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Compressed sensorimotor-to-transmodal hierarchical organization in schizophrenia

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Abstract

Background. Schizophrenia has been primarily conceptualized as a disorder of high-order cognitive functions with deficits in executive brain regions. Yet due to the increasing reports of early sensory processing deficit, recent models focus more on the developmental effects of impaired sensory process on high-order functions. The present study examined whether this pathological interaction relates to an overarching system-level imbalance, specifically a disruption in macroscale hierarchy affecting integration and segregation of unimodal and transmodal networks.

Methods. We applied a novel combination of connectome gradient and stepwise connectivity analysis to resting-state fMRI to characterize the sensorimotor-to-transmodal cortical hierarchy organization (96 patients *v.* 122 controls).

Results. We demonstrated compression of the cortical hierarchy organization in schizophrenia, with a prominent compression from the sensorimotor region and a less prominent compression from the frontal–parietal region, resulting in a diminished separation between sensory and fronto-parietal cognitive systems. Further analyses suggested reduced differentiation related to atypical functional connectome transition from unimodal to transmodal brain areas. Specifically, we found hypo-connectivity within unimodal regions and hyper-connectivity between unimodal regions and fronto-parietal and ventral attention regions along the classical sensation-to-cognition continuum (voxel-level corrected, $p < 0.05$).

Conclusions. The compression of cortical hierarchy organization represents a novel and integrative system-level substrate underlying the pathological interaction of early sensory and cognitive function in schizophrenia. This abnormal cortical hierarchy organization suggests cascading impairments from the disruption of the somatosensory–motor system and inefficient integration of bottom-up sensory information with attentional demands and executive control processes partially account for high-level cognitive deficits characteristic of schizophrenia.

Original Article

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Introduction

When 'dementia praecox' was first proposed to describe schizophrenia by Kraeplin in the late 19th century, cognitive deficit was regarded as the core component of the disorder (Dondé, Avissar, Weber, & Javitt, 2019), as evidenced by impaired function of higher-order brain regions, such as the prefrontal cortex (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Since then, perceptual deficits in the development of schizophrenia have been relatively ignored in the research field compared to the focus on the cognitive deficits. Although early

sensory deficits have been well described in the schizophrenia literature, they have often been attributed to failures of attention and other top-down mechanisms and not been emphasized within prevailing psychiatric models (Rassovsky, Green, Nuechterlein, Breitmeyer, & Mintz, 2005; van der Stelt, Frye, Lieberman, & Belger, 2004). Traditional top-down models emphasize higher-order cognitive deficit, which lead to deficient integration and organization of lower-level sensory information processes, as evidenced by the impaired casual forward influence of higher-order cognitive regions on sensory input regions during perception in schizophrenia (Dima et al., 2009; Dima, Dietrich, Dillo, & Emrich, 2010).

However, a growing number of studies demonstrate basic auditory and visual deficits significantly contribute to higher-order cognitive dysfunctions (Butler et al., 2007, 2009; Calderone et al., 2013; Dias, Butler, Hoptman, & Javitt, 2011; Dondé et al., 2019; Hoptman et al., 2018; Leitman et al., 2010), and intervention that directly targets the sensory processing impairments can drive substantial gains in higher-order cognition functions, in addition to improving sensory functions (Adcock et al., 2009; Biagianti, Fisher, Neilands, Loewy, & Vinogradov, 2016; Dale et al., 2016; Fisher, Holland, Merzenich, & Vinogradov, 2009). These findings highlight the importance of sensory processing dysfunction by 'bottom-up' dysregulation towards higher cognitive function in schizophrenia (Javitt, 2009*b*; Javitt & Freedman, 2015; Javitt & Sweet, 2015), in which the cognitive deficits in schizophrenia could be viewed as hierarchically organized, with deficits in early basic perceptual processes that localize to primary sensory brain regions propagating to higher-order brain cognitive regions contributing to subsequent higher levels functional impairment (Butler et al., 2007; Calderone et al., 2013; Dias et al., 2011; Leitman et al., 2010). Accordingly, recent models are gradually shifting the research focus more to the impaired developmental interactions between early sensory and high-order processes in schizophrenia (Javitt, 2009*b*; Javitt & Freedman, 2015; Javitt & Sweet, 2015). As such, the identification of neural mechanisms underlying the impaired functional integration between and within early sensory and cognitive brain systems is crucial to understand the pathophysiology mechanisms of schizophrenia, which ultimately helps guide future interventional approaches.

The aforementioned functional interaction can be explored by characterizing functional connectivity within and between different brain systems (Van Den Heuvel & Pol, 2010). Using resting-state functional connectivity (rsFC), researchers are able to observe abnormal FC within the high-order default, frontoparietal network as well as ventral attention network in schizophrenia (Dong, Wang, Chang, Luo, & Yao, 2018; Jiang et al., 2019; Liao et al., 2019; Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011). Aside from these abnormalities, an increasing number of rsFC studies suggest dysfunctional intrinsic connectivity within visual and somatosensory systems in this condition (Bordier, Nicolini, Forcellini, & Bifone, 2018; Chen et al., 2015, 2016; Dong et al., 2019; Jiang et al., 2015; Liu et al., 2018; Zhang, Guo, & Tian, 2019). In addition, a recent meta-analysis found altered resting-state regional brain activity both in high-order cognitive regions (e.g. default and ventral attention network) and regions in visual and sensorimotor network (Gong et al., 2020). Up to this point, only a few studies have looked at how sensory networks pathologically interact with higher-order association systems in schizophrenia (Berman et al., 2016; Hoptman et al., 2018; Kaufmann et al., 2015). In this more holistic view, brain dysfunction in schizophrenia is proposed to result from the abnormal hierarchical cerebral organization rather than from individual systems alone (Yang et al., 2016). However, detecting abnormality in the cerebral hierarchy organization represents a challenge, due to the limited number of approaches explicitly designed to evaluate hierarchical information propagation in the brain system.

Recent advances in neuroscience towards the understanding of brain organizational principles have highlighted a cortical hierarchy as a unifying functional mechanism for information processing in the primate and mouse brains (Burt et al., 2018; Chaudhuri, Knoblauch, Gariel, Kennedy, & Wang, 2015; Demirtaş et al., 2019; Fulcher, Murray, Zerbi, & Wang, 2019; Margulies et al., 2016; Mesulam, 2012; Paquola et al., 2019, 2020; Taylor, Hobbs, Burroni, & Siegelmann, 2015). Specifically, this mechanism refers to the functional system extending from primary sensorimotor to association areas, along which it increasingly represents more abstract and complex information in the brain. This hierarchical architecture facilitates segregated processing of specialized function domains (e.g. sensory and cognitive process), while also enabling a dynamic configuration and cross-communication of networks for more complex and integrated mental activity (Huntenburg, Bazin, & Margulies, 2018; Murphy et al., 2018; Sepulcre, Sabuncu, Yeo, Liu, & Johnson, 2012; Taylor et al., 2015). Investigating the cortical hierarchy provides an integrative window into the impairments of functional integration between and within early sensory processing and high-order cognitive functions in schizophrenia.

