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**Multivariate patterns of brain structure, brain function and symptoms in
schizophrenia**

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RESEARCH ARTICLE

Different shades of default mode disturbance in schizophrenia: Subnodal covariance estimation in structure and function

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Abstract

Schizophrenia is a devastating mental disease with an apparent disruption in the highly associative default mode network (DMN). Interplay between this canonical network and others probably contributes to goal-directed behavior so its disturbance is a candidate neural fingerprint underlying schizophrenia psychopathology. Previous research has reported both hyperconnectivity and hypoconnectivity within the DMN, and both increased and decreased DMN coupling with the multimodal saliency network (SN) and dorsal attention network (DAN). This study systematically revisited network disruption in patients with schizophrenia using data-derived network atlases and multivariate pattern-learning algorithms in a multisite dataset ($n = 325$). Resting-state fluctuations in unconstrained brain states were used to estimate functional connectivity, and local volume differences between individuals were used to estimate structural co-occurrence within and between the DMN, SN, and DAN. In brain structure and function, sparse inverse covariance estimates of network coupling were used to characterize healthy participants and patients with schizophrenia, and to identify statistically significant group differences. Evidence did not confirm that the backbone of the DMN was the primary driver of brain dysfunction in schizophrenia. Instead, functional and structural aberrations were frequently located outside of the DMN core, such as in the anterior temporoparietal junction and precuneus. Additionally, functional covariation analyses highlighted dysfunctional DMN-DAN coupling, while structural covariation results highlighted aberrant DMN-SN coupling. Our findings reframe the role of the DMN core and its relation to

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canonical networks in schizophrenia. We thus underline the importance of large-scale neural interactions as effective biomarkers and indicators of how to tailor psychiatric care to single patients.

KEYWORDS

default mode network proper, functional connectivity, machine learning, neuroimaging, schizophrenia, sparse inverse covariance estimation, structural covariance, sparsity

1 | INTRODUCTION

Schizophrenia is one of the most devastating medical conditions, affecting ~1% of the general population across cultures (Salomon et al., 2013). The clinical manifestations of schizophrenia reflect the disruption of a variety of higher-order cognitive processes (D'Argembeau, Raffard, & Van der Linden, 2008; DeLisi, 2001; Frith & Corcoran, 1996; Haggard, Martin, Taylor-Clarke, Jeannerod, & Franck, 2003), which are likely to be subserved by the association cortex (Buckner & Krienen, 2013; Spreng, Mar, & Kim, 2009; Stephan et al., 2016). A collection of associative cortical areas commonly linked with higher-level cognitive processes in both health and schizophrenia is the default mode network (DMN).

Several investigators have shown that dysfunction of the DMN in schizophrenia is linked to many of the positive and negative symptoms, such as delusional experiences, hallucinations, and disorganization of thought and behavior (Bluhm et al., 2007; Camchong, Lim, Sponheim, & MacDonald, 2009; Garrity et al., 2007; Rotarska-Jagiela et al., 2010; Whitfield-Gabrieli et al., 2009). DMN dysregulation in schizophrenia has been associated with deficits in higher-order cognitive processes from different symptom clusters, ranging from attention to social cognition (Holt et al., 2011; Northoff & Qin, 2011; Whitfield-Gabrieli & Ford, 2012). While ~23% of variation in liability for schizophrenia can be explained by genetic risk variants (Lee et al., 2012; Ripke et al., 2014), evidence suggests that up to 40% of the interindividual variance in functional connectivity patterns of the DMN is under genetic control (Glahn et al., 2010), suggesting patterns of DMN organization to be a clinically useful biomarker of schizophrenia.

Evolutionarily, regions of the association cortex, including the DMN, have increased their spatial distance from sensory-motor areas, allowing cognition to become more decoupled from perception-action cycles, a view known as the “tethering hypothesis” (Buckner & Krienen, 2013). Indeed, the DMN was recently shown to be located at a maximum distance from sensory-motor regions in both functional and topographical space (Margulies et al., 2016). These findings help explain why the DMN is particularly important for maintaining and manipulating abstract representations from downstream multimodal brain systems (Andrews-Hanna, Smallwood, & Spreng, 2014; Buckner, Andrews-Hanna, & Schacter, 2008; Konishi, McLaren, Engen, & Smallwood, 2015; Raichle, 2015). Based on this integrative account of DMN function, its importance as a diagnostic measure for many of the features of schizophrenia may emerge through its abnormal interactions with other neural systems.

Understanding how large-scale networks subserved and control higher-order cognition is an emerging agenda in psychiatric research (Jang et al., 2017; Medaglia, Lynall, & Bassett, 2015). In particular, reorganization of the coupling modes between the DMN, saliency network (SN), and dorsal attention network (DAN) has been repeatedly proposed to carry information about the cognitive states that is complementary to task-related neural activity increases and decreases in the same network (Bzdok et al., 2016b; Margulies et al., 2016). Therefore, this study systematically explored the dysfunctional couplings between the DMN, SN, and DAN in schizophrenia (White, Joseph, Francis, & Liddle, 2010; Woodward, Rogers, & Heckers, 2011).

Abnormal connectivity between large-scale networks and the DMN can provide insight into the longstanding “dysconnection hypothesis” that explains schizophrenia pathophysiology as coupling impairments due to context-dependent synaptic modulation (Friston, Brown, Siemerkus, & Stephan, 2016; Friston & Frith, 1995; Stephan et al., 2009a; Weinberger, Berman, Suddath, & Torrey, 1992). According to this pathophysiological concept, interregional coupling might be aberrant in schizophrenia because of impaired connective pathways. For instance, it has been proposed that the strength of dopaminergic projections to canonical brain networks is altered in schizophrenia (Lewis & Gonzalez-Burgos, 2006; Stephan et al., 2009). Such dysconnection of large-scale networks may contribute to positive symptoms through the failure of attentional reallocation and monitoring processes, but also to cognitive symptoms through impaired perceptual inference and disturbance of associative learning, as well as to negative symptoms due to inability of learning from and adapting to social environments. Together, these converging lines of evidence highlight that coupling patterns of canonical networks and the DMN may serve as an important biomarker for many aspects of the psychopathology of schizophrenia.

Although prior studies have highlighted the DMN as important in schizophrenia, the results have revealed a multifaceted and often inconsistent picture of how this large-scale network links to the major psychiatric disorder. Several studies have reported hypoconnectivity between regions of the DMN, such as between the posteromedial cortex (PMC) and the temporoparietal junctions (TPJ; Bluhm et al., 2007; Camchong, Lim, Sponheim, & MacDonald, 2011; Pankow et al., 2015). Other investigators instead reported hyperconnectivity within the DMN, such as between the medial prefrontal cortex and the PMC (Whitfield-Gabrieli et al., 2009; Zhou et al., 2007). Frequently inconsistent findings have also been published on pathological connectivity between the DMN and other commonly observed multimodal networks. For example, coupling of the DMN with the DAN as well as coupling between the DMN and the SN were reported as

pathologically decreased by some (White et al., 2010; Woodward et al., 2011) and as pathologically increased by others (Manoliu et al., 2013). Contradictory neural coupling findings have therefore been reported within the DMN of schizophrenia patients, as well as between the DMN and the other major brain networks including SN and DAN.

Given their intimate neurophysiological relationships and importance for disease, we studied the DMN and its pattern of coupling with the multimodal DAN and SN in schizophrenia adopting a comprehensive analysis strategy. First, because richer brain signals will be measured by taking into account the functional heterogeneity within the DMN at the subregional level, we deployed fine-grained topographical definitions from a recently completed DMN atlas as the (regions of interest (ROIs); Bzdok et al., 2013, 2015, 2016a; Eickhoff, Laird, Fox, Bzdok, & Hensel, 2016). Second, we extended the previous functional connectivity analyses between network parts to sparse inverse covariance estimation (Friedman, Hastie, & Tibshirani, 2008), which has recently been adapted for use in neuroimaging (Varoquaux, Gramfort, Poline, & Thirion, 2010). This under-exploited statistical framework, combined with benefits of using a large data-set, (i) offered increased interpretability by removing unimportant coupling relations, (ii) acknowledged the entire set of coupling relations instead of considering only pairs in isolation, and (iii) could account for the impact of third-party influences on each coupling relation. Third, the modeling approach is sufficiently abstract to allow for analogous analyses of the relationship between networks in both the functional (resting-state connectivity) and the structural (interindividual differences in brain volume) domain. Quantifying these aspects of structure-function correspondence underlying DMN aberration in schizophrenia aimed to complement previous connectivity investigations. We hypothesized that structural and functional interactions of DMN subnodes with two major brain networks provide insights into the mechanisms underlying schizophrenia psychopathology. That is, we expected the comparable quantification of neural network coupling in brain volume and function to allow zooming in on the multi-level disturbances underlying schizophrenia. This comprehensive analysis agenda allowed the formalization of complex correspondence between the neurobiological endophenotype and the clinical exophenotype in schizophrenia spectrum disorders.

2 | MATERIALS AND METHODS

2.1 | Data resources

This study considered magnetic resonance imaging (MRI) data from five different population samples acquired in Europe and USA: Aachen, Goettingen, Groeningen, Lille, and COBRE. Resting-state functional connectivity (RSFC) and voxel-based morphometric (VBM) data were collected from a total of 482 participants, 241 patients with schizophrenia and 241 healthy controls. Given the present goal to directly compare functional brain recordings and structural brain scans, we further considered only those participants who provided both RSFC and VBM in the database. These control and disease groups ($n = 325$) were matched for age within and across sites (see Supporting Information

Table S1 for details). No participant in the healthy group had a record of neurological or psychiatric disorders. Each participant in the schizophrenia group had been diagnosed by a board-certified psychiatrist in accordance with the clinical criteria of the International Classification of Diseases (ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). All acquisition sites used 3T MRI scanners (see Supporting Information Table S2 for details). For the acquisition of functional brain maps (i.e., RSFC), fMRI scans of blood-oxygen-level-dependent (BOLD) signal were recorded from the participants who were instructed to lie still during the scanning session and to let the mind wander. A post-scan interview confirmed that participants adhered to these instructions and did not fall asleep. For the acquisition of structural brain maps (i.e., VBM), 3D T1 MRI scans were recorded from each participant. All participants gave written informed consent to participate in the study, which was approved by the ethics committee of the RWTH Aachen University, Germany. Note that all phenotypic information has been anonymized for tabulation.

2.2 | Brain function: Resting-state fMRI

To measure functional activity of brain regions, we analyzed resting-state EPI (echo-planar imaging) scans from standard BOLD acquisitions (see Supporting Information Table S2 for details). The preprocessing was performed in SPM8 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK, <http://www.fil.ion.ucl.ac.uk/spm/>) run under MATLAB R2014a (Mathworks, Natick, MA). The first four brain scans were discarded to allow for magnetic field saturation. The EPI images were corrected for head movement by affine registration using a 2-pass procedure. To further reduce spurious correlations induced by motion, variance that could be explained by the head motion was removed from each voxel's time series. In particular, in adherence to previously published evaluations (Chai, Castanon, Ongur, & Whitfield-Gabrieli, 2012; Satterthwaite et al., 2013), we removed nuisance signals according to: (a) the 6 motion parameters derived from the image realignment, (b) their first derivatives, and (c) the respective squared terms (i.e., 24 parameter regression). These corrections have been shown to increase specificity and sensitivity of functional connectivity analyses and to detect valid signal correlation at rest. Motion correction was applied in all analyses. We did not perform global signal regression. Finally, the signal time series were band-pass filtered to preserve frequencies between 0.01 and 0.08 Hz, which have previously been associated with fluctuations of neuronal activity (Fox & Raichle, 2007; Lu et al., 2007), and are least impacted by physiological artifacts such as heart rate and respirations.

2.3 | Brain structure: Voxel-based morphometry (VBM) MRI

To measure the local brain volume across individuals, a high-resolution anatomical image was acquired from each participant using conventional scanning sequences. Anatomical scans were preprocessed with the VBM8 toolbox (<https://dbm.neuro.uni-jena.de/vbm>) in SPM8 using standard settings (DARTEL normalization to the ICBM-152 template,

affine and non-linear spatial normalization). Within a unified segmentation model (Ashburner & Friston, 2005), the brain scans were corrected for bias-field inhomogeneities. The brain tissue was segmented into gray matter, white matter, and cerebrospinal fluid, while adjusting for partial volume effects. We performed nonlinear modulation of segmented images to account for the amount of expansion and contraction applied during normalization using the nonlinear only modulation function within the VBM8 toolbox. The ensuing adjusted volume measurements represented the amount of gray matter corrected for individual brain sizes.

2.4 | Regions of interest

The DMN is essentially composed of four areas (which we henceforth refer to as network nodes), including the dorsomedial prefrontal cortex (DMPFC), the PMC, as well as the left and right TPJs (Buckner et al., 2008; Raichle et al., 2001). We note that the common approach is to examine the DMN with these nodes as targets of investigation (Du et al., 2016; Greicius, Krasnow, Reiss, & Menon, 2003; Whitfield-Gabrieli & Ford, 2012), assuming that the nodes of the DMN are functionally homogeneous. Nevertheless, the functional contribution of each individual node to the various abstract cognitive processes maintained by the overall network remains inconclusive (cf. Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Bado et al., 2014; Braga & Buckner, 2017). Indeed, there is recent empirical evidence that the individual nodes of the DMN segregate into distinct subnodes (Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). There is now accumulating support that neurobiologically meaningful subdivisions within each node of the DMN exist and could be profitably studied in the context of both healthy and abnormal human brain physiology.

Indeed, in a series of recent data-driven studies, the individual nodes of the DMN have been segregated into distinct subnodes based on local differences in functional interaction patterns with the rest of the brain, an established analysis technique called connectivity-based parcellation (Behrens et al., 2003; Eickhoff, Thirion, Varoquaux, & Bzdok, 2015). This technique assumes that a ROI may be divided into distinct subregions based on its whole-brain connectivity profiles. For each considered DMN node, connectivity-based parcellation has previously demonstrated a subdivision of the ROI into cluster with topographical boundary definitions, which can be reused in other studies.

Based on coherent whole-brain coupling profiles, the DMPFC was decomposed into two caudal and two rostral subnodes (Eickhoff et al., 2016). The PMC was partitioned into a ventral and dorsal subnode in the posterior cingulate cortex, one in the retrosplenial cortex (RSC) and one in the precuneus (Bzdok et al., 2015). Finally, the left and right TPJs of the DMN were decomposed into an anterior and a posterior subnode (Bzdok et al., 2013, 2016a). Adopting such a fine-grained perspective on DMN organization may provide new insights into the pathophysiology of schizophrenia. These node and subnode definitions of the DMN were used as three different ROI sets (cf. Supporting Information Table S3):

- First, we used the DMN atlas with the DMPFC, PMC, and both TPJs as composite nodes (4 ROIs), each collapsing its constituent subnodes (Figure 1a). The covariation analyses based on this ROI set examined the DMN at the conventional level of granularity: that is of network nodes. This served as a point of comparison for how this major brain network has most frequently been studied in previous brain-imaging research.
- Second, we used the full DMN atlas (12 ROIs) where the DMPFC, PMC, and the TPJs are represented as more fine-grained subnodes (Figure 1b). The DMPFC was segregated into a left and right caudal subnode and a rostro-ventral and rostro-dorsal part (left and right cDMPFC, rDMPFC, and rdDMPFC). Note that among the midline structures of the DMN, only the DMPFC yielded a division along the right versus left hemisphere in our DMN subnode atlas. The left and right TPJs were partitioned into an anterior and posterior subnode (left and right aTPJ and pTPJ). The PMC was parcellated into four subnodes, including the precuneus (PREC), the ventral and dorsal posterior cingulate cortex (vPCC and dPCC), and the RSC. The corresponding covariation analyses tested the hypothesis that the DMN can be shown to reveal richer structure in brain signals when measured by conventional MRI scanners at the level of network subnodes.
- Third, the DMN subnode atlas (12 ROIs) was supplemented by nodes from two multi-modal networks (Figure 1c): (i) the SN (Bzdok et al., 2012), including the midcingulate cortex (MCC), the bilateral anterior insula (AI) and the amygdala (AM), and (ii) the DAN (Rottschy et al., 2012), including the dorsolateral prefrontal cortex (DLPFC) and the intraparietal sulcus (IPS) bilaterally (9 additional ROIs outside of the DMN). Covariation analyses here examined the hypothesis that the DMN subnodes also display characteristic interactions with the nodes of other canonical brain networks. Indeed, the DAN and the SN have been implicated in attentional switching and reallocation of focus, processes that are markedly disrupted in schizophrenia (Luck & Gold, 2008; Maruff, Pantelis, Danckert, Smith, & Currie, 1996; Menon & Uddin, 2010; Potkin et al., 2009; Sato et al., 2003).

In sum, the covariation analyses of functional coupling (RSFC) and volumetric coupling (VBM) performed in this study were based on three different sets of previously established ROI. Collectively, the analyses are used to probe the DMN at different neuroanatomical resolutions and to systematically evaluate their relations to other major brain networks. All of the ROIs used in this study are available online for transparency and reuse via a NeuroVault permanent link (<http://neurovault.org/collections/2216/>).

