Altered Fronto-Temporal Functional Connectivity in Individuals at Ultra-High-Risk of Developing Psychosis

Youngwoo Bryan Yoon1*, Je-Yeon Yun2*, Wi Hoon Jung3,4, Kang Ik K. Cho1, Sung Nyun Kim2, Tae Young Lee4, Hye Yoon Park2, Jun Soo Kwon1,2,4*

1 Department of Brain and Cognitive Sciences, College of Natural Sciences, Seoul National University, Seoul, Republic of Korea, 2 Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea, 3 Department of Psychology, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America, 4 Institute of Human Behavioral Medicine, Seoul National University-Medical Research Center, Seoul, Republic of Korea

☯ These authors contributed equally to this work.
* kwonjs@snu.ac.kr

Abstract

Background
The superior temporal gyrus (STG) is one of the key regions implicated in psychosis, given that abnormalities in this region are associated with an increased risk of conversion from an at-risk mental state to psychosis. However, inconsistent results regarding the functional connectivity strength of the STG have been reported, and the regional heterogeneous characteristics of the STG should be considered.

Methods
To investigate the distinctive functional connection of each subregion in the STG, we parcelated the STG of each hemisphere into three regions: the planum temporale, Heschl’s gyrus, and planum polare. Resting-state functional magnetic resonance imaging was obtained from 22 first-episode psychosis (FEP) patients, 41 individuals at ultra-high-risk for psychosis (UHR), and 47 demographically matched healthy controls.

Results
Significant group differences (in seed-based connectivity) were demonstrated in the left planum temporale and from both the right and left Heschl’s gyrus seeds. From the left planum temporale seed, the FEP and UHR groups exhibited increased connectivity to the bilateral dorsolateral prefrontal cortex. In contrast, the FEP and UHR groups demonstrated decreased connectivity from the bilateral Heschl’s gyrus seeds to the dorsal anterior cingulate cortex. The enhanced connectivity between the left planum temporale and right dorsolateral prefrontal cortex was positively correlated with positive symptom severity in individuals at UHR ($r = .34, p = .03$).
Conclusions

These findings corroborate the fronto-temporal connectivity disruption hypothesis in schizophrenia by providing evidence supporting the altered fronto-temporal intrinsic functional connection at earlier stages of psychosis. Our data indicate that subregion-specific aberrant fronto-temporal interactions exist in the STG at the early stage of psychosis, thus suggesting that these aberrancies are the neural underpinning of proneness to psychosis.

Introduction

The superior temporal gyrus (STG) plays an important role in auditory perception and cognitive functions, including language [1], and impairment in this area has been identified as the core pathophysiology of psychosis [2, 3]. Patients with schizophrenia and first-episode psychosis (FEP) consistently exhibit decreased gray matter (GM) volume in the STG [4, 5] and abnormal language task-related functional connectivity networks within the STG [6–8]. Even before the onset of psychosis, an aberrant connection between the STG and prefrontal cortex was noted in individuals with an at-risk mental state (ARMS) during working memory tasks [8]. Furthermore, the degree to which the GM volume is reduced in the STG is associated with the onset of psychosis in ARMS individuals [9, 10]. These studies suggest that aberrations of the STG may be related to the pathological process of psychosis.

Previous studies have reported discrete patterns in the cytoarchitectonic organization [11, 12] and enzyme distribution [13] in the STG. They have also suggested that subregional differences in the architectonic arrangements influence its connectivity pattern to other areas of the brain [14, 15]. The STG consists of at least three histologically distinctive areas [16], and it can be anatomically divided into three different subregions [17] that exhibit different roles: the planum temporale (PT), Heschl’s gyrus (HG), and the planum polare (PP). Although few studies have carefully explored the various STG subregions, a volumetric study investigated progressive GM loss in the STG subregions in patients transitioning into psychosis. The study demonstrated a distinct pattern for each of the subregions and suggested the importance of assessing the STG by using a more detailed approach [18]. A functional anatomy study suggested that the STG subregions are projected to different parts of the brain and that these projections are involved in different language processing streams [19]. Meaningful studies have investigated the functional connection of the STG subregions in schizophrenia patients, further linking the aberrant connectivity to hallucinations. When comparing patients with and without auditory hallucinations, the aberrant functional connectivity of HG, increased connections to the frontoparietal region and decreased connections to the hippocampus and thalamus were reported among patients with auditory hallucinations [20]. A reduction in the functional connection of the PT with the temporal, parietal, and limbic regions was observed in schizophrenia patients and their relatives, which correlated with the tendency to experience hallucinations [21]. However, no study has revealed how each subregion is distinctively connected to other areas in the brain or how those connections interact with each other.