The present study aimed to examine how the impaired function and integration of both sensory and cognitive processes relates to macroscale cortical hierarchy in schizophrenia. We applied a novel combination of connectome gradient mapping (Margulies et al., 2016) and stepwise functional connectivity (SFC) analyses (Martínez et al., 2020; Sepulcre et al., 2012), which offer complementary characterization of hierarchical abnormalities in schizophrenia. In contrast to the common practice of partitioning brain regions into discrete communities with sharp boundaries, the gradient mapping approach, which is a non-linear decomposition of high-dimensional resting-state functional connectivity (rsFC), can identify brain functional hierarchies by representing brain connectivity in a continuous, low-dimensional space that places sensory and motor networks on one end and transmodal network on the other. This approach thus provides a more integrated vision on the rsFC anomalies in schizophrenia by capturing continuous spatial patterns of connectivity beyond segregated networks and provides simplified representation in terms of main dimensions to characterize the alteration of the macroscale cortical hierarchy in schizophrenia. SFC, developed earlier, has shown that brain hierarchy can also be understood as a sequence of steps in connectivity space. SFC was initiated from a priori-defined sensory seeds-based FC to further examine the hierarchical stream of information from unimodal sensory regions (visual, auditory, and somatosensory) to transmodal regions in schizophrenia patients and healthy controls. More importantly, SFC analytical approach allows for analysis of indirect FC (medium and large connectivity distances from the seed), which is thought to provide information integration about hierarchical flow across specific brain networks (Sepulcre, 2014). This approach thus enabled us to investigate the presence of atypical functional transitions from unimodal to multimodal cortical areas in schizophrenia. SFC is well-suitable to confirm the 'bottom-up' dysregulation of higher cognitive functions in this condition.

Table 1. Demographic characteristics of schizophrenia patients and controls

	Patients ($N = 96$)		Health controls ($N = 122$)		
Variables	Mean	S.D.	Mean	S.D.	p value
Age (years)	39.78	11.48	37.95	14.74	0.32
Gender (female : male)	30 : 66		41 : 81		0.71[a]
Handedness (right : left)	93 : 3		121 : 1		0.32[a]
Education (years)[b]	11.64	2.94	11.07	3.22	0.22
Chlorpromazine equivalents (mg/d)[c]	332.95	165.06			
Duration of illness (years)[d]	15.10	10.33	–	–	
PANSS-positive[e]	13.44	5.88	–	–	
PANSS-negative[e]	20.73	6.00	–	–	
PANSS-general[e]	28.22	5.81	–	–	
PANSS-total[e]	62.39	13.11	–	–	
FD	0.049	0.038	0.046	0.027	0.38

Notes:
FD, framewise displacements; PANSS, positive and negative syndrome scale.
[a]x^2 test.
[b]Data of 76 patients and 111 controls available.
[c]Data of 72 patients available and calculated using Woods method (Woods, 2003).
[d]Data of 88 patients available.
[e]Data of 64 patients available.

Based on the pathological mechanisms of 'bottom-up' dysregulation of higher cognitive functions and deficiency of top-down integration in schizophrenia mentioned above, and the initial observation of impaired connectivity between sensory and cognitive processes system in schizophrenia (Berman et al., 2016; Hoptman et al., 2018; Kaufmann et al., 2015), we hypothesized that the pathological interaction between sensory and cognitive processes in schizophrenia would be reflected by the expected abnormal macroscale cortical hierarchy in schizophrenia. To this end, we first constructed the macroscale cortical hierarchy at voxel level for each subject, and then conducted the statistical comparison between patients with schizophrenia (SZ) and health controls (HC) at voxel level with correction for multiple comparisons using the false discovery rate procedure. Finally, exploratory analyses examined possible correlations between altered gradient values, SFC values and clinical symptoms.

Methods

Participants

Patients were diagnosed with schizophrenia according to the structured clinical interview for DSM-IV Axis I disorders – clinical version (SCID-I-CV). Ninety-six schizophrenia patients and 122 healthy controls were included in the final analysis. See supplementary methods for details about participant recruitment. Demographic and clinical information of all participants is summarized in Table 1. Two groups did not show statistically significant differences in age, sex, education and handedness ($p > 0.3$). All patients received treatment with antipsychotics. All antipsychotic drugs were converted into chlorpromazine equivalents using Woods conversion (Woods, 2003). The mean illness duration is 15.1 years. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the Ethics Committee of the Clinical Hospital of Chengdu Brain Science Institute. Written informed consent was obtained from all subjects.

Data acquisition and image preprocessing

Structural and resting-state functional MRI data were acquired on a 3-T GE Discovery MR 750 scanner at the MRI Center of University of Electronic Science and Technology of China. See supplementary methods for details.

All preprocessing steps were consistent with our previous studies (Ding et al., 2019; Dong et al., 2020), see Fig. 1*a* and supplementary methods for details. To rule out the effects of head motion as much as possible, we conducted wavelet despiking processing, deleting data with high and frequent head motion, regressing out 24 motion parameters and taking relative motion as a covariate in statistical analysis. We did not conduct global signal regression (GSR) in the main analysis because GSR may distort between-group comparisons of inter-regional correlation (Saad et al., 2012). Besides, studies suggest that altered global signal is an important neuroimaging feature in schizophrenia (Hahamy et al., 2014; Yang et al., 2014). However, because GSR is still controversial, we repeated core analyses (gradient and SFC) with GSR in the control analyses. To reduce computational demands, the rsfMRI data were down-sampled to 4 mm isotropic voxels, resulting in 18 815 voxels. Subsequent gradient and SFC analyses were voxel-based calculation. Consistent with previous voxel-wise FC computation (Tomasi & Volkow, 2010), spatial smoothing was not conducted in the image preprocess step, but was conducted in postprocessing steps (6 mm) for gradient and SFC maps.

Connectivity gradient analyses

Gradient mapping techniques describe a continuous coordinate system at the systems level that place sensory and motor networks

