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REGULAR ARTICLE

# Enhancement of the left frontoparietal network through real-time functional magnetic resonance imaging functional connectivity–informed neurofeedback and its impact on working memory in schizophrenia: A pilot study

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**Aim:** Cognitive impairment in schizophrenia shows limited improvement with pharmacotherapy, indicating a need for effective treatment. The frontoparietal network supports working memory, and a biomarker has successfully predicted performance in patients, with the left frontoparietal network contributing the most to working memory. We hypothesized that enhancing functional connectivity in this network through real-time neurofeedback (NF) will improve working memory in patients with schizophrenia.

**Methods:** We conducted a two-arm, nonrandomized pilot study in patients with schizophrenia, with a NF group ($N = 11$) and a control N-back training group ($N = 11$). The NF training lasted 5 days (one session per day). The first session included baseline measurements, while the next four sessions involved training. The participants completed cognitive and clinical assessments and resting-state scans preintervention and postintervention. Our primary neural outcome was increased functional connectivity during NF, and the behavioral outcome was improvement in working memory, as indicated by scores on the digit-span backward task and working memory capability measured by the N-back task.

**Results:** The NF group showed increased functional connectivity within the left frontoparietal network during the final session. A significant correlation existed between functional connectivity and the improvement in the mean N-back level, indicating that enhancing this network can boost working memory. A group-by-time interaction effect improved post-intervention task score on the digit-span backward task in the NF group. In addition, post-NF scans indicated an enhanced resting-state functional connectivity within the left frontoparietal network.

**Conclusion:** These results highlight the potential of functional connectivity–informed NF as a novel therapeutic approach for improving working memory in schizophrenia.

**Clinical Trial Registration:** Japan Registry of Clinical Trials (UMIN000024831, jRCTs052180168, jRCTs032190244).

***Keywords:*** *biomarker, cognitive impairment, neurofeedback, schizophrenia, working memory.*

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Cognitive impairment in schizophrenia occurs before onset, progresses after onset, and is a predictor of functional prognosis.[1] However, the current treatment for schizophrenia relies predominantly on antipsychotic medications, which have limited efficacy in the treatment of cognitive impairment.[2] Therefore, new treatments are required to address these shortcomings.

Real-time functional magnetic resonance imaging (fMRI) neurofeedback (NF) has been reported to improve the symptoms of psychiatric disorders, such as depression,[3,4] tics,[5] schizophrenia,[6–14] autism spectrum disorder,[15] and phobia.[16] Biomarkers based on functional connectivity (FC) using resting-state fMRI have been developed to predict the diagnosis and symptoms of psychiatric disorders.[17–22] FC-informed NF is a promising and novel therapeutic approach that can directly intervene in disease- and symptom-specific FC derived from biomarkers.[23–25]

FC-informed NF (FCNef) induces changes in FC and behavioral performance. A randomized study involving two control groups of healthy participants reported persistent changes in resting-state

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functional networks for 2 months after FCNef.[26] Another randomized study of increased or decreased FC reported behavioral changes corresponding to the direction of FC changes and changes in the resting-state functional network in the increased FC group.[27] Furthermore, an FCNef study of subclinical depression targeting the FC between the left dorsolateral prefrontal cortex (DLPFC) and precuneus, which has been implicated as a diagnostic and symptomatic biomarker of depression,[17] reported improvements in Beck Depression Inventory-II (BDI-II) scores and brooding symptoms.[28] The FCNef approach has been successfully used to treat treatment-resistant depression.[29]

Real-time fMRI NF has been implemented for auditory hallucinations, theory of mind, and emotional cognition in schizophrenia; it reportedly controls activation in the target region and improves symptoms.[6–14] Moreover, the effectiveness of NF targeting activation of the left DLPFC for working memory in healthy participants has been reported.[30–33] However, in patients with schizophrenia, fMRI NF targeting working memory has not yet been reported.

We aimed to use the FCNef to improve working memory in patients with schizophrenia. The frontoparietal network has been consistently reported as a neural substrate for working memory.[34–37] Our approach was based on the working memory biomarker developed by Yamashita *et al.*,[36,38] which is a prediction model that estimates 3-back task performance, a measure of working memory capability, using FCs derived from resting-state imaging in healthy participants. When applied to resting-state scans of patients with schizophrenia, the predicted working memory capability was significantly correlated with performance on the Digit Sequencing Task of the Brief Assessment of Cognition in Schizophrenia, indicating that this biomarker could function in patients with schizophrenia. The biomarker comprised a weighted sum of 16 FC values selected from the intranetwork and internetwork connections of 18 networks identified in the study by Laird *et al.*,[39] with the greatest contribution (approximately 34%) from the FC within the left frontoparietal network (LFPN). Therefore, despite a notable contribution (approximately 20%) from the right frontoparietal network involving negative connectivity with the midbrain and superior parietal networks, this study focused on the LFPN because of its predominant contribution.

Building on this, we hypothesized that enhancing FC within the LFPN through FCNef would improve working memory in patients with schizophrenia. To test this hypothesis, we conducted a two-arm, nonrandomized controlled pilot study. The primary neural outcome was defined as increased LFPN FC values during FCNef, and the behavioral outcomes were improvements in working memory assessments, including the digit span backward task and the mean N-back level. Additionally, we were particularly interested in investigating resting-state FC changes within the LFPN because it is based on the Yamashita biomarker, which comprises resting-state FCs.

To our knowledge, this is the first study to use fMRI NF in Japanese patients with schizophrenia. To ensure safety as the primary objective, we collected multiple clinical and cognitive assessment measures to evaluate their effects on participants.

## Methods

### Study Structure

The participants were nonrandomly assigned to the FCNef and control groups to ensure that their age compositions did not differ significantly (Fig. 1a). Initially, all participants underwent adaptive N-back training for 5 consecutive days. In-depth preintervention training was aimed at maximizing performance gains through task repetition and minimizing learning effects during subsequent assessments. This task was also performed as a posttest and follow-up assessment.

We established a control group that performed the same N-back tasks as that executed during the NF run but outside the MRI scanner.

For preintervention and postintervention assessments, the FCNef group underwent MRI, as well as clinical and cognitive assessments, whereas the control group underwent only clinical and cognitive assessments. Furthermore, the FCNef group underwent follow-up assessments 1 to 3 months after the intervention, whereas the control group did not.

This study adhered to the Declaration of Helsinki and Clinical Trials Act (Act No. 16 of April 14, 2017). The study was conducted in accordance with the protocols approved by the Kyoto University Certified Review Board (YC1251) and the Committee on Medical Ethics of Kyoto University (R2223, C1251), including the Tokyo Medical and Dental University Hospital of Medicine, Clinical Research Center, and Certified Review Board (M2019-080). This study was registered with the Japan Registry of Clinical Trials (jRCTs052180168, jRCTs032190244) and the University Hospital Medical Information Network Clinical Trials Registry (UMIN000024831).

### Participants

We recruited 22 participants who had been diagnosed with schizophrenia or schizophrenia spectrum disorder based on the DSM-IV TR or DSM-5 criteria from the Department of Psychiatry, Kyoto University Hospital (KUHP), Japan, and the Department of Psychiatry, Tokyo Medical and Dental University (TMDU), Japan. The FCNef group comprised 11 participants (KUHP only) from 2017 to 2020, and the control group comprised 11 participants (KUHP: nine, TMDU: two) from 2021 to 2022. Details of the inclusion and exclusion criteria are provided in the Supporting Information Methods.

Written informed consent was obtained after a comprehensive description of the study had been provided. The participants were provided with financial compensation to participate in the study.

### Adaptive N-back Task

The adaptive N-back task was based on the single N-back task described by Jaeggi *et al.*[40] and was implemented in MATLAB R2007b (MathWorks Inc.). The modifications to the original task are detailed in Supporting Information Methods. The participants completed 40 rounds daily for 5 consecutive days (days 1–5), with one session per day. Each round consisted of 20 trials, displaying a letter at the center of the PC screen for 0.5 s every 3 s, repeated 20 + N times. Participants clicked on the mouse pad when the presented letter matched one N step earlier. At the end of each round, the performance (Pr) was calculated as Pr = hit rate − false alarm rate. If Pr ≥90, N increased by one in the next round; if Pr < 70, N decreased by one; and for 70 ≤ Pr < 90, N remained unchanged (Fig. S1). The performance in the previous round determines level N in the next round. Participants were informed that the task aimed to enhance their working memory and were provided with strategies, such as chunking, word matching, and consonant blending.

The mean N-back level represents the average N level across all 40 rounds in a session, reflecting the participants' optimal difficulty level for the N-back task and their working memory capability. The mean N-back level on the fifth day was used for preintervention assessment. This task was also used for the postintervention and follow-up assessments.