Whereas task-dependent functional network analyses could underestimate the networks not relevant to the task-dependent circuits, task-independent functional network analyses can identify submerged neural networks rather than an induced phenomenon, which enables us to understand the comprehensive properties of brain physiology [22]. Recently, instead of measuring functional networks across tasks, an alternative approach for measuring the spontaneous dynamics of the brain involves functional magnetic resonance imaging (fMRI) during the
Although few studies have investigated the resting-state network of the STG, moderate evidence suggests network alterations in the region. Some studies have directly explored the resting-state networks of the auditory perception areas in schizophrenia patients [20, 21, 24–26], and other studies have indirectly identified the networks within the auditory-associated area that are connected to other regions of the brain [27, 28]. However, there is inconsistency in the reports regarding the increased or decreased strength of connectivity within the auditory perception areas due to the non-homogeneous characteristics of the subregions in the temporal lobe [27].

We hypothesized that the discrepancy regarding the resting-state functional connectivity strength of the STG is caused by the different characteristics of each subregion. Given the advantages of resting-state studies and the distinctive role of STG subregional networks in individuals at an ultra-high-risk of developing psychosis, we compared the resting-state functional connectivity of the three subregions of the STG to the entire brain using the parcellated seeds of the STG according to the Destrieux atlas [17]. This led to the hypothesis that alterations in functional networks within the STG are closely related to psychosis progression; thus, the networks may demonstrate distinctive patterns in individuals at ultra-high-risk for psychosis (UHR) and in patients shortly after the onset of psychosis. In addition, the alteration is potentially associated with symptom severity. To directly examine the functional connectivity pattern of the entire brain with the STG, voxel-wise seed-based correlation analyses were applied during the resting-state by using different parts of the STG as seeds. Then, we extended our findings to characterize the circuit-level alterations associated with psychotic symptom severity. We will further explore how the presence of hallucinations is reflected in the altered connections. We expect our approach to unearth buried networks that were concealed by other task-dependent networks and monolithically defined seeds.

Materials and Methods

Participants

Twenty-four FEP patients, forty-two UHR individuals, and forty-eight healthy controls (HC) were selected. The FEP and UHR subjects were recruited from a longitudinal project to study individuals at a high risk for developing psychosis at the Seoul Youth Clinic, Seoul, Republic of Korea [29, 30]. For the present study, individuals were selected from the subject pool of the previous forty-one months (April 2010 to August 2013). The participants initially contacted the Seoul Youth Clinic via our website, telephone or referral from local clinics.

All participants were interviewed based on the Structured Clinical Interview for DSM-IV (SCID) Axis I [31] by experienced psychiatrists. The Positive and Negative Syndrome Scale (PANSS) [32] was applied to the FEP and UHR groups, and individuals scoring equal to or greater than 3 in the hallucinatory behavior subscale were considered to have hallucinations. The Korean version of the Wechsler Adult Intelligence Scale [33] was administered to all participants to assess their intelligence quotient (IQ).

The inclusion criteria for FEP were defined as individuals satisfying the diagnosis of brief psychotic disorder, schizophreniform disorder, schizophrenia or schizoaffective disorder according to the DSM-IV criteria and exhibiting symptoms for less than 1 year. All UHR subjects were assessed according to the Structured Interview for Prodromal Syndromes [34]. Our UHR subjects satisfied at least one of the prodromal states of psychosis criteria: attenuated positive syndrome (APS), brief intermittent psychotic syndrome (BIPS), and/or genetic risk with deterioration (GRD). APS is defined as the presence of any positive items on the Scale of Prodromal Symptoms (SOPS) [35] in the prodromal range, with an occurrence of the symptoms within the past year, or exhibiting attenuated psychotic symptoms upon at least one point
within the past year and showing these symptoms at one or more occasions per week for the past month. BIPS subjects exhibited at least one symptom from the positive items on the SOPS scale in the psychotic range, with symptoms initiated within the past 3 months and the presence of the symptoms several minutes a day at least once per month. GRD is defined as a significant decline in functioning, showing at least a 30% decrease in the Global Assessment of Functioning (GAF) scale over the past year, and individuals who have a genetic risk due to a first-degree relative with any psychotic disorder or schizotypal personality disorder [36].