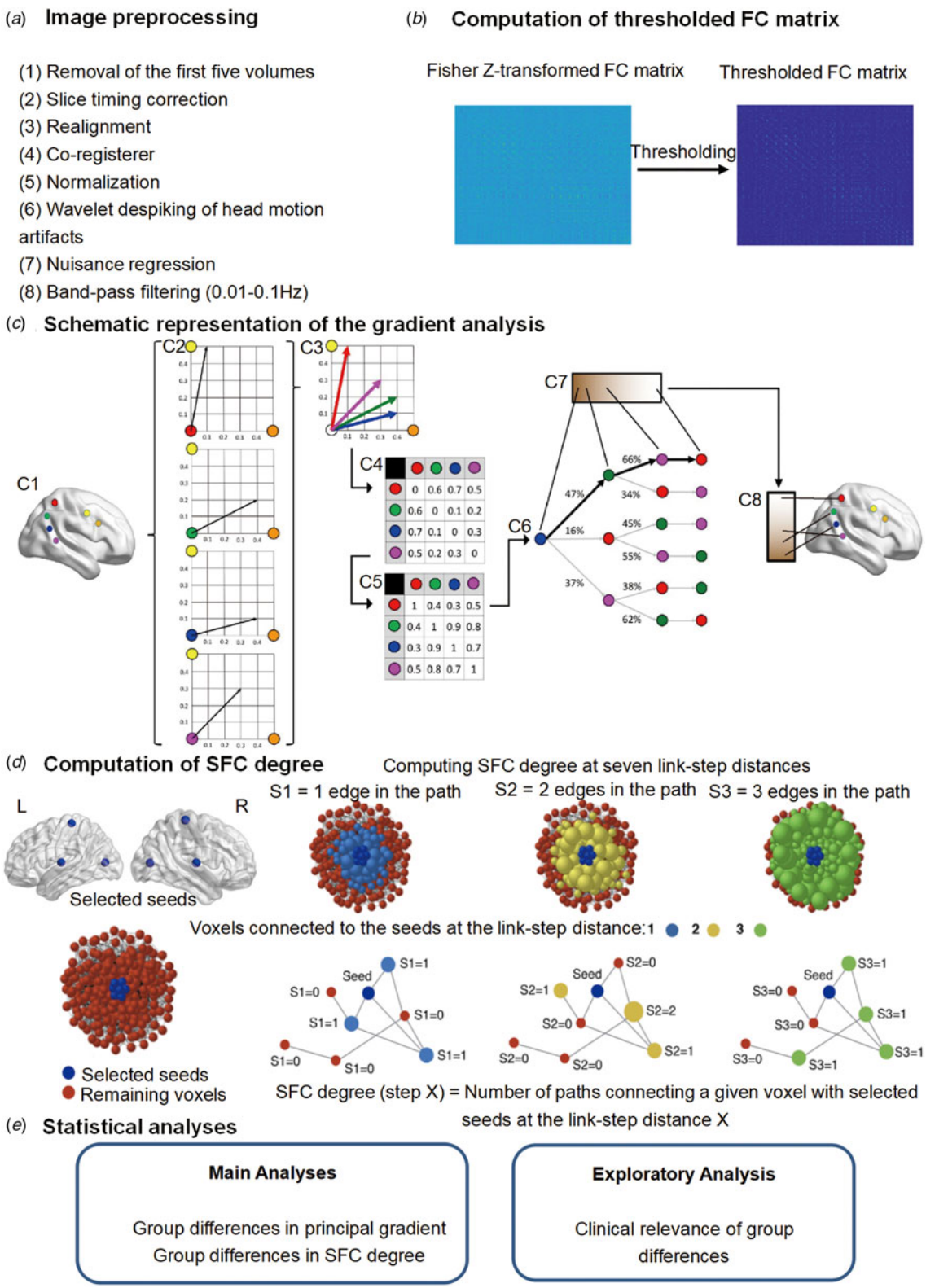

Fig. 1. Summary of workflow. (*a*) The steps for image preprocessing. (*b*) Computation of the thresholded FC. The thresholded FC was then submitted to the gradient and SFC analyses. (*c*) Schematic representation of gradient analysis. This example (C1) presents a schematic representation of gradient analysis. It illustrates the calculation of the principal functional gradient of four cerebral cortex voxels (red, green, blue, magenta) based on their functional connectivity with two target cerebral cortex voxels (yellow, orange). (C2) Connectivity from each cerebral cortex voxel (red, green, blue, magenta) to the two target cerebral cortex voxels (yellow, orange) is represented as a two-dimensional vector. (C3) All vectors can be represented in the same two-dimensional space. (C4) Cosine distance between each pair of vectors is calculated, and (C5) an affinity matrix is constructed as (1-cosine distance) for each pair of vectors. This affinity matrix represents the similarity of the connectivity patterns of each pair of voxels. (C6) A Markov chain is constructed using information from the affinity matrix. Information from the affinity matrix is thus used to represent the probability of transition between each pair of vectors. In this way, there will be higher transition probability between pairs of voxels with similar connectivity patterns. This probability of transition between each pair of vectors can be analyzed as a symmetric transformation matrix, thus allowing the

on one end and transmodel network on the other. This approach thus provides us a simplified representation in terms of main dimensions to characterize the alteration of the macroscale cortical hierarchy in schizophrenia.

First, the voxel-level connectivity matrix for each subject was computed using Fisher's Z-transformed Pearson's correlations (Fig. 1*b*). Based on previous studies (Dong et al., 2020; Guell, Schmahmann, Gabrieli, & Ghosh, 2018; Hong et al., 2019; Margulies et al., 2016), we thresholded the rsFC matrix with the top 10% of connections per row retained, whereas all others were zeroed. The negative connections were zeroed as well. Then, we used cosine distance to generate a similarity matrix that reflected the similarity of connectivity profiles between each pair of voxels. We used diffusion map embedding (Coifman et al., 2005), a nonlinear dimensionality reduction algorithm, to identify a low-dimensional embedding from a high-dimensional connectivity matrix. This methodological strategy has been proved to successfully identify relevant aspects of functional organization in the cerebral cortex in previous studies (Hong et al., 2019; Margulies et al., 2016). Figure 1*c* showed the schematic representation of the gradient analysis. The result of diffusion embedding is not one single mosaic of discrete networks, but multiple, continuous maps (gradients), which capture the similarity of each voxel's functional connections along with a continuous space. All gradients are orthogonal to each other and capture a portion of data variability in descending order.

To compare between the SZ and HC groups, we used an average connectivity matrix calculated from all patients and controls to produce a group-level gradient component template. We then performed Procrustes rotation to align the gradients of each participant to this template (Langs, Golland, & Ghosh, 2015). To maximize interpretability, we only used the first gradient component in our main analyses. The first gradient explains as much of the variance in the data as possible (~29%, online Supplementary Fig. S1) and, from a neurobiological point of view, represents a well-understood sensorimotor-to-transmodal organizational principle in the cerebral cortex connections. In addition, there's no consensus about the second gradient pattern among the previous studies (Bethlehem et al., 2020; Hong et al., 2019; Margulies et al., 2016). Furthermore, the second gradient extracted from functional connectivity data could not be reproduced as successfully as the principal gradient at the single-subject level (Guell et al., 2018). A supplementary exploratory analysis tested group differences using the second gradient component in our analysis. Further analyses based on the second gradient were outside of the scope.

Stepwise functional connectivity analyses

SFC analysis is a graph-theory-based method that detects both direct and indirect functional couplings from a defined seed region to other regions in the brain. More importantly, SFC analytical approach allows for analysis of indirect FC (medium and large connectivity distances from the seed), which is thought to provide information integration about hierarchical flow across specific brain networks (Martínez et al., 2020; Pretus et al., 2019; Sepulcre, 2014; Sepulcre et al., 2012). This approach thus enables us to investigate the presence of atypical functional transitions from unimodal to multimodal cortical areas within the framework of the cortical hierarchy in schizophrenia.