2.5 | Signal extraction

Using the three sets of ROIs described above, quantitative measures of functional activity and gray-matter volume differences were extracted within the DMN, DAN, and SN ROIs in every participant. Note that all analyses were constrained to these ROIs. For extracting relevant signal from a functional or structural brain scan, the ROIs served as

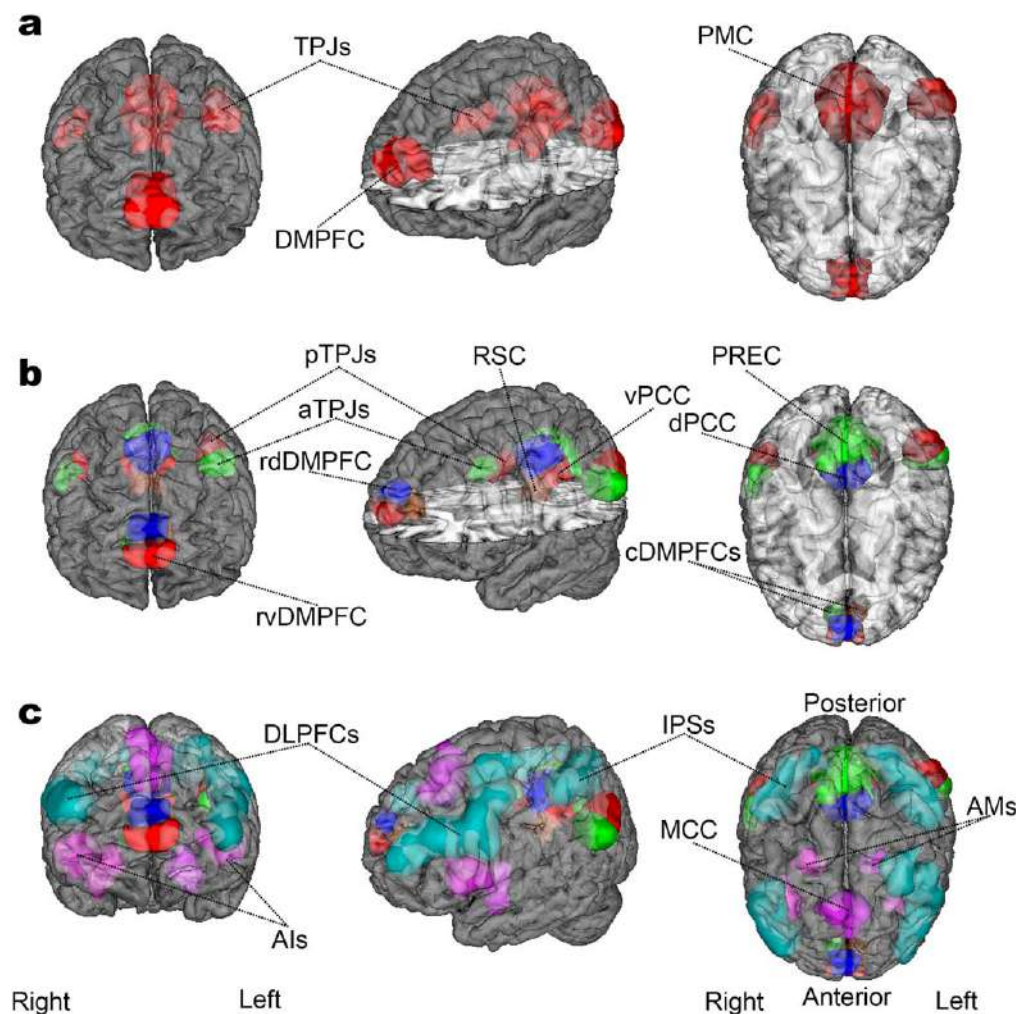


FIGURE 1 Target network definitions. The ROIs are rendered on the MNI standard brain with frontal, diagonal, and top views. (a) The DMN is represented by 4 ROIs, according to how the main network nodes are frequently studied in neuroimaging research. These comprise the DMPFC, PMC, and right/left TPJ. (b) The DMN nodes are subdivided into 12 ROIs accounting for the distinct subnodes in the DMN that were recently established (Bzdok et al., 2013, 2015, 2016a; Eickhoff et al., 2016). According to this prior work, the organizational core of the DMN (“DMN proper”) likely corresponds especially to its blue and red subnodes (the ventral and the dorsal PCCs, the left and right posterior TPJs, and the rostroventral and rostradorsal DMPFC). (c) The DMN subnodes are supplemented by 9 ROIs for the DAN (light green) and SN (purple), drawn from published quantitative meta-analyses (Bzdok et al., 2012; Rottschy et al., 2012). The DAN was composed of the DLPFC and IPS bilaterally. The SN included the MCC and the bilateral AI as well as AM. NeuroVault permanent link to all ROIs (21 in total) used in this study: <http://neurovault.org/collections/2216/>

topographic masks used to average the MRI signal across the voxels belonging to a given ROI. In RSFC, each target region was represented by the average BOLD signal across all voxels of that ROI. This feature-engineering strategy yielded as many functional brain variables as target regions in the ROI set for the participants. In VBM, each target region in the respective set of ROIs was represented by the average gray matter volume across all ROI voxels. Analogously, this way of engineering morphological brain features yielded as many volumetric brain variables per participant as the total number of ROIs in the current set. All ROI-wise functional or structural time series were transformed into z-scores by mean centering and unit-variance scaling. As part of the confound-removal procedure, variance that could be explained by the factors “site,” “age,” and “gender” as well as their two-way interactions was regressed out from the corresponding features.

2.5.1 | Measuring network covariation: Sparse inverse covariance estimation

Covariance has been argued to be a key notion when estimating the statistical dependencies characteristic of small-scale neural circuits and large-scale brain networks (Horwitz, McIntosh, Haxby, & Grady, 1995). In this study, we have performed formal inference of salient covariance relations in functional (i.e., RSFC) and volumetric (i.e., VBM) networks (or graphs, mathematically speaking) using sparse inverse covariance estimation. The automatic identification of networked organization in graphical models is an important step supporting the transition from descriptive statistics such as Pearson’s correlation coefficient to generative models that capture higher-order interactions. Here, the employed statistical estimator represents an adaptation of Lasso-like regression models (Tibshirani, 1996) to Gaussian graphical models

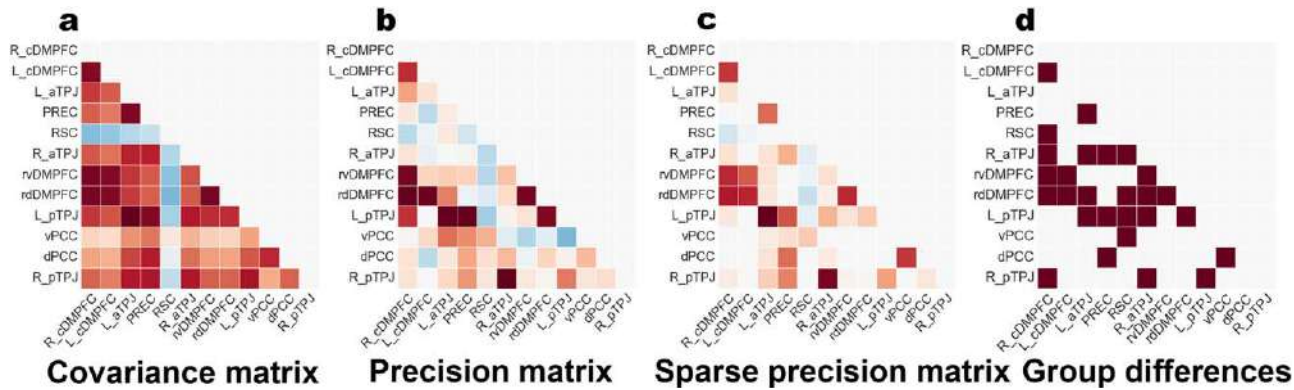


FIGURE 2 Network analysis workflow. Exemplary results illustrate the rationale of the statistical modeling framework. (a) The covariance matrix was computed with brain signals extracted from the DMN atlas. Each entry in this matrix indicates the linear relationship of each specific pair of target DMN nodes. (b) The precision matrix was computed by inverse covariance estimation (in this case without sparsity constraint). In contrast to the covariance matrix, the precision matrix captures the multiple relations between each of the pairs of target nodes while conditioning on the potential influence from the respective other nodes. (c) The parsimonious variant of the precision matrix was computed by sparse inverse covariance estimation with sparsity constraint. The additional modeling constraint improves interpretability by automatically reducing the network graph to the important network edges (non-zero strength, red or blue) and ignoring the irrelevant ones (zero strength, white). (d) The sparse precision matrices were computed separately in healthy controls and schizophrenic patients. Statistically significant group differences in coupling strengths (brown squares) were determined by nonparametric hypothesis testing. A significance test assessed group differences between all network relations at once. The entire analysis process was repeated for different network graph definitions (4 vs. 12 vs. 21 target nodes) and different imaging modalities (resting-state connectivity versus structural morphology)

(Friedman et al., 2008), an approach that has recently been adapted for application to neuroimaging data (Varoquaux et al., 2010). The validity of the derived probabilistic descriptions of the coupling properties in DMN function and volume was ascertained by cross-validation (three folds). These schemes ensured pattern generalization by measuring the goodness of fit in unseen data as a proxy for extrapolation to the general population (Shalev-Shwartz & Ben-David, 2014). This approach facilitated model selection for hyperparameter choice with an iteratively refined grid based on the log-likelihood score on left-out brain data (default parameters were chosen according to Varoquaux et al., 2010).

In a first step, we have computed the empirical covariance matrix (Figure 2a). This simple second-order statistic reflects how strongly the times series of ROI pairs covary (in terms of functional coupling in the RSFC analysis or volumetric coupling in the VBM analysis). The empirical covariance matrix is given by

$$\hat{\Sigma}_{\text{sample}} = \frac{1}{n} \chi^T \chi,$$

where $\chi \in \mathbb{R}^n \times p$ denotes the input dataset with p variables (i.e., functional brain signals averaged per ROI for the RSFC analysis and structural brain signals averaged per ROI for the VBM analysis) and n samples (i.e., brain scans). $\chi^T \chi$ denotes the inner product, the multiplication of the matrix χ with its transpose χ^T . The signed values in the covariance matrix indicate the direction of the linear relationship between two variables. This way of capturing the covariation in signal amplitude between any two ROIs was computed without statistically acknowledging the possible influence from the other ROIs. Every individual value in the covariance matrix can be viewed as a Pearson's linear correlation between each pair of ROIs, provided that the time series X were mean-centered and unit-variance scaled. Although the

strengths of correlation between time series of ROI pairs were considered in isolation, these covariation strength estimates were likely to be confounded with each other. For instance, a strong influence of ROI 1 on both ROI 2 and ROI 3 would entail high estimates of covariation between ROI 2 and ROI 3. This confound in the correlation structure between any two given target regions may therefore not accurately recover the underlying population-level coupling strength.

In a second step addressing this confound and enhancing neurobiological interpretability, we computed the partial correlations via the mathematical inverse of the covariance matrix, the so-called precision matrix (Figure 2b). The optimization objective is expressed by

$$\hat{K}_{\ell_1} = \operatorname{argmin}_{K \succ 0} \operatorname{tr} \left(K \hat{\Sigma}_{\text{sample}} \right) - \log \det K + \lambda \|K\|_1,$$

where $\hat{\Sigma}_{\text{sample}}$ is the empirical covariance matrix, $\|\cdot\|_1$ denotes the regularization constraint of putting an ℓ_1 norm on the matrix elements lying off the diagonal of the precision matrix K , and λ controls the amount of this sparsity constraint. In contrast to ordinary linear correlation or to the empirical covariance matrix described above, this matrix estimates the covariation between every two ROIs while conditioning on the potential influence of the remaining regions. In other words, the precision matrix obtains the direct covariation between two nodes within and between the DMN, SN, and DAN by accounting for partial correlations (Marrelec et al., 2006); unlike common linear correlation approaches, it does not privilege polysynaptic coupling patterns. Coming back to our toy example, we would thus obtain the conditionally independent proportion of covariation strength between ROI 2 and ROI 3 that is not explained by the conjoint influence from ROI 1. Despite its utility, this statistical approach is often challenging to apply in small samples (which is particularly the case of the VBM data in this study). In any dataset $\chi \in \mathbb{R}^n \times p$, considerable estimation errors can

arise when the number of unknown model parameters exceeds the number of samples by $n < \frac{1}{2} p(p+1)$.

To overcome erroneous eigenstructure, statistical conditioning was improved by imposing sparsity assumptions by means of ℓ_1 penalization (Figure 2c) of the inverse covariance estimation (Friedman et al., 2008; Hastie, Tibshirani, & Wainwright, 2015). In the case of multivariate Gaussian models, conditional independence between ROIs is given by the zero entries in the precision (i.e., inverse covariance) matrix. Incorporating this frequentist prior automatically reduces the model complexity by identifying the most important pairs of network nodes and ignoring the remainder. In the case of graphs, selecting those covariance parameters in the space of possible covariance models with sparse support (i.e., several zero-valued parameters in the graph) equates to limiting the number of graph edges. This sparse model estimation automatically balances the compromise between biasing towards model simplicity (hence, neurobiological interpretability) and obtaining optimal model fits to brain data. The degree of ℓ_1 penalization, controlled by the coefficient λ , was evaluated and selected in the cross-validation procedure. One important consequence of ℓ_1 penalization is that searching the covariance structure reduces to a convex problem with a unique solution. Hence, rerunning the sparse inverse covariance estimation with different random initializations of the model parameters will yield an identical solution each time.

In sum, detailed probabilistic models of network coupling were automatically derived from multisite brain data by using sparse inverse covariance estimation in both groups (i.e., healthy subjects and patients with schizophrenia). Models derived from RSFC data could be interpreted as summarizing the most important functional connections, while models derived from VBM data could be interpreted as summarizing the most important volumetric co-occurrences.

2.6 | Testing for significant disturbance in DMN covariation

Sparse inverse covariance estimation based on RSFC and separately on VBM was to be conducted separately in the healthy group and the group of patients with schizophrenia. Separate precision matrices were thus obtained in normal controls and people with schizophrenia. Statistical significance for group differences (Figure 2d) was assessed based on (family wise error, multiple-comparison corrected) p -values for the multivariate DMN covariation based on bootstrapping for nonparametric hypothesis testing (Miller et al., 2016; Smith et al., 2015). A series of bootstrap samples ($n = 1,000$) were drawn with replacement from the healthy brain data (i.e., RSFC data for functional connectivity and VBM data for the volumetric co-occurrence). For each of the thus generated 1,000 alternative dataset realizations, we performed all above steps of the sparse inverse covariance estimation (Efron & Tibshirani, 1994). This computation generated a null distribution of possible covariation estimates for every ROI-ROI relation in healthy individuals. Bootstrapping thus provided interval estimates that indicated how each coupling strength of the DMN was expected to vary in the general population (Hastie, Tibshirani, & Friedman, 2001).

Statistically significant differences between the healthy group and the group of patients with schizophrenia were then tested at the threshold corresponding to $p < 0.001$ by assessing whether the true coupling strength in individuals with schizophrenia was higher or lower than 99.9% of the coupling strengths in the healthy population. Note that, in VBM data, we have applied a more lenient threshold corresponding to $p < 0.05$, which led to statistical significance when structural covariation in schizophrenia exceeded the healthy distribution in 95% of the bootstrap samples. This is because the VBM analyses were performed in a small-sample scenario (i.e., as many brain images as participants), whereas the RSFC analyses were performed in a large-sample scenario (i.e., tens of thousands of brain images). In so doing significance testing for group differences, first in the functional covariation and then in the structural covariation, has been explicitly corrected for multiple testing, searching across all ROI pairs estimated (Miller et al., 2016; Smith et al., 2015).

3 | RESULTS

3.1 | Impact of studying nodes versus subnodes in the DMN

Based on brain measurements of functional connectivity (i.e., RSFC) in one set of analyses and structural co-occurrence (i.e., VBM) in another set of analyses, we initially examined whether subdividing traditionally studied DMN nodes into subnodes would provide richer information in brain signals. Based on 4 DMN nodes (Figure 1a) versus 12 DMN subnodes (Figure 1b), we therefore computed sparse inverse covariance estimates (i.e., precision matrices) and their statistically significant group differences (Figure 2).

In brain function as measured by RSFC, only the functional covariation between the right and the left TPJ of the DMN was determined to be significantly different between the healthy control and people with schizophrenia (Figure 3a). We then enhanced topographical granularity. Dividing the main nodes of the DMN into their constituent subnodes confirmed the observed effect (Figure 3b). We further observed that significant aberration did not involve the functional connectivity between the left anterior TPJ (aTPJ) and right posterior TPJ (pTPJ) subnodes. Importantly, a number of additional significant effects were not captured by the subnode-naïve connectivity analyses of the DMN.

In brain structure as measured by VBM, only the structural covariation between the PMC and the left TPJ node was significantly different between the control and disease groups (Figure 3c). Segmenting the composite DMN nodes into their distinct subnodes revealed that the observed effect could be more specifically credited to the morphological coupling between the left aTPJ and the precuneus (PREC) subnodes (Figure 3d). Once more, a number of additional differences in structural covariation were observed.

These preparatory analyses converged to the conclusion that neurobiologically meaningful information contained in fMRI and MRI signals is likely to remain hidden when using a general-purpose atlas to define the human DMN. Adopting a more fine-grained subnode atlas allowed detailing previously shown and discovered new covariation

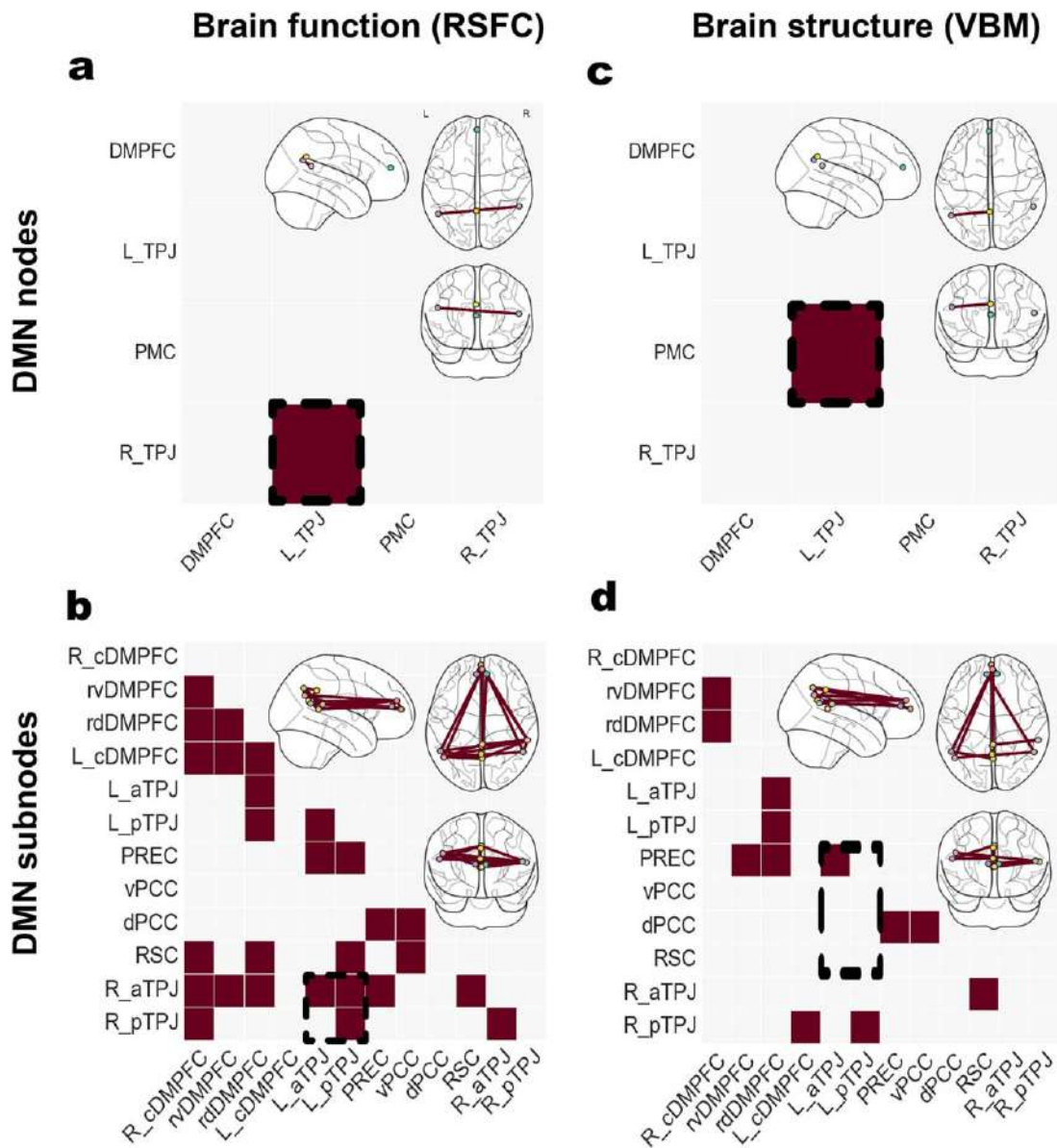


FIGURE 3 Studying nodes versus subnodes in the DMN. Significant differences in functional connectivity (left column, RSFC) and structural co-occurrence (right column, VBM). Schizophrenic patients and healthy controls were compared based on the usual DMN nodes (upper row) and the topographically more fine-grained DMN subnode atlas (lower row). Richer brain signals have been captured by the recent parcellation of the DMN nodes, resulting in a higher number of statistically significant group effects. Analysis approaches based on collapsed DMN nodes may therefore obfuscate disease-specific patterns in fMRI signals as indexed by resting-state connectivity and in MRI signals as indexed by VBM. The glass brains were created using the Nilearn Python package (Abraham et al., 2014)

effects in the DMN. This observation held true for both assessing functional coupling patterns (i.e., RSFC) and structural coupling patterns (i.e., VBM) in the DMN. Consequently, the remainder of the results section will focus on statistical analyses based on DMN subnodes.