At the time of enrollment, seventeen FEP patients were receiving antipsychotics. These patients were also receiving mood stabilizers (n = 1), antidepressants (n = 3), and anxiolytics (n = 8). None of the UHR subjects were medicated with antipsychotics or mood stabilizers, but they were receiving antidepressants (n = 4) and anxiolytics (n = 4).

HC subjects were recruited from internet advertisements. All HC were screened and confirmed using the SCID Non-patient Edition [37]. None of the HC had any history of a psychiatric disorder or any first- to third-degree biological relatives diagnosed with a psychiatric disorder. The participants were excluded if they were considered to have any of the following: i) a known history of a psychotic disorder, neurological illness, substance abuse, or considerable head injury; ii) evidence of a medical disease with documented cognitive sequelae; or iii) an intellectual disability (IQ below 70).

The present study was performed in accordance with the Declaration of Helsinki. This study was approved from the Institutional Review Board of Seoul National University Hospital. After providing a complete description of the study to the participants, written informed consent was obtained from each participant before study inclusion. For minors who were enrolled in this study, written informed consent was obtained from both the participants themselves and their caretakers or guardians.

Image Acquisition and Data Preprocessing

Functional and structural images were obtained with a Siemens 3T Trio MRI scanner (Siemens Magnetom Trio, Erlangen, Germany) using a 12-channel head coil. The T1-weighted anatomical image was acquired using magnetization prepared rapid gradient echo (echo time [TE] / repetition time [TR] = 1.89 / 1670 ms, field of view [FOV] = 250 mm, flip angle = 9°, matrix = 256 x 256, voxel size = 1.0 x 1.0 x 1.0 mm³, 208 slices). For each subject, we collected a rest scan comprising 116 contiguous echo-planar imaging (EPI) functional images (TE / TR = 30 / 3500 ms, FOV = 240 mm, flip angle = 90°, matrix = 128 x 128, voxel size = 1.9 x 1.9 x 3.5 mm³, 35 slices). During resting-state image acquisition, the participants were asked to relax with their eyes closed. To limit possible head movements and subsequent motion artifacts, cushions were used, and the participants were instructed to move as little as possible. The time required to collect the resting-state scans was 6 minutes and 58 seconds.

The first four echo-planar images were discarded. The remaining 112 contiguous EPI functional volumes were preprocessed using the Statistical Parametric Mapping software package, version 8 (SPM8; www.fil.ion.ucl.ac.uk/spm; Wellcome Department of Cognitive Neurology, London, UK). The images were first processed by slice-timing correction and subsequently realigned to correct for head motions. Two subjects from the FEP group, one subject from the UHR group and one subject from the HC group were excluded for exceeding the head motion criteria, i.e., translation > 2.5 mm and rotation > 2.5° in any directions. The functional volumes were then co-registered to each participant’s structural volumes. The images were segmented into GM, white matter (WM), and cerebrospinal fluid (CSF) partitions and were spatially normalized to the Montreal Neurological Institute (MNI) standardized space (http://www.mni.mcgill.ca/). The functional volumes were resampled to a 3 x 3 x 3 mm³ voxel size.
and spatially smoothed with a 6-mm full-width half-maximum (FWHM) isotropic Gaussian kernel.

The CONN-fMRI functional connectivity toolbox (V 14f, http://www.nitrc.org/projects/conn/) was used to remove confounding effects and for further analysis. For the nuisance regression, the head motion measured in 6 dimensions with their first derivatives, and the component-based noise correction (CompCor) [38] noise components were designated as nuisance variables. The CompCor strategy built in the CONN toolbox was used to increase the precision of the GM signal by erasing physiological noise, such as the heart rate and respiration signals, and to remove principal components from both the WM and CSF signals. In addition, the CompCor strategy is reported to remove motion-related artifacts effectively [39]. Subsequently, the linear trend was removed through the time course, and the band-pass filter (.008 < f < .09 Hz) was applied.