SFC analysis computes the number of functional paths between defined seed regions and every other voxel in the brain at successive numbers of relay stations or 'link-step' distances (Martínez et al., 2020; Sepulcre, 2014; Sepulcre et al., 2012). Hence, it complements connectivity gradient approaches by allowing voxel-level functional connections to be assessed at a range of intermediate relay stations. Following previous studies (Martínez et al., 2020; Pretus et al., 2019; Sepulcre et al., 2012), connectivity matrices were first filtered to include only positive correlations due to the ambiguous interpretation of negative correlations. After that, the connectivity matrices were further filtered to contain only correlations surviving a stringent false-discovery rate (FDR) correction ($q < 0.001$). Finally, we submitted the resulting FDR thresholded matrices to SFC analysis.

Given that deficits of visual, auditory, and somatosensory processing in schizophrenia were consistently observed [for reviews (Javitt, 2009*b*; Javitt & Freedman, 2015)], three bilateral primary sensory seed regions of interest (ROIs) including visual [MNI coordinates x, y, z: −14/10 (left/right), − 78, 8; (Brodmann 17, V1)], auditory [−54/58, −14, 8; (Brodmann 22, A1)] and somatosensory [−42/38, −29, 65; (Brodmann 3, hand area)] areas (Sepulcre et al., 2012), were defined as cubic regions of eight voxels each. To assess the degree of combined SFC of all sensory seeds irrespective of modality, a combined mask was constructed by combining information from all three primary sensory regions. The method is described in detail elsewhere (Martínez et al., 2020; Pretus et al., 2019; Sepulcre, 2014; Sepulcre et al., 2012) and schematically represented in Fig. 1*d*. The degree of SFC of a given voxel of the brain is defined as the number of functional paths connecting that voxel with an a priori selected seed region at a specific link-step distance. A link-step distance is defined as the number of edges that pertain to a path connecting a given voxel to the seed regions. At each link step, SFC maps were standardized to *Z*-scores by subtracting the mean and dividing by its standard deviation (S.D.) to yield SFC values. Therefore, each SFC map represents a relative increase of connectivity degree across different link-step distances. As demonstrated in previous studies (Buckner et al., 2009; Sepulcre et al., 2012), functional pathways 'collapse' into the cortical hubs of the adult human brain after link-step distances >7; accordingly, we constrained our SFC analysis to seven link-step distances.

Statistical and control analyses

General linear models were used to determine diagnostic differences (schizophrenia patients (SZ) *v.* HC) in dependent variables,

Fig1. contd

calculation of eigenvectors. (C7) Eigenvectors derived from this transformation matrix represent the principal orthogonal directions of transition between all pairs of voxels. Here, we illustrate the first resulting component of this analysis – the principal functional gradient of our four cerebral cortex voxels (red, green, blue, magenta) based on their connectivity with our two target cerebral cortex voxels (yellow, orange) progresses from the blue, to the green, to the magenta, to the red voxel. (C8) This order is mapped back into cerebral cortex map, allowing us to generate functional neuroanatomical descriptions. Of note, cerebral cortex functional gradients were calculated using functional connectivity values of each cerebral cortex voxel with the rest of cerebral cortex voxels (rather than between four voxels and only two target cerebellar voxels, as in this example). Vectors in our analysis thus possessed many more than just two dimensions, but cosine distance can also be calculated between pairs of high-dimensional vectors. Figure 1*c* is adapted from Guell et al. (2018). (*d*) Computation of the SFC. Figure 1*d* is adapted from Martínez et al.(2020). (*e*) Statistical analyses.

i.e. Z-normalized values of the principle (first) gradient scores, and SFC degree at each of the seven link-step distances with age, sex, handedness and mean FD controlled for each voxel. This was implemented in DPARBI toolbox (DPABI v4.1, http://rfmri.org/dpabi) (Yan, Wang, Zuo, & Zang, 2016). Two-sample *t* tests were calculated to determine diagnostic differences (schizophrenia patients (SZ) *v.* HC) in Z-normalized values of the principal (first) gradient scores, and SFC degree at each of the seven link-step distances. Age, sex, handedness and mean FD were set as covariates. The results for each test are reported at a voxel-based threshold corrected for false-discovery rate of multiple comparisons (FDR voxel-wise correction $p < 0.05$). We also imposed a minimum cluster extent of 20 voxels. All the results reported below are based on without global signal regression (GSR). GSR, confounding effect analyses of head motion and medication were performed to ensure robustness of the main findings, see supplementary methods for details.

Correlations between altered gradient scores, SFC degree, and clinical variables

As an exploratory investigation, to further examine the relationship between altered gradient scores, SFC degree, and clinical features, we calculated Pearson's correlations between gradient scores, SFC degree and the severity of clinical symptoms measured by PANSS (positive, negative, general psychopathology symptoms subscales and overall scores) in the patients' group. Analyses were computed in each region where the SZ and HC groups differed significantly in the statistical analyses. Given its high correlation with age, illness duration was not included separately in correlation analysis (Moser et al., 2018).

Data and code availability

The preprocessing software is freely available (DPABI v4.1, http://rfmri.org/dpabi) (Yan et al., 2016). The code for gradient analysis is openly available via the BrainSpace toolbox (http://brainspace.readthedocs.io) (de Wael et al., 2020). The code for SFC analysis is available via a direct request to Jorge Sepulcre. The results were visualized with BrainNet Viewer v1.7 (https://www.nitrc.org/projects/bnv/) (Xia, Wang, & He, 2013). The imaging and clinical data are made available via a direct request to the corresponding author (Cheng Luo). Sharing and re-use of imaging and clinical data need the expressed written permission of the authors and clearance from the relevant institutional review boards.

Results

The principal functional gradient of cerebral cortex in schizophrenia

The principal gradient of cerebral cortex FC showed a similar sensorimotor-to-transmodal gradient of cortical organization in HC and SZ (Fig. 2). It extended from primary cortices to transmodal areas. Of note, there was no significant difference between SZ and HC in the explained variance of the principal gradient (two-sample *t* test, $t = 0.86$, $p = 0.39$).

Compared to HC (Fig. 2 and Table 2), schizophrenia patients showed increased gradient values in regions of sensorimotor network and visual network, including bilateral post/precentral gyrus, posterior insula, middle occipital gyrus, and lingual gyrus; and decreased gradient scores in transmodal regions mainly belonging to FPN, i.e. middle frontal gyrus, superior frontal gyrus, inferior parietal lobule; also including a few regions in DMN (e.g. medial frontal gyrus, middle temporal gyrus and angular gyrus). Of note, cerebral cortex network allocations are based on Yeo network classification (Yeo, et al., 2011), which was also shown in the online Supplementary Fig. S2D. As shown in the scatterplot of Fig. 2*c*, functional gradient abnormalities in this case extended across the whole principal gradient spectrum. More specifically, higher principal gradient values in the SZ group were localized in the lowest pole of principal gradient (which corresponds to primary sensorimotor and visual processing areas), whereas lower values in the SZ group extended from the medium aspects to the highest pole of principal gradient (transmodal regions).