### MRI Acquisition

Imaging was conducted at the Advanced Telecommunications Research Institute International (ATR) Brain Activity Imaging Center using a 3T MRI scanner (Siemens MAGNETOM Prisma, Siemens) with a 32-channel head coil. T1-weighted structural images were acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: echo time (TE), 2.22 ms; repetition time (TR), 2400 ms; inversion time, 1000 ms; field of view (FOV), 256 × 240 mm; flip angle, 8°; matrix size, 320 × 300; resolution, 0.8 × 0.8 × 0.8 $mm^3$; and slice number, 256. The T2*-weighted gradient-echo planar sequence parameters for the NF, resting-state, and N-back task runs were as follows: TE, 30 ms; TR, 1000 ms; FOV, 200 × 200 mm; flip angle, 50°; matrix size, 100 × 100; resolution, 2 × 2 × 2 $mm^3$; slice number, 72 in interleaved order; multiband factor, 6; and scan time, 304 s (resting-state), 402 s (N-back task), and 512 s (NF). During the resting-state scans,

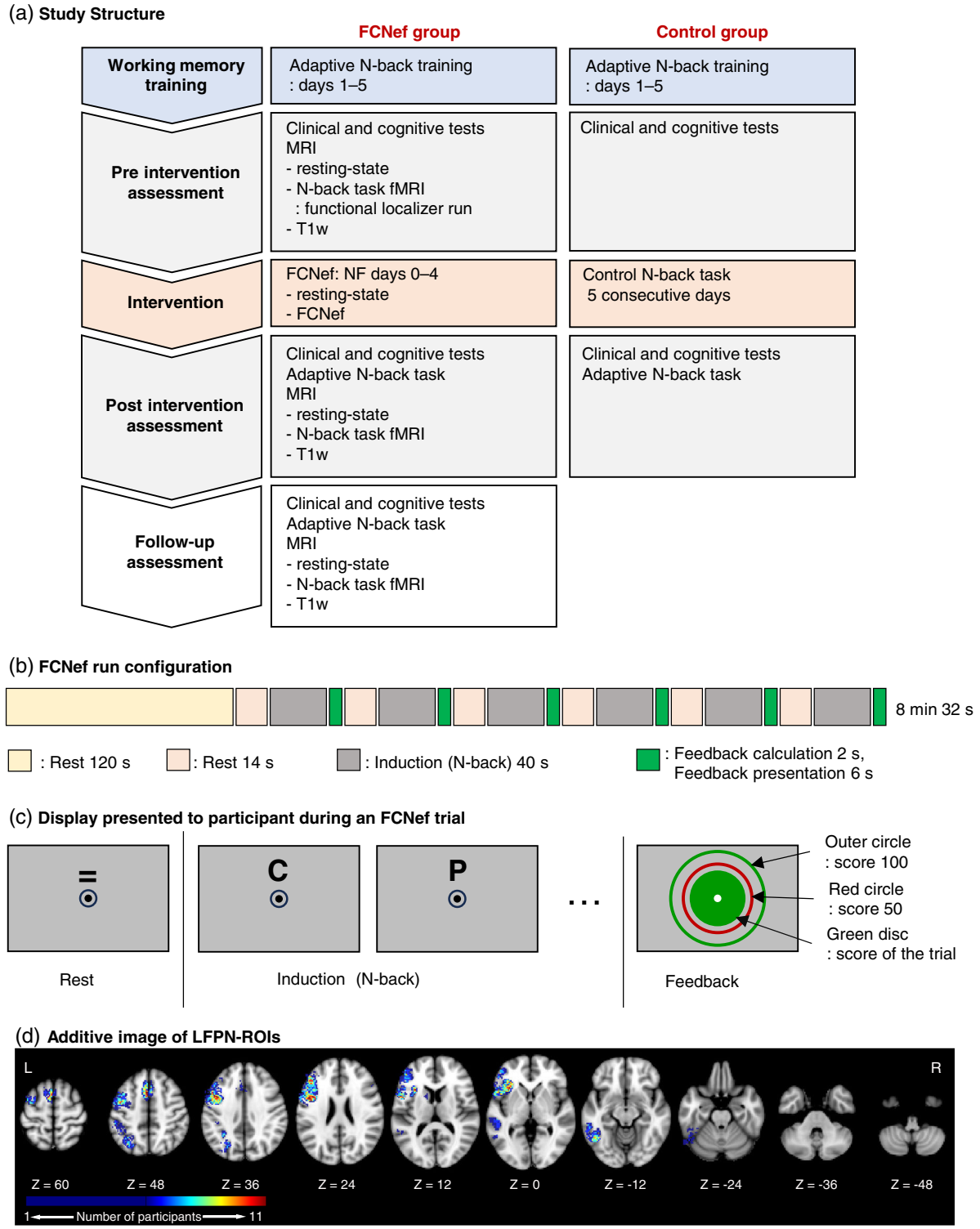


**Fig. 1** Overview of the study. **(a)** Participants were nonrandomly assigned to the FCNef and control groups. The control group performed the Control N-back task outside the MRI scanner. All participants initially underwent adaptive N-back training for 5 days. The FCNef group underwent MRI, clinical, and cognitive assessments, while the control group underwent only clinical and cognitive assessments. In addition, the FCNef group had follow-up assessments 1 to 3 months after intervention, whereas the control group did not. **(b)** The FCNef run comprised 120 s of rest, followed by six trials, with a total scan time of 8 min 32 s. Each trial consisted of rest (14 s), induction (40 s), feedback calculation (2 s), and feedback (6 s). Each session included five runs, with a total of 30 trials per session. **(c)** During the induction period, the N-back task was performed, and a letter was presented on the screen every 4 s (stimulus: 0.5 s, interstimulus interval: 3.5 s). A feedback score was provided in the form of a green disk. The red circle represents the baseline (NF day 0 mean, score 50), and the outer green circle represents the target (NF day 0 mean plus one SD, score 100). **(d)** The LFPN-ROI for each anatomical space was transformed into the MNI space, and the LFPN-ROI images in the MNI space for 11 participants in the FCNef group were summed. The LFPN-ROI included clusters in the Broca area and left insula, Wernicke area, left superior parietal lobule, and left medial frontal lobe. FCNef, functional connectivity–informed neurofeedback; fMRI, functional magnetic resonance imaging; LFPN-ROI, left frontoparietal network region of interest; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; NF, neurofeedback; T1w, T1-weighted image.

the participants were instructed to gaze at a fixation point at the center of the screen, minimize movement, and avoid thinking deeply about anything. The session order was as follows: for the pre-, post-, and follow-up MRI sessions, two resting-state runs preceded two N-back task runs with reversed-phase encoding, followed by T1-weighted runs. For the NF sessions, two resting-state runs with reversed phase-encoding blips preceded five NF runs with anterior-to-posterior phase-encoding.

### N-Back Task fMRI; Functional Localizer Run

We employed the N-back task for the localizer run, which is well documented for activating the LFPN.[41] The run comprised a block design with an initial rest period (20 s), followed by six trials of the N-back task (39 s) and rest between trials (26 s), totaling 402 s. During each rest period, the participants were instructed to focus on the fixation cross on the screen and avoid thinking deeply about anything. During the N-back task block, a letter was presented every 3 s (stimulus duration: 0.5 s, interstimulus interval: 2.5 s), totaling 13 stimuli. Participants were required to press a button when the presented letter matched the one that appeared N steps earlier. The letters were the same as those used in the adaptive N-back task.

The difficulty level of the localizer N-back task was selected from $N = 1$, 2, 3, and 4 and was individually adjusted to ensure proper activation of the LFPN. The mean N-back level on the fifth day of the adaptive N-back task was rounded to the nearest whole number, with a mean N-back level of 4.5 rounded to 4, and used as the N value in the localizer task. Literature suggests that patients with schizophrenia have only been tested on 0-, 1-, 2-, and 3-back tasks, with no known reports of 4-back or higher task performance.[34,42–44] We assumed a maximum preintervention mean N-back level of 4.5, and the task was not designed for 5-back or higher. The N-back task fMRI scan was conducted during the pre-FCNef, post-FCNef, and follow-up assessments.

### Region of Interest Definition for NF Training

The target region of interest (ROI) for the FCNef was individually created (LFPN-ROI) and defined as the region within the LFPN template (Laird *et al.*,[39] BrainMap ICN18) activated by the functional localizer and included in the gray matter (GM) mask. The LFPN template encompasses the left superior parietal lobule, left medial frontal lobule, left insula, and left Broca and Wernicke areas and correlates well with working memory and language tasks.[39]

Using the FMRIB Software Library (FSL) 5.0.10,[45–47] T1-weighted images were processed using the Brain Extraction Tool and FMRIB Automated Segmentation Tool, resulting in mask images of the whole brain, GM, white matter (WM), and cerebrospinal fluid (CSF). The outer edges of the GM, WM, and CSF masks were eroded to mitigate the partial volume effects.

Field maps and N-back task echo-planar imaging (EPI) scans were acquired using reversed phase–encoded blips to produce pairs of images with distortions in opposite directions. The susceptibility-induced off-resonance field was estimated using the FSL top-up tool.[46,48] The estimated b0 map was then applied to the EPI scans to correct for distortions. Subsequently, each EPI scan was registered to the anatomical space, coregistered to the standard brain, and subjected to motion correction, spatial smoothing with a 4.0-mm full-width half-maximum Gaussian kernel, intensity normalization, and high-pass temporal filtering (Gaussian-weighted least-squares straight fitting; $\sigma = 50.0$ s). Time-series statistical analysis estimated the beta maps using the FILM general linear model with explanatory variables for the N-back task via FEAT first-level analysis.[49] Furthermore, higher-level FEAT analysis was used to estimate voxels that were significantly activated in the LFPN template during the N-back task (uncorrected, $P < 0.001$). The obtained voxels were transformed into individual anatomical brain spaces via inverse deformation, masked by GM, and defined as the ROI for the FCNef intervention target (LFPN-ROI) (Fig. S2). Four ROIs were defined as LFPN, WM, CSF, and the whole brain. Figure 1d shows an additive image of the LFPN-ROIs.

