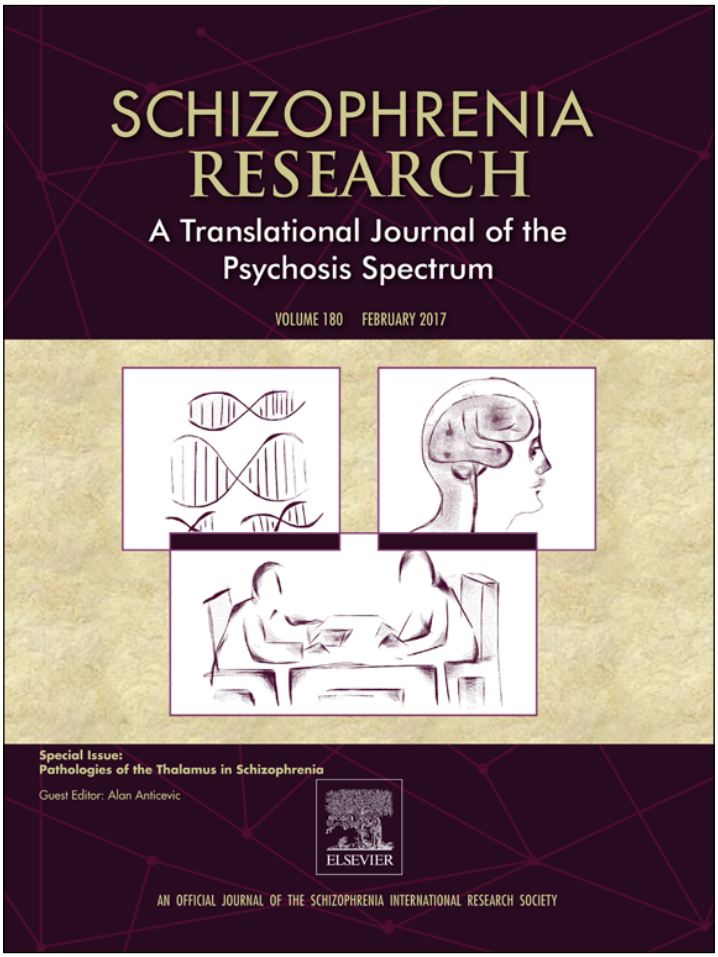

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Grey matter volume patterns in thalamic nuclei are associated with familial risk for schizophrenia

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ABSTRACT

Previous evidence suggests reduced thalamic grey matter volume (GMV) in patients with schizophrenia (SCZ). However, it is not considered an intermediate phenotype for schizophrenia, possibly because previous studies did not assess the contribution of individual thalamic nuclei and employed univariate statistics. Here, we hypothesized that multivariate statistics would reveal an association of GMV in different thalamic nuclei with familial risk for schizophrenia. We also hypothesized that accounting for the heterogeneity of thalamic GMV in healthy controls would improve the detection of subjects at familial risk for the disorder.

We acquired MRI scans for 96 clinically stable SCZ, 55 non-affected siblings of patients with schizophrenia (SIB), and 249 HC. The thalamus was parceled into seven regions of interest (ROIs). After a canonical univariate analysis, we used GMV estimates of thalamic ROIs, together with total thalamic GMV and premorbid intelligence, as features in Random Forests to classify HC, SIB, and SCZ. Then, we computed a Misclassification Index for each individual and tested the improvement in SIB detection after excluding a subsample of HC misclassified as patients. Random Forests discriminated SCZ from HC (accuracy = 81%) and SIB from HC (accuracy = 75%). Left anteromedial thalamic volumes were significantly associated with both multivariate classifications ($p < 0.05$). Excluding HC misclassified as SCZ improved greatly HC vs. SIB classification (Cohen's $d = 1.39$). These findings suggest that multivariate statistics identify a familial background associated with thalamic GMV reduction in SCZ. They also suggest the relevance of inter-individual variability of GMV patterns for the discrimination of individuals at familial risk for the disorder.

1. Introduction

The thalamus is comprised of numerous nuclei with sparse reciprocal connections, hence belonging to relatively independent circuits (Jones, 2007). The anatomical segregation of thalamic nuclei is reflected in their functional specialization. Accordingly, focal lesions yield different clinical correlates based on lesion localization (Pergola and Suchan, 2013). Consistent with the functional specialization of thalamic nuclei, post-mortem histology findings suggest that the volume of specific nuclei is reduced in patients with schizophrenia (SCZ) (reviewed by Alelu-Paz and Gimenez-Amaya, 2008; Pakkenberg et al., 2009). In particular, volume reductions in the mediodorsal thalamic nucleus (MD), pulvinar (Pul), anterior and midline thalamic nuclei (AT), and intralaminar nuclei (ILN) together explain the volume reduction of the entire thalamus (Byne et al., 2009). However, the small sample sizes limit the statistical power of post-mortem studies in SCZ.