Functional Connectivity Analysis

We measured the connectivity patterns of the regional mean time series in the resting-state fMRI data using six different seed regions-of-interests (ROI) located in the STG. Freesurfer image analysis (http://surfer.nmr.mgh.harvard.edu/) was used to parcellate the STG into six different ROIs in both hemispheres: HG, PT, and PP (S1 Fig). The six different ROIs of the STG were defined using the Destrieux atlas from the Freesurfer image analysis suite; thus, the seed locations were independent of our data [17].

The functional connectivity networks were measured in the EPI time series. Pearson’s correlation (bivariate) analyses were performed to estimate the connection from the seed ROIs to other voxels in the entire brain. By setting the explicit mask images, between-group comparisons could be performed among voxels presenting significant connectivity with each seed ROI. The explicit mask images were created by applying a cluster-level family-wise error (FWE) rate of $p < .05$ to correct for multiple comparisons over the entire brain. Then, three mask images from each group were combined; thus, all of the significant voxels of the 3 groups were included in a single explicit mask. The combined group explicit masks were applied to prevent potential bias by using the mask acquired from individuals in the psychosis spectrum or the healthy controls alone.

Significant between-group differences were compared by entering the (Fisher’s Z transformed) connectivity map of each ROI into a one-way analysis of variance (ANOVA) model. Regions of significant difference were defined by the clusters surviving the voxel-level height threshold of uncorrected $p < .001$ and the cluster-level extent threshold of $p < .05$ that was corrected for multiple comparisons using the FWE rate. For the post-hoc tests and correlation analyses, the Region of Interest Extraction Tool (http://software.incf.org/software/rex) in the CONN toolbox was used to extract Fisher’s Z transformed signal intensity values of the selected clusters. The post-hoc tests were executed using the Bonferroni correction. Correlation analyses were performed to explore the relationship among different functional connectivities and to measure the correlation between an individual’s connectivity intensities and clinical symptom scores from the PANSS. In addition, a two sample t-test was performed on the connectivity strength of individuals with and without hallucinations to compare the connectivity strength between each group.

Results

Demographic and Clinical Characteristics

No significant differences in age, gender, education level, handedness, or IQ were noted. The FEP group [duration of untreated psychosis: 0.54 ± 0.32 years] exhibited an increased
The PANSS total score ($p = .04$) and positive score ($p = .03$) in the PANSS scale, which indicated that these patients displayed worse symptom severity compared with the UHR group [duration of untreated prodromal positive symptoms [40]: 1.70 ± 1.49 years]. There were no significant differences in the hallucinatory behavior subscale in the PANSS in both the FEP and UHR groups ($p = .05$). Eleven of the 22 individuals from the FEP group and 12 of the 41 participants from the UHR group scored greater than or equal to 3 on the hallucinatory behavior subscale in the PANSS. The demographical and clinical characteristics are summarized (Table 1).

### Table 1. Demographic and Clinical Characteristics.

|                  | FEP ($n = 22$) | UHR ($n = 41$) | HC ($n = 47$) | Statistics |
|------------------|----------------|----------------|--------------|------------|
|                  | Mean     | SD           | Mean     | SD           | Mean     | SD           | $F / \chi^2$ | $p$        |
| Age (year)       | 22.73    | 4.89         | 20.78    | 2.52         | 22.09    | 2.96         | 2.995       | .054       |
| Gender (M / F)   | 9 / 13   |              | 29 / 12  |              | 28 / 19  |              | 5.312       | .070       |
| Education (year) | 13.32    | 1.94         | 13.17    | 1.22         | 13.94    | 1.55         | 3.010       | .053       |
| Handedness (R / L)| 20 / 2 |              | 37 / 4   |              | 43 / 4   |              | .041        | .980       |
| Estimated IQ     | 104.59   | 11.38        | 111.32   | 12.14        | 110.66   | 11.12        | 2.711       | .071       |
| Clinical rating scales | Mean     | SD           | Mean     | SD           | t         | $p$          |
| PANSS Total      | 68.09    | 10.41        | 61.27    | 13.19        | -2.099   | .040         |
| Positive         | 15.45    | 4.51         | 12.95    | 2.81         | -2.368   | .025         |
| Negative         | 17.41    | 4.62         | 16.24    | 5.66         | -1.673   | .187         |
| General          | 35.23    | 5.90         | 32.07    | 7.70         | 1.017    | .313         |
| GAF              | 48.36    | 8.77         | 50.51    | 7.56         |           |             |

