

RESEARCH ARTICLE

Predicting individual variability in task-evoked brain activity in schizophrenia

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Abstract

What goes wrong in a schizophrenia patient's brain that makes it so different from a healthy brain? In this study, we tested the hypothesis that the abnormal brain activity in schizophrenia is tightly related to alterations in brain connectivity. Using functional magnetic resonance imaging (fMRI), we demonstrated that both resting-state functional connectivity and brain activity during the well-validated N-back task differed significantly between schizophrenia patients and healthy controls. Nevertheless, using a machine-learning approach we were able to use resting-state functional connectivity measures extracted from healthy controls to accurately predict individual variability in the task-evoked brain activation in the schizophrenia patients. The predictions were highly accurate, sensitive, and specific, offering novel insights regarding the strong coupling between brain connectivity and activity in schizophrenia. On a practical perspective, these findings may allow to generate task activity maps for clinical populations without the need to actually perform any tasks, thereby reducing patients inconvenience while saving time and money.

KEYWORDS

cognitive function, Connectome, fMRI, machine learning, resting-state, schizophrenia

1 | INTRODUCTION

Understanding the differences between the brains of psychiatric patients and healthy individuals has been a major challenge for neuroscientists and psychiatrists, with specific efforts focused on schizophrenia (SCZ), because of its extreme clinical, social, and financial implications (Cloutier et al., 2016; Heinrichs & Zakzanis, 1998; McCutcheon, Reis Marques, & Howes, 2020; Velthorst et al., 2016). A vast body of evidence from over 20 years of neuroimaging studies in schizophrenia suggests that one of its underlying causes is a disruption in brain connectivity (Lynall et al., 2010; Van Den Heuvel & Fornito, 2014).

A broadly used approach to measure brain connectivity noninvasively is to detect brain regions that show high temporal correlation in

functional magnetic resonance imaging (fMRI) scans acquired at rest, that is, when no explicit task is introduced (rs-fMRI). This method can be used to explore the architecture of functional brain networks, often referred to as resting-state networks (RSN's) (Bijsterbosch, Smith, & Beckmann, 2017; van den Heuvel & Hulshoff Pol, 2010). Alterations in various RSN's that are associated with high cognitive functions, such as the default-mode (Whitfield-Gabrieli et al., 2009), salience (Palaniyappan, Simmonite, White, Liddle, & Liddle, 2013), and fronto-parietal (Godwin, Ji, Kandala, & Mamah, 2017) networks are consistently reported in schizophrenia. These alterations are in line with the substantial cognitive deficits and behavioral changes that are among the hallmarks of this condition (Heinrichs & Zakzanis, 1998; Knowles et al., 2015). Patients diagnosed with schizophrenia also

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demonstrate abnormal task-associated brain function compared to healthy individuals (Gur et al., 2002; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009) in several cognitive domains such as emotional response, decision making, response inhibition, and working memory.

Even though the abovementioned deficits in both functional connectivity and brain activity reported in schizophrenia may be in line with one another, they were traditionally studied mostly as two separate elements (Bijsterbosch et al., 2017). In the last few years, studies have been trying to bridge this gap and establish the claim that brain activation while performing different tasks is closely related to brain connectivity. Such studies, focusing mainly on young healthy adults, have shown that functional connectivity closely corresponds with task-derived measures, and that RSNs qualitatively resemble task-evoked networks at the group level (Cole, Bassett, Power, Braver, & Petersen, 2014; Krienen, Thomas Yeo, & Buckner, 2014; Smith et al., 2009). Furthermore, It has been demonstrated that by applying machine-learning based computational models, these RSNs can be used to predict differences in fMRI activation across a range of cognitive paradigms (Tavor et al., 2016), even for individuals with unique or unusual brain activation patterns. This highlights a strong coupling between brain connectivity and activity that can be captured at the level of individual participants.

The abovementioned findings suggest that the relationship between functional connectivity and task-evoked brain activity in healthy individuals may be a constant intrinsic trait rather than a transient state (Finn & Todd Constable, 2016). If it is in fact an intrinsic trait, it suggests that networks' organization could be mapped directly to brain function. This means that given a specific set of connectivity measures it will be possible to predict brain activation patterns in individuals regardless of their specific brain attributes and even if they suffer from a pathology that effects these attributes.

The idea that task-evoked brain activity can be predicted from task-free functional connectivity in both healthy individuals and patients was supported by a study which demonstrated that brain activity could be successfully predicted in patients awaiting neurosurgery (Parker Jones, Voets, Adcock, Stacey, & Jbabdi, 2017). However, these patients suffered from focal and well understood structural abnormalities. The question whether the close relationship between functional connectivity and brain activity is similar for individuals with brain pathologies that are more "diffuse" and "holistic," such as schizophrenia and other psychiatric disorders, remains unclear.

Successful predictions of task-evoked brain activity from task-free functional connectivity measures would allow reducing the fMRI protocol to a single rs-fMRI scan, instead of a series of demanding cognitive tasks. This would dramatically diminish scan time and inconvenience, and allow studying challenging populations that are usually not compliant with task performance, such as psychiatric patients (Fox & Greicius, 2010). But above all, this approach has the potential to deepen our understanding of how brain connectivity and activity are interrelated in the pathological brain and may further the understanding of the underlying mechanisms of schizophrenia.