In vivo studies with MRI using larger samples have shown significant grey matter volume (GMV) reduction in the thalamus of SCZ (Van Erp et al., 2015). However, a number of questions regarding the relationship between reduced thalamic volume and schizophrenia have not been addressed by the previous literature. First, it is not clear if reduced thalamic volume documented by imaging studies pertains to specific nuclei. In fact, the study of the thalamus as a whole does not take into account the functional and anatomical segregation of thalamic nuclei. On the other hand, examining GMV reduction in specific thalamic nuclei has led to controversial findings, possibly because assessing thalamic

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GMV requires specific imaging processing procedures (reviewed by Pergola et al., 2015).

Second, previous studies mostly employed univariate statistics. However, a substantial overlap is observed between patients and controls when evaluating single brain regions with univariate methods (Kambeitz et al., 2015). These procedures cannot test whether thalamic GMV estimates have a specific configuration across multiple nuclei that differentiates SCZ from healthy controls (HC). Multivariate statistics, instead, consider ensembles of brain regions at once to discriminate patients from controls. Even if individual components of complex brain patterns are not strongly associated with the illness, the multivariate pattern can be very sensitive in discriminating different populations (Kambeitz et al., 2015). For this reason, multivariate techniques are thought to yield greater sensitivity compared to univariate statistics (Zarogianni et al., 2013). Accordingly, these methods have been successful in identifying brain GMV patterns associated with diagnostic and prognostic variables in SCZ (Koutsouleris et al., 2012; Mourao-Miranda et al., 2012). However, to the best of our knowledge multivariate techniques have not been applied to study thalamic nuclei.

Third, it remains unclear whether thalamic GMV reduction is a trait associated with genetic risk for the disorder, or whether it is associated, for instance, with the clinical course of schizophrenia, i.e., state related. A common strategy to tackle this problem is investigating non-affected siblings of patients (SIB). SIB share on average 50% of genetic variation with patients and are free of disease-associated confounding variables. Therefore, studies with SIB are important to characterize intermediate phenotypes for schizophrenia, which are measures related to molecular genetics of the disease that are heritable, co-segregate with a psychiatric illness, yet are state-independent (Bertolino and Blasi, 2009; Gottesman and Gould, 2003). Notably, although thalamic GMV reduction is heritable (Den Braber et al., 2013) and is characteristic of SCZ (Van Erp et al., 2015), it is yet unclear whether it can be considered an intermediate phenotype for schizophrenia (Allen et al., 2009; Boos et al., 2007; Goldman et al., 2008; Honea et al., 2008). Recently, a meta-analysis including only six voxel-based morphometry (VBM) studies revealed reduced thalamic GMV in first-degree relatives of SCZ (Cooper et al., 2014). Thus, one reason for the lack of consensus on thalamic GMV reduction as an intermediate phenotype for schizophrenia may be that few VBM studies investigated specifically this brain region. Another reason may be that these studies do not take in account inter-individual variability in brain patterns of GMV, which is present also in healthy subjects and may be associated with genetic factors (Pergola et al., 2015). Indeed, genetic factors can be associated with phenotypes related to schizophrenia also in healthy populations, as indicated by several imaging genetics studies (Bertolino and Blasi, 2009).

Here, our aim was to investigate these topics. In particular, we examined GMV of individual thalamic nuclei in HC, SIB and SCZ and assessed with univariate statistics nuclei-specific GMV reductions within the thalamus. We did find specific GMV reductions, but consistent with prior evidence, we found no intermediate phenotype for schizophrenia. Then, we studied whether multivariate analyses provided greater sensitivity to detect thalamic phenotypes of familial risk for schizophrenia. We considered in the prediction also premorbid intelligence, which can be easily collected in a clinical setting and may be relevant to early-stage detection of schizophrenia (Kendler et al., 2016). Finally, we investigated whether taking into account inter-individual variability in thalamic patterns of GMV in healthy subjects may increase the detection power of greater familial risk for schizophrenia. With this aim, we removed HC with SCZ-like thalamic features from the HC sample; then, we assessed whether detection of subjects at greater familial risk for schizophrenia, i.e., SIB, improved. Here, we hypothesized that this procedure could enhance the sensitivity of risk detection analyses. Improved identification of at-risk subjects would also support the hypothesis that thalamic GMV is compromised in subjects at greater familial risk for schizophrenia.