### FC-Informed NF Procedure

FCNef was administered for 5 consecutive days with intermittent feedback. NF day 0 involved baseline FC measurements without feedback, whereas NF days 1 to 4 comprised the training period. We adopted an explicit approach, which is common in clinical populations,[50,51] by informing participants that the study aimed to "improve their working memory" and provide strategies for NF. The instructions for participants before the FCNef sessions are described in the Supporting Information Methods. The NF run included an initial rest and six subsequent trials, each comprising a preinduction rest, induction, feedback calculation, and feedback presentation (Fig. 1b). The term "online" refers to the processing of fMRI scans transferred in real-time, particularly during NF runs. Online preprocessing was time-limited and differed from N-back and resting-state runs.

### Online Processing and Calculation of Feedback Score

#### NF Training Day 0: Baseline FC

NF training day 0 (NF day 0) included baseline FC measurements without feedback. Online data preprocessing was performed using proprietary software implemented in MATLAB 2007b (MathWorks Inc.), incorporating the statistical parametric software package SPM12 (Wellcome Trust Centre for Neuroimaging; https://www.fil.ion.ucl.ac.uk/spm/). Before the NF run, the ROIs defined in the anatomical space were transformed into a functional space on each training day, and one EPI volume was scanned and coregistered to the skull-stripped T1-weighted image from the pre-FCNef MRI. Inverse transformations were then applied to four ROIs: the LFPN, WM, CSF, and whole brain. During the NF run, each EPI volume was transferred to the analysis computer in real time. Each volume was realigned with the reference volume (the first volume of the run). Volumes displaying framewise displacements >0.5 mm were censored.[52] Subsequently, the data were denoised through linear regression using 18 parameters, including six body motion parameters, WM, CSF, the whole brain, and their derivatives. Finally, the residuals were applied to a bandpass filter ranging from 0.0078 to 0.3 Hz (Fig. S3).

Forty volumes were obtained during the induction period to perform motion regression appropriately. The mean signal of the LFPN-ROI during the rest period (at the beginning of the run) was subtracted from the signal from the same ROI during the induction period to obtain a better baseline for the relevant signal, and voxel-wise blood oxygen (BOLD) signal time courses were extracted within the LFPN-ROI. Subsequently, the FC value was calculated as the mean voxel-wise correlation within the LFPN-ROI as follows. The time series for each voxel was correlated with every other voxel within the mask, and this calculation was repeated for every voxel in the mask. Correlation coefficients were transformed into Fisher $z$ values, which were averaged within the mask. The mean voxel-wise correlation coefficient was consistent with the FC calculation within the same network in Yamashita *et al.*'s biomarker.[36,38] Taking the spatially weighted averages of multiple FCs in brain circuit biomarkers, as used in our FCNef, reduces within-subject variation and improves signal-to-noise ratio.[53]

The mean and SD of the FC values on NF day 0 were calculated as $FC_{baseline}$ and $SD_{baseline}$.

#### NF Training Days 1–4: Calculating Feedback Score

Scores (0–100) were obtained from the FC values during the induction period and visually represented on a screen as the size of the green disk during feedback (Fig. 1c). Bonuses (0–¥100 per trial) were provided according to the scores, with a maximum of ¥3000 per day in addition to the basic fee.

The processing steps were applied to those used on NF day 0. At the end of each induction period, the voxel-wise correlation

coefficient during the induction period within the LFPN-ROI was calculated as $FC_{target}$ and converted into a score using the following method:

$$score = 50 \times \left( \frac{FC_{target} - FC_{baseline}}{SD_{baseline}} \right) + 50$$

Scores above 100 were rounded to 100, and those below 0 were rounded to 0. $FC_{baseline}$ was set at a score of 50, and $FC_{baseline}$ plus or minus SD was set at 100 or 0.

### N-back Task Training for Control Group

This task was based on the N-back task used in NF and spanned 5 consecutive days. It was executed using Presentation Software v20.3 Build 02.25.19 (Neurobehavioral Systems, Inc.). Each round lasted 492 s, beginning with 120 s of rest, followed by six trials: rest (14 s), N-back task (40 s), and post-task review (8 s). The initial rest period featured a fixation point at the center. During the task, a letter was displayed every 4 s for 0.5 s, with no display during the review. The same letters were used in the NF runs. The N level was determined in a manner similar to the functional localizer run. Bonuses of up to ¥1000 per day were awarded based on the correct answer rates during training on days 1 to 4. Instructions for the participants are provided in the Supporting Information Methods.

### Experimental Measures

Working memory capability was assessed using the mean N-back level in the adaptive N-back task, digit span backward task from the Wechsler Adult Intelligence Scale 3rd revision (WAIS-III),[54] and Spatial Working Memory (SWM) task[55] from Cantab (Cambridge Cognition, United Kingdom). The other cognitive tests were as follows: digit span forward task from WAIS-III for attention and working memory, Trail Making Test (TMT) part B[56] and Cantab SWM[55] task strategy for executive function, Rivermead Behavioral Memory Test (RBMT) immediate story and delayed story recall[57,58] for verbal learning and memory, TMT part A[56] for speed of information processing, and Cantab Reaction Time[59] five-choice mean movement time, and five-choice mean reaction time for motor and mental response speeds. Schizophrenia symptoms and functioning and quality of life were assessed using the Positive and Negative Syndrome Scale (PANSS),[60] the 21-item Peters *et al.* Delusion Inventory (PDI),[61] BDI-II,[62] Global Assessment of Functioning (GAF),[63] and the Japanese version of the Schizophrenia Quality of Life Scale (JSQLS).[64,65] PANSS analysis using a five-factor model, preprocessing of resting-state scans, and calculation of FC are described in the Supporting Information Methods.

### Statistical Analysis

Statistical analyses were conducted using SPSS version 26 (IBM), and all tests were two-tailed, with a significance level of 0.05. Demographic and clinical variables between the groups were evaluated using the Student *t* test for continuous variables and the Fisher exact test for categorical variables. The dependent variables included age, illness duration, chlorpromazine-equivalent antipsychotic dose, premorbid IQ, sex, and the socioeconomic status of the participants and their parents. The independent variables were group (FCNef or control).

Demographic and clinical variables, including age and sex, showed no significant differences between groups and were not included as covariates in the analysis. A paired *t* test was used to analyze changes in the online mean FC from NF days 0 to 4, with online FC as the dependent variable and time (NF days 0 and 4) as the independent variable. Similarly, a paired *t* test was used to analyze the changes in resting-state FC from pre-FCNef to post-FCNef, with resting-state FC as the dependent variable and time (pre-FCNef and post-FCNef) as the independent variable. These comparisons were conceptually independent and analyzed separately without correction, as online and resting-state FC reflect distinct neural states.

Associations were evaluated using the Pearson correlation coefficient for the following comparisons: (1) changes in the online mean FC from NF days 0 to 4 and changes in the working memory assessments from pre-FCNef to post-FCNef, with false discovery rate (FDR) correction[66] applied for multiple comparisons; (2) changes in resting-state FC from pre-FCNef to post-FCNef and working memory assessments from pre-FCNef to post-FCNef with FDR corrections were applied for multiple comparisons; and (3) changes in online mean FC from NF day 0 to day 4 and changes in resting-state FC from pre-FCNef to post-FCNef were analyzed separately without correction, as this test did not involve working memory assessments and was considered an independent hypothesis. Age and sex were not included as covariates in the correlation analysis because no established knowledge suggests their impact on intervention-induced FC changes.

Group comparisons of changes in cognitive and clinical assessments from preintervention to postintervention were performed using repeated-measures ANOVA with a two-factor mixed design. The dependent variables were the clinical and cognitive assessment scores. The within-subject factor was time (preintervention or postintervention), and the between-subject factor was group (FCNef or control). FDR correction was applied for multiple comparisons. The Bonferroni method was used for multiple comparison corrections in the analysis of the interaction effects. This pilot study included multiple clinical and cognitive evaluation scales for safety assessment, and the risk of type II errors increased owing to multiple comparison corrections.[67] To mitigate this risk, we indicated any indicators meeting the criterion of uncorrected $P < 0.05$ in the manuscript and figures and discussed them carefully in the Discussion section.

A one-factor repeated-measures ANOVA was conducted on the pre-FCNef and post-FCNef and follow-up assessments in the FCNef group. The dependent variables were the clinical and cognitive assessment scores, with time (pre-FCNef, post-FCNef, and follow-up) as the within-subject factor. The Dunnett post hoc test was used to compare each time point with the preintervention assessment. FDR correction was applied for multiple comparisons among the measures.

### Effect Size Calculation for Paired *t* Test

For the paired *t* test, the effect size index dz. was calculated using G*Power 3.1.9,[68,69] dz. represents Cohen *d* corrected for the correlation of paired data, and was computed using the following formula:

$$dz = \frac{|\mu_{x-}\mu_y|}{\sqrt{\sigma_x^2 + \sigma_y^2 - 2\rho^{xy}\sigma_x\sigma_y}},$$

where $\mu_x$ and $\mu_y$ represent the population mean, $\sigma_x$ and $\sigma_x$ represent the population SD, and $\rho_{xy}$ represents the correlation between the two random variables.