In the current study, we aim to investigate the relationship between functional connectivity and task-evoked brain activity in SCZ patients

by predicting task-evoked brain activity from task-free functional connectivity measures. First, we asserted the differences between patients and controls in both task-evoked brain activity and resting-state functional connectivity. Then, we trained a prediction model based on functional connectivity measures extracted from task-free scans of healthy controls and applied the model to predict working memory task-evoked brain activity in SCZ patients. We demonstrate accurate predictions in terms of sensitivity, represented by high overlap between predicted and actual brain activation maps, and specificity, represented by accurate prediction of individual-unique activation patterns.

2 | MATERIALS AND METHODS

2.1 | Participants

The dataset was acquired in Sheba Medical Center, Ramat-Gan, Israel. It originally consisted of 112 participants: 89 healthy volunteers and 23 patients diagnosed with schizophrenia (SCZ). All participants were 18–55 years old Hebrew speakers and had no history of neurological conditions (no significant age difference between groups, $P = .113$). The control participants had no history of psychiatric conditions. The research protocol was approved by the Institutional Review Board of Sheba Medical Center. All participants signed an informed consent form. Nine healthy volunteers and three SCZ patients were excluded from the study due to insufficient task performance or the lack of vital MRI scans. The final dataset used for analysis consisted of 80 healthy volunteers and 20 patients. Clinical and demographic characteristics are described in Table 1. Individual level characteristics for SCZ group are described in Table S1.

2.2 | Clinical assessment

All participants in the SCZ group met the criteria for schizophrenia according to DSM-5 and were diagnosed by a psychiatrist. Symptoms

TABLE 1 Clinical and demographic characteristics. SCZ = patients diagnosed with schizophrenia

	Control (N = 80)	SCZ (N = 20)
Age (years) Mean (STD)	33.67 (11.79)	29.3 (6.39)
Gender % male	56.25	80
PANSS total Mean (STD)	–	50.64 (12.83)
PANSS general Mean (STD)	–	23.47 (5.47)
PANSS positive Mean (STD)	–	11 (4.99)
PANSS negative Mean (STD)	–	16.18 (5.16)

severity was evaluated using the Positive and Negative Syndrome Scale (PANSS) for schizophrenia (Kay, Fiszbein, & Opler, 1987). Out of 20 patients, 17 had available PANSS scores. Average clinical scores are described in Table 1 and individual scores in Table S1.

2.3 | fMRI working memory task

All participants conducted the widely used fMRI working memory (WM) N-back task (Livny et al., 2018; Owen, McMillan, Laird, & Bullmore, 2005). Differences between control participants and SCZ patients in this task have been reported consistently, in both brain activation patterns and task performance (Jansma, Ramsey, Van Der Wee, & Kahn, 2004; Krieger, Lis, Cetin, Gallhofer, & Meyer-Lindenberg, 2005; Whitfield-Gabrieli et al., 2009). A detailed description of the task design can be found in Supporting Information and Figure S1.

2.4 | MRI acquisition

Participants underwent an MRI session which included anatomical, task-fMRI and rs-fMRI scans. Scans were acquired on a 3 Tesla whole body MRI system (GE Signa HDxt, version 16 VO2) equipped with an eight-channel head coil.

Anatomical high-resolution (1mm^3 , Matrix size 256×256 , FOV 25.6 cm) images of the entire brain were acquired, using a standard 3D inversion recovery prepared fast spoiled gradient echo pulse (FSPGR) T1 weighted sequence. Additional anatomical sequences (T2w and fluid-attenuated inversion recovery [FLAIR]) were acquired for radiological screening.

Working memory task functional scans were acquired with a T2*-weighted gradient-echo echo-planar protocol (GE-EPI) using the following parameters: TR = 3 s; TE = 30–35 ms; matrix size 64×64 , FOV 22×22 cm, and up to 40 contiguous oblique axial slices covering the whole brain. The resulting voxel size was 3.4 mm^3 .

Rs-fMRI protocol was almost similar to the task fMRI protocol, except that TR was reduced to 2 s and scan time was 9:53 min. Participants were instructed to close their eyes during the scan.

2.5 | fMRI preprocessing and individual statistics

fMRI preprocessing (see Figure 1) for both rs-fMRI and N-back task was carried out using FMRIB Software Library (FSL v5.0.10) (Smith et al., 2004) and included high-pass filtering at 0.01 Hz, correction for motion artifacts, linear registration to the T1w anatomical scan, nonlinear registration to 152MNI space, and smoothing with 5 mm gaussian kernel. Residual noise was cleaned using FMRIB's ICA-based Xnoiseifier (FIX) (Griffanti et al., 2014), which is a semi-automatic ICA based method to identify and remove structured noise from fMRI scans. Motion confounds (24 parameters) were regressed out the data in that process. Then each scan was resampled onto the set of 91,282

“grayordinates” (Glasser et al., 2013) in standard space which was used for surface representation using the HCP's Connectome Workbench visualization and discovery tool (Marcus et al., 2011). Individual-level statistical analysis was performed using the FEAT pipeline in FSL (Woolrich, Ripley, Brady, & Smith, 2001). Task activation maps were generated for the 2back > 0back contrast representing brain activity associated with working memory (Owen et al., 2005) for each participant.