2. Materials and methods

2.1. Participants

We recruited 400 Caucasian subjects: 96 SCZ (DSM-IV-TR) selected among consecutive outpatients at the University Hospital of Bari; 55 SIB, 249 HC. Table 1 reports demographic information. Exclusion criteria for all groups 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 SIB and 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 eight weeks (chlorpromazine equivalents mean ± SD: 561 ± 303 mg/day). All participants gave their informed consent following the Declaration of Helsinki. All procedures were approved by the ethics committee of Bari University Hospital.

2.2. Demographics, neuropsychology, and clinical assessment

Groups were not matched for gender and age, therefore the effect of these variables was factored out in all univariate and multivariate analyses. The Italian version of the *Wide Reading Achievement Test*, revised (Sartori et al., 1997; abbreviated as TIB throughout the article) was used to assess pre-morbid intelligence. Participants were screened for *Socioeconomic Status Index* (Hollingshead, 1975), and *Edinburgh Handedness Inventory* (Oldfield, 1971), to model possible confounds in the study. Moreover, we assessed the severity of clinical symptoms of SCZ with the *Positive and Negative Syndrome Scale* test (PANSS; Kay et al., 1987; PANSS total score mean ± SD: 76 ± 18, range = 41–110).

2.3. Imaging data acquisition and preprocessing

MR data were acquired with a General Electric (Milwaukee, WI) 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: TE = min-full; flip angle 6°; bandwidth 31.25; field of view 250 mm; matrix size 256 × 256; 124 contiguous 1.3 mm thickness axial slices; voxel size = 0.9 × 0.9 × 1.3 mm; acquisition time 6′08″.

Only images free of visible artifacts and of neurological abnormalities, as assessed by a board-certified neuroradiologist (TP), were included in the study. Data were preprocessed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm) as previously reported (Di Giorgio et al., 2014; see Supplemental material). Images were resampled to 1.1 mm^3 isotropic voxels to match the acquisition volume, and smoothed slightly with a Gaussian kernel of 3 mm full-width at half maximum (FWHM). Since thalamic nuclei are relatively small, it is critical to adjust smoothing parameters to limit the inflation of spatial correlation between voxels belonging to adjacent nuclei.

2.4. Imaging data analysis

As a first step, we performed a VBM analysis in order to investigate the association between thalamic GMV and diagnosis with a between-subjects ANCOVA using SPM8 (Di Giorgio et al., 2014; Supplemental material). We corrected statistics for multiple comparisons using FWE $p < 0.05$ (extent threshold: 50 voxels). Then, we performed a thalamic region of interest (ROI) analysis. We used a published atlas ("The Thalamus Atlas": Krauth et al., 2010; Jakab et al., 2012), which previous research found consistent with histologic sections (Morel, 2007), with focal stroke localization (Danet et al., 2015; Pergola et al., 2013a), and with functional cluster localization (Pergola et al., 2013b; Antonucci et al., 2016). The ROIs available in "The Thalamus Atlas" refer to specific nuclei. However, with small ROIs, the definition of the borders may be

Table 1
Demographic variables of the samples included in the study.

	HC[a]	SIB[b]	SCZ[c]	Test	p-Value
Gender [M/F]	138/111	23/32	67/29	$\chi^2_2 = 11.8$	0.003
Age [mean (SD[d])]	31 (8.4)	35 (8.9)	33 (7.7)	$F_{2,397} = 7.2$	<0.001
Edinburgh Inventory [mean (SD)]	0.69 (0.48)	0.77 (0.40)	0.73 (0.42)	$F_{2,334} = 0.7$	0.50
Hollingshead [mean (SD)]	31 (15)	28 (15)	27 (16)	$F_{2,334} = 2.1$	0.12
TIB[e] [mean (SD)]	115 (4.1)	107 (7.9)	104 (8.8)	$F_{2,314} = 80$	<0.001

[a] Healthy controls.
[b] Non-affected siblings of patients.
[c] Patient with schizophrenia.
[d] Standard deviation.
[e] Italian version of the Wide Reading Achievement Test.

unreliable with respect to inter-individual variability (Pergola et al., 2013c; Pergola et al., 2016). Therefore, we combined these ROIs using Marsbar (Brett et al., 2002). Based on the adjacency of thalamic nuclei and their connectivity patterns (Barbas et al., 2013; Pergola et al., 2012), we defined fourteen ROIs, i.e. seven for each hemisphere: anterior/midline nuclei (AT); MD; ILN; ventrolateral nucleus (VL); ventral anterior region (VA); geniculate nuclei (GN); pulvinar (Pul) (see Supplemental material for further details). Additionally, we used an ROI including all thalamic nuclei to control for total thalamic GMV. Finally, we summarized GMV estimates using the first principal component of the GMV volume in each voxel of the ROIs.