The subsequent functional and structural covariation analyses were performed in two complementary flavors. Intra-network analyses performed sparse inverse covariance estimation based on the 12 subnodes from the DMN atlas (Figure 1b). Cross-network analyses performed the same multivariate modeling of network coupling but extended the 12 DMN subnodes with nine nodes from the DAN and the SN, which are two multimodal networks known to closely interact with the DMN (Figure 1c). Hence, intra-network analyses exposed the

coupling differences in the DMN between healthy controls and people with schizophrenia at the subnode level. This work was extended in cross-network analyses to characterize the interplay between the DMN and two other multimodal large-scale networks.

3.2 | Intranetwork covariation in brain function

We systematically detailed the neural coupling fluctuations within the DMN in people with schizophrenia and healthy controls during the resting-state (i.e., RSFC). The functional intra-network analyses (Figure 5 and Supporting Information Fig. S1 upper row) revealed the right aTPJ as the subnode with the highest number of significantly disrupted

functional connections in the DMN. Eight out of 11 connectivity targets of the right aTPJ were disturbed, including connections to three subnodes in the DMPFC, the right pTPJ, both subnodes in the left TPJ, as well as the PREC and the RSC. The subnode with the second highest number of functional disturbances was the rostr-dorsal DMPFC (rdDMPFC) subnode. Seven out of 11 of its connection targets were significantly affected in people with schizophrenia including the right and left caudal DMPFC (cDMPFC), the rostr-ventral DMPFC (rvDMPFC), the RSC subnode as well as both subnodes in the left TPJ and the right aTPJ. Further, the right cDMPFC and the left pTPJ subnodes in the DMN exhibited 6 out of 11 affected connections. Both shared common aberrations to the RSC, to the rdDMPFC, and to the two right TPJs as connectivity targets. Conversely, the ventral and dorsal posterior cingulate cortex (vPCC and dPCC) in the DMN showed only 2 out of 11 significantly altered functional connections to other DMN subnodes. Both were restricted to connectivity targets in the PMC.

Regarding the direction of aberrant functional coupling, the right aTPJ was hyperconnected with the left TPJs and the rvDMPFC, while it was hypoconnected toward the RSC, PREC, rdDMPFC, and left pTPJ. DMPFC subnodes were hypoconnected with each other in patients compared to the healthy group. A set of further hypoconnections were observed involving significant aberrations of the right pTPJ and the PREC with other subnodes.

In sum, multivariate connectivity analyses based on functional resting-state fluctuations illustrated statistically significant disturbances in 27 out of 60 connections between subnodes of the DMN in patients with schizophrenia. Among these, the right aTPJ exhibited the highest and the vPCC and dPCC the lowest number of affected coupling strengths with other parts of the DMN.

3.3 | Across-network covariation in brain function

We then tested for group differences in the functional coupling between the DMN and the multimodal networks DAN and SN (Figures 4a and 5 and Supporting Information Fig. S1, second row). Importantly, after adding the nodes from the other two macroscopic brain networks for computing precision matrices, the overall pattern of covariation remained similar. In the intranetwork versus across-network analyses, the differences in functional covariation between DMN subnodes were not statistically significant at $p < 0.05$ (dependent *t*-test). These observations support the notion that the functional connectivity patterns delineated by sparse inverse covariance estimation on RSFC data are relatively robust to changes in the size and definition of the network graph (i.e., which nodes are included).

Regarding the DAN, the left IPS displayed the highest number of edges that were significantly disturbed in patients. Nine out of 20 connectivity targets were affected. These included six subnodes in the DMN (rdDMPFC, dPCC, both left TPJs, right aTPJ, and PREC) and nodes in the other two networks including the mid-cingulate cortex (MCC), the right AM and the right IPS. The left DLPFC in the DAN also showed disrupted connectivity with 8 out of 20 targets. These included six DMN subnodes (right cDMPFC, rvDMPFC, rdDMPFC, RSC, and both left TPJs) as well as nodes of the SN including the left AI and

MCC. The right IPS, in turn, showed seven affected connections, including DMN subnodes (rdDMPFC, left aTPJ, both right TPJs, PREC) and DAN nodes (left IPS and right DLPFC), but no part of the SN. Similar to its left-hemisphere counterpart, the right DLPFC showed six affected connections, including nodes of the SN (MCC, right AI), only one node of the DAN (right IPS), as well as several DMN subnodes (rdDMPFC, both left TPJs).

Regarding the SN, the MCC displayed 6 out of 20 functional connections disturbed in schizophrenia patients, including several DMN subnodes (left and right cDMPFC, and RSC) and nearly the entire DAN (left and right DLPFC, left IPS), but no other part of the SN. The left AI was the second most affected node with four aberrant connections, including only one DMN subnode (left cDMPFC), one DAN node (left DLPFC), and two SN nodes (right AI, left AM). The right AM in turn showed only three affected connections with the DMN (right cDMPFC, RSC) and DAN (left IPS). The right AI showed three affected connections with the DMN (dPCC), the DAN (right DLPFC), and the SN (left AI). Finally, the left AM had only two affected connections with the DMN (rvDMPFC) and the SN (left AI). As a general observation, the highest number of functional disruptions therefore appeared between the DMN and the DAN.

Regarding the directionality of functional coupling aberration, the right DLPFC of the DAN was hypoconnected with the DMN, whereas the left DLPFC and the default network were hyperconnected except with the rdDMPFC. As a similar pattern, the right IPS of the DAN was mostly hypoconnected with the DMN, except with the left aTPJ, while the left IPS was mostly hyperconnected except with the left pTPJ and the PREC. As to the SN, only the MCC and the right AM exhibited hypoconnectivities with the DMN, with the right cDMPFC and the RSC, respectively.

Summing up the present findings in functional connectivity data within and from the DMN, we made several observations. First, the right aTPJ emerged as a potential driver of perturbations to network coupling observed in schizophrenia, especially when focusing on functional covariation within the DMN (i.e., intranetwork analysis). Importantly, this subnode of the DMN has been repeatedly reported not to be part of the functional core of this canonical network (Bzdok et al., 2013; Mars et al., 2012). Second, many of the subnodes, here identified to drive dysfunction in schizophrenia, are not part of what is emerging to be a default-mode network proper. According to previous studies, such a stricter topographical definition of the DMN core does most likely not include the left and right anterior TPJs, the PREC (Bzdok et al., 2015; Margulies et al., 2009), the left and right cDMPFC (Eickhoff et al., 2016), or the RSC (Bzdok et al., 2015). Indeed, parts of the DMN core, the vPCC and dPCC, were among the least dysfunctional target regions in both intra- and across-network analyses. Third, the functional abnormalities in schizophrenia frequently manifested between commonly observed macroscopic networks, especially between the DMN and the DAN.

3.4 | Intranetwork covariation in brain structure

We conducted an analysis in the domain of brain structure using the VBM data that was analogous to the assessments of brain function.

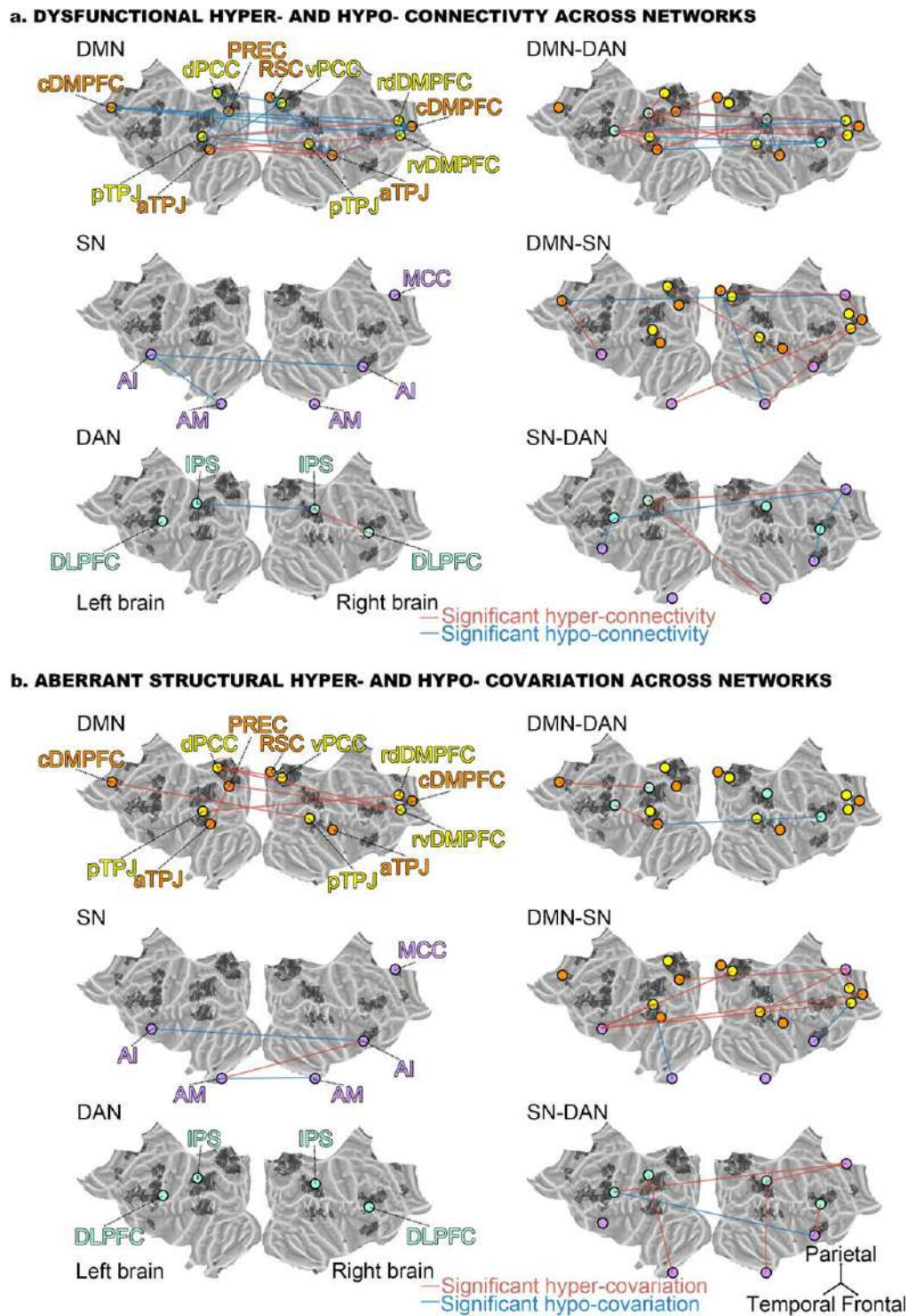


FIGURE 4 Dysfunctional connectivity and aberrant structural covariation across networks. Depicts the significant increase (red lines) or decrease (blue lines) in functional connectivity (a) or in structural co-occurrence (b) comparing schizophrenic to healthy subjects in the across-network RSFC analyses (cf. Supporting Information Fig. S1). Circles represent regions of interest in the DMN (orange), the “DMN proper” (yellow), the SN (purple), and the DAN (light green). The left column shows the differences within each network, while the right column displays differences between two networks. The connectivity findings show that the dysfunctional connectivities within the DMN include several subnodes that are not part of the “DMN proper.” While the functional coupling between the DMN and the SN is partly disrupted, the functional connectivity between the DMN and the DAN is particularly disturbed. Furthermore, the connectivities within and between the SN and the DAN remain largely intact. The covariance findings show that the deviant structural covariations within the DMN involve several subnodes not part of the “DMN proper.” The volumetric relationships between the DMN and the SN are also more disrupted than between any other network pair. Collectively, the findings emphasize internetwork dysregulation rather than exclusive disturbance of the DMN core parts. Flat brains were generated using PyCortex (Gao, Huth, Lescroart, & Gallant, 2015)

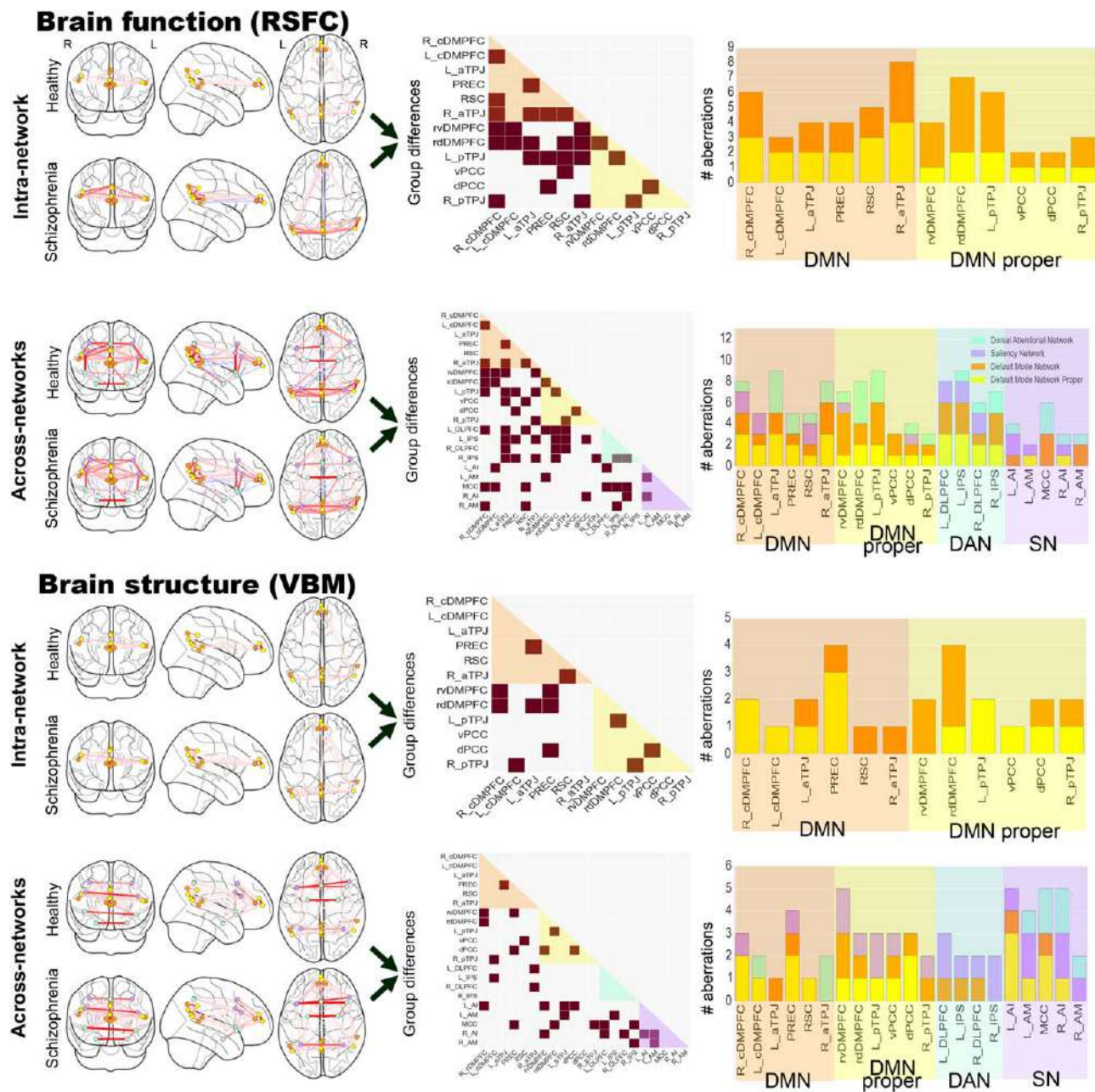


FIGURE 5 DMN aberrations in schizophrenia are specific to subnodes. Functional connectivity (RSFC) and structural co-occurrence (VBM) measurements were used to compute sparse inverse covariance estimation separately in healthy and schizophrenic individuals (left column). We conducted intra-network analyses (i.e., DMN subnode atlas) and across-network analyses (i.e., DMN subnode atlas augmented by nodes of the DAN and SN). Statistically significant group differences (brown squares in middle column) between the normal and diagnosed individuals are shown as derived from sparse inverse covariance estimation. The number of subnode-specific dysregulations (right column) is shown as counts when viewed from the DMN proper (yellow), other DMN parts (orange), DAN (light green), and SN (purple). The findings make apparent that schizophrenia pathophysiology may be relatively more driven by across-network effects and effects outside of the DMN proper. The glass brains were created using the Nilearn Python package (Abraham et al., 2014)

We thus investigated the inter-individual morphological variability within the DMN in healthy subjects and patient with schizophrenia. The structural co-occurrence results from covariation analyses on VBM data were then also evaluated for statistically significant group differences.