Note: FEP, first-episode psychosis; UHR, ultra-high-risk for psychosis; HC, healthy control; IQ, Intelligence quotient. PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning

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Each seed region exhibited distinct functional connectivity patterns (Fig 1). The significant spatial group differences of the three groups revealed by the one-way ANOVA model were observed in the left PT and in the right and left HG seed-to-brain networks. Five regions from the left PT seed, 2 regions from the right HG seed, and 3 regions from the left HG seed demonstrated significant group differences. The UHR group demonstrated an intermediate strength between the FEP and HC groups in the 7 of the 10 altered functional connectivities. No statistical significance was observed for the seed-to-brain networks from the right PT as well as the right and left PP seeds. Information regarding the clusters demonstrating significant differences and the post-hoc analysis results is summarized (Table 2 and Fig 2).

### Relationship among the Functional Connectivities

In the FEP group, the increased connections between the left PT and the right dorsolateral prefrontal cortex (DLPFC) and decreased connections between the left HG and the dorsal anterior cingulate cortex (ACC) were negatively correlated with each other ($r = -.48$, $p = .02$).
Association between the Functional Connectivities and Symptom Severity

In the UHR individuals, the level of increased connection strength between the left PT seed and the right DLPFC was positively associated with overall positive symptom severity as assessed by the PANSS ($r = .34$, $p = .03$) (Fig 3A). The enhanced connectivity in the UHR participants was positively correlated with the hallucinatory behavior subscale in the PANSS ($r = .33$, $p = .03$). Among individuals in the FEP and UHR groups, there were significant differences in the degree of the augmented connection between individuals with ($n = 23$) and without
### Table 2. Between Group Difference in Functional Connectivity of Superior Temporal Gyrus.

| Seed Region                  | Brain Region                      | MNI Coordinate (x, y, z) | Size of Clusters | Cluster P value (FWE corrected) | Group Functional Connectivity | Mean SD | FEP-HC | UHR-HC | FEP-UHR |
|------------------------------|-----------------------------------|--------------------------|------------------|-------------------------------|------------------------------|---------|--------|--------|---------|
| Left planum temporale        | Right Primary Motor Cortex        | +58 -04 +34             | 165              | .039                          | FEP-HC                       | 0.12    | 0.15   | <0.01  | <0.01   |
|                             | UHR-HC                            |                          |                  |                               |                              | 0.04    | 0.16   | <0.01  | <0.01   |
|                             | FEP-UHR                           |                          |                  |                               |                              | 0.20    | 0.16   | <0.01  | <0.01   |
|                             |                                    |                          |                  |                               |                              | 0.04    | 0.16   | <0.01  | <0.01   |
| Right Dorsolateral prefrontal cortex | -40 +52 -24                     | 190                     | 0.021            | 1.00                          |                              | 0.01    | 0.12   | <0.01  | <0.01   |
| Left Dorsolateral prefrontal cortex | -38 +50 +22                     | 155                     | 0.023            | 1.00                          |                              | 0.06    | 0.16   | <0.01  | <0.01   |
| Left Middle temporal gyrus   | Right Dorsolateral prefrontal cortex | +42 -05 -30            | 105              | 0.023            | 1.00                          | 0.08    | 0.14   | <0.01  | <0.01   |
| Left Superior temporal gyrus | Right Dorsolateral prefrontal cortex | +48 -44 +06           | 280              | 0.040            | 1.00                          | 0.19    | 0.12   | <0.01  | <0.01   |
| Left Heschl's gyrus          | Left Insular cortex               | -38 -14 +12            | 170              | 0.051            | 1.00                          | 0.08    | 0.12   | <0.01  | <0.01   |
| Left Heschl's gyrus          | Left Insular cortex               | -44 -14 +12            | 151              | 0.011            | 1.00                          | 0.01    | 0.12   | <0.01  | <0.01   |
| Left Heschl's gyrus          | Left Putamen                       | -32 -16 -02            | 151              | 0.011            | 1.00                          | 0.01    | 0.12   | <0.01  | <0.01   |

**Note:** FWE, family-wise error; FC, functional connectivity; FEP, first-episode psychosis; UHR, ultra-high-risk for psychosis; HC, healthy control.