2.4.1. Univariate statistics

We used IBM® SPSS® Statistics Version 20 to analyze GMV estimates extracted from each thalamic ROI. We computed a repeated measures ANCOVA with *diagnosis* (HC, SIB, SCZ) and *gender* as between-subjects factors, *side* (left, right) and *ROI* (7 levels) as within-subjects factors, and total thalamic GMV, as well as first- and second-order terms of age as covariates. We used Greenhouse-Geisser correction for violation of sphericity where appropriate. We corrected post-hoc tests with Bonferroni's rule (seven tests, see Results). Furthermore, we asked whether thalamic GMV was associated with antipsychotic treatment (Dazzan et al., 2005). To this aim, we computed Pearson's correlations between GMV estimates in thalamic nuclei and antipsychotic dose, measured in chlorpromazine equivalents.

2.4.2. Multivariate statistics

We used Random Forests (Breiman, 2001), a supervised *machine learning* algorithm, to identify multivariate patterns related to the different diagnostic categories. Thalamic ROI GMV estimates and total thalamic volume were used as features in a multivariate analysis to predict diagnosis (HC vs. SIB, HC vs. SCZ, SIB vs. SCZ). We marginalized these features for gender and for linear as well as quadratic terms of age. Furthermore, we used as feature premorbid intelligence to increase the accuracy of the prediction, as previously done (Karageorgiou et al., 2011). We used 70% of available data, balanced between classes, to build training sets and to grow Random Forests classifiers. We bootstrapped the training set 100 times. Then, we used the left out 30% to evaluate performances of grown Random Forests (see Supplemental materials for details). We assessed whether the algorithm outperformed random classifiers in the test set. To this aim, we obtained a null distribution of performances by permuting class labels (100 runs). We used Cohen's *d* and Wilcoxon Rank test to compare the performances in test obtained by the two classifiers (test and null distribution). Finally, we assessed the importance of each feature in discriminating between classes on the whole sample (Supplemental material).

2.4.3. Relevance of thalamic multivariate patterns to familial risk for schizophrenia

In order to investigate how variability of thalamic GMV patterns in the HC population impacts on classification of at risk individuals, we first computed a Misclassification Index (MI), i.e., the rate of inaccurate classification, for each individual (Supplemental material). Then, we clustered individuals based on the MI into true/false negatives/positives (depending on whether they were correctly or incorrectly classified as HC or SCZ; see Supplemental material). Thus, we split HC into true negatives (TN, i.e., HC classified as such) and false positives (FP, i.e., HC classified as SCZ). We removed FP to test the performance of the TN vs. SIB classification (Supplemental material). We computed Cohen's *d* effect size measure of the distance between the distributions and assessed the significance of the difference between models using Wilcoxon Rank test. Also in this classification, we assessed accuracy in the test set and obtained a null distribution to model chance level (as described in Section 2.4.2).

3. Results

The whole-brain VBM analysis yielded a significant main effect of *diagnosis* on the GMV at the level of the right thalamus (MNI = 8,−12,8; cluster extent = 363; $F_{2,394} = 17$; FWE-corrected $p < 0.05$). Both HC and SIB had greater thalamic GMV compared to SCZ (Supplemental Fig. 1). Other brain regions surviving the statistical threshold are reported in Supplemental Table 1.

3.1. Univariate analysis

Fig. 1 shows the z-transformed scores representing the deviation from the mean of GMV estimates in each diagnostic group for the thalamic regions studied. Repeated measures ANCOVA performed on thalamic ROIs yielded a significant main effect of *diagnosis* ($F_{2,391} = 4.6$, $p = 0.011$) and a significant *ROI* × *diagnosis* interaction ($F_{4.7,925} = 2.8$, $p = 0.017$). No other interactions with *diagnosis* were significant. To resolve the *ROI* × *diagnosis* interaction we pooled data across levels of *side* and performed seven univariate ANOVAs (one per ROI) with the same covariates included above and set $\alpha = 7.1 \times 10^{-3}$ (Bonferroni correction). GMV estimates in bilateral MD differed significantly between diagnostic groups ($F_{2,391} = 8.0$, $p = 3.9 \times 10^{-4}$). Post-hoc tests revealed that reduced volume estimates were found in SCZ compared to HC ($p < 0.001$) and SIB ($p = 0.003$). No other effects survived Bonferroni correction. No significant correlation between ROI GMV and chlorpromazine equivalents was observed for any thalamic ROI (all $p > 0.05$).