2.6 | fMRI group analysis

As mentioned above, group differences in brain activity between healthy and SCZ participants in the N-back task are well documented (Jansma et al., 2004; Krieger et al., 2005; Whitfield-Gabrieli et al., 2009). However, it is important to validate that such differences are found in our specific dataset in order to ensure that successful prediction is not simply a result of no variability between the groups. In order to test for group differences in task evoked brain activation, group level analysis was performed using FSL's FEAT pipeline. Z-score activation maps depicting group differences in brain activation were created using FMRIB's local analysis of mixed effects (FLAME) (Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). The activation maps were then thresholded using a Gaussian-two-Gammas mixture model (Beckmann & Smith, 2004), where the Gaussian represents the noise and the two Gamma distributions represent positive and negative activations. The positive and negative thresholds are chosen to correspond to the medians of the two Gamma distributions.

2.7 | Functional connectivity-based classification

It is well established that SCZ patients demonstrate altered patterns of brain connectivity compared to controls (Lynall et al., 2010; Van Den Heuvel & Fornito, 2014; Whitfield-Gabrieli et al., 2009). Before exploring the predictability of task-evoked activity from connectivity measures, we aimed to assert these differences in our dataset. In order to achieve this, we trained a classifier to distinguish between controls and SCZ based on functional connectivity measures.

Feature extraction for classification was conducted by averaging the preprocessed rs-fMRI time courses within each of 100 cortical parcels, where each parcel was assigned to one of seven brain networks, according to a parcellation by Schaefer et al. (Schaefer et al., 2018). Pearson's correlation coefficients were calculated for each dyad of parcels, resulting in 4950 correlation scores, which were used as features for the classification model. All features were normalized by removing the mean and scaling to unit variance.

Then, we utilized an elastic-net logistic regression model in order to classify each participant to either patient or control. The L1/L2 ratio ($\alpha = 0.7$) and the regularization factor ($\lambda = 0.77$) were chosen in a stratified fivefold cross-validation procedure. In order to determine chance level rates and utilize them to test for statistical significance