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Fig 2. Significant difference in functional connectivity among groups. The differences among individuals with first-episode psychosis (FEP), ultra-high-risk for psychosis (UHR), and the healthy controls (HC) were revealed by one-way ANOVA ($p < .05$, family-wise error rate corrected). Significant differences...
auditory hallucination \((n = 40) (p = .02)\) (Fig 3B). None of aberrant connectivity showed a significant association with the lengths of the prodromal syndrome in the UHR group.

**Discussion**

This study investigated the resting-state functional connectivity network within the subregions of the STG in FEP and UHR individuals to explore subregion-specific alterations in connectivity. The widespread disorganization of networks, including the frontal area, as measured by the aberrant strength of the functional connectivity, was evident in both the FEP and UHR groups with the left PT and in the right and left HGs. Notably, the strength of the altered network between the left PT and the right DLPFC in the UHR group correlated with psychotic symptom severity. To our knowledge, the present study is the first to report the disorganization in fronto-temporal functional connectivity in both FEP and UHR individuals during the resting-state. Taken together, our results suggest that the alteration in fronto-temporal functional connectivity is evident at the earliest stages and the prodromal stages of psychosis.

The hyperconnectivity between the left PT and the bilateral DLPFC and the hypoconnectivity between the bilateral HG and the dorsal ACC demonstrate the existence of disorganized functional connections between the prefrontal cortex and the STG. The disconnection hypothesis of schizophrenia comprises not only hypoconnectivity, which refers to decreased interactions between regions, but also hyperconnectivity, which represents reinforcement between regions [41–43]. Previously, both hyper- and hypoconnectivity in fronto-temporal functional connectivity have been reported [6, 24, 27, 44, 45], and our results demonstrate the distinctive fronto-temporal connectivity patterns in different subregions of the STG and are thus consistent with previous findings. No significant difference in fronto-temporal connectivity strength was noted between the FEP and UHR groups; however, all of the altered fronto-temporal connections demonstrated the highest degrees of dysconnectivity in the FEP individuals, and intermediate values were noted in the UHR group. These results resemble previous studies.

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**Fig 3. Associations between functional connectivity strength and symptom severity.**

(A) Scatterplot of the correlation between the overall positive symptom severity and altered functional connectivity of the ultra-high-risk for psychosis (UHR) subject group \((r = .34, p = .03)\): Fisher’s Z transformed connectivity strength between the left planum temporale (PT)–right dorsolateral prefrontal cortex (DLPFC) \((x\) axis) and the overall positive symptom scale score of Positive and Negative Syndrome Scale (PANSS) \((y\) axis). (B) Bar plot of the mean functional connectivity strength (Fisher’s Z transformed) of the hallucination group \((n = 23)\) and non-hallucination group \((n = 40)\) among individuals in the FEP and UHR groups \((p = .02)\).
investigating WM disconnections [46] and fronto-temporal functional connectivity during working memory tasks in UHR and FEP subjects [8].

The hyperconnectivity between the left PT and the right DLPFC was positively correlated with the overall positive symptom severity, as measured by the PANSS, among the UHR individuals (Fig 3A). The relationship between the disorganization in neural activity and the positive symptoms has been discussed for decades [47]. In particular, the hyperconnectivity of the neural circuitry is thought to be due to excessive attention to inconsequential information [48]. We suggest that the excessive attention induces positive symptoms, which are consequences of impairment in selective attention [49]. Additionally, the relationship between hyperconnectivity and hallucinatory symptom severity was analyzed, and a positive correlation among UHR individuals was observed. There were significant differences in the degree of hyperconnectivity between participants with or without hallucinatory symptoms among the FEP and UHR groups (Fig 3B). A meta-analysis revealed that the core regions responsible for hallucinations are the regions related to speech production, whereas an individual's hallucinatory trait is associated with the speech perception areas [50]. The DLPFC is involved in numerous high-level functions, including speech perception [51]. Collectively, an enhanced connection between both speech perception regions leads to an exaggerated attention to irrelevant cues, which contributes to an individual's proneness to hallucinations. However, we were unable to reveal an association between the positive symptom severity and aberrant fronto-temporal connectivity in the FEP group. The differences in fronto-temporal connections between the FEP and HC groups were greater than those between the UHR and HC groups. We hypothesize that the more severely altered connections or medications in FEP individuals influenced the positive symptoms in a more complex manner; thus, the relationship between a single aberrant connection and positive symptom severity was potentially blurred.