3.2. Multivariate classification

Table 2 reports the performance of Random Forests classifiers. Test set performances were significantly higher than the null distribution, with large Cohen's *d* effect size (Balanced Accuracy: HC vs. SCZ, Cohen's $d = 5.3$, $p < 2.2 \times 10^{-16}$; HC vs. SIB, Cohen's $d = 2.7$, $p < 2.2 \times 10^{-16}$; SIB vs. SCZ, Cohen's $d = 1.3$, $p < 2.2 \times 10^{-16}$). The right MD was the most important thalamic region when discriminating SCZ from SIB and HC, whereas GMV estimates in the left AT discriminated SIB from HC (Table 3). Notably, the left AT also discriminated SCZ from HC. Thus, the left AT was the only thalamic ROI differentiating HC from both SIB

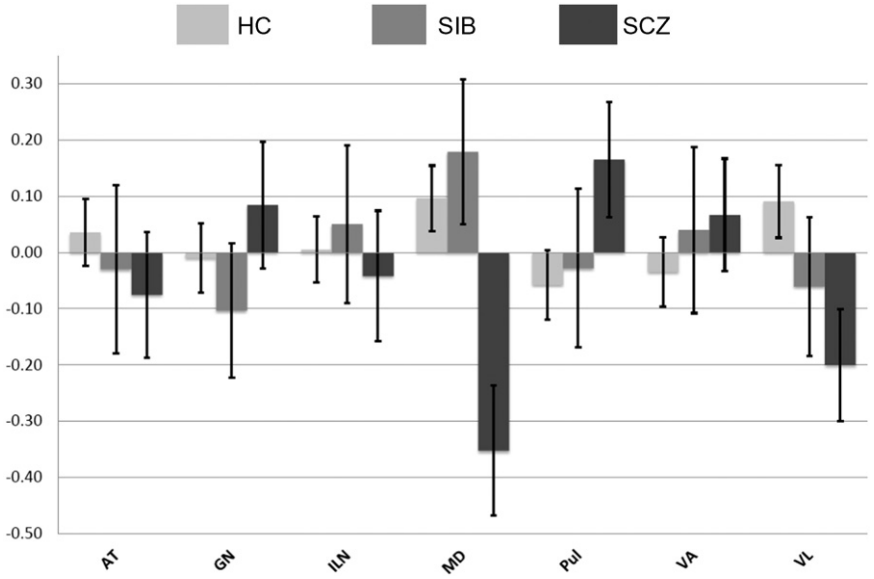

Fig. 1. Graph showing grey matter volume estimates in different thalamic ROIs. The bars represent standardized residuals of grey matter volume estimates marginalized for gender, linear and quadratic terms of age, and total thalamic grey matter. Error bars represent the standard error of the mean. The effect in the mediodorsal nucleus (MD) survives Bonferroni correction for multiple comparisons. Abbreviations: HC = healthy controls; SIB = non-affected siblings of patients; SCZ = patients with schizophrenia; AT = anterior thalamus and midline nuclei; GN = geniculate nuclei; ILN = intralaminar nuclei; Pul = pulvinar; VA = ventral anterior region; VL = ventrolateral nuclei.

and SCZ. The ranking of the variables highlights that individual thalamic ROIs were more potent predictors of diagnosis compared to GMV estimates in the whole thalamus (Table 3).

3.3. Relevance of thalamic multivariate patterns to schizophrenia risk detection

We asked whether removing HC with high MI would improve SIB detection. K-means clustering identified two clusters (split value = 0.5). Thus, we identified 43 HC who were more often classified as SCZ than as HC (false positive, FP). Table 4 shows a comparison of demographic variables between true positives (TP), false negatives (FN), true negatives (TN), and FP. We found that lower socio-economic status characterized FP relative to TN. We also observed a significant difference in handedness between the subgroups of patients correctly and incorrectly classified. Furthermore, we found that FN received lower doses of antipsychotics compared with TP. The difference was marginally significant ($p = 0.069$), in spite of an equally severe symptomatology.