To better characterize the altered pattern of sensorimotor-transmodal hierarchical gradient, global histogram analyses were performed. As shown in the right bottom corner of Fig. 2*c*, this analysis revealed that there was a prominent compression of the lowest portion of the principal functional gradient and a less prominent compression of the highest portion of the principal functional gradient. Furthermore, Kolmogorov–Smirnov test (Matlab function) indicated that the distribution of SZ group gradient values was significantly different from the distribution of HC group gradient values ($p < 0.001$, ks2stat = 0.08). To quantitatively demonstrate the overall compression, we tested whether there was a linear correlation between X and X−Y per spatially corresponding voxel (X represents voxel-level gradient values in SZ group mean map, i.e. red histogram of Fig. 2*c*, Y represents voxel-level gradient values in HC group mean map, i.e. blue histogram of Fig. 2*c*, and X−Y represents differences of gradient values between SZ and HC mean map per spatially corresponding voxel). We found there was a significant correlation between X−Y and X ($r = 0.51$, $p < 0.001$), which suggested the overall gradient value compression in SZ group compared to HC group. In the same logic, we tested the compression of transmodal pole and sensorimotor pole, we found the correlation value in sensorimotor pole ($r = 0.53$, $p < 0.001$) was higher than transmodal pole ($r = 0.10$, $p < 0.001$), which suggested there was a prominent compression of sensorimotor regions and a less prominent compression of transmodal regions.

Connectivity gradient analysis provides a description of the connectome where each voxel is located along a gradient according to its connectivity pattern. Voxels with similar connectivity patterns are located close to one another along a given connectivity gradient. Therefore, the gradient value represents information about the spatial pattern in the embedding space – shifts in value are not 'more' or 'less,' but rather reflect changes in relative similarity within a latent dimension, i.e. the similarity of functional connectivity patterns along each dimension ('gradient'). The gradient values are a scalar, and for this reason significant gradient value alterations in schizophrenia reflect the extent to which the patient group deviates from the HC group. Our interest here was the different spatial distributions of cortical hierarchy between two groups. Interestingly, our finding of compressed cerebral cortical functional gradients suggested a less differentiated global hierarchical organization, i.e. diminished network differentiation in schizophrenia, in which there is a relatively stronger shift in functional affiliation from visual–sensorimotor towards transmodal regions in gradient space.

The SFC degree in schizophrenia

The SFC degree showed a similar spatial transition pattern along the sensation-to-cognition continuum in SZ and HC (Fig. 3*a*).

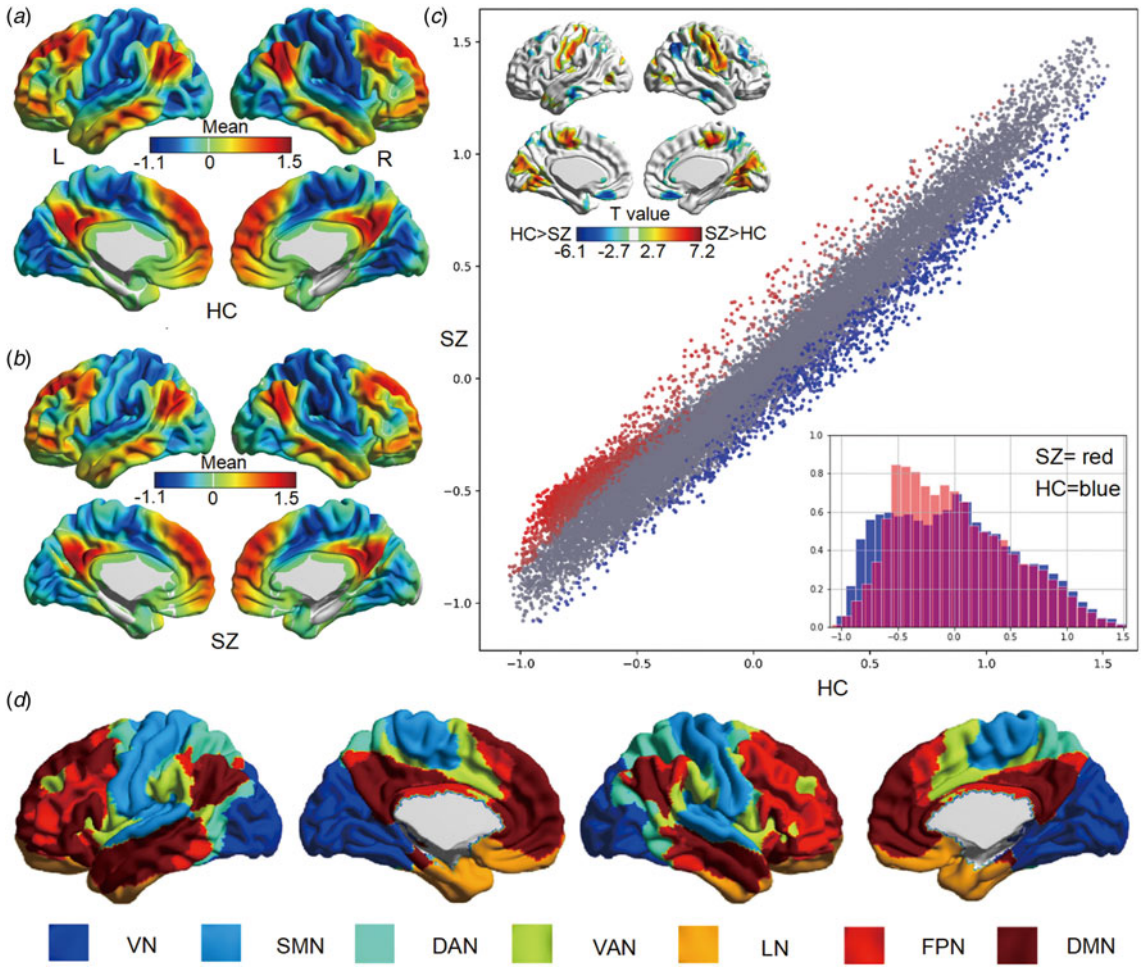

Fig. 2. Group mean patterns and statistical differences in the cerebral principal functional gradient. (*a*) Mean gradient pattern in HC. (*b*) Mean gradient pattern in SZ. (*c*) Significant group differences between SZ and HC. Scatterplot represents cerebral gradient of SZ (y axis) v. cerebral gradient of HC (x axis). Scatterplot colors correspond to significant group differences map as shown in top left corner of Fig. 2*c*: higher gradient value in SZ (red), and lower gradient value in SZ (blue) compared to HC. Compressed gradient pattern in SZ is shown in density histograms in bottom right corner of Fig. 2*c*. All results are shown after FDR correction ($p < 0.05$). (*d*) Yeo network classification (Yeo et al., 2011).