## Results

### Demographic and Clinical Characteristics

No significant differences were observed between the two groups regarding demographic or clinical characteristics (Table S1). One participant in the FCNef group was left-handed, whereas all other participants were right-handed. One participant in the FCNef group missed the follow-up assessments because of scheduling difficulties (Fig. S4). The socioeconomic status of the parents of one participant was not confirmed.

One control group participant had a mean N-back level of 5.525 on the pretest, exceeding the assumed maximum of 4.5 (as described in the N-Back Task fMRI section). We identified this score as an outlier and excluded it from analysis. The average mean N-back level for

included participants was 2.464 (SD = 0.927), with 5.525 corresponding to the mean + 3.3 SD.

During the adaptive N-back training, there was a significant improvement seen in the mean N-back level for the time factor and nonsignificant effects for the interaction and group factors. The details are provided in Supporting Information Results and Fig. S5.

### Changes in Online Mean FC During FC-Informed NF: Evaluating Training Success

The mean FC value on NF day 0 was 0.050 (SD = 0.026), which increased to 0.068 (SD = 0.023) on NF day 4 (Fig. 2). A paired *t* test revealed a significant difference between NF days 0 and 4 (t [10] = 2.357, *P* = 0.040), with a 95% confidence interval (CI) of 0.001 to 0.036 and dz. = 0.71. We compared only NF days 0 and 4, when the greatest effect was expected. Although 30 trials were scheduled daily, the average number of trials per session was 28.7 (SD = 4.5, ranging from 6 to 30) owing to experimental time constraints and participant fatigue. One participant missed NF day 4 of the FCNef; therefore, NF day 3 data were substituted in the analysis. All other participants were present on all days. A sensitivity analysis of substitution was conducted, and the results remained consistent across all approaches (Supporting Information Results). For the feedback scores, see Supporting Information Results and Fig. S6.

### Correlation Between Changes in Online FC and Working Memory Tests

The Pearson correlation coefficient was *r* = 0.69 between the change in mean N-back level (from pre-FCNef to post-FCNef) and the change in mean FC value (from NF days 0–4), with a significant *P*-value of 0.019 and a 95% CI of 0.15 to 0.91 (Fig. 3a). After applying multiple comparison corrections, the results remained statistically significant (false discovery rate–adjusted *P*-value [pFDR] = 0.038). The Pearson correlation coefficient was *r* = 0.32 between the change in the digit span backward task (from pre-FCNef to post-FCNef) and the mean FC value (from NF days 0–4), with a *P*-value of 0.35 (pFDR = 0.35) and a 95% CI of −0.35 to 0.77 (Fig. 3b). One participant missed NF day 4 of the FCNef; therefore, NF day 3 data were substituted in the analysis.

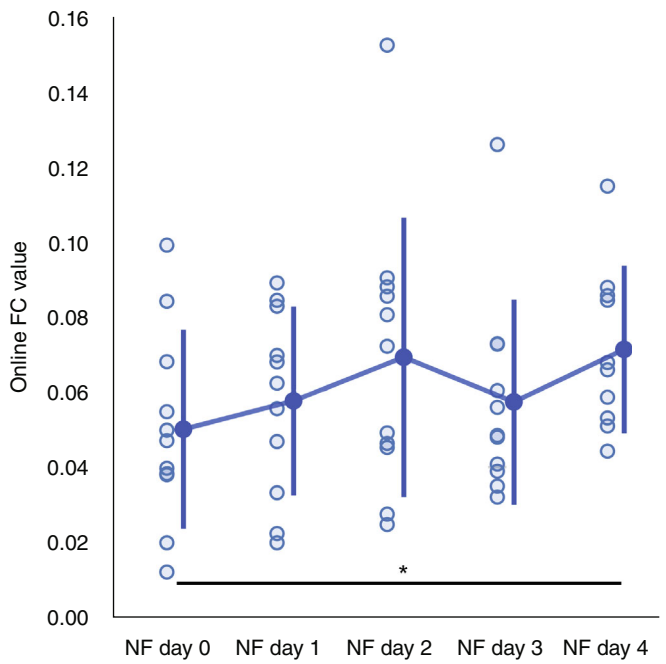


**Fig. 2** Changes in online mean FC values during FCNef. The color-filled dots depict the participants' mean FC values for each session, and the error bars depict the SD. The noncolored dots indicate the FC values of individual participants. Thirty trials were performed in each session, and the dots represent the average FC values per participant for each session. A paired *t* test revealed a significant difference between NF days 0 and 4 (t [10] = 2.357, *P* = 0.040), with a 95% CI of 0.001 to 0.036 and dz. of 0.71. Statistical significance was set at *P* < 0.05*. CI, confidence interval; FC, functional connectivity; FCNef, functional connectivity–informed neurofeedback; NF, neurofeedback.

### Changes in Resting-State FC From Pre-FCNef to Post-FCNef

The pre-FCNef mean FC value was 0.206 (SD = 0.023) and the post-FCNef mean FC value increased to 0.252 (SD = 0.073) (Fig. 4a). A paired *t* test identified a significant difference (t [10] = 2.270, *P* = 0.047), with a 95% CI of 0.000856 to 0.0922 and a dz. of 0.684. The Pearson correlation coefficient was *r* = 0.13 between changes in resting-state FC and online FC (from NF days 0 to 4), with a *P*-value of 0.71 and a 95% CI ranging from −0.51 to 0.68 (Fig. 4b).

### Association Between Changes in Resting-State FC and Working Memory Tests

Between resting-state FC changes and mean N-back level changes, the Pearson correlation coefficient was *r* = 0.26, with a *P*-value of 0.44 (pFDR = 0.44) and 95% CI ranging from −0.40 to 0.74 (Fig. 4c). Between changes in resting-state FC and changes in the digit span backward task, the Pearson correlation coefficient was *r* = 0.43, with a *P*-value of 0.19 (pFDR = 0.38) and 95% CI ranging from −0.23 to 0.82 (Fig. 4c).

### Changes in Preintervention and Postintervention Assessments Between FC-Informed NF and Control Groups

ANOVA identified an interaction effect on the digit span backward task (F [1, 19] = 5.24, *P* = 0.034, partial $\eta^2$ = 0.216; Table 1, Fig. 5a). However, after applying multiple comparison corrections, the effect was no longer statistically significant (pFDR = 0.63). The interaction analysis results were as follows: the FCNef group's mean score on the digit span backward task was 6.1 (SD = 1.7) preintervention and 7.1 (SD = 2.3) postintervention; the control group's mean score on the task was 5.9 (SD = 2.2) preintervention and 5.6 (SD = 2.8) postintervention. When the group factor was FCNef, a significant difference was observed in the time factor (pre < post, *P* = 0.019 [95% CI, 0.18–1.82]), and when the group factor was controlled, no significant difference was observed in the time factor (*P* = 0.47). No significant group differences were found for the time factor preintervention (*P* = 0.83) or postintervention (*P* = 0.19).

Differences were found in the time factor, while nonsignificant differences were found for the group factor or interaction effect in the following assessments: PANSS cognitive factor (*P* = 0.037, F [1, 19] = 5.01, partial $\eta^2$ = 0.21), TMT Part B (*P* = 0.028, F [1, 19] = 5.63, partial $\eta^2$ = 0.23), BDI-II (*P* < 0.001, F [1, 19] = 20.77, partial $\eta^2$ = 0.52), RBMT story immediate recall (*P* = 0.005, F [1, 19] = 10.07, partial $\eta^2$ = 0.35), and RBMT story delayed recall (*P* = 0.002, F [1, 19] = 13.23, partial $\eta^2$ = 0.41) (Table 1, Fig. 5b–f). After applying multiple comparison corrections, the RBMT story immediate recall (pFDR = 0.033), delayed recall (pFDR = 0.02), and BDI-II (pFDR = 0.004) remained significant. Mean BDI-II scores were decreased in the FCNef group (from 17.2 [SD = 10.9] to 12.5 [SD = 8.5]), control group (from 13.5 [SD = 7.3] to 10.8 [SD = 7.4]), and all participants (from 15.4 [SD = 9.3] to 11.7 [SD = 7.9]). For the RBMT story immediate recall, the mean scores increased in the FCNef group (from 9.2 [SD = 5.8] to 12.2 [SD = 5.3]), control group (from 7.7 [SD = 4.5] to 9.7 [SD = 6.2]), and all participants (from 8.5 [SD = 5.2] to 11.0 [SD = 5.7]). Similarly, mean delayed recall scores increased in the FCNef group (from 8.0 [SD = 5.6] to 11.1 [SD = 4.0]), control group (from 7.1 [SD = 4.0] to 8.5 [SD = 5.0]), and all participants (from 7.5 [SD = 4.8] to 9.9 [SD = 4.6]).