After removing FP from the analysis, the accuracy of the classification TN vs. SIB improved by approximately 5%, reaching 80.9% (SD = 3.8; Cohen's $d = 1.39$; W = 15,720,000, bootstrap: $p = 1.4 \times 10^{-11}$; Fig. 2). The effect size of the improvement of SIB detection following removal of FP indicates a very strong effect of the procedure. Test set performances of TN vs. SIB classification were higher than chance, with large Cohen's d effect size (Balanced Accuracy: Cohen's $d = 3.8$, $p < 2.2 \times 10^{-16}$). Also in this analysis, left AT GMV was the only thalamic ROI significantly associated with classification accuracy ($p = 0.047$).

4. Discussion

The present study aimed to investigate the association between thalamic GMV patterns and risk for schizophrenia. First, we found with univariate analysis that specific thalamic nuclei differentiated HC from SCZ but not from SIB, most prominently the MD. This finding suggests that GMV reduction in the MD using this statistical approach is associated with the disease but not with familial risk for schizophrenia. Second, multivariate analyses supported the idea that GMV reduction in the MD are state-related, i.e., found in SCZ but not in SIB, but also revealed a thalamic structural pattern discriminating HC from both SIB and SCZ. The left AT was the most important thalamic region associated with

Table 2
Performance of multivariate classifiers in discriminating HC, SIB and SCZ based on thalamic features and premorbid intelligence. Accuracies are reported as mean (standard deviation).

Set	Measure	HC[a] vs. SCZ[c]	HC vs. SIB[b]	SIB vs. SCZ
Training set performance	CV accuracy	79.7 (6.7)	73.3 (9.0)	71.9 (12.4)
	Sensitivity	66.2	51.3	79.4
	Specificity	85.1	77.1	56.4
Test set performance	Accuracy	81.0 (3.3)	75.1 (3.9)	63.7 (5.4)
100 re-samplings	Sensitivity	69.7 (8.4)	58.2 (13.1)	72.9 (10.1)
	Specificity	85.2 (4.5)	78.8 (5.1)	47.6 (12.1)
	Balanced Accuracy[d]	77.5 (4.1)	68.5 (6.1)	60.2 (5.3)
Test set NULL distribution	Accuracy	60.0 (4.8)	66.4 (5.0)	53.9 (8.3)
(100 re-samplings with permutations of training set labels)	Sensitivity	27.1 (10.7)	27.9 (11.6)	61.1 (12.0)
	Specificity	71.9 (5.5)	74.7 (5.9)	41.1 (13.2)
	Balanced Accuracy[d]	50.0 (5.8)	51.3 (6.1)	51.1 (8.2)

[a] Healthy controls.
[b] Non-affected siblings of patients.
[c] Patients with schizophrenia.
[d] (Sensitivity + Specificity) / 2.

Table 3
Features importance discriminating HC, SIB and SCZ. Significant features are in white background.

	HC_a vs. SCZ_c		HC vs. SIB_b		SIB vs. SCZ	
Rank	Features	*p* value	Features	*p* value	Features	*p* value
1	TIB_d	0.0001	TIB	0.0001	MD-right	0.0001
2	MD_e-right	0.0007	AT-left	0.0292	MD-left	0.0997
3	VL_f-right	0.0008	Whole thalamus	0.1307	Whole thalamus	0.1216
4	ILN_g-right	0.0009	GN-right	0.2472	TIB	0.1408
5	MD-left	0.0030	VA-right	0.2586	GN-right	0.1632
6	AT_h-left	0.0057	Pul-left	0.3021	ILN-left	0.2389
7	Whole thalamus	0.0111	AT-right	0.3307	GN-left	0.2859
8	AT-right	0.0186	ILN-right	0.3537	ILN-right	0.3171
9	VA_i-right	0.0450	GN-left	0.3704	VLright	0.3722
10	GN_j-right	0.0491	Pul-right	0.4609	AT-left	0.4077
11	ILN-left	0.0585	VA-left	0.4913	VA-right	0.5069
12	VL-left	0.1507	VL-left	0.4940	Pul-right	0.5908
13	Pul_k-left	0.2220	ILN-left	0.5060	VA-left	0.6630
14	Pul-right	0.2798	VL-right	0.5162	VL-left	0.7154
15	VA-left	0.3587	MD-left	0.6353	Pul-left	0.8969
16	GN-left	0.5875	MD-right	0.6771	AT-right	0.9733

a = healthy controls.
b = non-affected siblings of patients.
c = patients with schizophrenia.
d = Italian version of the Wide Reading Achievement Test.
e = mediodorsal nucleus.
f = ventrolateral nucleus.
g = intralaminar nuclei.
h = anterior/midline nuclei.
i = ventral anterior region.
j = geniculate nuclei.
k = pulvinar.

familial risk for schizophrenia, thus not all thalamic nuclei showed a state-related GMV decrease. This finding suggests the relevance of multivariate thalamic GMV patterns as an intermediate phenotype for schizophrenia. Third, removing HC who deviated from the healthy population for thalamic patterns and premorbid intelligence dramatically increased the accuracy of discrimination of at-risk individuals from HC.

