schizotypal traits during adolescence. *Behaviour Genetics* **41**, 499–511.

Ettinger U, Meyhofer I, Steffens M, Wagner M and Koutsouleris N (2014) Genetics, cognition, and neurobiology of schizotypal personality: a review of the overlap with schizophrenia. *Frontiers in Psychiatry* **5**, 18.

Ettinger U, Mohr C, Gooding DC, Cohen AS, Rapp A, Haenschel C and Park S (2015) Cognition and brain function in schizotypy: a selective review. *Schizophrenia Bulletin* **41** (Suppl. 2), S417–S426.

Fanous AH, Neale MC, Gardner CO, Webb BT, Straub RE, O'Neill FA, Walsh D, Riley BP and Kendler KS (2007) Significant correlation in linkage signals from genome-wide scans of schizophrenia and schizotypy. *Molecular Psychiatry* **12**, 958–965.

Ferguson BR and Gao WJ (2014) Development of thalamocortical connections between the mediodorsal thalamus and the prefrontal cortex and its implication in cognition. *Frontiers in Human Neuroscience* **8**, 1027.

Fonseca-Pedrero E, Debbane M, Ortuno-Sierra J, Chan RCK, Cicero DC, Zhang LC, Brenner C, Barkus E, Linscott RJ, Kwapil T, Barrantes-Vidal N, Cohen A, Raine A, Compton MT, Tone EB, Suhr J, Muniz J, Fumero A, Giakoumaki S, Tsaousis I, Preti A, Chmielewski M, Laloyaux J, Mechri A, Lahmar MA, Wuthrich V, Laroi F, Badcock JC and Jablensky A (2018) The structure of schizotypal personality traits: a cross-national study. *Psychological Medicine* **48**, 451–462.

Fornito A, Yucel M, Patti J, Wood SJ and Pantelis C (2009) Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophrenia Research* **108**, 104–113.

Gilbert CD and Sigman M (2007) Brain states: top-down influences in sensory processing. *Neuron* **54**, 677–696.

Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL, Bullmore E and Fox PT (2008) Meta-analysis of gray matter

anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biological Psychiatry* **64**, 774–781.

Gooding DC, Matts CW and Rollmann EA (2006) Sustained attention deficits in relation to psychometrically identified schizotypy: evaluating a potential endophenotypic marker. *Schizophrenia Research* **82**, 27–37.

Guloksuz S and van Os J (2018) The slow death of the concept of schizophrenia and the painful birth of the psychosis spectrum. *Psychological Medicine* **48**, 229–244.

Hollingshead AA (1975) *Four-factor index of Social status. Unpublished manuscript*, New Haven, CT: Yale University.

Jakab A, Blanc R, Berenyi EL and Szekely G (2012) Generation of individualized thalamus target maps by using statistical shape models and thalamocortical tractography. *American Journal of Neuroradiology* **33**, 2110–2116.

Johns LC and van Os J (2001) The continuity of psychotic experiences in the general population. *Clinical Psychology Review* **21**, 1125–1141.

Jones EG (2007) *The Thalamus*. Cambridge, UK; New York: Cambridge University Press, 1708.

Kambeitz J, Kambeitz-Ilankovic L, Leucht S, Wood S, Davatzikos C, Malchow B, Falkai P and Koutsouleris N (2015) Detecting neuroimaging biomarkers for schizophrenia: a meta-analysis of multivariate pattern recognition studies. *Neuropsychopharmacology* **40**, 1742–1751.

Kerns JG and Becker TM (2008) Communication disturbances, working memory, and emotion in people with elevated disorganized schizotypy. *Schizophrenia Research* **100**, 172–180.

Krauth A, Blanc R, Poveda A, Jeanmonod D, Morel A and Szekely G (2010) A mean three-dimensional atlas of the human thalamus: generation from multiple histological data. *Neuroimage* **49**, 2053–2062.

Kuhn M (2008) Caret package. *Journal of Statistical Software* **28**, 1–26.

Kuhn S, Schubert F and Gallinat J (2012) Higher prefrontal cortical thickness in high schizotypal personality trait. *Journal of Psychiatric Research* **46**, 960–965.

Lenzenweger MF (2015) Thinking clearly about schizotypy: hewing to the schizophrenia liability core, considering interesting tangents, and avoiding conceptual quicksand. *Schizophrenia Bulletin* **41** (Suppl. 2), S483–S491.

Lynall ME, Bassett DS, Kerwin R, McKenna PJ, Kitzbichler M, Muller U and Bullmore E (2010) Functional connectivity and brain networks in schizophrenia. *Journal of Neuroscience* **30**, 9477–9487.

Mechelli A, Price CJ, Friston KJ and Ashburner J (2005) Voxel-based morphometry of the human brain: methods and applications. *Current Medical Imaging Reviews* **1**, 105–113.

Meehl PE (1989) Schizotaxia revisited. *Archives of General Psychiatry* **46**, 935–944.