The structural intra-network analyses (Figure 5 and Supporting Information Fig. S1, third row) revealed DMN subnodes in the PREC and the rdDMPFC as the target regions with highest structural

disturbances in people with schizophrenia. For the PREC, 4 out of 11 volumetric co-occurrence relations were affected, including the medial frontal pole (rvDMPFC and rdDMPFC), dPCC, and left aTPJ. The rdDMPFC in turn showed four affected volumetric relations, including the right cDMPFC, both left TPJ subnodes, and the PREC. Conversely, only a single disturbed structural relation with other parts of the DMN was found for the right aTPJ, left cDMPFC, vPCC, and RSC.

The large majority of structural coupling aberrations were hypercovariations between DMN subnodes. Specifically, all PMC subnodes, including the PREC, both pTPJs, the right aTPJ and cDMPFC exhibited only hypercovariations. Further, the left aTPJ was hypoconnected with the rdDMPFC and the right cDMPFC was hypoconnected with the rvDMPFC.

In sum, the intranetwork analyses of structural co-occurrence illustrated that the DMN subnode atlas was instrumental in identifying fine-grained differences in morphological deviations in a large group of people diagnosed as schizophrenic. Healthy and diagnosed subjects showed statistically significant differences in a fifth of the volumetric coupling relations within the DMN (12 out of 60). This result stands in contrast to the higher number of functional aberrations found in the corresponding analyses in the functional imaging arm of the study (RSFC).

3.5 | Across-network covariation in brain structure

We finally tested for group differences in structural covariation between the DMN and the DAN and SN (Figures 4b and 5 and Supporting Information Fig. S1, lowest row). Concurrent with the functional covariation analyses, the overall pattern of structural coupling was similar when computing the precision matrices after taking into account the nodes of the DAN and SN. In the intranetwork versus across-network analyses, the differences in structural covariation between DMN subnodes were not statistically significant at $p < 0.05$ (dependent t -test). As another global observation, none of the structural analyses showed any negative covariation in the healthy or disease group, in contrast to the various positive and negative coupling results observed in the functional covariation analyses. Moreover, we again showed a lower overall number of statistically significant volume differences in people with schizophrenia (31 significant abnormalities) compared with the corresponding group differences in brain function (61 significant abnormalities).

Regarding the DAN, we identified the left DLPFC as exhibiting statistically significant differences between healthy controls and people with schizophrenia in 3 out of 20 volumetric relations. These included the right aTPJ, MCC, and right AI. Congruently, the DLPFC in the right hemisphere also exhibited affected volumetric relations with the right aTPJ and the right AI. Further, the right and left IPS both showed impaired volumetric coupling with the AM of the same hemisphere. While the right IPS was also disrupted in its volumetric relation with the MCC, the left IPS displayed another impaired relation with the left cDMPFC.

Regarding the SN, the MCC as well as left and right AI of this same commonly observed multimodal network showed the highest number of impaired volumetric couplings (besides rvDMPFC). All three SN nodes showed disturbed relations with subnodes in the DMPFC. More specifically, left AI exhibited four affected relations, including the right cDMPFC, the rvDMPFC, the vPCC, the left pTPJ, and the right AI. The AI in the right hemisphere instead showed affected relations with rvDMPFC, left AI, left AM, as well as the right and left DLPFC. The MCC had five affected volumetric relations including the rdDMPFC,

the PREC, the left DLPFC, as well as the IPS and pTPJ in the right hemisphere. Finally, both AM showed dysfunctional structural coupling among each other as well as to the IPS in the same hemisphere, while the left AM showed additional abnormalities with the right AI and the left pTPJ. As a general observation, the highest number of structural disruptions emerged between the DMN and the SN.

Consistent with the intranetwork analysis in brain structure, patients mostly exhibited significant hypercovariations between the DMN and the other canonical networks. Specifically, both the MCC and the right AI, the most disrupted SN nodes towards the DMN, exhibited only hypercovariations while the SN exhibited hypocovariations with the DMN only from the left AM and the right AI.

In sum, major brain networks, such as the DAN and SN, demonstrated specific volumetric coupling relations with distinct subnodes of the DMN that were shown to be impaired in schizophrenia. Importantly, only a few subnodes of the DMN proper showed statistically significant group differences. Similar to the present finding in brain function, the morphological properties of the DMN proper were found to be more intact than many other parts of the graph. Moreover, nodes of the SN were most impaired among all three networks and featured most aberrations with coupling partners of the DMN proper.

4 | DISCUSSION

Our study suggests that dysconnectivity and dysregulation anchored in the DMN is a neurobiological hallmark of schizophrenia spectrum disorders. Adopting a systems neuroscience approach, we aimed at reconciling coupling within the highly associative DMN and its coupling with the multimodal saliency and dorsal attention networks. We combined meta-analytically defensible network definitions and recently developed machine learning methods for multivariate discovery of primary covariation patterns. Network coupling was investigated in two domains, first, based on brain measurements of functional resting-state fluctuations (i.e., RSFC) and second, based on structural brain morphology (i.e., VBM). Applying an identical modeling strategy to observed functional fluctuations and volumetric differences facilitated conclusions across neurobiological levels, including their third-party coupling influences. Functional covariation analyses revealed extended disturbances related to the right anterior TPJ and the DAN. In contrast, structural covariation analyses emphasized disturbances related to the precuneus in the PMC and the SN. These findings emphasize disturbed coupling between the DMN and other large-scale networks rather than exclusive dysregulation of core parts within the DMN. Collectively, our results suggest that some previously inconsistent findings may be reconciled by using a DMN atlas with subnode resolution to recover currently under-appreciated, physiologically meaningful covariation patterns in schizophrenia.

4.1 | Covariation patterns mostly altered by cortical areas that are not part of the “DMN proper”

Covariation analyses applied to resting-state fluctuations within and from the DMN identified the right anterior TPJ subnode as featuring a

particularly high number of coupling perturbations in people diagnosed as schizophrenic, especially in the functional intranetwork analyses. Recent brain parcellation studies have associated the anterior portions of the TPJs with externally focused evaluation of visual, auditory, tactile, and other preprocessed sensory input as well as maintenance of perception-action cycles associated with the SN (Bzdok et al., 2013, 2016a; Glasser et al., 2015; Humphreys & Ralph, 2015; Mars et al., 2012). Hence, this investigation at subnode granularity points to an aberration of multimodal integration of perception-action cycles, more closely linked to DAN and SN function, rather than to imagination-based thought processes, more closely linked to DMN function (Hassabis, Kumaran, & Maguire, 2007; Wang et al., 2017). This quantitative evidence potentially relates to several clinical manifestations of schizophrenia, such as false subjective beliefs (delusion), perceiving unreal stimuli (hallucinations), awkward sensations (paresthesia), concentration difficulties, as well as disorganized speech and motor movement.

Across structural covariation analyses, the PREC emerged as one of the most impaired DMN nodes. The PREC is anatomically located in the parietal lobe and is thought to subservise visuomotor processes, such as those necessary for attentional shifting, reaching movements, and hand-eye coordination (Margulies et al., 2009; Mesulam, 1981; Stephan et al., 1995). These cognitive associations ascribed to the PREC can indeed be related to several schizophrenia symptoms, especially loss of train of thought, impairments in executive function, working memory, and memory retrieval, as well as psychogenic motor abnormalities (catatonia). Both anterior TPJs and the PREC are similarly believed to govern context-dependent reorganization of large-scale networks (Bzdok et al., 2013; Cavanna & Trimble, 2006; Downar, Crawley, Mikulis, & Davis, 2000; Seghier, 2013).

As a general conclusion, functional and structural findings agreed in emphasizing that (i) the communication within the medial core of the DMN in prefrontal and cingulate regions was relatively preserved in the examined patients and (ii) the dysfunction of schizophrenia substantially involves subnodes that do not belong to what is emerging to be a default mode network proper. Such a stricter topographical definition of the DMN excludes the anterior left and right TPJ, the PREC (Bzdok et al., 2015; Margulies et al., 2009), the RSC closer to the limbic system (Braga & Buckner, 2017; Bzdok et al., 2015; Vogt & Laureys, 2005), and the caudal DMPFCs closer to the anterior cingulate cortex (Eickhoff et al., 2016; Vogt & Pandya, 1987). Instead, our definition of the DMN core includes the ventral and the dorsal PCCs, the left and right posterior TPJs, and the rostroventral and rostradorsal DMPFC. Both the ventral and dorsal PCCs were identified among the least dysfunctional areas across all present analyses.

Collectively, these data suggest that dysfunctions in the DMN that underpin schizophrenia pathology do not emerge from the core of the network, but are reflected in the coupling of the subnodes of the larger network, regions that prior work has implicated as participating in large-scale networks other than the DMN. In particular, our study highlights disturbed internetwork communication, focused on the right anterior TPJ and PREC, as candidate drivers of the disease process that underpins schizophrenia.

4.2 | Discrepancies between volumetric and functional aberration patterns in schizophrenia

In the context of schizophrenia, network analyses have frequently been performed on either functional brain measurements (Liu et al., 2008; Lynall et al., 2010; Yu, Sui, Kiehl, Pearlson, & Calhoun, 2013) or structural brain measurements (Konrad & Winterer, 2008; van den Heuvel, Mandl, Stam, Kahn, & Pol, 2010). Direct investigations of the volume-function correspondence in long-distance coupling have been less frequent (But see: Clos, Rottschy, Laird, Fox, & Eickhoff, 2014; Honey et al., 2009; Kelly et al., 2012).

This study departs from previous single-modality investigations by applying identical covariation analyses to RSFC and VBM data to facilitate neurobiological conclusions independent of differences in the employed statistical models. We did not find strong evidence that these neurobiological domains show analogous patterns when considering the DMN in isolation or its interplay with the DAN and SN. In the functional domain, for instance, the right anterior TPJ was the overall most affected subnode, while the PREC and the right dorsal DMPFC exhibited the strongest disruptions in the structural domain. These findings suggest that neural disturbances in schizophrenia are a result of heterogeneous changes in cortex architecture that do not map in a simple way to patterns of neural communication. In addition, these regularities emphasize abnormalities in schizophrenia between networks rather than within the DMN core.

Given that the DMN is believed to exert control over the subordinate DAN and SN (Carhart-Harris & Friston, 2010; Margulies et al., 2016), it is exciting that our results revealed a dissociation in their disrupted links in the structural and functional network analyses. DMN interactions with the SN were more consistently altered in brain morphology (VBM), whereas DMN interactions with the DAN emerged as more consistently altered in brain function (RSFC) in patients with schizophrenia. Congruently, previous quantitative meta-analysis on schizophrenia and other psychiatric populations highlighted aberration in the SN across volumetric neuroimaging studies (Goodkind et al., 2015) and dysfunction in the DAN in large amounts of functional neuroimaging studies (McTeague et al., 2017). Both inter-individual differences in local brain volume (e.g., Draganski et al., 2004) and fluctuations in resting-state patterns (e.g., Rosenberg et al., 2015) have been shown to offer reliable correlates of success and failure in specific cognitive performances (Kanai & Rees, 2011). Differences in the executive control performance between healthy individuals were related to cortical thickness differences in the SN extending into parts of the DMN (Westlye, Grydeland, Walhovd, & Fjell, 2011). The present pathological increases in structural DMN-SN coupling may therefore provide insight into a longer-term compensatory mechanism due to impaired executive function in patients with schizophrenia. In contrast, the present patterns of pathological increases and decreases in functional DMN-DAN coupling may uncover a multifaceted dysbalance in allocating attentional resources to internal thought and emotion (cf. Shim et al., 2010; Whitfield-Gabrieli et al., 2009). Thus, previous isolated findings are reconciled by our integrative analysis pipeline that situated detailed disruption patterns in the context of top-level DMN control on intermediate multimodal networks.

Although we did not find a close mapping between structure and function, in both domains we found evidence that corroborates the dysconnection hypothesis of schizophrenia (Friston et al., 2016; Friston & Frith, 1995; Stephan et al., 2009; Weinberger et al., 1992) as a central pathophysiological component that could underlie schizophrenia spectrum disorders. Together, our findings support an account of the pathophysiology of schizophrenia in which abnormal integrity of long-range connections prevent integration of information from systems that support the maintenance of cognitive sets, such as mediated by the SN, or the dynamic allocation of cognitive resources, such as mediated by the DAN (Dosenbach et al., 2006; Seeley et al., 2007).

4.3 | Future directions

More globally, the overwhelming majority of mental disorders are known to show some disturbance of the DMN (Broyd et al., 2009; Whitfield-Gabrieli & Ford, 2012). Yet, we deem it unlikely that brain disorders with diverging clinical phenotypes are caused by identical neurobiological disease mechanisms. Rather, the numerous brain disorders affecting the DMN are perhaps more realistically framed to underlie a stratification of partly overlapping pathophysiologies (cf. Calhoun et al., 2011; Meda et al., 2012; Öngür et al., 2010). Investigating the DMN at an increased level of topographic granularity may be a prerequisite for identifying the DMN dysregulation specific to each major psychiatric disorder. A variety of neurobiologically distinct types of DMN aberration may expose brain phenotypes that enable effective stratification of patients with schizophrenia in clinical practice (Brodersen et al., 2011). If successful in schizophrenia, this analysis framework may scale to other major psychiatric disorders.

Moreover, our approach leveraging sparse inverse covariance estimation has several advantages, including enhanced interpretability, statistically privileging direct network influences, and interoperability across different brain-imaging modalities. However, the employed statistical model is inherently blind to interaction partners outside of the network graph and disregards higher-order interaction between the nodes in the network graph (Ganmor, Segev, & Schneidman, 2011; Giusti, Ghrist, & Bassett, 2016; Giusti, Pastalkova, Curto, & Itskov, 2015). That is, our analysis strategy was able to consider all targeted internodal relations simultaneously but assumed network interaction to be only composed of a set of dyadic partners. Going beyond pair-wise covariation in network analysis would be an exciting future extension of this work (Bassett & Sporns, 2017).

5 | CONCLUSION

Conventional brain-imaging measurements of the highly associative DMN were shown to carry fine-grained information about its coupling relation to other macroscopic brain networks. We could thus conclude that schizophrenia may not be explained by a primary dysfunction in the backbone of the DMN ("default mode network proper"). Schizophrenia psychopathology may not only be due to deficits within the DMN but especially also to deficits between the DMN and other multimodal networks including the SN and DAN. Further, by leveraging

state-of-the-art machine learning techniques for a direct juxtaposition of functional and structural covariation patterns, we provide empirical evidence for complementary disease mechanisms in schizophrenia patients. These first steps towards a more integrative approach to study DMN disturbance may be critical to chisel out the "dysconnection" pathophysiology potentially underlying schizophrenia.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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SUPPORTING INFORMATION APPENDIX

"Different shades of default mode disturbance in schizophrenia:
Subnodal covariance estimation in structure and function."

Jérémy Lefort-Besnard, Danielle S. Bassett, Jonathan Smallwood, Daniel Margulies, Birgit Derntl, Oliver Gruber, Andre Aleman, Renaud Jardri, Gaël Varoquaux, Bertrand Thirion, Simon B. Eickhoff and Danilo Bzdok

Contents:

1. Supplementary Tables (3)

2. Supplementary Figures (1)

1. Supplementary tables

Supplementary Table 1: Demographic information on participants

Site	Group	Age	Age Difference (p value)	Female	Male	n	N
Groningen	HC	31.6		13	19	32	
Groningen	SZ	33.6	0.476	13	19	32	64
Göttingen	HC	31.9		7	22	29	
Göttingen	SZ	32.0	0.978	6	27	33	62
Aachen	HC	33.2		3	10	13	
Aachen	SZ	35.1	0.682	3	11	14	27
Lille	HC	29.0		5	11	16	
Lille	SZ	33.3	0.048	6	9	15	31
COBRE	HC	35.8		23	50	73	
COBRE	SZ	38.2	0.270	13	55	68	141
Σ	HC	33.4		51	112	163	
	SZ	35.3	0.491	41	121	162	325