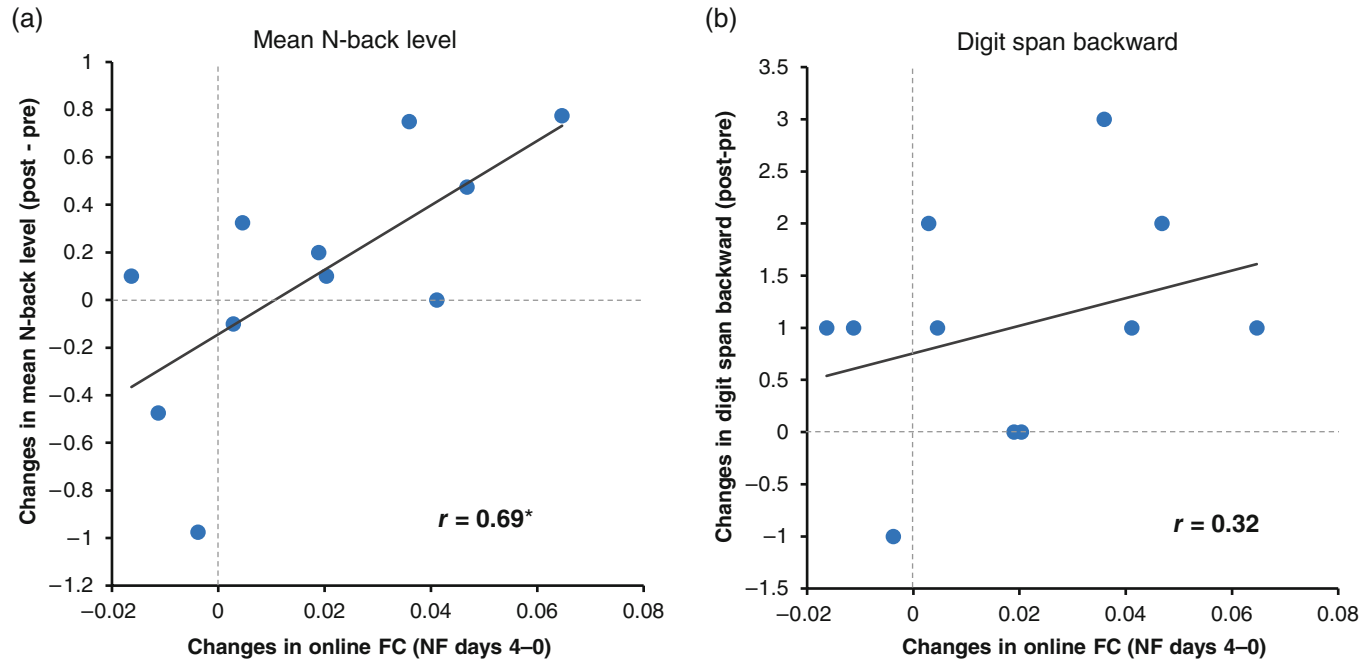


**Fig. 3** Associations between online FC changes during FCNef and working memory tests improvement. The scatter plots represent the change in FC value from NF day 0 to NF day 4 during NF on the horizontal axis and the change in working memory test scores from pre-FCNef to post-FCNef on the vertical axis. **(a)** Pearson correlation coefficient was $r = 0.69$ between the change in mean N-back level (from pre-FCNef to post-FCNef). The change in the mean FC value (from NF days 0 to 4), with a significant $P$ value of 0.019 (pFDR = 0.038) and a 95% CI of 0.15 to 0.91, indicated that the more successfully participants enhanced their FC, the more their mean N-back level improved. **(b)** Pearson correlation coefficient was $r = 0.32$ between the change in the digit span backward task (from pre-FCNef to post-FCNef) and the change in the mean FC value (from NF days 0 to 4), with a $P$ value of 0.35 (pFDR = 0.35) and a 95% CI of −0.35 to 0.77. Statistical significance was set at $P < 0.05$*. CI, confidence interval; FC, functional connectivity; FCNef, functional connectivity–informed neurofeedback; NF, neurofeedback; pFDR, false discovery rate–adjusted $P$-value.

### Follow-up Assessments in the FC-Informed NF Group

A follow-up MRI scan was performed 1 to 3 months after NF completion with a mean interval of 57 days (SD = 20 days, range: 31–82 days). Cognitive and clinical assessments were performed within 1 week of the MRI. One participant missed the follow-up assessment because of scheduling difficulties and was excluded from the statistical tests. A time effect was observed for TMT Part B (F [2, 18] = 4.006 [$P = 0.036$], pFDR = 0.18; partial $\eta^2 = 0.308$) (Table 2), PANSS cognitive factor (F [2, 18] = 3.613 [$P = 0.048$], pFDR = 0.192; partial $\eta^2 = 0.286$), RBMT story immediate recall (F [2, 18] = 7.018 [$P = 0.006$], pFDR = 0.053; partial $\eta^2 = 0.438$), delayed recall (F [2, 18] = 6.377 [$P = 0.008$], pFDR = 0.053; partial $\eta^2 = 0.415$), and BDI-II (F [2, 18] = 7.082 [$P = 0.005$], pFDR = 0.053; partial $\eta^2 = 0.440$). These effects were not significant after applying multiple comparison corrections. The mean LFPN FC on resting-state imaging at follow-up was higher than pre-FCNef but lower than post-FCNef (Fig. S7). ANOVA did not identify significant time effects (F [2, 18] = 1.576 [$P = 0.234$], partial $\eta^2 = 0.149$).

## Discussion

A two-arm, nonrandomized, controlled pilot study of connectivity-informed NF designed to enhance FC within the LFPN was conducted to improve working memory in patients with schizophrenia. The FC value of the LFPN in the FCNef group significantly increased on NF day 4 compared with that on NF day 0 (Fig. 2), indicating successful NF training. A significant correlation was found between the increase in FC values from NF days 0 to 4 and the improvement in the mean N-back level post-FCNef. The more the FCNef participants enhanced their FC, the more their mean N-back level improved. When comparing improvements in the cognitive and clinical assessments of the FCNef group with those of the control group, an interaction effect was observed in the digit span backward task. The FCNef group demonstrated markedly improved scores on the post-FCNef task compared with the pre-FCNef task. In the resting-state images scanned on a different day from the NF intervention, the FC values within the LFPN were significantly increased post-FCNef compared with pre-FCNef.

We assumed that the FCNef group would show improvements in two working memory assessments (mean N-back level and digit span backward task) compared with the control group and that increased FC during FCNef would correlate with these improvements. However, while digit span backward task scores improved remarkably post-FCNef, they did not correlate significantly with increased online FC. Conversely, the mean N-back level was significantly correlated with increased online FC, but did not improve post-FCNef.

A repeated-measures ANOVA of the mean N-back level revealed no main effects or interactions, indicating no group differences in the pattern of performance change between the FCNef and control groups and no significant improvement from preintevention to post-intervention (Table 1). However, a significantly strong positive correlation (0.69) was found between changes in FC values (from NF days 0–4) and changes in the mean N-back level (pre-FCNef to post-FCNef) (Fig. 3a). The mean N-back level improved with adaptive N-back training preceding NF (Fig. S2). Even after improving task performance through in-depth training, the performance improved with the degree of FC enhancement, suggesting that those who can enhance LFPN FC during FCNef can improve their working memory.

Upon comparing the improvements in the cognitive and clinical assessments of the FCNef group with those of the control group, an interaction effect was observed in the digit span backward task (Table 1, Fig. 5a). Notably, the FCNef group exhibited a pronounced improvement in the post-FCNef task, suggesting that the improvement was attributable to FCNef rather than repeated testing or the N-back task implemented as the FCNef strategy. However,