A divergent trend was observed between the left PT to bilateral DLPFC and the bilateral HG to dorsal ACC networks. In addition, the FEP group exhibited decreased connectivity to the insula via the bilateral HG seeds. The ACC and the insula comprises the salience network [52]. The reduced functional connection in the salience network are related to the information processing disturbance in schizophrenia and are regarded as the core pathology of the disease [53, 54]. One possible explanation for the dissimilar trend in fronto-temporal functional connections could be attributed to our brain's compensatory mechanism when the reduced functional connectivity between the HG and salience network triggers an abnormal increase in top-down control. Evidence supporting this notion was evident in the FEP group, where a negative correlation between the left PT to right DLPFC and the left HG to dorsal ACC connections was noted. The interaction between the auditory cortex and subregions of the salience network were also assessed by electrophysiological studies analyzing mismatch negativity (MMN) [55–58], which is considered a potent biomarker of psychosis [59]. The present findings revealed a decreased interaction between the auditory cortex and the salience network and thus extend our previous electrophysiological studies, which demonstrated a decreased MMN in UHR individuals [60, 61].

There are meaningful studies reporting aberrant connectivity between the prefrontal area and temporal area during various tasks [8, 44, 62]. We expand these task-induced network studies by demonstrating aberrant connections between the prefrontal and temporal areas during the resting-state. Resting-state research is expected to better reflect the trait of brain physiology by presenting comprehensive fluctuations in intrinsic brain activity [63]. Therefore, our findings demonstrate an alteration in the spontaneous neural activity rather than evoked disorganization. Furthermore, the resting-state better represents the phenomenology of schizophrenia compared with the task-induced neural activity [64]. Because our findings were obtained from FEP and UHR individuals, we suggest that the aberrant connectivity, which has been consistently reported between the temporal and frontal lobes in schizophrenia patients, potentially
existed from earlier stages of the illness. Our results conclusively show that the alteration in fronto-temporal functional connectivity is a trait noted in individuals at early or prodromal psychosis and that the aberrant connection is rather intrinsic. These findings suggest that the functional disjunction is a candidate phenotype for the transition to psychosis.

Our study includes a few limitations. First, although none of our UHR participants were receiving antipsychotics, 17 of our 22 FEP participants were taking antipsychotics. However, we did not observe a significant difference in connection strength in the disease-affected connections between FEP patients taking antipsychotics and FEP patients who were not administered antipsychotics. Regardless, the effect of medication on connectivity should be investigated in further studies. Second, compared with our UHR and HC groups, a relatively smaller number of FEP individuals were included in our study. No significant group differences in the right PT and bilateral PP seeds were noted, and the between-group differences of these seed-based connections may be underestimated due to the small size of the FEP group. Third, an association between functional connectivity strength and symptom severity was only noted in the UHR group. Our UHR group exhibited significantly milder positive symptom severity compared with the FEP group. This fact could potentially serve as one of the strengths of our study. The UHR group exhibited symptoms at a subthreshold for psychosis, which suggests that the enhancement in connectivity is not the consequence of severe psychotic symptoms. To validate our conclusions, a longitudinal effect of enhanced connections to positive symptoms, including hallucinations, should be verified in a follow-up study.

In summary, our results identified altered temporal and cortical functional connectivity in FEP patients and UHR individuals. Disorganized fronto-temporal connectivity was observed in both groups, and such disorganization was associated with psychotic symptom severity. By highlighting fronto-temporal functional connectivity alterations in early psychosis patients and UHR individuals, our results clarify the controversy regarding hyper- or hypoconnectivity in resting-state fronto-temporal functional connectivity. Furthermore, the aberrant fronto-temporal connections were associated with psychotic symptom severity, thus emphasizing the clinical significance of the circuit in the progression of psychosis. Together with additional studies emphasizing the role of the STG in individuals at ultra-high-risk of developing psychosis, our study extends the previous studies by underscoring the role of the STG as the core hub for functional interactions with other areas of the brain.

Supporting Information
S1 Fig. Placement of primary seed region of interest (ROI). The ROIs are overlaid on a standard neuroanatomical template. (TIF)

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Author Contributions
Conceived and designed the experiments: YBY JYY WHJ JSK. Performed the experiments: YBY JYY KKC. Analyzed the data: YBY. Wrote the paper: YBY JYY SNK. Performed all participants recruitment and screening: TYL SNK HYP.
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