Supplementary Table 2: Information on MRI scanning sites

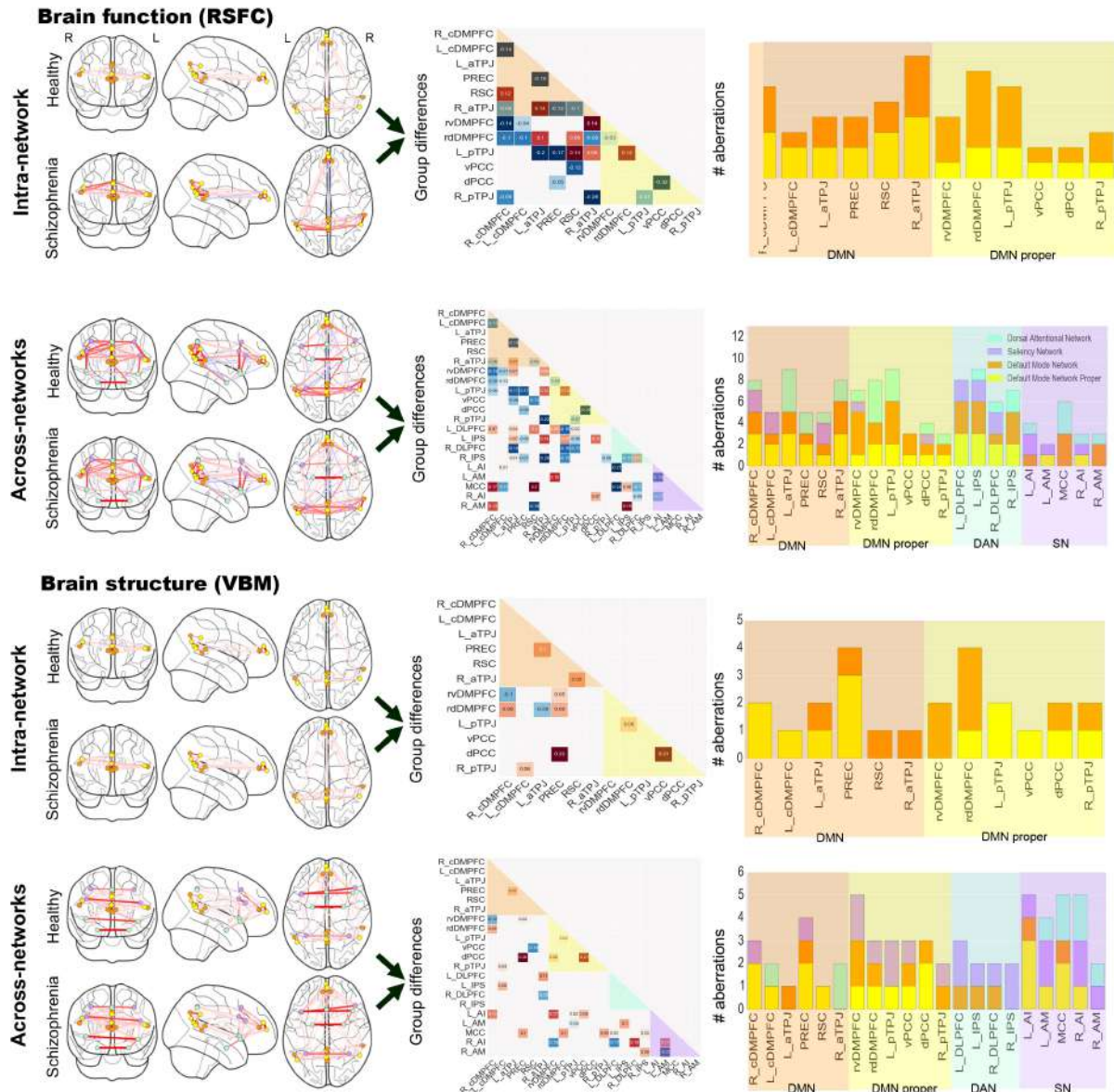
Place	Aachen	Gröningen	Göttigen	Lille	COBRE
Scanner	Siemens 3T TrioTim	Philips Achieva 3 T	Siemens TrioTim	Philips Achieva 3T	Siemens 3T TrioTim
TR (ms)	2000	2400	2000	1000	2000
TE (ms)	28	28	30	9,6	29
Number of slices	34	43	33	45	32
Slice- thickness (mm)	3,3	3	3	3,4	3,5
Gap (mm)	3,6	n.a	0,6	n.a	1
Flip-angle	77	85	70	9	
Voxel-size (mm3)	n.a	n.a	n.a	3,219 x 3,219 x 3,4 mm	3 x 3 x 4mm3
Orientation	Axial	Axial	Axial	Sagittal	Axial
In-plane resolution (mm2)	3.6 x 3,6	3,44 x 3,44	3 x 3	n.a	3,75 x 3,75
Cross hair	Yes	No, eyes closed	Yes	No, eyes closed	Yes

Supplementary Table 3: coordinate per ROIs

	seeds definition	Full name	x	y	z	number voxel
DMN nodes	DMPFC	Dorsomedial prefrontal cortex	0	55,86	14,6	318
	PMC	Posterior Medial cortex	-0,3	-53,67	29,3	1518
	R_TPJ	Right temporo-parietal junction	55,56	-47,31	16,73	239
	L_TPJ	Left temporo-parietal junction	-49,66	-57,94	24,9	376
DMN subnodes	R_cDMPFC	Caudal right dorsomedial prefrontal cortex	6,82	49,02	13,43	44
	rvDMPFC	Rostro-ventral dorsomedial prefrontal cortex	-0,6	61,05	9,84	100
	rdDMPFC	Rostro-dorsal dorsomedial prefrontal cortex	0,97	55,46	21,08	74
	L_cDMPFC	caudal left dorsomedial prefrontal cortex	-6,36	48,57	13,78	42
	PREC	Precuneus	1,08	-63,02	37,97	357
	vPCC	Ventral posterior cingulate cortex	-0,35	-57,15	20,97	291
	dPCC	Dorsal posterior cingulate cortex	0,057	-46,48	34,76	420
	RSC	Retrosplenial cortex	1,26	-44,26	9,96	82
	R_aTPJ	Anterior right temporo-parietal junction	58,62	-38,85	16,16	98
	R_pTPJ	Posterior right temporo-parietal junction	53,32	-54,5	17,47	119
	L_aTPJ	Anterior left temporo-parietal junction	-52,14	-53,32	20,48	163
	L_pTPJ	Posterior left temporo-parietal junction	-47,76	-61,48	28,28	213
DAN	L_DLPPFC	Left dorsolateral prefrontal cortex	-40,75	15,96	31,22	966
	R_DLPPFC	Right dorsolateral prefrontal cortex	46,25	26,46	24,26	505
	R_IPS	Right intraparietal sulcus	36,39	-51,63	46,05	373
	L_IPS	Left intraparietal sulcus	-33,78	-51,44	47,49	565
SN	R_AM	Right amygdala	27,59	-4,1	-19,73	172
	L_AM	Left amygdala	-23,04	-4,46	-19,64	157
	R_AI	Right anterior insula	42,57	18,03	-5,8	309
	L_AI	Left anterior insula	-41,42	16,8	-0,84	218
	MCC	Mid cingulate cortex	0,11	19,69	46	338

2. Supplementary Figures

Supplementary figure 1:



DMN aberrations in schizophrenia are specific to subnodes.

Functional connectivity (RSFC) and structural co-occurrence (VBM) measurements were used to compute sparse inverse covariance estimation separately in healthy and schizophrenic individuals (*left column*). We conducted intra-network analyses (i.e., DMN subnode atlas) and across-network analyses (i.e., DMN subnode atlas augmented by nodes of the DAN and SN). Statistically significant group differences (*squares in the middle column*) with direction and intensity of the differences (*shades of blue for hyper-coupling, shades of red for hypo-coupling*) between the normal and diagnosed individuals are shown in the

precision matrix of the schizophrenia group. The number of subnode-specific dysregulations is shown as counts when viewed from the DMN proper (*yellow*), other DMN parts (*orange*), DAN (*light green*), and SN (*purple*). The findings make apparent that schizophrenia pathophysiology may be relatively more driven by across-network effects and effects outside of the DMN proper. The glass brains were created using the Nilearn Python package (Abraham et al., 2014).

ARTICLE

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Patterns of schizophrenia symptoms: hidden structure in the PANSS questionnaire

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Abstract

The clinical presentation of patients with schizophrenia has long been described to be very heterogeneous. Coherent symptom profiles can probably be directly derived from behavioral manifestations quantified in medical questionnaires. The combination of machine learning algorithms and an international multi-site dataset ($n = 218$ patients) identified distinctive patterns underlying schizophrenia from the widespread PANSS questionnaire. Our clustering approach revealed a negative symptom patient group as well as a moderate and a severe group, giving further support for the existence of schizophrenia subtypes. Additionally, emerging regression analyses uncovered the most clinically predictive questionnaire items. Small subsets of PANSS items showed convincing forecasting performance in single patients. These item subsets encompassed the entire symptom spectrum confirming that the different facets of schizophrenia can be shown to enable improved clinical diagnosis and medical action in patients. Finally, we did not find evidence for complicated relationships among the PANSS items in our sample. Our collective results suggest that identifying best treatment for a given individual may be grounded in subtle item combinations that transcend the long-trusted positive, negative, and cognitive categories.

Introduction

Schizophrenia psychopathology is characterized by variability in several clinical aspects. Three symptom groups are commonly thought to be predominant: positive, negative and cognitive^{1,2}.

The investigation of the pathophysiological processes leading to schizophrenia symptoms involves the use of standardized rating scales. Various psychological instruments were proposed to quantitatively describe schizophrenia phenomenology. Such clinical assessment tools include the *Scale for the Assessment of Negative Symptoms*³, the *Negative Symptom Assessment*⁴, the *Scale for*

*the Assessment of Positive Symptoms*⁵, the *Schedule for Deficit Syndrome*⁶ and the *Brief Psychiatric Rating Scale*⁷. These questionnaires were mostly developed to assess two major dimensions of the psychopathology: the positive and negative syndromes^{3,5,8–10}. However, psychometric standardization has not been attested to most of these assessment scales^{11,12}. The same goes for the validity of these clinical assessment tools, including the inter-rater reliability, the assessment that the scale's score is not influenced by confounds of no interest, and the coherence of its construction.

In particular, Kay and colleagues¹³ have developed the *Positive And Negative Syndrome Scale* (PANSS) to increase the measure's replicability and objectivity as well as enable direct comparison between positive, negative and more general symptom facets (i.e., cognitive, mood, motor and thought process abnormalities symptoms). The PANSS consists of 30 items. Each item is rated on a

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seven-point severity scale. The authors have categorized the symptoms into three dimensions. The first two item dimensions capture the positive and negative syndromes consisting of seven different items each. The 16 other items constitute the third item dimension to grasp the general psychopathology. The ensuing instrument presents specified interview guidelines and assessment criteria enhancing the objectivity and replicability of the symptom descriptions. Taken together, the specified PANSS interview allowed enhancing inter-rater reliability, while the inclusion of a third dimension facilitates comparison to other mental disturbances. These added features may explain why the PANSS is today among the most widely used psychometric tools for the evaluation of schizophrenia symptoms.

Despite its widespread adoption, the structure of the PANSS questionnaire is a topic of ongoing debate. The current version of the PANSS questionnaire comprises three subscales. Yet, using principal component analysis (PCA) approaches, several authors suggested different subscales that regroup covarying questionnaire items may yield a better description of heterogeneous schizophrenia symptoms^{14–16}. Such quantitative findings have revealed a complex and often inconsistent picture of how the PANSS questionnaire subscales might describe psychiatric patients. For instance, Daneluzzo and colleagues¹⁵ advanced a three-subscale subdivision of schizophrenia symptoms, whereas Kay and Sevy¹⁷ reported a solution with seven subscales. Nevertheless, most studies proposing alternative subdivisions of the PANSS have reported five-subscale solutions¹⁸. In other words, the collection of previous studies revisiting the PANSS provides convincing evidence for the potential of various alternative conceptualizations of schizophrenia symptom dimensions.

To develop and improve symptom scales, factor-analysis procedures were an important statistical tool¹⁹. In psychology, such multivariate techniques for identifying sources of variation are often applied in the construction of multi-scale questionnaires to determine many-to-many mapping of which items belong to which degree to which scales. Regarding the study of the PANSS questionnaire, PCA was applied for more than half a century to explore the underlying organization of the PANSS questionnaire. Yet, the strong assumptions underlying PCA (i.e., orthogonality) may for instance preclude identification of other rich candidate descriptions of capturing symptoms constellations of a given patient with schizophrenia. Therefore, we hypothesized that the inconsistencies in the previous questionnaire analyses can be reconciled by expanding the repertoire of previously used statistical tools.

Our comprehensive analytic strategy emphasized prediction performance and thus clinical relevance. We

used approaches that concentrate on prediction to find generalizable predictive patterns which could enable improvements of clinical workflows. The present investigations thus extended previous research in three ways: First, we more comprehensively explored the underlying organization of the PANSS questionnaire. Second, we focused on the predictability of questionnaire item at the level of single individuals. Third, we charted the possibility of higher-order relationships among questionnaire items. Combined with benefits of using a large data set, this analysis framework offers a more complete understanding of the underlying form and clinical predictability of the commonly used PANSS questionnaire.

Methods

Data resources

We revisited the underlying structure of the PANSS questionnaire based on behavioral data from eight different schizophrenia samples acquired in Europe and the USA (see Supplementary Table 1 for details). The behavioral assessments were collected from a total of 218 patients, including 154 males and 64 female subjects. The distribution of the PANSS questionnaire responses in our sample was homogeneous (Fig. 1).

Identifying the hidden item stratification: principal component analysis

PCA is the most commonly applied data-analysis method that was previously used to discover hidden factors of variation in the PANSS questionnaire. The majority of previous studies revisiting the PANSS reported five-component solutions. We hence compared the similarities between the five PCA directions extracted from our patient sample and the five latent components found in other psychiatric populations^{20–22}.

Identifying hidden group structure: k-means clustering

We applied a k-means clustering algorithm to automatically partition patient symptom profiles into homogeneous groups. In contrast to PCA, k-means is a method identifying one-to-many mappings²³: each patient is a member of exactly one group. We used "NbClust"²⁴, an established R package that simultaneously applied 30 cluster validity metrics. This approach provided complementary indications of the number of groups most supported by the patient data. Among all indices (using the method "median") and according to the majority rule, the best number of clusters was 3. That is, the most robust three groups were expressed in the final clustering solution. Therefore, three patient groups of distinct symptom profiles were automatically extracted as it provided a useful fit to our clinical sample.

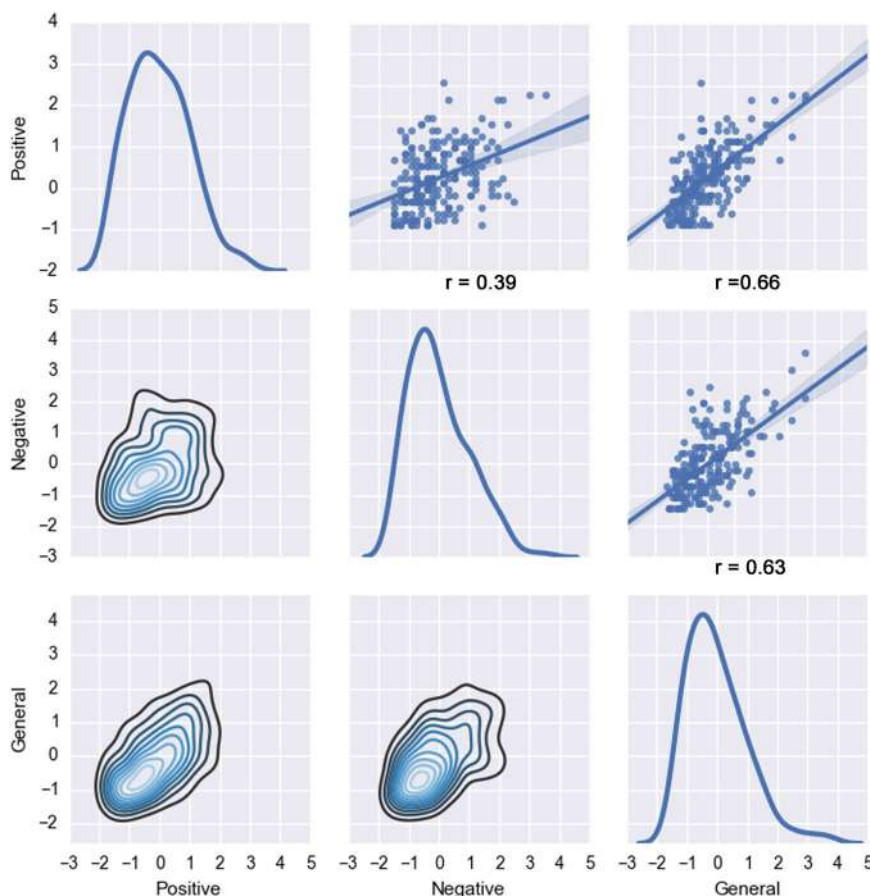


Fig. 1 Distribution of questionnaire responses by PANSS categories. In the examined schizophrenia patients, the item scores were summarized by the positive, negative, and general symptom groups structuring the questionnaire. That is, we plotted the standardized items scores mean of each symptom group (positive, negative, and general). Diagonal: the curves represent the individual distribution of the positive, negative and general symptoms items scores. Top-right: the three scatter plots display the linear dependencies between the positive and the negative, the positive and the general, and the general and the negative symptoms items scores and the linear regression of the data sample (with the correlation coefficient r noted below). Lower-left: plots the density estimates between each variable. Item responses were z-scored to put them on a same par for comparability

Identifying predictive structure: sparse logistic regression

The goal of PCA and k-means was to discover interesting symptoms patterns as measured by PANSS items such as underlying structure and relationship among schizophrenia patients. Complementing these insights in a next step, we applied a modeling technique that emphasizes both prediction performance and automatic identification of the most relevant items.

To achieve this goal, we capitalized on the pattern-learning algorithm *sparse logistic regression*²⁵. The sparsity constraint was imposed in form of an l_1 regularization. Such a constraint in the optimization objective automatically detects relevant features “on-the-fly” during model estimation. The l_1 penalty term, calibrated by the hyper-parameter λ , is designed to control the parsimony criterion and its shrinkage regularization on the learned model weights. This penalized (negative) log likelihood of

the logistic regression objective is given by:

$$-\frac{1}{N} \sum_{i=1}^N \log \left(1 + e^{-y_i f(x_i; \beta_0, \beta)} \right) + \lambda \|\beta\|_1$$

where x_i represents a given patient’s PANSS scores, y_i is his/her schizophrenia severity group defined as the median-split of his/her PANSS total score (0 as mild, 1 as severe), β_0 is the intercept, and β is the weight attached to each questionnaire item, the right part of the equation corresponds to the l_1 penalty term controlled by the hyper-parameter λ . The item selection behavior depends on the choice of this tuning parameter²⁶. The hyper-parameter selection was based on the data in a principled fashion using nested cross-validation. In a common grid of candidate parameter choices, the value of λ was varied logarithmically from 3.5 to 1.0 in log-space with 16 steps.

The member in the model family that yielded highest prediction accuracy (i.e., generalization performance) for each candidate of λ was selected. In other words, the goal here was not to select the best hyperparameter. Rather, we charted a space of candidate λ to explicitly investigate the transition from low to high sparsity. In this way, the quantitative investigation detected subsets of items that were most predictive for schizophrenia severity. Finally, we further detailed this analysis with an examination of the learning curve to assess the predictive model performance as a function of increasing sample size.

Testing for complex relationships among the PANSS items

The k-means method (cf. above) extracted latent structure dormant in the data regardless of symptom severity measures. Sparse logistic regression (cf. above) in turn selected the most predictive variables but this predictive algorithm was not convenient to uncover hidden non-linear relationships between the questionnaire items. We combined exploration of more sophisticated item-item relationships with evaluating prediction performance using non-linear predictive algorithms. In this way, we tested the hypothesis of existing higher-order relationships between the PANSS responses and their usefulness for prediction. We compared the performance of linear models to the performance of models able to exploit non-linear structure in the questionnaires. We complemented this analysis with accuracy-sample-size examination by computing learning curve for each pattern-learning model. Three linear models (ridge regression, logistic regression, and support vector machine) were benchmarked against three models allowing looking for higher-order interactions (k nearest neighbor, random forest and adaptive boosting; see Supplementary Methods for more details). Again, schizophrenia severity was defined as the median-split of the PANSS total score (0 as mild, 1 as severe) representing a categorical summary of the constituent continuous scores.