Taken together, the present evidence suggests that the thalamus is involved in schizophrenia as an ensemble of multiple regions, and reveals that specific thalamic nuclei may be associated with familial risk for this brain disorder.

4.1. Involvement of the thalamus in schizophrenia

GMV estimates in the bilateral MD and AT were both significant predictors of HC vs. SCZ classification. Nevertheless, it remains the case that GMV reduction in the MD was state-associated in the present investigation, and not associated with familial risk for schizophrenia. Instead, the finding that GMV in the left AT ranked among the top predictors of familial risk for schizophrenia (e.g., reduced both in SIB and SCZ) suggests that this feature may be a heritable trait associated with the disease. This finding is consistent with the most recent meta-analysis currently available on this topic, in which structural and functional alterations in first-degree relatives of SCZ compared to controls were localized in the left anterior dorsal thalamus (Cooper et al., 2014). Our findings are also consistent with post-mortem evidence indicating reduced neuronal counts in the AT (Byne et al., 2006; Young et al., 2000) and with imaging evidence of decreased neuronal integrity (Jakary et al., 2005) in the AT of SCZ. Morphometric evidence also points to altered shape of the anterior tip of the thalamus (Ananth et al., 2002; Gilbert et al., 2001; Hazlett et al., 1999; Qiu et al., 2009). The left laterality of our finding on the AT is consistent with previous observations (Csernansky et al., 2004; Okada et al., 2016) and also with thalamus-specific findings on genetic liability to schizophrenia (Brucato et al., 2015). It has been proposed that genetic variation associated with schizophrenia may partly overlap with that associated with lateralized brain structure, leading to lateralized findings in studies of schizophrenia (Ocklenburg et al., 2015).

Notably, the ROI we used includes the anterior and midline thalamic nuclei. Both nuclei groups are extensively connected with the medial temporal lobe (Aggleton and Brown, 1999; Cassel and de Vasconcelos,

Table 4
Differences between correctly and incorrectly classified samples of healthy controls and patients with schizophrenia.

	SCZ[a]			HC[b]		
	TP[c]	FN[d]	*p* value[e]	TN[f]	FP[g]	*p* value[e]
Gender {M/F}	47/19	20/10	n.s.	110/96	28/15	n.s.
Age {mean (SD[h]) [range]}	33 (7.9) [17, 58]	33 (7.5) [21, 47]	0.67	31 (8.0) [21, 57]	32 (10) [22, 57]	0.57
Edinburgh Inventory {mean (SD) [range]}	0.7 (0.4) [−0.89, 1]	0.5 (0.5) [−1, 1]	0.046	0.6 (0.5) [−1, 1]	0.6 (0.5) [−0.83, 1]	0.9
Hollingshead {mean (SD) [range]}	23 (15) [0, 69]	26 (22) [0, 64]	0.80	28 (19) [0, 69]	19 (13.5) [0, 45]	0.004
Chlorpromazine equivalents {mean (SD) [range]}	613 (305) [80, 1438]	458 (269) [50, 900]	0.069			
PANSS total score {mean (SD) [range]}	76 (17) [41, 110]	78 (22) [44, 110]	0.30			

[a] Patients with schizophrenia.
[b] Healthy controls.
[c] True positives.
[d] False negatives.
[e] Mann-Whitney *U* test.
[f] True negatives.
[g] False positives.
[h] Standard deviation.

2015). Because of their small size and elusive localization, these nuclei have not been thoroughly investigated for their association with schizophrenia (Byne et al., 2009). The present findings are thus relevant to theoretical models which posit a central role of the anterior and midline nuclei in schizophrenia based on thalamo-hippocampal connections (Lisman et al., 2010; Lisman, 2012).