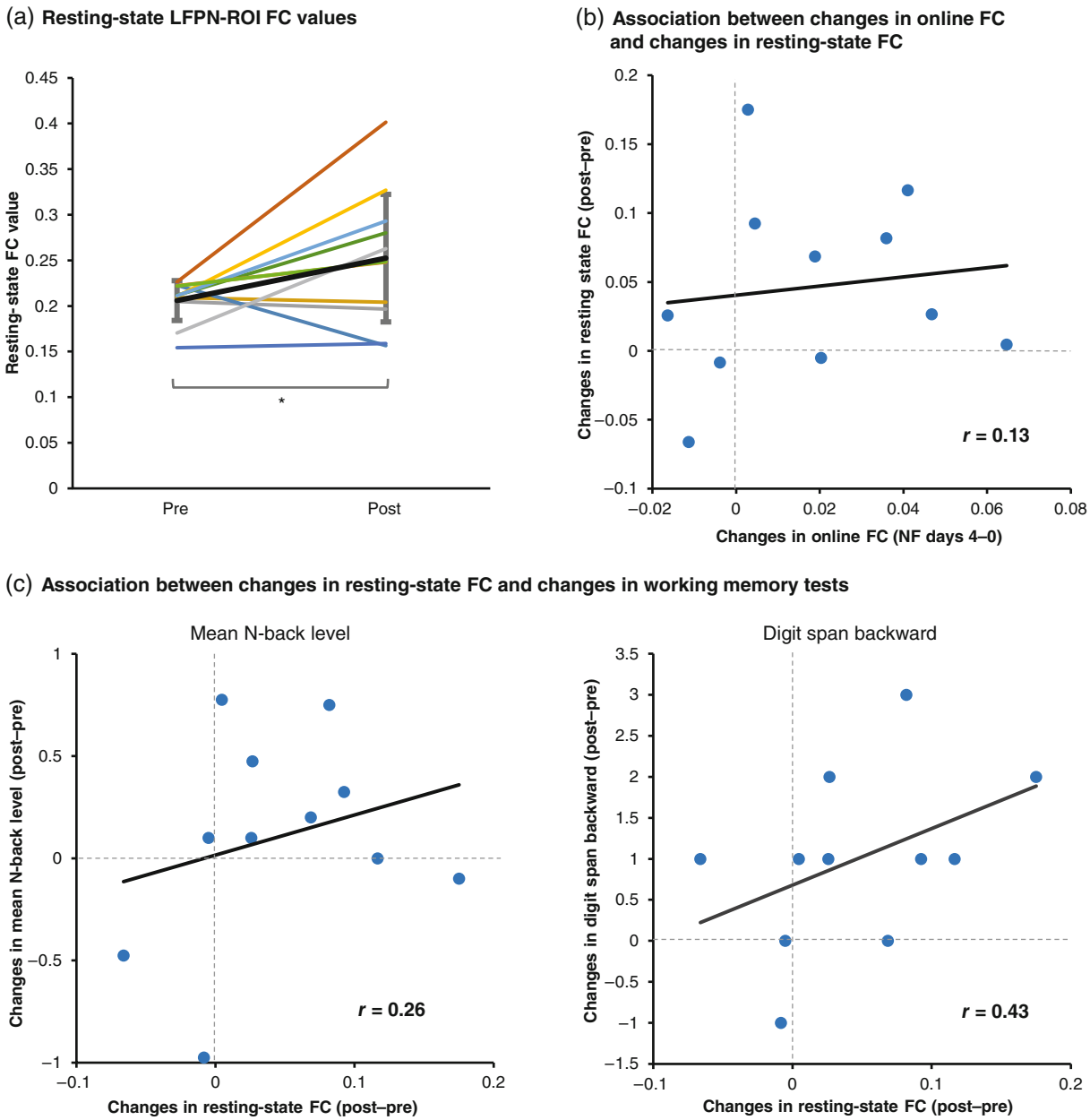


**Fig. 4** Changes in resting-state LFPN-ROI FC from pre-FCNef to post-FCNef: associations with online FC changes and working memory test scores. **(a)** The black line represents the mean of the group, the error bars depict the SDs, and the colored lines illustrate the individual changes. A significant difference was observed between the mean resting-state FC within the LFPN-ROI pre-FCNef and post-FCNef (paired *t* test, t [10] = 2.27, $P = 0.047$). Significant difference: $P < 0.05$* **(b)** The scatter plot of the change in FC from NF day 0 to NF day 4 during NF on the horizontal axis and the change in resting-state FC within the LFPN-ROI from pre-FCNef to post-FCNef on the vertical axis. Pearson correlation coefficient was $r = 0.13$, with a *P*-value of 0.71 and 95% CI ranging from −0.51 to 0.68. **(c)** The left scatter plot depicts the changes in resting-state FC within the LFPN-ROI from pre-FCNef to post-FCNef on the horizontal axis, whereas the change in the mean N-back level from pre-FCNef to post-FCNef is represented on the vertical axis. The Pearson correlation coefficient was $r = 0.26$, with a *P*-value of 0.44 (pFDR = 0.44) and a 95% CI ranging from −0.40 to 0.74. The right scatter plot illustrates the change in the digit span backward task from pre-FCNef to post-FCNef on the vertical axis. The Pearson correlation coefficient was $r = 0.43$, with a *P*-value of 0.19 (pFDR = 0.38) and a 95% CI ranging from −0.23 to 0.82. A moderately nonsignificant correlation was observed. FC, functional connectivity; FCNef, functional connectivity–informed neurofeedback; LFPN-ROI, left frontoparietal network region of interest; NF, neurofeedback; pFDR, false discovery rate–adjusted *P*-value.

the improvement in digit span backward task score did not significantly correlate with the increase in online FC (r = 0.32, Fig. 3b).

Decreased digit span backward task scores have been reported in patients with schizophrenia.[36,70] In the WAIS-III standardization sample, the mean score for patients with schizophrenia was 5.76 (SD = 1.91), which was significantly lower than that of the healthy controls (mean = 7.19, SD = 2.62).[71] In our study, preintervention mean scores were 6.1 (SD = 1.7) for FCNef, 5.9 (SD = 2.2) for controls, and 6.0 (SD = 1.9) overall—comparable to or slightly higher than those reported for patients with schizophrenia. Postintervention, the FCNef group improved to 7.1 (SD = 2.3), with a 95% CI difference of 0.18 to 1.82, reaching a level similar to healthy controls in the WAIS-III data set. However, slight differences in the age distribution in the WAIS-III data set (mean: 38.2 [SD = 6.1])[72] and our study (mean: 38.1 [SD = 8.5]) require cautious interpretation. Notable improvement was observed in the FCNef group.

A significant main effect of time was observed for the BDI-II and RBMT story immediate and delayed recall (Table 1, Fig. 5d–f),

**Table 1.** Clinical and cognitive outcomes at the preintervention and postintervention assessments

| | Pre | | | | Post | | | | Main effect | | | | Interaction | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | FCNef ($N = 11$) | | Control ($N = 10$) | | FCNef ($N = 11$) | | Control ($N = 10$) | | Time | | Group | | Time by group | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | *F* value | *P*-value | *F* value | *P*-value | *F* value | *P*-value |
| Working memory | | | | | | | | | | | | | | |
| Digit span backward | 6.1 | 1.7 | 5.9 | 2.2 | 7.1 | 2.3 | 5.6 | 2.8 | 1.519 | 0.233 | 0.786 | 0.386 | 5.240 | 0.034† |
| Mean N-back level | 2.65 | 1.17 | 2.26 | 0.56 | 2.76 | 1.18 | 2.25 | 0.64 | 0.266 | 0.612 | 1.265 | 0.275 | 0.353 | 0.560 |
| SWM between error | 43.5 | 39.8 | 32.7 | 13.2 | 42.5 | 37.0 | 26.6 | 18.4 | 2.215 | 0.153 | 1.069 | 0.314 | 1.143 | 0.298 |
| Attention/working memory | | | | | | | | | | | | | | |
| Digit span forward | 10.5 | 2.1 | 10.1 | 2.2 | 10.2 | 1.8 | 10.3 | 1.6 | 0.019 | 0.892 | 0.021 | 0.885 | 0.801 | 0.382 |
| Executive function | | | | | | | | | | | | | | |
| TMT (Part B) | 152.0 | 87.2 | 139.7 | 44.0 | 123.6 | 58.8 | 122.7 | 32.8 | 5.628 | 0.028‡ | 0.072 | 0.791 | 0.357 | 0.557 |
| SWM strategy | 31.8 | 10.0 | 34.7 | 4.7 | 31.1 | 9.1 | 30.6 | 8.1 | 3.435 | 0.079 | 0.124 | 0.728 | 1.677 | 0.211 |
| Verbal learning | | | | | | | | | | | | | | |
| RBMT story immediate recall | 9.2 | 5.8 | 7.7 | 4.5 | 12.2 | 5.3 | 9.7 | 6.2 | 10.073 | 0.005*§ | 0.843 | 0.370 | 0.403 | 0.533 |
| Verbal memory | | | | | | | | | | | | | | |
| RBMT story delayed recall | 8.0 | 5.6 | 7.1 | 4.0 | 11.1 | 4.0 | 8.5 | 5.0 | 13.232 | 0.002*¶ | 0.812 | 0.379 | 1.850 | 0.190 |
| Speed of information processing | | | | | | | | | | | | | | |
| TMT (Part A) | 104.8 | 28.7 | 107.9 | 21.6 | 105.3 | 31.2 | 93.1 | 23.2 | 3.444 | 0.079 | 0.171 | 0.684 | 3.895 | 0.063 |
| RTI five-choice movement time | 493.1 | 110.9 | 475.8 | 107.9 | 498.9 | 152.3 | 463.3 | 126.6 | 0.051 | 0.824 | 0.249 | 0.624 | 0.371 | 0.550 |
| RTI five-choice reaction time | 358.6 | 111.2 | 330.6 | 69.5 | 337.3 | 74.0 | 324.3 | 69.7 | 2.835 | 0.109 | 0.332 | 0.571 | 0.847 | 0.369 |
| Clinical symptoms, QOL | | | | | | | | | | | | | | |
| PANSS Total | 57.7 | 16.4 | 54.3 | 12.2 | 50.0 | 11.0 | 51.9 | 11.5 | 3.032 | 0.098 | 0.025 | 0.877 | 0.839 | 0.371 |
| PANSS Positive | 13.7 | 4.4 | 13.5 | 3.3 | 11.4 | 3.9 | 12.6 | 5.1 | 3.198 | 0.09 | 0.099 | 0.756 | 0.643 | 0.432 |
| PANSS Negative | 15.9 | 4.8 | 14.6 | 4.2 | 14.7 | 3.8 | 13.7 | 2.9 | 1.485 | 0.238 | 0.580 | 0.456 | 0.027 | 0.871 |
| PANSS General | 28.1 | 8.9 | 26.2 | 5.8 | 23.9 | 4.9 | 25.6 | 5.7 | 2.463 | 0.133 | 0.002 | 0.967 | 1.382 | 0.254 |
| PANSS Cognitive | 9.6 | 2.3 | 9.0 | 2.4 | 8.0 | 2.3 | 7.7 | 1.7 | 5.010 | 0.037†† | 0.334 | 0.570 | 0.037 | 0.849 |
| GAF | 55.4 | 11.3 | 54.6 | 11.3 | 56.8 | 13.5 | 57.0 | 13.4 | 0.495 | 0.490 | 0.004 | 0.951 | 0.03 | 0.865 |
| JSQLS | 46.1 | 21.2 | 46.2 | 14.1 | 43.6 | 20.2 | 43.5 | 17.0 | 0.943 | 0.344 | 0.000 | 0.997 | 0.001 | 0.977 |
| BDI-II | 17.2 | 10.9 | 13.5 | 7.3 | 12.5 | 8.5 | 10.8 | 7.4 | 20.774 | <0.001**‡‡ | 0.516 | 0.481 | 1.548 | 0.229 |
| PDI | 6.6 | 7.1 | 6.4 | 4.6 | 6.5 | 6.7 | 4.8 | 3.0 | 3.336 | 0.084 | 0.137 | 0.715 | 2.657 | 0.120 |

Significant differences are indicated as follows: pFDR <0.05*, pFDR <0.01**.
All *P*-values are uncorrected. The FDR method was applied for multiple comparisons, and the adjusted *P*-values are as follows: †, 0.63; ‡, 0.14; §, 0.033; ¶, 0.02; ††, 0.148; ‡‡, 0.004.
BDI-II, Beck Depression Inventory-II; FCNef, functional connectivity–informed neurofeedback; FDR, false discovery rate; GAF, Global Assessment of Functioning; JSQLS, Japanese version of the Schizophrenia Quality of Life Scale; PANSS, Positive and Negative Syndrome Scale; PDI, 21-item Peters et al. Delusions Inventory; pFDR, false discovery rate–adjusted *P*-value; QOL, quality of life; RBMT, Rivermead Behavioral Memory Test; RTI, Reaction Time Index; SWM, Spatial Working Memory; TMT, Trail Making Test.