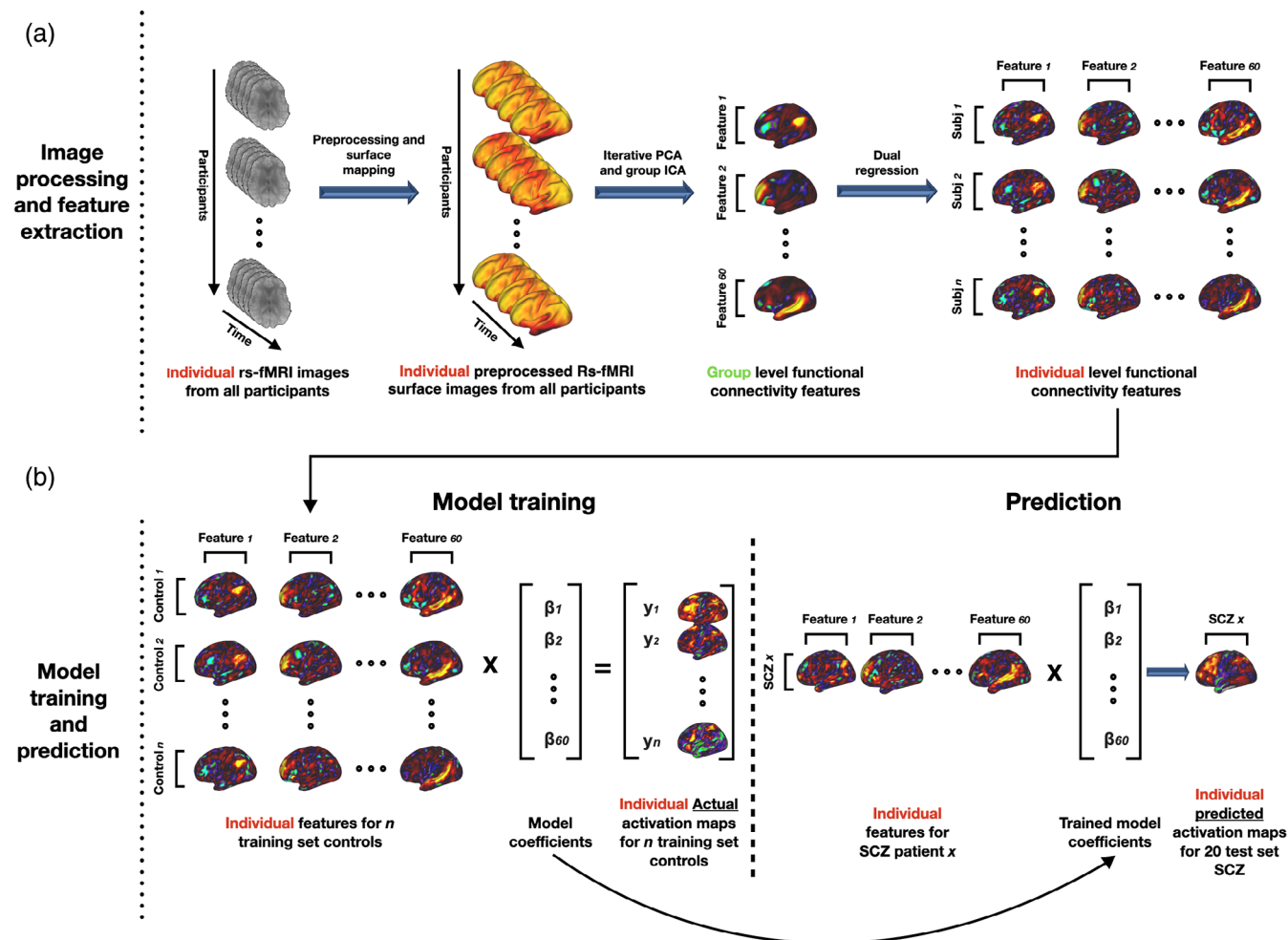


FIGURE 1 Prediction pipeline: (a) fMRI preprocessing and feature extraction included iterative principal component analysis (PCA) followed by group independent component analysis (ICA) to yield group level functional connectivity maps (features). Then, dual regression was applied to generate individual-level features. (b) Our GLM based prediction model was trained on features extracted solely from healthy controls (training set) and validated using a leave-one-out routine. Last, the trained model was applied on the SCZ patients (test set) and yielded a predicted activation map for each participant. Note that the process described in panel B was conducted separately for each of 50 nonoverlapping brain parcels to yield a whole cortex predicted activation map (see Supporting Information)

we used a 5,000 iterations permutation test in which our classification labels (control or SCZ) were shuffled randomly. We calculated four scores to determine prediction success: AUC (Area under the receiver operating characteristics curve), accuracy, sensitivity and specificity. For more details see Supporting Information.

To explore which features contributed most to the classification, we sorted them by the absolute classification beta value. To ensure the robustness of the results we repeated this procedure 1,000 times and averaged the beta values across all iterations. Then, we extracted the 100 features that contributed most to the classification.

2.8 | Prediction of task activity from functional connectivity measures

The prediction pipeline was adapted from Tavor et al. (2016). We used data from 80 control participants as a training set. Feature

extraction included dimensionality reduction of preprocessed rs-fMRI maps by iterative group principal component analysis (PCA) (Smith, Hyvärinen, Varoquaux, Miller, & Beckmann, 2014), yielding 200 group level principal components. Next, group-level spatial independent component analysis (ICA) (Beckmann, DeLuca, Devlin, & Smith, 2005) was carried out on cortical data using fast ICA (Hyvärinen, 1999) to define a set of 60 cortical group-level functional connectivity maps. Then dual regression (Beckmann, Mackay, Filippini, & Smith, 2009) was performed on the group level connectivity maps to generate individual-level functional connectivity maps that were used as features for the prediction model.

A linear model was used to map the functional connectivity features to the individual task-evoked activation maps. The model was trained only on the 80 healthy controls training set. Regression coefficients (betas) were calculated for each participant, and then, for performance validation purposes, averaged for $n - 1$ participants each time to execute a leave-one-out (LOO) prediction routine to generate

a predicted task activation map for each control participant. Then, the trained model was utilized to predict task activation maps in 20 SCZ patients that were kept out in previous steps. A detailed description of the prediction pipeline be found in Figure 1 and Supporting Information.

3 | RESULTS

3.1 | N-back working memory task group differences

Group differences between SCZ patients and healthy controls in the 2back > 0back contrast of the N-back task were tested. As expected, significant differences in activation were found in various cortical regions. Healthy controls displayed higher activation mainly in areas that correspond with the fronto-parietal network (Thomas Yeo et al., 2011) such as the dorsolateral prefrontal cortex (DLPFC), medial frontal cortex, inferior parietal lobule and posterior temporal regions. SCZ patients displayed significantly higher activations mostly in occipital visual areas and in the left insula. These group differences are presented in Figure 2. In order to ensure that the observed group differences are not originated from residual head motion differences between the groups, we repeated the analysis while controlling for absolute and relative head motion measures estimated by FSL's MCFLIRT. This procedure had almost no effect on the observed group differences. For more details see Figure S2.

3.2 | Functional connectivity-based classification

We used an elastic-net logistic regression classifier to explore the ability to successfully classify our participants as either control or SCZ using rs-fMRI derived functional connectivity measures. In order to

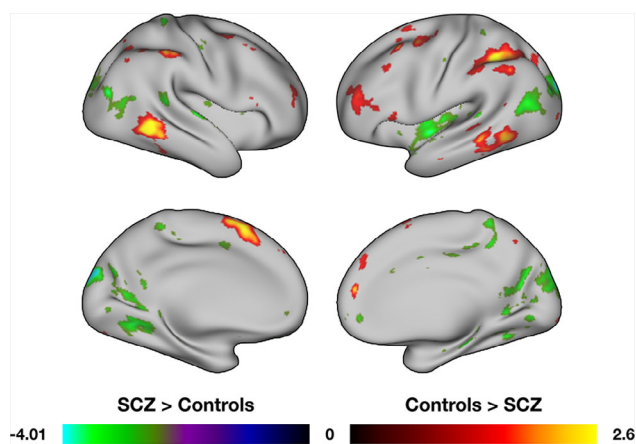


FIGURE 2 Brain activation maps showing group differences between control and SCZ in the 2back > 0back contrast. The maps are thresholded using Gaussian-two-Gammas mixture model. The positive threshold was set as $Z = 1.08$ and the negative as $Z = -2.41$

test the statistical significance of our classification we performed a permutation test and used it to compute chance level rates for 4 classification performance scores. All scores were found significant compared to the computed chance level: $AUC = 0.845$ ($p = .0002$), $Accuracy = 0.76$ ($p = .0002$), $Sensitivity = 0.8$ ($p = .0004$) and $Specificity = 0.75$ ($p = .0006$). These results indicate successful classification of participants into control and SCZ using functional connectivity features (Figure 3a and Figure S3).