Code availability

All analysis scripts of the present study are readily accessible to the reader online (<https://github.com/JLefortBesnard/Panss2018>). See Supplementary Methods for more details.

Results

Factor-structure identified with PCA

In a preparatory analysis, we replicated results from the most often used statistical approach for latent-factor modeling of the PANSS questionnaire administered to schizophrenia patients (SFig. 1). Our findings from the five-component solution were found to be virtually identical to the previously reported findings in other schizophrenia populations^{20–22}.

Properties of patient groups hidden in PANSS questionnaire

Previous research on dimensional many-to-many PCA directions was complemented by assigning each patient to only one dominant constellation of PANSS items in a one-to-many fashion. Each patient was assigned to one and only one k-means cluster. Patients within a cluster were maximally similar, while patients from different clusters are maximally diverging in their symptom constellation.

This approach exposed three distinct symptom clusters that grouped the patients: the first group harbored low expression for each questionnaire item, the second group included several quite prominent items scores and the third one displayed a heavy affection on the negative scale (Fig. 2): (i) the first group included patients who scored rather low on most items (maximum 2 points on average). (ii) the second group included patients who scored high (more than 2.5 points on average) on three positive items (delusions, hallucinatory behavior, and suspiciousness/persecution), one negative item (difficulty in abstract thinking) and four general items (anxiety, guilt feelings, depression, and unusual thought content). (iii) The third group included patients scoring high (more than 3 points on average) on three positive items (delusions, hallucinatory behavior, and suspiciousness/persecution), five negative items (blunted affect, emotional withdrawal, passive/apathetic social withdrawal, difficulty in abstract thinking, and lack of spontaneity and flow of conversation), and three general symptom items (anxiety, depression and motor retardation).

Yet, as an exploratory pattern-discovery approach, k-means yield clusters without formal guarantee to offer predictive discriminability between patients that were not part of the present schizophrenia sample^{27,28}. A natural next step of the present study therefore consisted in estimating the predictability of schizophrenia severity from PANSS questionnaire items.

Isolating the most predictive items in the PANSS questionnaire

A predictive pattern-learning algorithm (sparse logistic regression) was used to automatically identify item subsets in the PANSS questionnaire that are most informative about telling mild versus severe schizophrenia apart in future patients. The parsimony constraint of this statistical model allowed isolating the most important items to make useful predictions in single psychiatric patients. With systematically varying parsimony constraint, a series of algorithms estimations was carried out to predict schizophrenia severity (defined as the median-split of the PANSS total score) based on the symptom scales (Fig. 3a, c).

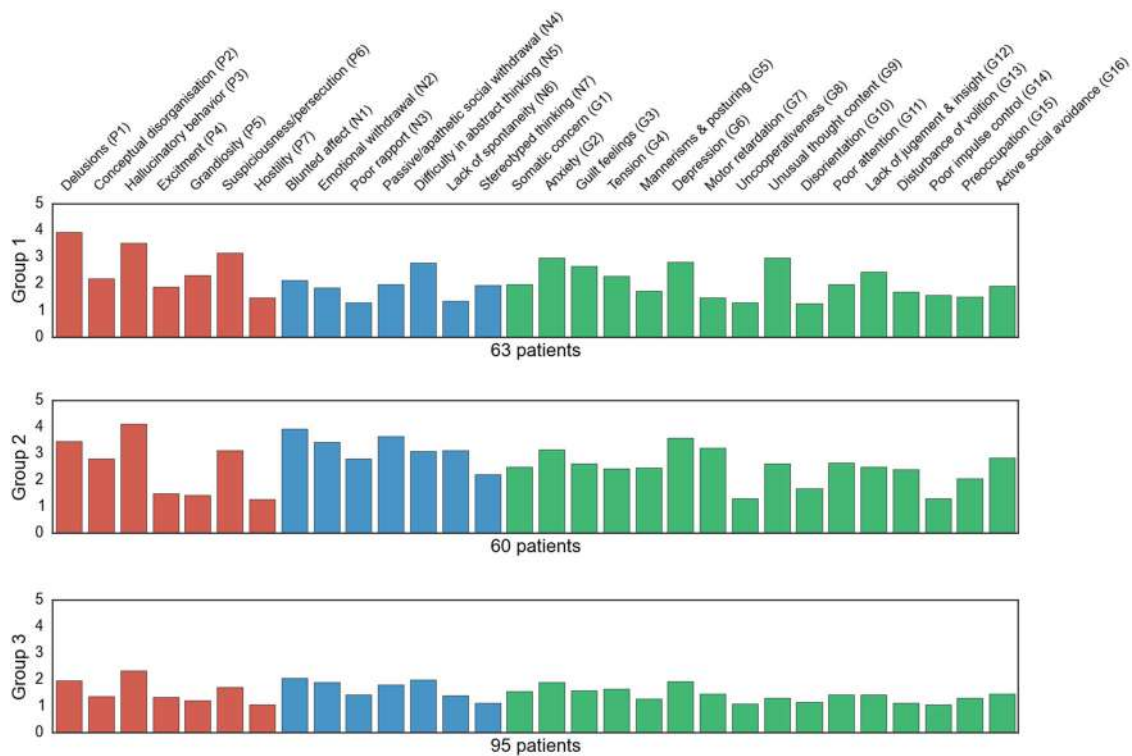


Fig. 2 Three patient groups with distinct symptom profiles. Three patient groups were extracted from the data using automatic clustering. Each row represents one data-derived symptom group with a distinct profile of patients. The weights (x axis) of each bar (PANSS item on the y axis) are automatically determined given the relative importance of the items for a particular group. The red bars are the item scores of the PANSS positive scale in the respective cluster, the *blue* ones are the item scores of the PANSS negative scale and the green bars are the item scores of the PANSS general psychopathology scale. Three different subtypes appeared: a profile including patients with low score for each item (group 3), a profile including patients with very high scores on a number of items related to each type of symptomatology (i.e., negative, positive, and general symptoms, group 1) and a profile including patients scoring very high on items associated with negative symptoms (group 2). In sum, these results suggest a discriminative hidden structure in the PANSS items not only based on a dimensional but also on a categorical aspect of the PANSS

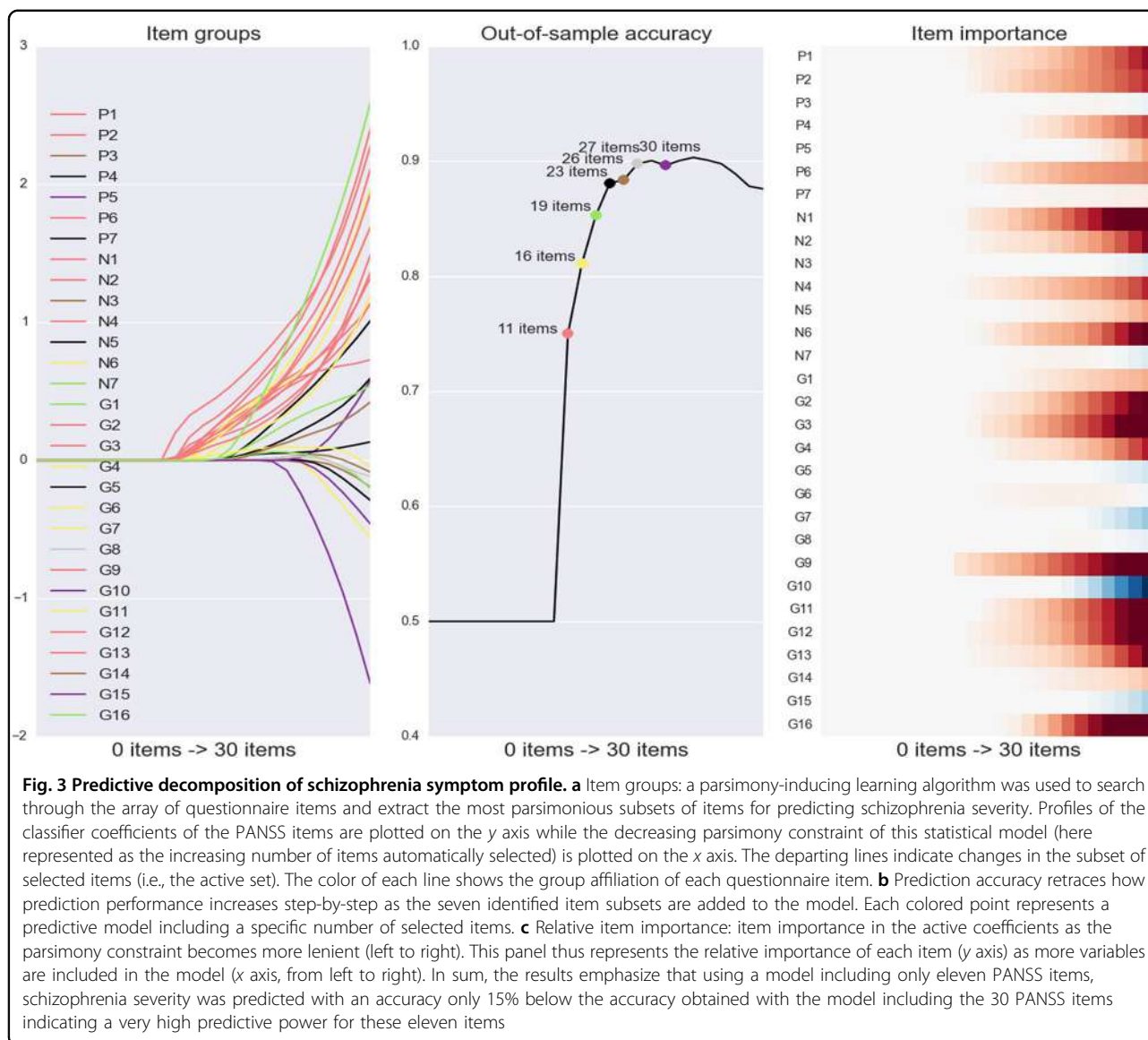
Our analysis strategy extracted eleven of the overall 30 items as the most predictive PANSS subset and achieved quite effective prediction of schizophrenia severity (75% accuracy). This essential subset included two items associated with negative symptoms (blunted affect, passive/apathetic social withdrawal), three items associated with positive symptoms (delusions, conceptual disorganization, suspiciousness/persecution), two items associated with emotional symptoms (emotional withdrawal, anxiety), one item associated with social discomfort (guilt feelings), and three items associated with cognitive symptoms (unusual thought content, lack of judgment and insight, and disturbance of volition).

As we relieved the parsimony constraint step-by-step, six other solutions were found that isolated further questionnaire items subsets predictive of schizophrenia severity (Fig. 3b), with 16, 19, 23, 26, 27, and 30 automatically selected items. These subsets reached a prediction accuracy (out-of-sample prediction performance) of 81%, 85%, 88%, 88%, 90% and 90% in new patients, respectively.

As a final step, we analyzed the learning curve to assess the predictive model performance as a function of increasing available sample size (SFig. 2). The performance of the model continuously improved after the training size exceeded 100 patients. This observation suggested that data from more than 100 individuals are beneficial to learn from a powerful predictive model for schizophrenia from behavioral data. The finding also indicated that our multi-site dataset allowed for richer descriptions of the patterns hidden in the PANSS questionnaire.

Testing for complex relationships among the PANSS items

The parsimony-inducing predictive algorithm was a linear model that could only capture how each PANSS item individually contributed to schizophrenia disease, while statistical approaches able to appreciate non-linear structure allow detecting items that together modulate disease severity. To test the hypothesis of existing higher-order interaction between the PANSS items, we compared the prediction performance on schizophrenia severity



(defined as the median-split of the PANSS total score) of different linear models (ridge regression, logistic regression, and support vector machine) to the prediction performance of different non-linear ones (k nearest neighbor, random forest, and adaptive boosting) (Fig. 4). Furthermore, we investigated the scaling behavior of each pattern-learning model (SFig. 3).

The three linear models—ridge regression, logistic regression, and support vector machine—obtained on average a better performance with respectively 93%, 92%, and 92% accuracy. Instead, the models looking for higher-order interactions—k nearest neighbor, random forest and adaptive boosting—obtained on average 87%, 91%, and 87%. Furthermore, the variance was higher for the non-linear model performances (average standard

deviation: 4.6%) than within the linear model performances (average standard deviation: 3.3%).

Considering the learning curve of the linear models showed that a plateau is reached at 60 patients for two of them (logistic regression and support vector machine) and 130 for the ridge regression giving support to the claim that linear models are proper to extract knowledge in our sample size. On the same line, the k-nearest neighbor training score started to diverge from the test score when given more than 120 patients while the random forest reached a plateau at 130 patients. However, it appears clearly that adaptive boosting keeps on learning and predicting better with more data involved in the fitting.

As a general observation, the linear models predicted more accurately on average with less variance on our

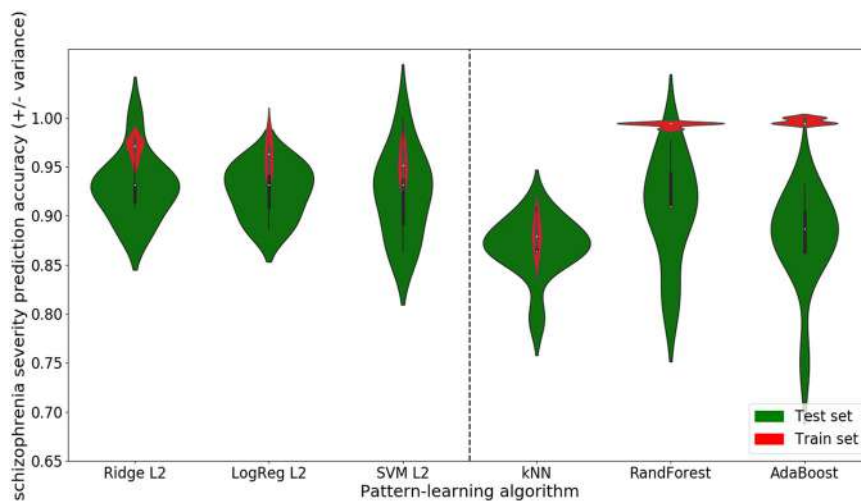


Fig. 4 Probing complex relationships among the PANSS items. We explored the hypothesis that more complex patterns may explain relationships between the different PANSS items. We thus compared the predicting performance of models looking for additive effects (left side) to the prediction performance of models looking for higher-order effects (right side). The red violin plots display the in-sample accuracies (train set) while the green plots display the generalization performance (test set). The width of the violins illustrates the density of the obtained performances. For instance, the shape of the first green violin plot on the right side (skinny on each end and wide in the middle) indicates that the obtained accuracies are highly concentrated around the median. The height of the violins indicates the variability (i.e., range of the obtained accuracies). Short violins represent a slight while long violins represent a substantial variability. Linear models including the ridge regression (*Ridge L2*), the logistic regression (*LogReg L2*), and the support vector machine (*SVM L2*) are plotted on the left side of the dashed bar. Non-linear models including the k nearest neighbor (kNN), the random forest (RandForest) and the adaptive boosting (AdaBoost) are plotted on the right side. As a general observation, the green violin plots of the linear models indicate on average a better performance with less variance thus appear to be more adapted to this setting. These results suggest that the PANSS items are perhaps mostly individually predictive as much as this evidence is supported by our multi-site patient dataset

patient sample, suggesting that the PANSS items are predominantly predictive for disease severity based on their one-by-one scores. However, this claim might be limited to the size of our sample and increasing the sample size may likely improve the predictive accuracy of non-linear models such as adaptive boosting.

Discussion

The PANSS questionnaire is pervasively used in psychiatry but has been repeatedly proposed to require revision. We provide a comprehensive characterization for quantifying the different typologies of psychopathology in schizophrenia patients from a multi-site data collection. Furthermore, our study emphasizes the relevance of the questionnaire as behavioral information valuable to effectively predict schizophrenia severity in single individuals. On the one hand, we found that dimensional partitions are candidate fingerprints underlying discrete schizophrenia profiles as it was emphasized in our automatic structure-discovery approaches. On the other hand, an automatic variable-selection algorithm revealed a most important subset of eleven most predictive PANSS items. This quintessential PANSS subset encompassed various parts of the spectrum of schizophrenia symptoms confirming that the different facets of schizophrenia could be

shown as useful in robust single-subject predictions for these psychiatric patients. Collectively, our results suggest that some previously inconsistent findings may be reconciled by using an extended repertoire of modern data-analysis tools.

Extracting predictive subsets of PANSS items

As a primary focus of the present investigation, we automatically identified the most predictive PANSS items of schizophrenia severity. A subselection of the 30 total PANSS items predicted schizophrenia severity with an accuracy of 75% which is only 15% below the accuracy obtained using the full PANSS questionnaire (90%) in our multi-site sample of 218 patients. The eleven items included two items associated with negative symptoms, three items associated with positive symptoms, two items associated with emotional symptoms, one item associated with social discomfort, and three items associated with cognitive symptoms. In sum, this core subset of questionnaire items was highly predictive of schizophrenia severity and presents a quintessential summary of eleven items tapping into parts of the whole spectrum of schizophrenia symptomatology.

Over the past century, the most common practice to understand the risk of developing a mental disorder was

to look for the psychopathology's underpinnings by investigating the contribution of each potentially accountable variable to a specific mental disease. However, several advantages arise from predicting behavior (i.e., to accurately forecast behaviors that have not yet been observed) including the ability to test the relevance of existing theories and to discover new mechanisms²⁹. Furthermore, a number of successful studies often focused on prediction, rather than placing a premium on scientific discovery. For instance, Koutsouleris and colleagues³⁰ used support vector machines to predict the clinical outcomes of individuals in at-risk mental states of psychosis by showing relevance of predictive patterns of whole-brain neuroanatomical abnormalities that could forecast psychosis onset. Recently, Ramsay and colleagues³¹ performed a penalized regression variant and found that global cognition, education, and gender were predictive of improvement on global cognition following a cognitive training in schizophrenia patients, while the explanatory modeling, in the example of Pearson correlation and classical linear-regression-type analyses, did not find any relationship. Therefore, a strategy aiming at prediction appears to be an attractive complementary approach to enable improvements of clinical workflows.