Nieuwenhuis M, van Haren NE, Hulshoff Pol HE, Cahn W, Kahn RS and Schnack HG (2012) Classification of schizophrenia patients and healthy controls from structural MRI scans in two large independent samples. *Neuroimage* **61**, 606–612.

Nieuwenhuis M, Schnack HG, van Haren NE, Lappin J, Morgan C, Reinders AA, Gutierrez-Tordesillas D, Roiz-Santianez R, Schaufelberger MS, Rosa PG, Zanetti MV, Busatto GF, Crespo-Facorro B, McGorry PD, Velakoulis D, Pantelis C, Wood SJ, Kahn RS, Mourao-Miranda J and Dazzan P (2017) Multi-center MRI prediction models: predicting sex and illness course in first episode psychosis patients. *Neuroimage* **145**, 246–253.

Okada N, Fukunaga M, Yamashita F, Koshiyama D, Yamamori H, Ohi K, Yasuda Y, Fujimoto M, Watanabe Y, Yahata N, Nemoto K, Hibar DP, van Erp TG, Fujino H, Isobe M, Isomura S, Natsubori T, Narita H, Hashimoto N, Miyata J, Koike S, Takahashi T, Yamasue H, Matsuo K, Onitsuka T, Iidaka T, Kawasaki Y, Yoshimura R, Watanabe Y, Suzuki M, Turner JA, Takeda M, Thompson PM, Ozaki N, Kasai K and Hashimoto R (2016) Abnormal asymmetries in subcortical brain volume in schizophrenia. *Molecular Psychiatry* **21**, 1460–1466.

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* **9**, 97–113.

Pergola G, Selvaggi P, Trizio S, Bertolino A and Blasi G (2015) The role of the thalamus in schizophrenia from a neuroimaging perspective. *Neuroscience and Biobehavioral Reviews* **54**, 57–75.

Pergola G, Trizio S, Di Carlo P, Taurisano P, Mancini M, Amoroso N, Nettis MA, Andriola I, Caforio G, Popolizio T, Rampino A, Di Giorgio A, Bertolino A and Blasi G (2017) Grey matter volume patterns in thalamic nuclei are associated with familial risk for schizophrenia. *Schizophrenia Research* **180**, 13–20.

Peters SK, Dunlop K and Downar J (2016) Cortico-striatal-thalamic loop circuits of the salience network: a central pathway in psychiatric disease and treatment. *Frontiers in Systems Neuroscience* **10**, 104.

Pratt JA, Morris B and Dawson N (2018) Deconstructing schizophrenia: advances in preclinical models for biomarker identification. In: Pratt J, Hall J (eds) *Biomarkers in Psychiatry. Current Topics in Behavioral Neurosciences*, vol 40. Springer, Cham.

Pynn LK and DeSouza JF (2013) The function of efference copy signals: implications for symptoms of schizophrenia. *Vision Research* **76**, 124–133.

Raine A (1991) The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin* **17**, 555–564.

Rozycki M, Satterthwaite TD, Koutsouleris N, Erus G, Doshi J, Wolf DH, Fan Y, Gur RE, Gur RC, Meisenzahl EM, Zhuo C, Ying H, Yan H, Yue W, Zhang D and Davatzikos C (2017) Multisite machine learning analysis provides a robust structural imaging signature of schizophrenia detectable across diverse patient populations and within individuals. *Schizophrenia Bulletin* **44**, 1035–1044.

Salomon R, Bleich-Cohen M, Hahamy-Dubossarsky A, Dinstien I, Weizman R, Poyurovsky M, Kupchik M, Kotler M, Hendler T and Malach R (2011) Global functional connectivity deficits in schizophrenia depend on behavioral state. *Journal of Neuroscience* **31**, 12972–12981.

Salvador R, Radua J, Canales-Rodriguez EJ, Solanes A, Sarro S, Goikolea JM, Valiente A, Monte GC, Natividad MDC, Guerrero-Pedraza A, Moro N, Fernandez-Corcuera P, Amann BL, Maristany T, Vieta E, McKenna PJ and Pomarol-Clotet E (2017) Evaluation of machine learning algorithms and structural features for optimal MRI-based diagnostic prediction in psychosis. *PLoS ONE* **12**, e0175683.

Schmitt LI, Wimmer RD, Nakajima M, Happ M, Mofakham S and Halassa MM (2017) Thalamic amplification of cortical connectivity sustains attentional control. *Nature* **545**, 219–223.