Feature importance analysis revealed that out of the top 100 contributing features, 56 were inter-hemispheric connections and 44 intra-hemispheric: 25 in the left hemisphere and 19 in the right. Out of the 56 inter-hemispheric connections, 31 were homotopic, meaning they connected nodes that are assigned to the same network in different hemispheres. Therefore, the proportion of homotopic connections in the top 100 contributing features was 31% and 70% in the top 10, even though they amount to only 8% of the total features used for classification. Figure 3b presents the top 100 contributing features on a circular graph. Each edge in the graph is a feature used for the classification, and its importance is depicted by the color in grayscale. Each node is colored by networks according to the parcellation by Schaefer et al. (2018) (Section 2, Figure 3b and Figure S4). To further explore the important role homotopic connections have in differentiating SCZ patients from healthy controls we repeated the classification using only homotopic connections as features. This process improved our classification ability even more: $AUC = 0.887$, ($p = .0002$), $Accuracy = 0.82$ ($p = .0002$), $Sensitivity = 0.8$ ($p = .0002$), $Specificity = 0.825$, ($p = .0002$) (see Figure S5, Figure S6 and Table S2).

3.3 | Task-evoked brain activity prediction

Our GLM-based prediction model was trained on 80 healthy controls. Using a leave-one-out routine, a predicted cortical activation map was created for each participant in the training set. Then the trained model was used to predict cortical activation maps in the test set that consisted of 20 SCZ patients. Exemplar maps showing the predicted and actual activations and the substantial overlap between them in both control and SCZ groups can be found in Figure 4a.

We calculated the correlations between the actual and predicted activation maps of all participant pairs (Figure 4b). The diagonal of the resulting correlation matrix represents correlations between the predicted and actual activation maps of the same participant (diagonal correlations). The rest of the matrix represents correlations between predicted and actual activation maps of different participants (off-diagonal correlations). The accuracy score was calculated as the average Pearson correlation between participants' actual and predicted activation maps ($Mean = 0.544$, $Median = 0.589$, $SD = 0.193$). The specificity score was defined as the diagonality index, calculated as the average difference between diagonal and off-diagonal correlations ($DI = 0.063$). Diagonality of the correlation matrix that indicates high prediction specificity was quantitatively verified by a Kolmogorov-Smirnov test between diagonal and off-

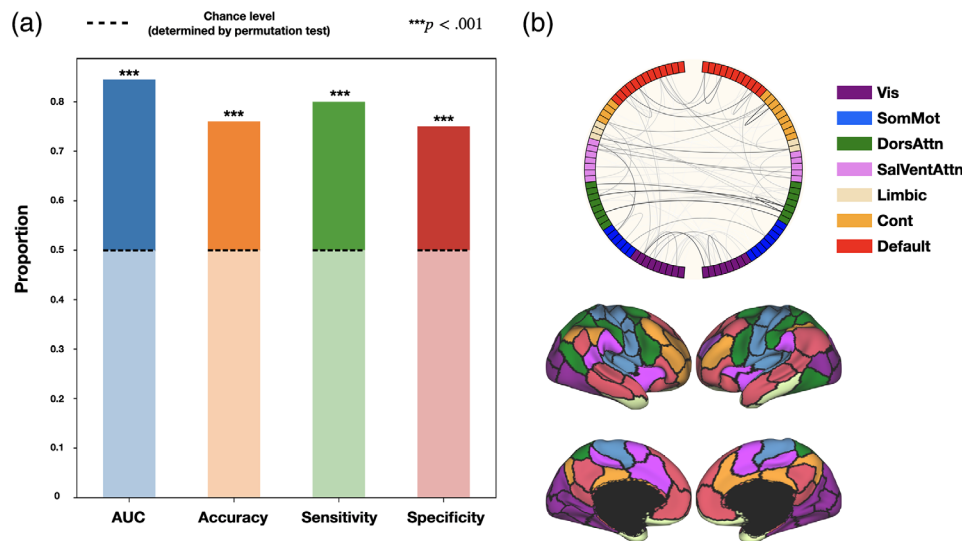


FIGURE 3 Classification of participants into control and schizophrenia groups. (a) Results of a permutation test designed to determine classification success, evaluated by 4 scores: area under the ROC curve (AUC), accuracy, sensitivity and specificity. Computed chance level for each score is marked by a dashed line. (b) A circular graph showing the 100 edges that contributed most to the classification. Features importance is depicted by the color in grayscale (i.e., darkest edges contributed most). Each half of the plot represents one hemisphere. The nodes are colored according to the parcellation by Schaefer et al. (2018)

diagonal correlations, in which diagonal correlations were found significantly higher ($D = 0.25$, $p < .0001$). A histogram of diagonal and off-diagonal values is shown in Figure 4c. In order to further quantify prediction specificity, we calculated the proportion of participants for whom the diagonal correlation was highest, that is, their actual activation map resembled their own predicted map more than any other predicted map. The diagonal correlation was highest for 90% (72 out of 80) of the control group and 85% (17 out of 20) of the SCZ group (Figure 4d).