4.2. Insight from multivariate approaches

The comparison of multivariate with univariate results yields a convergent indication that GM estimates in the MD differ between groups. This finding is consistent with previous evidence from post-mortem (Byne et al., 2009) and imaging studies (Pergola et al., 2015). However, the multivariate analysis yielded greater sensitivity because it revealed multiple thalamic ROIs associated with diagnosis of schizophrenia. For instance, not only the MD, but also adjacent thalamic ROIs were associated with HC vs. SCZ classification (AT, VL, ILN), when all ROIs and premorbid intelligence were taken into account as a pattern. Notably, the performance of the classifiers aligns with previous findings (Zarogianni et al., 2013; Kambeitz et al., 2015), even though only a small part of the brain was used for the prediction. Importantly, only when considering the thalamus as an ensemble of distinct ROIs, an association between GMV reduction and familial risk was found.

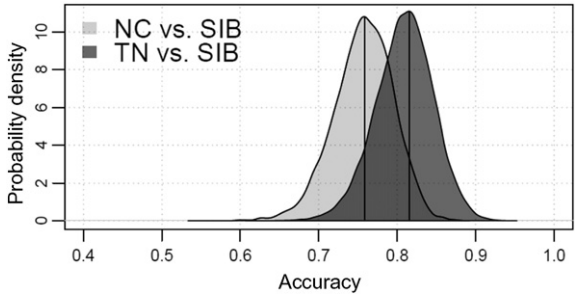

Fig. 2. Improvement of the classification following removal of misclassified healthy controls. The graph represents the accuracy of the classifications on the x-axis and probability density on the y-axis. HC with high misclassification rate were excluded in the TN vs. SIB classification. The distributions are based on 10,000 bootstrap runs. Abbreviations: HC = healthy controls; SIB = non-affected siblings of patients with schizophrenia; TN = true negatives, i.e., HC classified as such when compared with patients with schizophrenia on thalamic grey matter volume patterns.

4.3. Relevance of the findings for the identification of at-risk individuals

Misclassified individuals did not suffer from any psychiatric disorder, but their multivariate patterns were more similar to those typical of SCZ than of HC. Subpopulations of HC like the one identified here may confound studies aimed to detect intermediate phenotypes for schizophrenia. This hypothesis is supported by the finding that removing these participants greatly improved the HC vs. SIB classification. It is important to highlight that misclassified HC were identified by comparing their features with SCZ, and not with SIB. The improvement of test performance obtained by filtering the control population emphasizes the role of thalamic GMV patterns in selecting a more informative base of knowledge. The present evidence suggests that misclassification analysis could be employed to highlight observations which may undermine the sample homogeneity and, therefore, the sensitivity and robustness of the inferred results. A possible application of this approach is the study with imaging genetics of specific subgroups of individuals defined based on brain features rather than on diagnostic categories (Koutsouleris et al., 2015).

4.4. Limitations

Our samples were not homogeneous for age and gender. We took into account linear and non-linear relationships between these confounding variables and GMV, but it is still possible that the heterogeneity of these variables decreased the signal to noise ratio. Unfortunately, it would not have been possible to match these variables without dramatically reducing the sample sizes of the SCZ and SIB groups. Moreover, the thalamic parceling we performed was based on an atlas rather than on individual segmentation of thalamic nuclei. To increase the reliability of our assessment, we excluded the borders between ROIs to focus on their core, which is less susceptible to inter-individual variation than the borders.

5. Conclusions

In this study we parceled the thalamus in several ROIs and examined the association between GMV estimates in these ROI and diagnosis of schizophrenia with univariate and multivariate approaches. We found that multivariate approaches combined with thalamic parceling and premorbid intelligence explain a significant portion of the differences between diagnostic groups and carry information related with familial risk for schizophrenia. The findings highlight the suitability of multivariate approaches for identification of intermediate phenotypes for schizophrenia and the role of the thalamus in this brain disorder.

Conflict of interest

Giulio Pergola is the academic supervisor of a collaborative research project with Hoffman-La Roche, Ltd. All other authors report no potential conflicts of interest.

Contributors

GP, PDC, AB, and GB designed the study. ST, PT, MM, MAN, IA, GC, TP, AR, ADG, AB, and GB collected the data. GP, ST, PDC, MM, NA, MAN, IA, GC, TP, ADG, AB, and GB performed the analyses. GP, PDC, PT, MM, NA, GC, ADG, AB, and GB interpreted the results. GP, PDC, AB, and GB wrote the manuscript. All authors critically revised the manuscript, proofread it, and prepared it for submission.

Role of the funding source

The funding sources had no role in the design of the study, in data collection and analysis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2016.07.005.

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