Schwarz E, Doan NT, Pergola G, Westlye LT, Kaufmann T, Wolfers T, Brecheisen R, Quarto T, Ing AJ, Di Carlo P, Gurholt TP, Harms RL, Noirhomme Q, Moberget T, Agartz I, Andreassen OA, Bellani M, Bertolino A, Blasi G, Brambilla P, Buitelaar JK, Cervenka S, Flyckt L, Frangou S, Franke B, Hall J, Heslenfeld DJ, Kirsch P, McIntosh AM, Nothen MM, Papassotiropoulos A, de Quervain DJ, Rietschel M, Schumann G, Tost H, Witt SH, Zink M and Meyer-Lindenberg A and Imagemend Consortium (2019) Reproducible grey matter patterns index a multivariate, global alteration of brain structure in schizophrenia and bipolar disorder. *Translational Psychiatry* **9**, 12.

Sherman SM (2016) Thalamus plays a central role in ongoing cortical functioning. *Nature Neuroscience* **19**, 533–541.

Takahashi T, Suzuki M, Zhou SY, Nakamura K, Tanino R, Kawasaki Y, Seal ML, Seto H and Kurachi M (2008) Prevalence and length of the adhesio interthalamica in schizophrenia spectrum disorders. *Psychiatry Research* **164**, 90–94.

Taurisano P, Romano R, Mancini M, Di Giorgio A, Antonucci LA, Fazio L, Rampino A, Quarto T, Gelao B, Porcelli A, Papazacharias A, Ursini G, Caforio G, Masellis R, Niccoli-Asabella A, Todarello O, Popolizio T, Rubini G, Blasi G and Bertolino A (2014) Prefronto-striatal physiology is associated with schizotypy and is modulated by a functional variant of DRD2. *Frontiers in Behavioral Neuroscience* **8**, 235.

Tien AY (1991) Distributions of hallucinations in the population. *Social Psychiatry and Psychiatric Epidemiology* **26**, 287–292.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B and Joliot M (2002) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* **15**, 273–289.

van den Heuvel MP, Mandl RC, Stam CJ, Kahn RS and Hulshoff Pol HE (2010) Aberrant frontal and temporal complex network structure in schizophrenia: a graph theoretical analysis. *Journal of Neuroscience* **30**, 15915–15926.

van Erp TG, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, Agartz I, Westlye LT, Haukvik UK, Dale AM, Melle I,

https://doi.org/10.1017/S0033291719001430 Published online by Cambridge University Press

Hartberg CB, Gruber O, Kraemer B, Zilles D, Donohoe G, Kelly S, McDonald C, Morris DW, Cannon DM, Corvin A, Machielsen MW, Koenders L, de Haan L, Veltman DJ, Satterthwaite TD, Wolf DH, Gur RC, Gur RE, Potkin SG, Mathalon DH, Mueller BA, Preda A, Macciardi F, Ehrlich S, Walton E, Hass J, Calhoun VD, Bockholt HJ, Sponheim SR, Shoemaker JM, van Haren NE, Hulshoff Pol HE, Ophoff RA, Kahn RS, Roiz-Santianez R, Crespo-Facorro B, Wang L, Alpert KI, Jonsson EG, Dimitrova R, Bois C, Whalley HC, McIntosh AM, Lawrie SM, Hashimoto R, Thompson PM and Turner JA (2016) Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecular Psychiatry* **21**, 547–553.

van Os J, Linscott RJ, Myin-Germeys I, Delespaul P and Krabbendam L (2009) A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological Medicine* **39**, 179–195.

Vollema MG and Hoijtink H (2000) The multidimensionality of self-report schizotypy in a psychiatric population: an analysis using multidimensional Rasch models. *Schizophrenia Bulletin* **26**, 565–575.

Vollema MG and Postma B (2002) Neurocognitive correlates of schizotypy in first degree relatives of schizophrenia patients. *Schizophrenia Bulletin* **28**, 367–377.

Vollema MG, Sitskoorn MM, Appels MC and Kahn RS (2002) Does the Schizotypal Personality Questionnaire reflect the biological-genetic vulnerability to schizophrenia? *Schizophrenia Research* **54**, 39–45.

Vukadinovic Z (2014) NMDA receptor hypofunction and the thalamus in schizophrenia. *Physiology and Behavior* **131**, 156–159.

Walter EE, Fernandez F, Snelling M and Barkus E (2016) Genetic consideration of schizotypal traits: a review. *Frontiers in Psychology* **7**, 1769.

Woodward TS, Leong K, Sanford N, Tipper CM and Lavigne KM (2016) Altered balance of functional brain networks in schizophrenia. *Psychiatry Research* **248**, 94–104.

Zarogianni E, Moorhead TW and Lawrie SM (2013) Towards the identification of imaging biomarkers in schizophrenia, using multivariate pattern classification at a single-subject level. *Neuroimage: Clinical* **3**, 279–289.

Zarogianni E, Storkey AJ, Johnstone EC, Owens DG and Lawrie SM (2017) Improved individualized prediction of schizophrenia in subjects at familial high risk, based on neuroanatomical data, schizotypal and neurocognitive features. *Schizophrenia Research* **181**, 6–12.

https://doi.org/10.1017/S0033291719001430 Published online by Cambridge University Press