To determine which features contributed most to the prediction, the regression coefficient (beta) value of each feature was averaged across all training set participants. The features were then sorted by absolute beta value. A bar plot of average beta values and the top 5 contributing features is shown in Figure 5.

We calculated correlations between prediction sensitivity (diagonal correlations) and PANSS scores: positive symptoms ($r = -.13$, $p = .61$), negative symptoms ($r = .23$, $p = .37$), general pathology ($r = .2$, $p = .44$) and total score ($r = .12$, $p = .63$). All correlations were found statistically insignificant (using $P < .05$), indicating that our predictive ability did not depend on symptoms severity.

4 | DISCUSSION

In the current study, we tested the hypothesis that abnormalities in brain function in SCZ are closely associated with, and can be predicted by, brain connectivity. We provide the first evidence for successful predictions of fMRI task-evoked brain activity in psychiatric patients. Furthermore, the prediction was obtained using a model trained on healthy controls exclusively. Our results suggest that the

relationship between functional connectivity and task-evoked brain activity is a stable intrinsic trait, and that the functional organization of brain networks inferred from task-free fMRI scans can be mapped directly to task-evoked brain function, regardless of individual-specific brain attributes such as a diagnosed brain pathology.

Our findings are in line with previous literature describing schizophrenia as a disorder of brain connectivity (Lynall et al., 2010; Van Den Heuvel & Fornito, 2014; Whitfield-Gabrieli et al., 2009). Along with the growing body of evidence linking connectivity directly to task-evoked brain activity (Cole et al., 2014; Saygin et al., 2012; Smith et al., 2009; Tavor et al., 2016) and cognitive function (Godwin et al., 2017; Hampson, Driesen, Skudlarski, Gore, & Constable, 2006), the current study provides support to the claim that abnormal brain activation patterns and altered cognitive function, which are widely reported in schizophrenia, may correspond directly to changes in the architecture of connectivity-derived brain networks. The successful predictions of task-evoked brain activity from task-free functional connectivity measures suggest that the abnormalities observed in SCZ in task-performance and the related brain activity are manifested at the level of functional connectivity. Therefore, it is important to deepen our understanding of the mechanism underlying these connectivity alterations, that may be a potential target for developing biomarkers or disease modifying interventions (Fox & Greicius, 2010).

Importantly, we demonstrated predictions that are both sensitive and specific. This is a core issue when trying to make individual predictions because it is cardinal to not only predict the shared variance across all individuals, but also account for the variance that is unique for every individual. Modern “dimensional” approaches, such as the Research Domain Criteria approach spearheaded by the National Institute of Mental Health (NIMH) (Cuthbert & Insel, 2010), calls to