In steps 1 and 2, sensory-related seeds display a regional–local FC along with the unimodal areas, e.g. somatomotor and visual cortex. From 3 to 7 link-step distances, sensory-related seeds showed gradual transitions towards multimodal integration areas (e.g. dorsal anterior cingulate cortex and frontal eye field, frontoinsular cortex), and eventually displayed convergent to the cortical hubs regions (e.g. dorsolateral prefrontal, inferior lateral parietal cortex, medial prefrontal cortex, posterior cingulate cortex / precuneus or the lateral temporal cortex).

Statistical comparison indicated that at link-step distance 1, corresponding to classic seed-based FC analysis, patients with schizophrenia showed reduced SFC degree between the unimodal seeds and visual and sensorimotor systems, i.e., bilateral middle occipital gyrus, lingual gyrus and pre/postcentral gyrus (online Supplementary Table S1 and Fig. 3*b*). Interestingly, this reduced SFC pattern was consistently observed across all link-steps distances (steps 2–7). Increased SFC degree was found between unimodal seeds and frontoparietal regions, i.e. middle/superior frontal gyrus, inferior parietal lobule, supramarginal gyrus, and dorsal precuneus), and ventral attention regions (dorsal anterior cingulate cortex and bilateral anterior insular cortex/central opercular cortex) at early and medium link-step distances (steps 1−4). However, this increased SFC degree gradually faded in the remaining link-step maps (steps 5−7).

Control analyses

Control analyses found GSR, micro head movements and medication did not significantly affect trends of overall results (gradient and SFC analyses), which ensured robustness of main results, see online Supplementary Fig. S2−S3 and supplementary results for details.

Association among altered gradient, SFC and clinical severity of symptoms in schizophrenia

The severity of clinical symptoms was related to decreased functional gradient values in ventral medial frontal gyrus, left anterior insula and left precuneus (online Supplementary Table S2 and Fig. S4). Across all the link-step distances, most of the significant correlations fit the following rule: for those regions involved in high-order cognitive function (i.e. superior frontal gyrus, anterior insular cortex), increased SFC degree was associated with less clinical severity. Accordingly, for those regions involved in sensory processing function, i.e. pre/postcentral gyrus and visual areas,

Table 2. Group differences in principal functional gradient values

Brain regions	*T* value	Voxels (k)	MNI coordinates		
			X	*Y*	*Z*
Patients >Controls					
L Middle/inferior temporal gyrus	5.21	42	−48	4	−32
L/R Lingual gyrus/middle occipital gyrus	5.47	895	−8	−60	0
R Middle occipital gyrus/middle temporal gyrus	4.25	39	48	−72	0
L Middle occipital gyrus/middle temporal gyrus	4.38	39	−44	−76	4
R Posterior insula	4.43	26	36	−16	12
L Posterior insula	4.30	21	−44	−24	16
L/R Pre/postcentral gyrus	7.19	1235	48	−16	40
			−40	−20	44
Patients <Controls					
L Fusiform gyrus/temporal lobe	−3.82	25	−20	0	−44
L Middle/inferior temporal gyrus	−5.64	96	−68	−24	−16
R Inferior/middle temporal gyrus	−5.00	99	60	−20	−20
Medial frontal gyrus	−5.91	101	0	36	−24
R Anterior insula/superior temporal gyrus	−3.64	20	52	8	−4
R Middle frontal gyrus	−6.09	227	32	32	52
R Anterior cingulate gyrus	−3.33	27	4	36	20
L Anterior insula	−4.25	22	−32	20	12
R Supramarginal gyrus/inferior parietal lobule	−4.22	39	68	−32	24
L Inferior parietal lobule/angular gyrus/supramarginal gyrus	−5.94	144	−52	−52	56
L Middle frontal gyrus	−3.34	22	−40	36	36
R Inferior parietal lobule/angular gyrus/precuneus/supramarginal gyrus	−5.87	435	44	−60	56
L Middle frontal gyrus	−4.83	39	−28	20	60
L Precuneus	−4.47	48	−12	−60	76
R Superior frontal gyrus	−3.62	23	32	8	68

Notes: L, left side of brain; R, right side of brain. Results are reported using a voxel-wise FDR threshold of $p < 0.05$ and an additional cluster-size threshold of $k = 20$.

increased SFC degree correlated with greater clinical severity. There is an exception in the left middle frontal gyrus at link-step 4, where increased SFC degree was associated with greater clinical severity. It should be noted that, most of these findings were only seen at uncorrected levels ($p < 0.05$). Given the exploratory nature of these associations, one should remain cautious when interpreting these results.

Discussion

Recent emerging models and rapidly growing empirical studies emphasize the impaired function and integration of both the early sensory and cognitive processing in understanding the pathophysiology of schizophrenia. Investigating the fundamental sensorimotor-to-transmodal cortical hierarchy organization in schizophrenia would provide critical and integrative experimental evidence for these models. The present study used a novel combination of connectome gradient and SFC analyses to characterize the macroscale cortical hierarchy organization in schizophrenia. In summary, the gradient analysis identified a significantly reduced network differentiation, i.e. gradient compression, in which there is a prominent compression from the sensorimotor system of the cortical hierarchy and a less prominent compression from the higher-level systems such as FPN and DMN. The SFC approach further suggested reduced network differentiation related to atypical functional transitions from unimodal to multimodal cortical areas in schizophrenia. Altogether, the present study provided converging evidence for abnormal cortical hierarchy organization as a system-level substrate underlying the pathological interaction of early sensory and cognitive function in schizophrenia. The findings indicated that impairments at different hierarchical processing steps, especially the foci of effects emphasize that disrupted somatosensory–motor systems may cascade into the higher-order cognitive deficits, which are the hallmark characteristic of schizophrenia.

The cascading effects of early sensory deficits along the sensation-to-cognition continuum

Intriguingly, the present study found a selective gradient compression pattern of the sensorimotor system in the compressed cortical hierarchy organization. Recently, a significant paradigm shift in the research field of schizophrenia has begun to emerge,