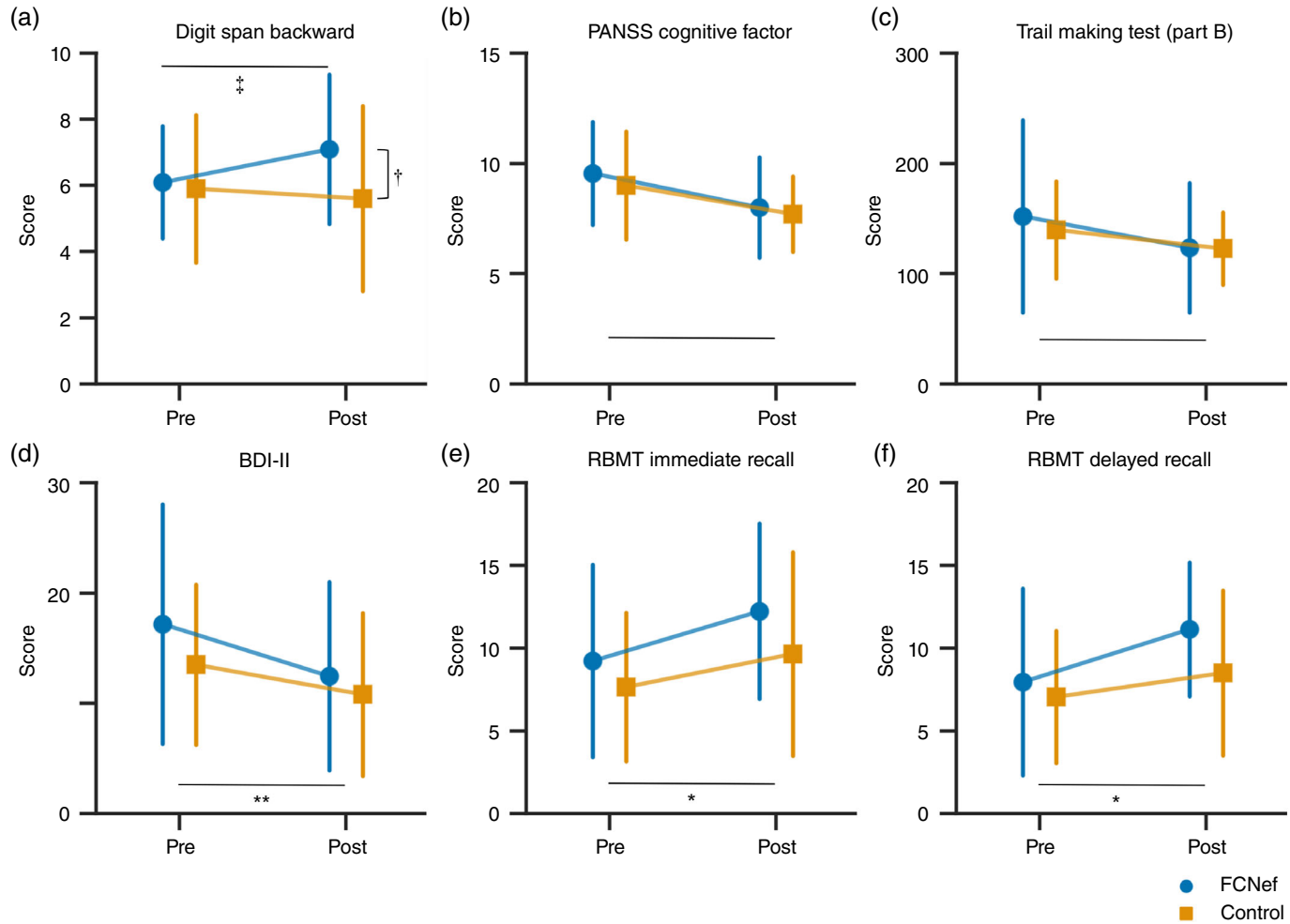


**Fig. 5** Longitudinal changes in cognitive and clinical tests for FCNef and control groups. The graphs show the clinical and cognitive test scores of each group before and after intervention. Blue and orange lines represent the FCNef and control groups, respectively. The mean score for each group is depicted by a dot (FCNef group) or a square (control group), and the SD is represented by an error bar. **(a)** ANOVA identified an interaction effect on the digit span backward task (F [1, 19] = 5.24 [$P = 0.034$†], pFDR = 0.63; partial $\eta^2 = 0.216$). The interaction analysis results were as follows: the FCNef group's mean score on the digit span backward task was 6.1 (SD = 1.7) preintervention and 7.1 (SD = 2.3) postintervention; the control group's mean score on the task was 5.9 (SD = 2.2) preintervention and 5.6 (SD = 2.8) postintervention. When the group factor was the FCNef, a significant difference was observed in the time factor (pre < post, $P = 0.019$‡ [95% CI, 0.18–1.82]). When the group factor was controlled, no significant difference was observed in the time factor ($P = 0.47$). No significant group differences were found for the time factor preintervention ($P = 0.83$) or postintervention ($P = 0.19$). **(b)–(f)**. Significant differences were found for the time factor, while nonsignificant differences were found for the group factor or interaction effect in the following assessments: PANSS cognitive factor ($P = 0.037$, F [1, 19] = 5.01; partial $\eta^2 = 0.21$), TMT part B ($P = 0.028$, F [1, 19] = 5.63; partial $\eta^2 = 0.23$), BDI-II ($P < 0.001$, F [1, 19] = 20.77; partial $\eta^2 = 0.52$), RBMT story immediate recall ($P = 0.005$, F [1, 19] = 10.07; partial $\eta^2 = 0.35$), and RBMT story delayed recall ($P = 0.002$, F [1, 19] = 13.23; partial $\eta^2 = 0.41$). The mean scores of these scales improved after the intervention. After applying multiple comparison corrections, the RBMT story immediate recall (pFDR = 0.033), delayed recall (pFDR = 0.02), and BDI-II (pFDR = 0.004) remained significant. Significant difference: pFDR <0.05*, pFDR <0.01**. BDI-II, Beck Depression Inventory-II; FCNef, functional connectivity–informed neurofeedback; PANSS, Positive and Negative Syndrome Scale; pFDR, false discovery rate–adjusted *P*-value; RBMT, Rivermead Behavioral Memory Test; TMT, Trail Making Test.

although no group-by-time interactions were noted. These assessments revealed worse scores in patients with schizophrenia than in healthy controls.[73–75] The observed reductions in BDI-II scores, implying nonspecific intervention effects, may be due to the participants perceiving the continuous involvement of researchers (medical professionals) during the intervention as supportive or a source of relief. The RBMT story immediate and delayed recall tests are similar to logical memory tests and are known to show learning effects from repeated testing.[76] Improvements in the results of these tests may be attributed to learning effects and N-back task training during the intervention. Notably, no significant deterioration was observed in the clinical and cognitive assessment results compared with those in the control group.

Resting-state LFPN FC values were significantly increased post-FCNef compared with pre-FCNef. These resting-state scans were performed on a different day from the NF and started at the beginning of the imaging protocol, potentially reflecting intrinsic activation. Contrary to our expectations, no correlation was observed between the changes in online FC values (from NF days 0–4) and resting-state FC values (pre-FCNef to post-FCNef). The relatively small sample size may have affected the results. Our target LFPN-ROI included the insula and ventrolateral prefrontal cortex (Fig. 1d), regions implicated in NF learning,[77] which may influence resting-state FC changes. A more comprehensive study involving a larger sample size and resting-state imaging of a control group may provide deeper insights into the mechanisms underlying this transfer effect.