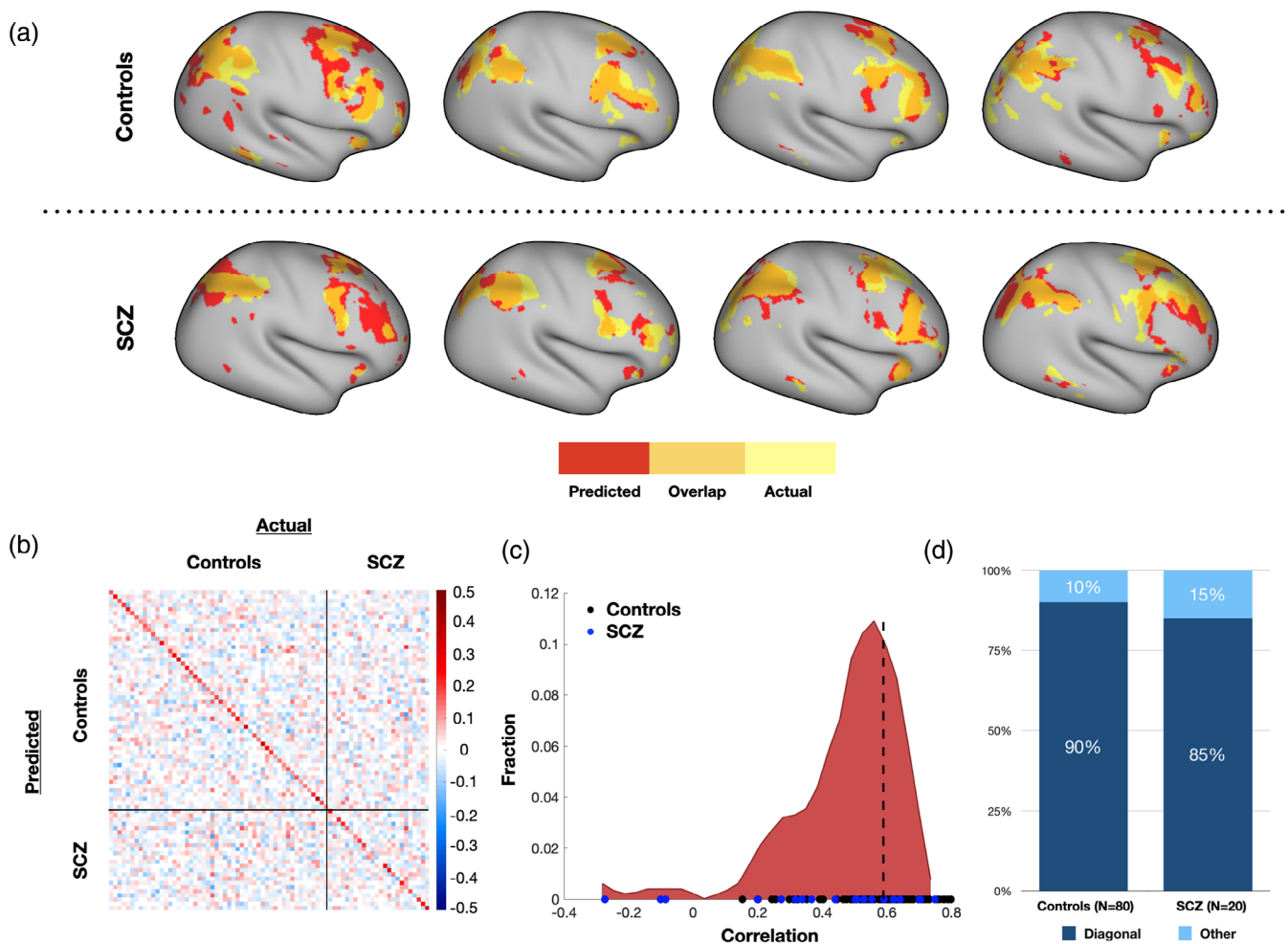


FIGURE 4 N-back task-evoked brain activity prediction. (a) Predicted (red) and actual (yellow) task activation maps and the substantial overlap between them (orange) for 4 control and 4 SCZ participants. (b) Correlations between predicted and actual activation maps. Rows and columns are normalized by removing the mean in order to account for higher variability in actual than predicted maps. The diagonal represents correlations between predicted and actual maps in the same individuals, hence the diagonality of the matrix indicates high prediction specificity. (c) Off-diagonal values histogram. The markers on the x-axis are the diagonal values (SCZ in blue and control in black). The dashed line indicates the median of diagonal correlations. (d) The proportion of participants in each group that the diagonal (individual-specific) prediction was the most accurate one for them

move from statistically based dichotomic diagnoses towards describing individual specific phenotypes as a continuum. Understanding that these approaches will become more and more prominent in psychiatric research, we must be able to draw individual-level conclusions that will ultimately not rely on dichotomic diagnosis (Finn & Todd Constable, 2016). The current study goes hand in hand with these approaches, as our findings suggest a framework in which we rely upon learning the unique relationship between an individual's connectivity and brain activation patterns and therefore do not have to train the prediction model on diagnosed patients in order to predict their brain activation patterns. Hence, our ability to make such predictions will not be affected if the criteria for diagnosis change dramatically.

The ability to predict task-evoked brain activity in one population (or dataset), using a model trained on another, is worth considering in relation to recent debates on fMRI analyses reliability. Recent publications suggest that the reliability of task-fMRI paradigms may be

inadequate, resulting in an inaccurate estimation of task-evoked brain activations (Elliott et al., 2020; Zuo, Xu, & Milham, 2019). The method described here could be used to train prediction models on task-fMRI data that was collected following rigorous reliability standards (Elliott, Knodt, Caspi, Moffitt, & Hariri, 2021; Kragel, Han, Krainak, Gianaros, & Wager, 2021; Zuo et al., 2019), and then utilize these models to predict task-evoked brain activity in other datasets. Therefore, we may provide the opportunity to produce reliable predictions of task-evoked brain activity at the level of the single participant, without any task actually being performed.

We examined the differences between the SCZ and control groups in both functional connectivity and task-evoked brain activity, in order to confirm that our predictive ability could not be explained by the lack of variability between the groups. We showed that the healthy controls and SCZ patients in the current dataset can be accurately differentiated based on functional connectivity measures. This