Given the benefit of such analysis framework, we automatically extracted the most predictive items from the PANSS questionnaire. The eleven items highly predictive of schizophrenia severity corroborate results from previous clinical studies. In fact, the five dimensions underlying the psychopathology of schizophrenia often reported in different samples^{20–22,32–34} are comparable with the five symptom domains encompassed by the eleven highly predictive items. This overlap implies that similar underlying determinants of schizophrenia were uncovered by the two complementing approaches (i.e., the explanatory and the predictive strategies). In sum, these extracted symptom constellations, corroborating previous findings, might thus be relevant for further investigations related to disease trajectory.

The PANSS questionnaire is a gold standard for quantifying schizophrenia symptoms but has been repeatedly noted to require further improvement: Indeed, the PANSS questionnaire has been criticized for being lengthy³⁵. In fact, 30–40 min are required for the PANSS assessment¹³. Our results show that assessing only a third of this questionnaire may be sufficient for making accurate statements about psychopathological features of schizophrenia patients. This highly predictive subset of PANSS items could help to obtain a fast diagnostic of clinical/psychopathological severity which has several advantages. These benefits include (i) saving clinician time without sacrificing effectiveness, (ii) reducing the time taken for assessing symptoms severity and thereby saving patients time, and (iii) economic advantages such as savings in

national health expenditure, increased physician income or reduction of physician work hours.

Extracting subgroup categories from the PANSS

Using a clustering method, three types of distinct, clinically meaningful symptom categories emerged. A first profile with low expression for each questionnaire item, a second profile with some items scoring really high, and a third profile with a heavy affection on the negative scale. Providing evidence that a major difference between patients is the extent of the negative symptoms, our results also provide support for the possible clinical effectiveness of the subtypes.

Diagnostic manuals such as the DSM and the ICD highlight the focus on ensuring an effective communication of diagnoses between clinicians rather than capturing diagnoses that align well with biological reality. Given that schizophrenia is today widely acknowledged to be a spectrum disorder, modeling schizophrenia intermediate phenotypes (i.e., biological markers) is of great interest. Supplementing discrete disease definition in form of categorical and dimensional additions is an emerging mindset among many clinicians and researchers. Given that clinical subgroups of schizophrenia are often thought as disjoint from each other, we opted for adding “categorical” constraint to the analysis for discovering latent relationships between the PANSS items.

Even though PCA is the most often used statistical framework, a few existing studies also applied a clustering method to extract information from the PANSS. Rolls and colleagues³⁶ for instance, also applied a clustering method to a sample of patients diagnosed with schizophrenia. Three types of profile were also identified including a positive and high negative symptoms profile, a positive and intermediate negative symptoms profile and a positive and low negative symptoms profile. Each profile scored high on positive symptoms which was not the case in our study. However, both their results and ours provide evidence that the extent of negative symptoms underlies a major difference between patients. Other authors³⁷ also identified three subgroups in another schizophrenia sample identical to the three profiles that became apparent in our sample with in addition a fourth subgroup including patients scoring high only on positive items. Here, unlike our findings, positive symptoms were relevant to distinguish schizophrenia patients. Nonetheless, as in our study, dimensional partitions as well as negative symptoms were found to underlie discrete schizophrenia profiles.

In sum, our results corroborate previous findings suggesting latent structure in the PANSS items mostly based on negative symptom items. Our results have repeatedly emphasized relevance of blunted affect, apathetic social withdrawal, and emotional withdrawal items which were

found to be highly predictive of schizophrenia severity in our previous analysis. Moreover, these automatically extracted patient symptom constellations potentially endorse the possibility of existing schizophrenia subtypes.

Exploring complex patterns in the PANSS

We investigated the idea that more elaborate statistical relationships among questionnaire items may explain the response variability among patients with schizophrenia. We looked for both additive (i.e., linear) and interaction effects. Additive effects imply that the effect produced by two or more symptoms produce a total effect the same as the sum of their individual effects. Interaction effects mean that the combined effect is not additive. In fact, it is widely assumed that higher-order interactions between vulnerabilities triggered by the environment such as growing up in an urbanized area³⁸ and vulnerabilities conferred by genes such as *NRG1*³⁹ are important in the etiology of schizophrenia and may result in this major psychiatric disorder³⁸. Nonetheless, the very successful genome-wide association studies (GWAS) have been mostly grounded in additive models and thus blind to such interaction effects. In other words, common GWAS applications investigate the separate effect of each individual gene on overall disease vulnerability.

To test the hypothesis of similar interaction effects at the behavioral level as captured by PANSS responses, we compared the prediction accuracy of models looking for additive effects to models able to identify higher-order effects for possible enhanced prediction performance. Furthermore, we detailed this analysis with an examination of each model's learning curve to assess the predictive model performance as a function of increasing sample size. We found that in our patient sample, PANSS questionnaire items give information about the outcome (i.e., schizophrenia severity) in an additive manner. Indeed, the prediction performance obtained when looking for such additive effects was more consistently higher than when looking for higher-order effects. In sum, the linearity assumption seems to be appropriate given the higher obtained performance as indicated by currently available schizophrenia sample sizes. Nonetheless, our results also suggest that increasing sample size in future studies might be beneficial to extract higher-order effects between items of the PANSS.

Our results emphasizing additive effects between PANSS items, as much as supported by our multi-site patient cohort, have several clinical implications. First, to the best of our knowledge, our study is the first appropriate empirical evidence that validates the strategy of previous research of similar sample size. Indeed, previous PANSS studies have focused on simple effects underlying the questionnaire and our results legitimate this view. Second, our findings support the predictive validity of the

extracted subset of highly predictive PANSS items. Finally, these quantitative results suggest that schizophrenia severity is directly proportional to the PANSS questionnaire items. Indeed, such outcomes indicate that simple statistical relationships (e.g., simple correlation) underlie the PANSS items and are sufficient to extract knowledge in such sample size. These simple processes underlying the PANSS evaluation with its relation to schizophrenia severity can be decomposed into parts and reassembled into the same thing easing the interpretation. In sum, emphasizing linear effects underlying the PANSS questionnaire, this exploration endorses our analytic strategy while validating the statistical design of previous PANSS studies.

Conclusion

Our research exposes a subset of the PANSS items to be highly effective in detecting severe schizophrenia patients. This most predictive fraction of the PANSS items potentially allows for pragmatic, fast and cost-effective early intervention in schizophrenia in a future of precision psychiatry. As another consequence of our findings, identifying the best treatment for a given individual may not be grounded in positive, negative, or cognitive symptoms. Instead, subtle item combinations that transcend these categories may represent a more appropriate focus to better allocate treatment choices to a particular patient.

Schizophrenia, as a highly variable syndrome and major psychiatric disorder, is an important target for personalized medicine. This possible future requires that prevention and treatment strategies should take patient-specific aspects of clinical symptoms into account. Putting a premium on patient group and clinical tool predictability should facilitate procedural streamlining and enhance clinical care and alleviate economic costs. Individualizing treatment can better allocate health-care expenditures for treatments only effective in specific subpopulation of schizophrenia patients. Our results offer new quantitative insights into stratification of schizophrenia populations and might help for the development of improved clinical guidelines and workflows.

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SUPPORTING INFORMATION APPENDIX

"Patterns of Schizophrenia Symptoms: Hidden Structure in the PANSS Questionnaire"

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Renaud Jardri, Iris Sommer, Bertrand Thirion, Danilo Bzdok

Contents:

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2. Supplementary results (1 page)
3. Supplementary discussion (1 pages)
4. Supplementary figures (3 pages)
5. Supplementary table (1 page)
6. Bibliography (1 page)

1. SUPPLEMENTARY METHODS

Data resources

We revisited the underlying structure of the PANSS questionnaire based on behavioral data from eight different schizophrenia samples acquired in Europe and the USA: Goettingen, Groningen, Lille, Utrecht, Tuebingen, COBRE, as well as two different samples from Aachen (see Supplementary Table 1 for details). The behavioral assessments were collected from a total of 218 patients, including 154 males and 64 female subjects. Three patients were excluded from the study due to missing items scores in the PANSS questionnaire. The mean age across the eligible participants was 35.3 years (S.D. = 11.42; ranging from 18 to 65), which did not yield a statistically significant difference between males and females ($p=0.26$). Each subject has been diagnosed by a board-certified psychiatrist in accordance with the clinical criteria of the International Classification of Diseases (ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). All patients underwent a 40-45min semi-structured clinical interview with a medical doctor, after which the clinician rated the patient on the 30 PANSS items. The distribution of the PANSS questionnaire responses in our sample was homogeneous (Fig. 1). Ethics approvals were obtained from the ethics committee of each site's university.

Identifying the hidden item stratification: Principal component analysis

PCA is the most commonly applied data-analysis method that was previously used to discover hidden factors of variation in the PANSS questionnaire. We therefore applied the same statistical approach to our sample of schizophrenia patients as a point of comparison to previous research.

PCA summarizes the PANSS items scores into a smaller number of representative variables that collectively explain most of the variability across the set of original questionnaire items. The idea is that not all of the 30 PANSS items are equally effective in describing schizophrenia symptoms. PCA seeks weighted combinations of the items that are as interesting as possible, where the concept of *interesting* is measured by the amount that patient scores vary along each emerging dimension. More concretely, PCA explored the relationships between the 30 questionnaire items

and exhibits them as a linear combination of uncorrelated variables called *principal components*. Each such component of symptom variation is represented as a set of specific weights for the questionnaire items, one item weight for each hidden variability component. All weights of a given component are typically non-zero in contrast to the sparse modeling approach below. The weights of the first principal component define the most important source of variation that is as close as possible to the patient symptom scores as its direction is indicative of how response profiles vary the most. In other words, the first principal component i) captures a maximum of the information contained in the set of PANSS items, ii) identifies a direction along which the patient scores vary the most, and iii) provides the linear fit that is closest to the patients' clinical profile. The second principal component, in turn, is a linear combination of the PANSS items that is uncorrelated with the first principal component and extracts the largest direction of variance under this constraint. The strategy is analogous for the third and all subsequent extracted components. Each additional principal component must ensure uncorrelatedness to the previous ones while explaining the largest portion of unexplained variance.

The majority of previous studies revisiting the PANSS reported five-component solutions. We hence compared the similarities between the five PCA directions extracted from our patient sample and the five latent components found in other psychiatric populations (1-3).

Identifying hidden group structure: k-means clustering

We applied a k-means clustering algorithm to automatically partition patient symptom profiles into homogeneous groups. PCA and k-mean pursued complementary statistical goals in our study, although both these structure-discovery methods simplify the response items into a smaller number of summary scores. While PCA extracts representations of the data explaining most of the variance, k-means finds homogeneous groups among the observed symptom profiles from the patients. Here, the goal was to partition patients into discrete groups so that patients within each group are quite similar to each other in terms of their salient symptoms, while patients in different groups are maximally different from each other. In other words, this common clustering technique automatically establishes k groups that are internally coherent in their presented symptoms but as different as possible from each other. In contrast to PCA, k-means is a method identifying one-to-many mappings (4): each patient is a member of exactly one group. k-means seeks to partition patient symptom profiles into a number of non-overlapping patient groups. k-means requires to prespecify the desired number of groups k. We thus used "NbClust" (5), an established R package that simultaneously applied 30 cluster validity metrics. This approach provided complementary indications of the number of groups most supported by the patient data. Among all indices (using the method "median") and according to the majority rule, the best number of clusters was 3. That is, the most robust three groups were expressed in the final clustering solution. Therefore, three patient groups of distinct symptom profiles were automatically extracted as it provided a useful fit to our clinical sample.

Identifying predictive structure: Sparse logistic regression

The goal of PCA and k-means was to discover interesting symptoms patterns as measured by PANSS items such as underlying structure and relationship among schizophrenia patients. Complementing these insights in a next step, we applied a modeling technique that emphasizes both prediction performance and automatic

identification of the most relevant items. That is, we wanted to fit a model that i) relates the item scores to the severity of schizophrenia, with the aim of accurately predicting the response for future patient (i.e., out-of-sample prediction) and ii) finds the most parsimonious subsets of predictive PANSS items.

To achieve this goal, we capitalized on the pattern-learning algorithm *sparse logistic regression* (6). On the one hand, this predictive learning algorithm estimates the separating hyperplane (i.e., a linear function) that distinguishes patients with more severe versus more mild schizophrenia symptoms. The outcome y is defined by the severity of schizophrenia. The severity is characterized by the median-split of the PANSS total score (0 as mild, 1 as severe) as it was the categorical summary of the constituent continuous scores. On the other hand, the imposed sparsity constraint identifies a minimal subset of features (i.e., items of the PANSS questionnaire) that is most informative about the differences between patients. While computing a vector of weights associated with the items, similar to linear regression, this approach aims to reduce the weights of items that have little discriminatory value to exactly zero (a feature's weight equal to zero has no effect on the prediction outcome). This procedure results in a subselection of items which have high joint discriminatory power to separate patients with severe versus mild symptoms. In this way, sparse logistic regression extends previous PANSS investigations by automatic *variable selection* (7). Its benefit is rooted in its clear algorithmic definition leading to formal and rigorous choices in automatic variable selection. This additional constraint enforcing parsimony of response items is particularly useful in our study, as it helps pointing to subset of items most predictive of schizophrenia severity. As a result, our modeling findings obtained from the sparse logistic regression are much easier to interpret.

The sparsity constraint was imposed in form of an ℓ_1 regularization. Such a constraint in the optimization objective automatically detects relevant features “on-the-fly” during model estimation. The ℓ_1 penalty term, calibrated by the hyper-parameter λ , is designed to control the parsimony criterion and its shrinkage regularization on the learned model weights. This penalized (negative) log likelihood of the logistic regression objective is given by:

$$-\frac{1}{N} \sum_{i=1}^N \log(1 + e^{-y_i f(x_i; \beta_0, \beta)}) + \lambda \|\beta\|_1$$

where x_i represents a given patient's PANSS scores, y_i is his/her schizophrenia severity, β_0 is the intercept, and β is the weight attached to each questionnaire item, the right part of the equation corresponds to the ℓ_1 penalty term controlled by the hyper-parameter λ . The item selection behavior depends on the choice of this tuning parameter. Indeed, the sparse logistic regression shrinks the coefficient estimates more toward zero and performs always more aggressive variable selection with increasing λ . The hyper-parameter selection was based on the data in a principled fashion using nested cross-validation. In a common grid of candidate parameter choices, the value of λ was varied logarithmically from 3.5 to 1.0 in log-space with 16 steps. The member in the model family that yielded highest prediction accuracy (i.e., generalization performance) for each candidate of λ was selected. In this way, the quantitative investigation detected subsets of items that were most predictive for schizophrenia severity. In other words, the goal here was not to select the best hyperparameter. Rather, we charted a space of candidate λ to explicitly investigate the transition from low to high sparsity.

Finally, we further detailed this analysis with an examination of the learning curve to assess the predictive model performance as a function of increasing sample size. To this

end, we computed the prediction accuracy for the sparse logistic regression for predicting schizophrenia severity in a series of increasing patient subsets for model training.

Testing for complex relationships among the PANSS items

The k-means method (cf. above) extracted latent structure dormant in the data regardless of symptom severity measures. Sparse logistic regression (cf. above) in turn selected the most predictive variables but this predictive algorithm was not convenient to uncover hidden non-linear relationships between the questionnaire items. We combined exploration of more sophisticated item-item relationships with evaluating prediction performance using non-linear predictive algorithms. In this way, we tested the hypothesis of existing higher-order relationships between the PANSS responses and their usefulness for prediction. We compared the performance of linear models to the performance of models able to exploit non-linear structure in the questionnaires. We complemented this analysis with accuracy-sample-size examination by computing learning curve for each pattern-learning model. Three linear models (ridge regression, logistic regression, and support vector machine) were benchmarked against three models allowing looking for higher-order interactions (k nearest neighbor, random forest and adaptive boosting). Again, schizophrenia severity was defined as the median-split of the PANSS total score (0 as mild, 1 as severe) representing a categorical summary of the constituent continuous scores.

Among the linear predictive pattern-learning algorithms, the ridge regression is commonly used as a shrinkage method. This model encourages small absolute weights on each item which emphasized the most predictive PANSS items, while linear support vector machines mapped the items as points in space so that items of separate categories (predictive of a mild or a severe schizophrenia) were divided by a maximal gap between the patients.

Regarding the non-linear models, the k nearest neighbor estimator uses the k closest training examples (in our case, the closest patient symptom profiles) in the feature space, while the output is determined by a majority vote across these most similar training examples. In other words, the guessed severity for a given new schizophrenia patient can thus be derived from the schizophrenia severity of the k closest patients in the training set. Further, the random forest algorithm is an ensemble learning method that operates by constructing a multitude of decision trees and outputs its prediction estimate that is the committee decision across all trees. The severity of schizophrenia symptoms in a given patient was thus derived based on the most consistently predicted outcome of the built decision trees. As the last non-linear prediction algorithm, the adaptive boosting algorithm starts by fitting a model on the dataset and then fits additional copies of that model on the same dataset but where the weights of incorrectly judged instances are adjusted such that subsequent fine-tuning of models focusses more on difficult cases.

Code availability

Python was selected as scientific computing engine. Capitalizing on its open-source ecosystem helps enhance replicability, reusability, and provenance tracking. Scikit-learn (8) provided efficient, unit-tested implementations of state-of-the-art statistical learning algorithms (<http://scikit-learn.org>). All analysis scripts of the present study are readily accessible to the reader online (<https://github.com/JLefortBesnard/Panss2018>).

2. SUPPLEMENTARY RESULTS

Comparison to previous hidden-factor investigations

In a preparatory analysis, we replicated the most often used statistical approach for latent-factor modeling of the PANSS questionnaire administered to schizophrenia patients (SFig. 1). We computed the five dominant components of variation in our multi-site sample using PCA analogous to previous studies (1-3). Our findings from the five-component solution were found to be virtually identical to the previously reported findings in other schizophrenia populations (1-3).