A moderate but not statistically significant correlation coefficient (0.43) was observed between changes in resting-state LFPN FC and changes in the digit span backward task from pre-FCNef to post-FCNef (Fig. 4c). This association corresponds to the relationship demonstrated for a working memory capability biomarker based on resting-state FC within the LFPN, as indicated by Yamashita

**Table 2.** Clinical and cognitive outcomes in the FCNef group at follow-up assessments

| | Pre-post | | | | Pre-follow | | Main effect | | Dunnett test | |
|---|---|---|---|---|---|---|---|---|---|---|
| | FCNef ($N = 11$) | | FCNef ($N = 11$) | | FCNef ($N = 10$) | | Time | | Pre-post | Pre-follow |
| | Mean | SD | Mean | SD | Mean | SD | *F*-value | *P*-value | *P*-value | *P*-value |
| Working memory | | | | | | | | | | |
| Digit span backward | 6.1 | 1.7 | 7.1 | 2.3 | 6.9 | 2.0 | 3.217 | 0.064 | 0.043 | 0.174 |
| Mean N-back level | 2.65 | 1.17 | 2.76 | 1.18 | 2.61 | 1.21 | 1.396 | 0.273 | 0.794 | 0.469 |
| SWM between errors | 43.5 | 39.8 | 42.5 | 37.0 | 34.0 | 29.7 | 2.176 | 0.166 | 0.985 | 0.135 |
| Attention/working memory | | | | | | | | | | |
| Digit span forward | 10.5 | 2.1 | 10.2 | 1.8 | 10.2 | 1.6 | 0.124 | 0.884 | 0.956 | 0.956 |
| Executive function | | | | | | | | | | |
| TMT (Part B) | 152.0 | 87.2 | 123.6 | 58.8 | 108.5 | 47.3 | 4.006 | 0.036† | 0.112 | 0.025 |
| SWM strategy | 31.8 | 10.0 | 31.1 | 9.1 | 33.9 | 7.8 | 0.470 | 0.543 | 0.956 | 0.720 |
| Verbal learning | | | | | | | | | | |
| RBMT story immediate recall | 9.2 | 5.8 | 12.2 | 5.3 | 11.2 | 5.1 | 7.018 | 0.006‡ | 0.003 | 0.053 |
| Verbal memory | | | | | | | | | | |
| RBMT story delayed recall | 8.0 | 5.6 | 11.1 | 4.0 | 9.4 | 5.1 | 6.377 | 0.008§ | 0.004 | 0.241 |
| Speed of information processing | | | | | | | | | | |
| TMT (Part A) | 104.8 | 28.7 | 105.3 | 31.2 | 91.0 | 30.2 | 1.748 | 0.202 | 0.827 | 0.346 |
| RTI five-choice movement time | 493.1 | 110.9 | 498.9 | 152.3 | 471.9 | 179.2 | 0.310 | 0.645 | 0.998 | 0.706 |
| RTI five-choice reaction time | 358.6 | 111.2 | 337.3 | 74 | 337.1 | 71.9 | 0.550 | 0.586 | 0.531 | 0.984 |
| Clinical symptoms, QOL | | | | | | | | | | |
| PANSS Total | 57.7 | 16.4 | 50.0 | 11.0 | 56.3 | 17.5 | 3.064 | 0.072 | 0.073 | 0.987 |
| PANSS Positive | 13.7 | 4.4 | 11.4 | 3.9 | 12.2 | 5.3 | 2.205 | 0.139 | 0.090 | 0.559 |
| PANSS Negative | 15.9 | 4.8 | 14.7 | 3.8 | 16.5 | 4.5 | 0.985 | 0.393 | 0.517 | 0.912 |
| PANSS General | 29.1 | 8.9 | 23.9 | 4.9 | 27.6 | 9.4 | 2.585 | 0.103 | 0.124 | 0.994 |
| PANSS Cognitive | 9.6 | 2.3 | 8.0 | 2.3 | 9.5 | 2.8 | 3.613 | 0.048¶ | 0.051 | 0.990 |
| GAF | 55.4 | 11.3 | 56.8 | 13.5 | 53.9 | 9.9 | 0.450 | 0.548 | 0.843 | 0.860 |
| JSQLS | 46.1 | 21.2 | 43.6 | 20.2 | 37.8 | 17.1 | 1.315 | 0.293 | 0.716 | 0.211 |
| BDI-II | 17.2 | 10.9 | 12.5 | 8.5 | 11.8 | 10.2 | 7.082 | 0.005†† | 0.011 | 0.006 |
| PDI | 6.6 | 7.1 | 6.5 | 6.7 | 3.7 | 5.0 | 1.344 | 0.279 | 0.996 | 0.273 |

All *P*-values are uncorrected. The FDR method was applied for multiple comparisons, and the adjusted *P*-values are as follows: †, 0.18; ‡, 0.053; §, 0.053; ¶, 0.192; ††, 0.053.

BDI-II, Beck Depression Inventory-II; FCNef, functional connectivity–informed neurofeedback; FDR, false discovery rate; GAF, Global Assessment of Functioning; JSQLS, Japanese version of the Schizophrenia Quality of Life Scale; PANSS, Positive and Negative Syndrome Scale; PDI, 21-item Peters et al. Delusions Inventory; QOL, quality of life; RBMT, Rivermead Behavioral Memory Test; RTI, Reaction Time Index; SWM, Spatial Working Memory; TMT, Trail Making Test.

*et al.*[36,38] Meanwhile, a weak and nonsignificant correlation was observed between the changes in resting-state LFPN FC and mean N-back level from pre-FCNef to post-FCNef (Fig. 4c). The small sample size may have affected the varying results among working memory assessments.

In the follow-up assessments, the increase in resting-state FC and improvement in the digit span backward task declined but remained higher than in the pre-FCNef assessment. However, the interpretation is limited by the variability in time intervals between post-FCNef and follow-up assessments and the absence of a control group.

Previous studies using fMRI NF for emotion recognition,[6] auditory hallucinations,[8–12] theory of mind,[14] and attempts to increase anterior cingulate cortex activity[7] have reported successful score increases during NF, with some studies showing correlations between neural and behavioral changes.[6,8,10,12,14] Similarly, our study demonstrated increased FC during NF and a correlation between neural and behavioral changes. Impaired neural plasticity has been well documented.[78] Our results indicate that increased LFPN FC is associated with improved working memory, suggesting a potential neural plasticity in schizophrenia. In addition, working

memory predicts community living and social functioning in patients with schizophrenia.[79,80] Although improvements in working memory might have contributed to these outcomes, this short-term study could not assess them. Future studies should explore the long-term impacts on social functioning and quality of life.

Moreover, our biomarker-based FCNef study demonstrated a neural-behavioral correlation with longitudinal changes, highlighting the significance of the biomarker. The correlation between the improvement in the mean N-back level and increased FC within the LFPN raises the possibility of a causal relationship between the LFPN and working memory. In the future, causal inference may be further explored using the FCNef and decoded NF.[24,81]

This study has several limitations that warrant further investigation. First, the small sample size limited the statistical power of the study, reduced its ability to detect actual effects, and increased the risk of type II errors. Moreover, random noise may have influenced the results, given the variability in cognitive, clinical, and FC measures. Second, the nonrandomized study design, differences in study duration, and variations in experimental facilities may have introduced systematic differences in confounding variables such as baseline cognitive ability, medication status, or socioeconomic factors, potentially compromising the validity of the comparisons. Third, the absence of MRI and follow-up assessments in the control group limited our ability to determine whether the improvements observed in the FCNef group were specific to NF. Fourth, this study lacked double-anonymized and sham feedback. Performing the same N-back task without brain activity feedback served as a mental rehearsal control outside the scanner, as described by Sorger *et al*.[82] While this controlled for the strategy's behavioral effects, it did not account for the placebo effect of training in a high-tech environment, motivational influences, or a sense of accomplishment from successful control. Moreover, the absence of double anonymization may have biased both the participants' task behaviors and the researchers' interpretations of the results. Fede *et al*.[51] recommended two control conditions: sham feedback and no NF. Fifth, the effects of anticholinergics and benzodiazepines have not yet been fully examined. Future studies should consider these factors.

In summary, the present fMRI NF in patients with schizophrenia was conducted safely, with no adverse events or worsening of symptoms, compared with the control group. This study highlights the potential of FCNef to enhance FC within the LFPN as a novel therapeutic approach for improving working memory in patients with schizophrenia. In addition to improvements in working memory, further development of NF targeting schizophrenia symptoms that do not respond adequately to antipsychotic medications is expected in the future.[83] Moreover, with the accessibility of large MRI databases for various neuropsychiatric disorders,[84] the development of FC-based biomarkers and FCNef for these disorders is likely to gain momentum.

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## Disclosure statement

Mitsuo Kawato is the inventor of patents related to FC-informed NF. The original assignee of the patents (Japanese patent No. 6722845, No. 7140348, US 12020427) was ATR. The corresponding author (Hidehiko Takahashi) is one of the Editors-in-Chief of *Psychiatry and Clinical Neurosciences*, and a co-author (Toshiya Murai) is an editorial board member of *Psychiatry and Clinical Neurosciences*. To minimize bias, they were excluded from all editorial decision-making related to the acceptance and publication of this article. Editorial decision-making was handled independently by Editor-in-Chief Tadafumi Kato. Hidehiko Takahashi has received collaborative research funding from XNef and ATR. Jun Miyata received joint research funds from XNef (supported by Shionogi Pharma). Yujiro Yoshihara has received joint research funds from ATR and XNef (supported by Shionogi Pharma). The other authors report no conflicts of interest.

## Author contributions

YY, MY, HI, and HT designed the study. YK, TA, YY, MY, HN, MS, TK, JM, TM, and HT collected the data. YK and TA performed data analysis. YK wrote the original draft of the manuscript. YK, TA, YY, MY, HN, MS, TK, JM, MK, TM, HI, and HT reviewed and revised the manuscript.

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## Supporting Information

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