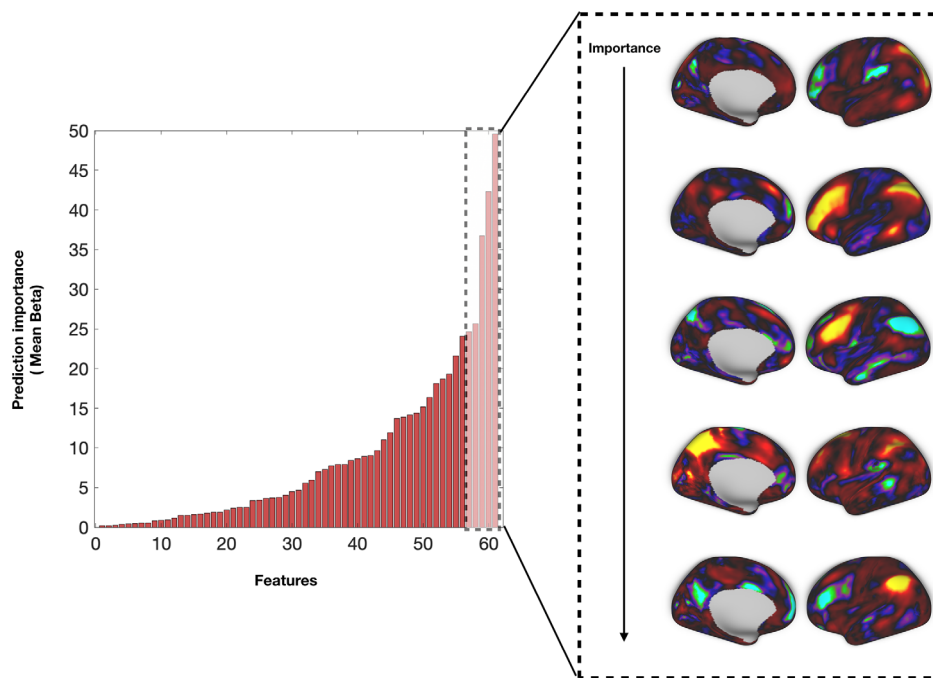


FIGURE 5 Features (connectivity maps) that were used for prediction of brain activity, sorted by their importance for prediction (determined by absolute GLM regression coefficient value). Surface representation of the top five contributing features is also presented

finding is consistent with previous studies that performed classification of SCZ and controls based on functional connectivity measures (Anderson & Cohen, 2013; Cetin et al., 2016; Li et al., 2020).

When examining feature importance, we noticed that homotopic connections, meaning connections between areas within the same network in both hemispheres, are cardinal for classification. As evidence, their proportion in the top 100 important connections is 31%, and 70% of the top 10, while their proportion from the total features is only 8%. Moreover, when we used only homotopic connections as features, our classification ability improved. These findings are consistent with previous studies that demonstrated reduction in homotopic functional connectivity in SCZ patients (Hoptman et al., 2012; Li, Xu, Zhang, Hoptman, & Zuo, 2015), and even in their siblings (Guo et al., 2014), and therefore highlight the need to better understand alterations in homotopic connectivity in schizophrenia.

As for the task-evoked brain activity results, we found differences between SCZ patients and healthy controls in the N-back working memory task, in line with previous studies (Jansma et al., 2004; Krieger et al., 2005; Whitfield-Gabrieli et al., 2009). Even though task fMRI findings in schizophrenia seem to be rather inconsistent, a large body of evidence has reported a reduction of brain activity in areas related to the fronto-parietal network (Thomas Yeo et al., 2011), such as the DLPFC and the inferior parietal lobule, when working memory is a major factor in the performed task (Eryilmaz et al., 2016). These are brain regions that are highly associated with working memory, thus it is not surprising that patients demonstrated reduced activity in these regions. When examining the features that contributed most to task prediction, many of them are also associated with the fronto-parietal network, which is also in line with the major role this network plays in working memory and other high cognitive functions (Dodds, Morein-Zamir, & Robbins, 2011). It is important to note though that if

other tasks would have been used, we would expect that different functional networks might better predict their activation.

There are a few methodological issues that should be considered when interpreting our results. The first is related to the quality of the imaging data. While originally the predictability of brain activity from connectivity was demonstrated on very high quality datasets (provided by the HCP) (Tavor et al., 2016), the acquisition of the current dataset did not meet the same standard in terms of temporal and spatial resolution, as often happens with clinical data. However, the fact that we were still able to show accurate predictions emphasizes that the relations between brain connectivity and activity are very robust and could therefore be detected even with sub-optimal data. Nevertheless, it might be possible to get even more accurate results with a larger higher-quality dataset. Such datasets with higher temporal resolution and more datapoints may also enable us to use more advanced machine-learning algorithms to improve prediction success. Another issue is one that almost all fMRI schizophrenia studies suffer from: the fact that we use long MRI protocols and a demanding cognitive task creates a bias towards high functioning patients that might not be a good representation of the population (Fox & Greicius, 2010). To validate that this issue is not cardinal in our study, we showed that our ability to make individual-specific predictions does not depend on symptoms severity scores (PANSS). We also note that due to the relatively modest size of the SCZ group we could not use it as a training set, and therefore cannot rule out that prediction may further improve by training a “SCZ specific” model. However, the fact that we demonstrate accurate predictions in both controls and patients using the same model supports our hypothesis that such a “disorder specific” model is not necessary to achieve individual specific prediction of task-evoked brain activity. Finally, it is important to generalize our findings beyond schizophrenia to other psychiatric conditions. To

achieve this, a large dataset of various fMRI tasks performed by patients diagnosed with various conditions should be collected. On the same note, we hope other researchers would utilize our publicly available method on their own datasets to examine its replicability on different clinical populations.

5 | CONCLUSIONS

We demonstrate a framework for predicting fMRI task-evoked brain activity in SCZ using a training set consisting of healthy controls exclusively. This may be a promising approach for studying connectivity and brain function in SCZ, as it allows drawing conclusions that typically require hours of tedious scanning and task performance, with only one short MRI scan at rest. Moreover, our results support the notion that interrelations between functional connectivity and brain activity do not depend on transient factors. Rather, they may be an intrinsic trait underlying the functional and the resulting behavioral abnormalities in SCZ. Therefore, while functional connectivity and task-fMRI may be highly informative on their own, future studies should not consider brain activity and connectivity as two different elements but try to understand how they integrate and interact in the healthy as well as the pathological brain.

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CONFLICT OF INTEREST

The authors have no conflict of interests to disclose.

ETHICS APPROVAL

The research protocol was approved by the Institutional Review Board of Sheba Medical Center. All participants signed an informed consent form.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. All analysis codes are available in GitHub (<https://github.com/nivtik/schizPredict>).

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SUPPORTING INFORMATION

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