The present PCA decomposition of PANSS items explained 52% of the variance across symptom scales. This result in our sample is similar to what was found in previous studies: 52% (2), 51% (3), up to 57% of variance explained (1). The component most associated with negative symptom items captured the largest amount of the total variance (26%). Several PANSS items were found to be important in both the first component extracted from our dataset and in the first component derived from other patient samples (1-3). This first component was mostly associated with negative symptom items, including disturbance of volition, passive/apathetic social withdrawal, active social avoidance, motor retardation, and emotional withdrawal from the highest to the lowest absolute association. Our second component exhibited most associations with various positive symptom items (10% explained variance). Three items with relevant weights were found both in our component as well as in the component associated with positive symptom items discovered in previous studies (1-3). These items included grandiosity, unusual thought content, and delusions (from highest to lowest weight relevance). The three remaining components explained approximately 5% of the variance each. A component associated with excitement symptoms had two highly weighted items in common with the excitement-related component of previous studies including from the highest to the lowest absolute association poor impulse control and uncooperativeness (1-3). The five items preoccupation, mannerisms and posturing, stereotyped thinking, conceptual disorganization, lack of judgement and insight (ordered from the highest to the lowest absolute weight) were found relevant in our fourth component as well as in previously reported components mostly associated with cognitive symptom (1-3). Finally, the fifth component exposed three relevant items that were also highlighted in the component related to emotional discomfort symptom in previous studies (1-3), including tension, somatic concern, and preoccupation (from the highest to the lowest absolute weight).

In sum, carrying out PCA on PANSS questionnaires from a large schizophrenia sample led to virtually identical directions of variation patterns underlying symptom combinations as in previous factor modeling investigations. Furthermore, the discovered variability components that explained most of the variance prominently included PANSS items associated with negative symptom. Instead, PANSS items from the positive and general scales were more inconsistently emphasized across the components of variation, which is in line with previous findings (1-3).

3. SUPPLEMENTARY DISCUSSION

Extracting continuous axes in the PANSS

Our investigation set out by replicating the often reported latent-factor results obtained from the principal components of the PANSS questionnaire administered to schizophrenia patients. To evaluate correspondence with a stream of previous PANSS studies, we extracted five most dominant components in our sample. In agreement with previous research, these five directions of variation indicated that symptomatology varies along negative, positive, excitement, cognitive and emotional discomfort symptoms items from the highest to the lowest influence.

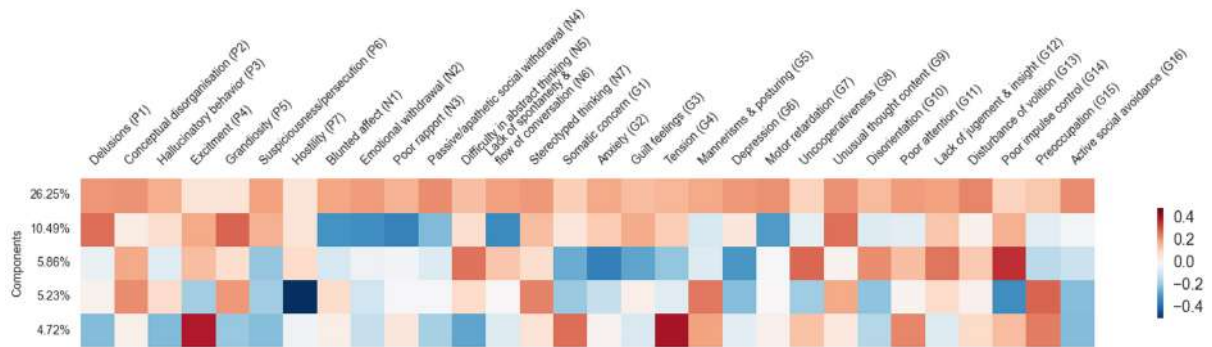
Over more than 30 years, insightful information about schizophrenia psychopathology was obtained through the extraction of hidden dimensions in the PANSS questionnaire using an essentially identical statistical tool: principal component analysis. Most studies of clinical behavior have probed item patterns of five overarching components underlying the PANSS questionnaire. An overwhelming majority of previous studies reported a component with relevant loadings on negative symptom items as explaining most of the variance (1-3). Here, we replicated this recurring finding across over a dozen of previous PANSS questionnaire investigations. Indeed, most of the response variability was explained by the component with relevant loadings on negative symptoms items. This first component can be viewed as the direction along which the patient scores are highly variable. Another recurring finding includes a component with relevant loadings on positive symptom items which was also replicated in our sample (1-3). The three other components were also similar to the previous findings as their loadings emphasized variation over an excitement, cognitive, and emotional discomfort syndrome. In this set of preparatory analyses, our results confirmed virtually identical symptom gradients underlying PANSS questionnaire scores suggesting similarities in the underlying properties present in our multi-site dataset and those present in samples from other PANSS investigations.

Analogous to previous studies (1-3), our sample analysis revealed no item associated with positive symptoms that has high loadings in the first component associated with negative symptoms. This observation corroborates previous findings supporting the notion that the negative symptoms represent a source of variation separate from other symptom aspects in schizophrenia. Indeed, across studies, negative symptoms consistently emerged as a separate factor (9). Instead, across previous PCA analyses, PANSS items from the positive and general scales were more inconsistently associated with components of variation (1-3). Explanations for the observed divergences may include that different subgroups of schizophrenia patients differ less systematically in their symptom patterns that are different from the negative symptoms.

In sum, our results are in line with the pentagonal model of representation of PANSS, which defines five hidden factors summarizing schizophrenia patients PANSS scores (3). The pentagonal model includes variation over negative, positive, activation, dysphoric mood and autistic preoccupation symptoms items which mostly corroborate other findings (1, 2) including ours. We indeed obtained five virtually identical directions of variation patterns underlying PANSS questionnaire scores. In other words, we have shown that our sample harbors very similar emerging properties than most of the previously explored schizophrenia patients samples.

4. SUPPLEMENTARY FIGURES

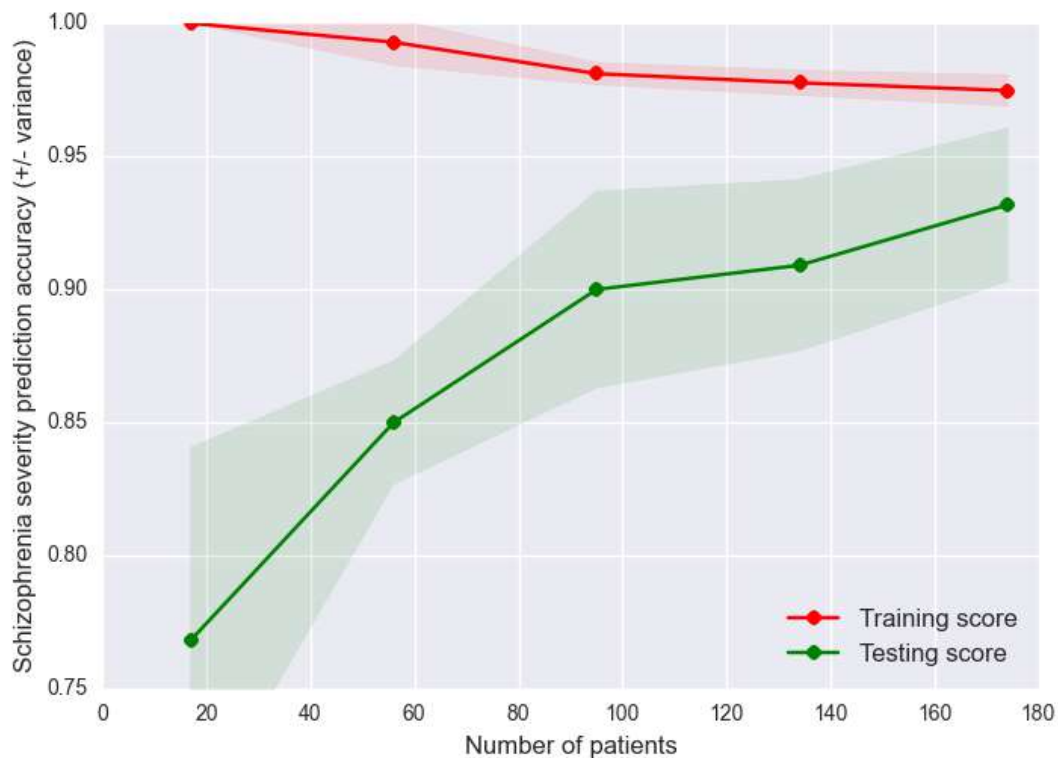
Supplementary figure 1



Replication of the previous PCA approaches to decomposing PANSS questionnaire.

We carry out commonly used principal component analysis to derive five components of variation in the PANSS questionnaire data in our patient sample. Each component and its ratio of explained variance are shown. Each row shows the item relevance (weights) for each component. The findings confirmed earlier descriptions of five components, each closely and specifically associated with a particular schizophrenia symptom including negative, positive, excitement, cognitive and emotional discomfort symptoms. Among these, we obtained one component roughly corresponding to each group of symptoms. Our five-component solution was virtually identical to the components found in a series of previous hidden factor decompositions in schizophrenic patient samples (1-3).

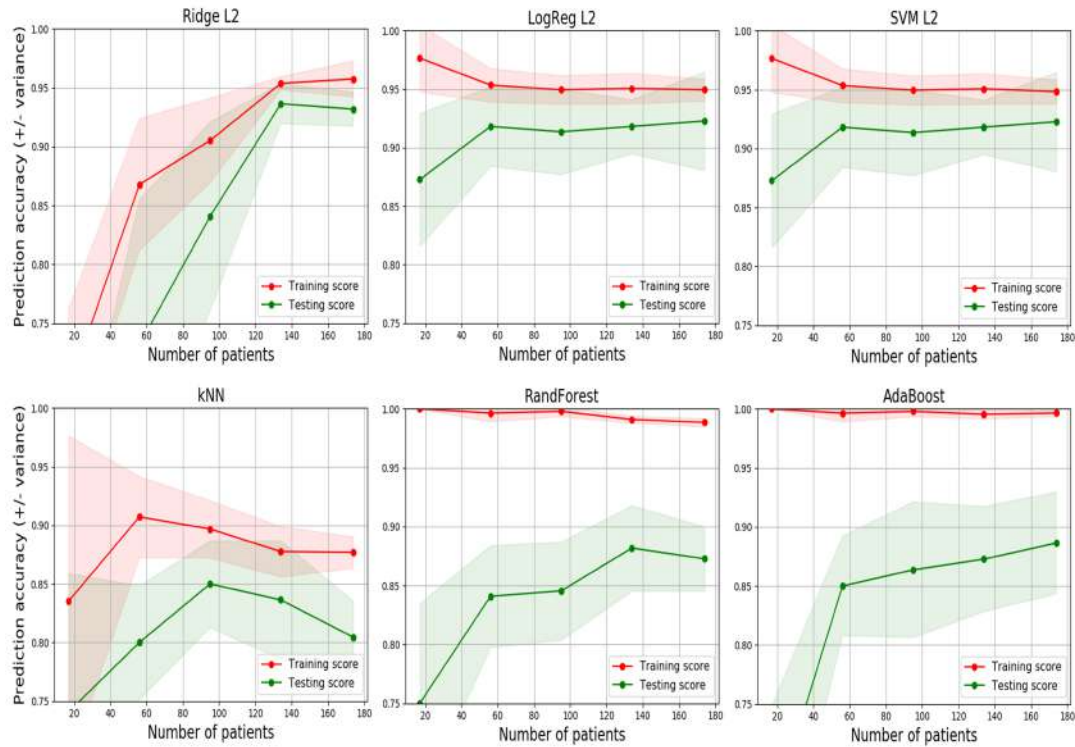
Supplementary figure 2



Scaling of schizophrenia prediction accuracy with increasing patients.

A learning curve is a representation of performance of the learning algorithm with always bigger subsets of the data at hand. The number of patients included is plotted on the x axis while the y axis displays the obtained accuracy for each specific setting (5 splits of the total amount of available data). The *red line* represents the average in-sample (i.e., *training score*) accuracy, while the green line represents the average generalization performance (i.e., *testing score*). The green and red shadows represent the accuracy standard deviations. Performance in the training set higher than performance in the testing set is to be expected since the training score can dramatically overestimate the test score. Indeed, the learning algorithm learns from the training data and therefore is optimistically biased while the test score represents the efficiency of the model applied to unseen data. While recruitment of more patients would likely further improve the performance of the learning algorithms, we can observe that gathering 90 subjects is a good tradeoff between the needed amount of data and achieving a fair classifier performance.

Supplementary figure 3



Scaling of linear and non-linear prediction accuracy with increasing patients.

We explored the learning behavior of each model with always bigger subsets of the data at hand, in the same fashion as the analysis in supplementary figure 2. The learning curve of each linear model (Ridge Regression, Logistic Regression and SVM) is plotted on the first row while the learning curve of each non-linear model (kNN, Random Forest, and Adaptive Boosting) is plotted on the second row. The number of patients whose data is considered is given on the x axis, while the y axis displays the obtained accuracy for each specific setting (5 splits of the total amount of available data). The *red line* represents the average in-sample (i.e., *training score*) accuracy, while the green line represents the average expected generalization performance (i.e., *testing score*). The green and red shadows represent the accuracy standard deviation. We can observe that gathering around 130 subjects is a good tradeoff between the needed amount of data and achieving a fair classifier performance for both the linear and non-linear models. On the other hand, recruitment of more patients may likely further improve the performance in more data-hungry non-linear models, such as the AdaBoost.

5. SUPPLEMENTARY TABLE

Supplementary table 1:

Sites	# patients	# male	# female	Age (M)	Age (Std)	Age onset (M)	Age onset (Std)
Aachen	28	20	8	36,57	9,79	27,68	8,61
Groningen	32	19	13	32,97	11,19	25,78	9,27
Utrecht	23	13	10	35,46	9,78	25,28	6,08
Goetingen	36	29	7	32,06	9,81	25,61	8,16
Tuebingen	9	4	5	32,11	9,37	23	0
Lille	18	11	7	33,89	7,65	22,89	2,59
Cobre	72	58	14	38,17	13,89	23,61	5,95
TOTAL	218	154	64	35,3	11,42	24,83	5,06

6. SUPPLEMENTARY BIBLIOGRAPHY

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Cheers and thanks again, to all of you.

Affidavit according to § 5 (1) for Data Retention

Erklärung § 5 Abs. 1 zur Datenaufbewahrung

Hiermit erkläre ich, dass die dieser Dissertation zu Grunde liegenden Originaldaten

- bei mir, Lefort-Besnard Jeremy, 21 Rochusstraße, 52062 Aachen, Germany
- und
- bei meinem Betreuer, Prof. Dr. Dr. Danilo Bzdok, Klinik für Psychiatrie, Psychotherapie und Psychosomatik, des Universitätsklinikums Aachen,

hinterlegt sind.

Affidavit according to § 5 (1) and (2), and § 11 (3) 12 of the doctoral studies regulations

I, Lefort-Besnard Jeremy, hereby declare on oath, that I have contributed a significant part, and thus majority, of the publication:

Lefort-Besnard J. (candidate), Bassett S.D., Smallwood J., Margulies S.D., Derntl B., Gruber O., Aleman A., Jardri R., Varoquaux G., Thirion B., Eickhoff B.S., Bzdok D. (supervisor): Different shades of default mode disturbance in schizophrenia: Subnodal covariance estimation in structure and function; Human Brain Mapping; 2017, 39:644–661.

The contributions to the publications were as follows:

Names ->	Candidate: Jeremy Lefort-Besnard	Danielle Bassett	Jonathan Smallwood	Daniel Margulies	Birgit Derntl	Oliver Gruber	Andre Aleman	Renaud Jardri	Gael Varoquaux	Bertrand Thirion	Simon Eickhoff	Co-Authors	Doctoral supervisor: Danilo Bzdok	Sum (%)
Study supervision													100	100
Study design/conception													100	100
Data manipulation	50												50	100
Data visualization	50												50	100
Vizualization insights		10	10	10	10	10	10	10	10	10	10	100		100
Statistical evaluation	50												50	100
Statistical insights		10	10	10	10	10	10	10	10	10	10	100		100
Delivery of materials					12,5	12,5	12,5	12,5				50	50	100
Interpretation of data evaluation	80	1	1	1	1	1	1	1	1	1	1	10	10	100
Writing/draft of the manuscript	100													100
Correction of the manuscript		1	1	1	1	1	1	1	1	1	1	10	90	100

The position as the first author obviously arises from this significant contribution.

Signature of the doctoral candidate

As supervisor and corresponding author I confirm the statements of Lefort-Besnard Jeremy and as a representative of the collaborative partners (Bassett S.D., Smallwood J., Margulies S.D., Aleman A., Jardri R., Varoquaux G., Thirion B.)

Signature of the doctoral supervisor

As co-author I endorse the statement of Prof. Dr. Dr. Bzdok
Names and signatures of all German speaking co-authors (allowed on separate pages)

Birgit Derntl

Oliver Gruber

Simon Eickhoff

Affidavit according to § 5 (1) and (2), and § 11 (3) 12 of the doctoral studies regulations

I, Lefort-Besnard Jeremy, hereby declare on oath, that I have contributed a significant part, and thus majority, of the publication:

Lefort-Besnard J. (candidate), Varoquaux G., Derntl B., Gruber O., Aleman A., Jardri R., Sommer I., Thirion B., Bzdok D. (supervisor): Patterns of Schizophrenia Symptoms: Hidden Structure in the PANSS Questionnaire; Translational Psychiatry; In press.

The contributions to the publications were as follows:

Names ->	Candidate: Jeremy Lefort-Besnard	Gael Varoquaux	Birgit Derntl	Oliver Gruber	Andre Aleman	Renaud Jardri	Iris Sommer	Bertrand Thirion	Co-Authors	Doctoral supervisor: Danilo Bzdok	Sum (%)
Study supervision										100	100
Study design/conception										100	100
Data manipulation	50									50	100
Data visualization	50									50	100
Vizualization insights		14,3	14,3	14,3	14,3	14,3	14,3	14,3	100		100
Statistical evaluation	50									50	100
Statistical insights		14,3	14,3	14,3	14,3	14,3	14,3	14,3	100		100
Delivery of materials			10	10	10	10	10		50	50	100
Interpretation of data evaluation	80	1,43	1,43	1,43	1,43	1,43	1,43	1,43	10	10	100
Writing/draft of the manuscript	100										100
Correction of the manuscript		1,43	1,43	1,43	1,43	1,43	1,43	1,43	10	90	100

The position as the first author obviously arises from this significant contribution.

Signature of the doctoral candidate

As supervisor and corresponding author I confirm the statements of Lefort-Besnard Jeremy and as a representative of the collaborative partners (Varoquaux G., Aleman A., Jardri R., Sommer I, Thirion B.)

Signature of the doctoral supervisor

As co-author I endorse the statement of Prof. Dr. Dr. Bzdok
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Birgit Derntl

Oliver Gruber