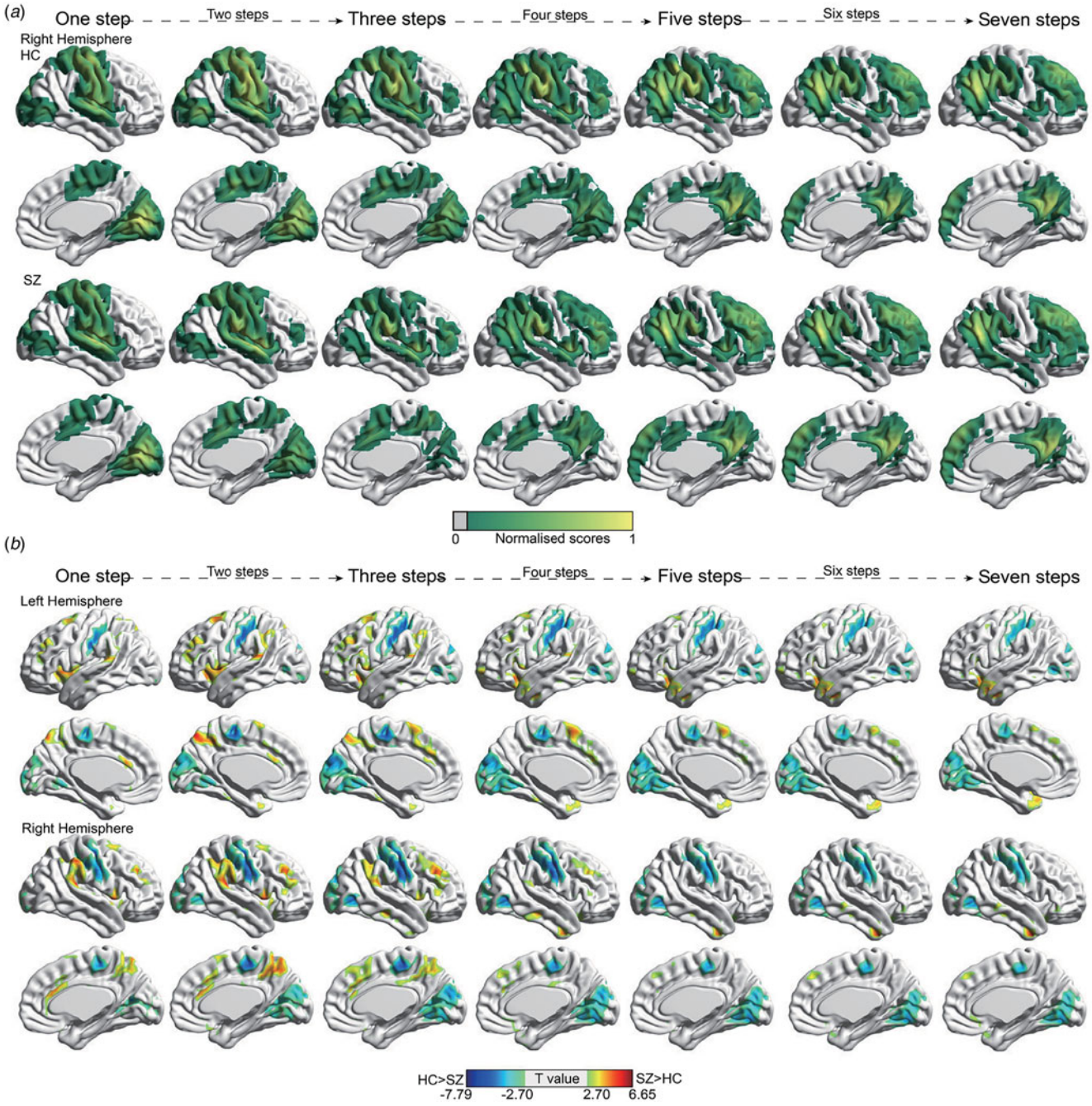

Fig. 3. Group patterns and differences in stepwise functional connectivity degree. (*a*) Stepwise functional connectivity patterns in HC and patients with schizophrenia (one-sample *t* tests with $p < 0.001$ uncorrected). In the normalized color scale, 0 represents nonsignificant results ($p < 0.001$), and 1 is the maximum value corresponding to the smallest *p* value. Given the results of the left hemisphere are similar to those on the right hemisphere, we only show the results of the right hemisphere for visualization. (*b*) Group differences between schizophrenia and HC in stepwise functional connectivity degree. All results are shown after FDR correction ($p < 0.05$).

according to which early regions of the sensory pathway may result in 'bottom-up' dysregulation of higher cortical function (Javitt, 2009*a*, *b*; Javitt & Freedman, 2015; Javitt & Sweet, 2015). Further complementing this view, neurophysiology findings indicate that the bottom-up propagation of deficits from early sensory to higher-level processes in schizophrenia occurs even when top-down processes remain intact (Dias et al., 2011). Similarly, some recent rsFC and structural studies found that the connectivity deficits of visual and sensorimotor pathway can be detected even when the associative regions, like FPN and DMN, failed to reach statistical significance in schizophrenia (Bordier et al., 2018; Chen et al., 2015; Guo et al., 2014; Jørgensen et al., 2016; Liu et al., 2018; Zhang et al., 2019). Our findings of prominent cortical network compression in the sensorimotor and visual systems therefore provides an integrative basis to support previous reports of impaired early sensory processing in schizophrenia. More importantly, this result extends previous findings by showing that the abnormality of early sensory processing is not purely

anchored on local functional circuits but rather affects overarching hierarchical cerebral organization, which reflects its global and widespread influence on brain information transitions in schizophrenia.

Furthermore, the SFC findings strengthened global and widespread influence of the early sensory processing on brain information transitions in schizophrenia by demonstrating that the pattern of hypo-connectivity within visual and sensorimotor systems across all (early, medium and large) link-step distances along the sensation-to-cognition continuum. SFC at the 1 (early) link-step distance corresponded to classic seed-based FC analysis. Overall, hypo-connectivity within visual and sensorimotor systems at the 1 link-step distance are largely compatible with the existing seed-based rsFC as well as more sophisticated network-based and/or graph theory analyses in schizophrenia (Bordier et al., 2018; Chen et al., 2015; Duan et al., 2019; Kaufmann et al., 2015; Liu et al., 2018; Skåtun et al., 2017). In line with the prominent compression from the sensorimotor and visual system, our stable observation of hypo-connectivity within visual and sensorimotor systems across all link distances suggests an impaired ability to decode early information coming from early sensory regions in schizophrenia. Moreover, the degraded quality of early sensory input would persist, propagate and form the cascading effects along the whole sensation-to-cognition continuum, affecting higher-order integrative networks at subsequent stage of the cortical hierarchy in schizophrenia. These findings provide novel and integrative evidence to support the propagation of sensory deficits to higher cognitive functions in schizophrenia (Calderone et al., 2013; Dondé, Silipo, Dias, & Javitt, 2019; Javitt, 2009*b*; Leitman et al., 2010).

The dys-myelination hypothesis of schizophrenia proposed that abnormalities in myelination in the central nervous system may underpin or facilitate the pathogenesis and progress of schizophrenia (Hakak et al., 2001; Karoutzou, Emrich, & Dietrich, 2008). Interestingly, a recent study found reduced intracortical myelin in highly myelinated low-level sensory and motor regions in schizophrenia, which could cause disinhibition of sensory input, resulting in abnormal propagation of degraded quality of early sensory input to other cortical areas (Jørgensen et al., 2016). This finding thus provided evidence to further support the cascading effects of early sensory deficits along the sensation-to-cognition continuum. Considering both variations of intracortical myelin and FC across the entire cortex follow the general principle of macroscopic gradients (Paquola et al., 2019), future studies integrating the connectomics and myelin feature within gradients-based framework would be especially significant and deepen our understanding of how dysfunctional sensory processing involved in the pathophysiology mechanisms of schizophrenia.

In addition, although deficit of early sensory processing systems is not emphasized within prevailing psychiatric models, our findings are in parallel to the recent neurobiological findings of abnormal early sensory processing which characterize individuals' variability in psychopathology and cognitive impairment across multiple psychiatric disorders (Elliott, Romer, Knodt, & Hariri, 2018; Kebets et al., 2019). So far, with some notable exceptions in neurophysiological studies, hypothesis-driven fMRI studies have primarily targeted high-order brain networks. Consistent with the previous observation of prominent motor pole compression in cerebellar hierarchy (Dong et al., 2020), the present data-driven findings encourage future research to expand the neuroscientific view in schizophrenia and give more attention to sensory processing deficits characterization. Further investigation along these lines would deepen our understanding of the pathophysiology of schizophrenia.

Inefficient integration of bottom-up sensory information with top-down processes

We also found that schizophrenia patients showed hyper-connectivity between unimodal sensory seeds and frontoparietal–ventral-attention regions at the early and medium link distances along the sensation-to-cognition continuum. Several previous seed-based or ROI-based FC studies provide preliminary evidence for sensory networks pathologically interacting with higher-order association systems in the literature of schizophrenia (Berman et al., 2016; Hoptman et al., 2018; Kaufmann et al., 2015). In a more holistic view, we extend the previous studies by showing that this pathological interaction between sensory networks and higher-order association systems exists in the hierarchical information flow, not limited in directed communication (1 link-step). Supporting the cascading effects of sensory process deficits on subsequent high-order cognitive process impairment, our hyper-connectivity may further suggest that the integration of bottom-up sensory information with attentional demands and executive control processes in the sensation-to-cognition continuum is more effortful or less efficient in schizophrenia than in healthy populations.

This inefficient integration process is also characterized by the overall compression of the principal sensorimotor-to-transmodal hierarchy organization, which reflects diminished separation between sensory systems (e.g. visual and sensory regions) involved in the immediate environment and transmodal cognitive systems (e.g. frontoparietal regions) that support complex cognitive inferences. The effective brain function is supported by the maintenance of subnetworks segregation as well as their integration (Wig, 2017). Therefore, the diminished network differentiation would unavoidably result in ineffective functional specialization, leading to a blurred boundary between externally oriented immediate environment and internally abstract cognitive processing (Murphy et al., 2018; Northoff & Duncan, 2016), which further contributes to the inefficient integration of bottom-up sensory information with top-down processes. Because functional gradients analysis provides a very low-dimensional representation of resting-state connectivity to capture the fundamental corticocortical connectome hierarchy, the compressed corticocortical connectivity hierarchy organization extended previous observations of disturbances in corticocortical connectivity (Phillips et al., 2011), by providing an integrative/holistic neuroscientific perspective to understand the disrupted corticocortical connectivity in schizophrenia.

Critically, these cortical hierarchy abnormalities showed trend associations with the severity of clinical symptoms. Specifically, for those regions involved in high-order cognitive function (i.e. superior frontal gyrus, anterior insular cortex), abnormality of hierarchy value was associated with less clinical severity. Accordingly, for those regions involved in sensory processing function, i.e. pre/postcentral gyrus and visual areas, abnormality of hierarchy value correlated with greater clinical severity. These associations might further highlight the importance of cascading impairments of sensory processing and less efficient integration between sensory and cognitive processing to understand the clinical profiles of schizophrenia (Javitt, 2009*b*; Javitt & Freedman, 2015). However, given the exploratory nature of these associations, one should remain cautious when interpreting these results.

These results encourage future studies to further verify these exploratory associations.

Implications for future treatment studies

Finally, results reported here also encourage future studies to develop novel intervention strategies, such as complementary sensory-based therapies, which may help to correct early sensory dysfunction and thus further facilitates the remediation of high-order function in schizophrenia. Cognitive training must address limitations in perceptual/pre-attentive processing first (for a review see Vinogradov, Fisher, & de Villers-Sidani, 2012). This hope was preliminarily bolstered by some finding of learning-induced neuroplasticity, in which training in early auditory or visual processes results in substantial gains in verbal or visual cognitive processes through 'bottom-up' tuning of the neural systems (Adcock et al., 2009; Biagianti et al., 2016; Dale et al., 2016; Fisher et al., 2009; Hochberger et al., 2019; Surti, Corbera, Bell, & Wexler, 2011). In addition, considering the strong associations between audiovisual temporal processing deficits and clinical symptomatology (Stevenson et al., 2017), for example, auditory hallucinations (Hugdahl, 2009), training aimed at multisensory temporal processing may help relieve clinical symptoms through increasing the individual experience level of perceptual integration in patients with schizophrenia. This hope was also preliminarily supported by our recent works (He et al., 2018; Yang et al., 2018), in which the music intervention (listening to Mozart music), as a type of the auditory input, improved the functional integration in VAN and sensorimotor network in schizophrenia.

Limitation and future direction

Notwithstanding its implications, the main limitations of this study should be acknowledged. A main limitation in the current study, as well as many other clinical imaging studies in the field, is the effect of antipsychotic drugs. While we cannot eliminate completely the potential confounding effects of medication, chlorpromazine equivalents were not associated with the altered gradient or SFC scores. Due to the use of the cross-sectional research design, we did not establish the developmental trajectories of altered cortical hierarchy in schizophrenia. Because altered sensory-motor FC abnormalities have been consistently observed in clinical-high risk, early-stage including drug-naive first-episode, and chronic schizophrenia (Berman et al., 2016; Dong et al., 2019; Du et al., 2018; Guo et al., 2014; Jiang et al., 2015; Luo et al., 2020), it is possible that the prominent compression from the sensorimotor portion of the cortical hierarchy is present at different stages of the illness, possibly ranging from pre-clinical to early and late stages of the disorder. Future longitudinal studies may evaluate the development of cortical hierarchy in schizophrenia across time. And, a supplementary exploratory analysis for the second gradient value in our data showed group differences in the regions of sensorimotor network and visual network, which was similar to the findings in principle gradient value (online Supplementary Fig. S5). This further highlighted the critical role of disorganization of the sensorimotor and visual system in the pathophysiology of schizophrenia. Further testing of this difference is beyond the scope of the current study. However, the findings reported here hint at the possibility of the cerebral cortical functional gradient alterations in schizophrenia beyond the principal gradient of functional connectivity.

Conclusions

The present study provided novel system-level substrate underlying the pathological interaction of early sensory and cognitive function in schizophrenia, i.e. the compression of sensorimotor-to-transmodal cortical hierarchy organization. Within the framework of the compressed cortical hierarchy organization, a cascade of impairments stemming from the disrupted somatosensory–motor system and inefficient integration of bottom-up sensory information with attentional demands and executive control processes may partially account for high-level cognitive deficits of schizophrenia. While top-down processing is certainly deficient in schizophrenia, future investigations of bottom-up dysfunction will further clarify the underlying causes of cognitive deficits in this disorder and promote the development of new treatment intervention.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721002129.

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Conflict of interest. None.

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