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# Plasticity of DNA methylation, functional brain connectivity and efficiency in cognitive remediation for schizophrenia

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ABSTRACT

Cognitive remediation (CR) is predicated on principles of neuroplasticity, but the actual molecular and neurocircuitry changes underlying cognitive change in individuals with impaired neuroplastic processes is poorly understood. The present study examined epigenetic-neurocircuitry-behavioral outcome measures in schizophrenia, before and after participating in a CR program that targeted higher-order cognitive functions. Outcome measures included DNA methylation of genes central to synaptic plasticity (CpG sites of Reelin promoter and BDNF promoter) from buccal swabs, resting-state functional brain connectivity and topological network efficiency, and global scores of a cognitive battery from 35 inpatients in a rehabilitative ward (18 CR, 17 non-CR) with similar premorbid IQ to 15 healthy controls. Baseline group differences between healthy controls and schizophrenia, group-by-time effects of CR in schizophrenia, and associations between the outcome measures were tested. Baseline functional connectivity abnormalities within the frontal, fronto-temporal and fronto-parietal regions, and trending decreases in global efficiency, but not DNA methylation, were found in schizophrenia; the frontal and fronto-temporal connectivity, and global efficiency correlated with global cognitive performance across all individuals. Notably, CR resulted in differential changes in Reelin promoter CpG methylation levels, altered within-frontal and fronto-temporal functional connectivity, increasing global efficiency and improving cognitive performance in schizophrenia, when compared to non-CR. In the CR inpatients, positive associations between the micro to macro measures: Reelin methylation changes, higher global efficiency and improving global cognitive performance were found. Present findings provide a neurobiological insight into potential CR-led epigenetics-neurocircuitry modifications driving cognitive plasticity.

## 1. Introduction

An urgent issue in schizophrenia research today is the treatment of cognitive impairment, which affects daily functioning and is a source of long-term morbidity (Green et al., 2004; Insel, 2010). Cognitive remediation (CR) is a learning-based intervention that shows small-to-medium effects on improving global cognitive deficits in schizophrenia (Keshavan et al., 2014; Wykes, 1998). While the approaches to cognitive remediation vary across clinics, cognitive remediation is premised on the principle of neuroplasticity, i.e., the brain possesses remarkable adaptive abilities to environmental cues throughout life, and that cognitive training is a strong positive stimulus of adaptive neural

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mechanisms (Kaneko and Keshavan, 2012; Medalia and Choi, 2009). However, the exact neurobiological adaptations underlying CR in schizophrenia, a severe disorder with disturbed neuroplastic mechanisms (Falkai et al., 2015), are unclear to date, and neuroscience-informed CR—quantitative markers that can determine the optimal duration, frequency and intensity of CR that engender maximal cognitive improvements in patients—remains a distant goal.

Pioneering positron tomography work of schizophrenia patients before and after CR had focused on activity in the frontal lobe, providing important proof-of-concept data that CR *can* remodel the brain of patients despite chronicity of illness (Penades et al., 2000; Wykes, 1998). Subsequent seminal work using task-based fMRI found task-evoked activation changes in many regions distributed across the brain, including the prefrontal cortices, after CR (Haut et al., 2010; Keshavan et al., 2017; Penadés et al., 2013; Subramaniam et al., 2014). The variability in task paradigms and analysis methods used across the studies (Haut et al., 2010; Keshavan et al., 2017; Penadés et al., 2013; Subramaniam et al., 2014), and the small sample size in many studies (some less than ten per group), however, hampers identification of a consistent pattern of brain changes following CR.

Resting-state fMRI (rs-fMRI) permits the study of ongoing, spontaneous brain activity in the absence of a task. As the brain consumes a fifth of the body's energy even “at rest”, it has been opined that these slow and synchronous brain waves during rest yields a richer source of brain information than task-related brain activation (Fox and Raichle, 2007). Resting-state activity also captures individual differences in brain activity during task performance (Tavor et al., 2016). Rs-fMRI has rapidly gained popularity in the study of clinical populations, including schizophrenia, because it circumvents the difficulties patients face in performing cognitively-demanding tasks; task performance-related confounds such as practice effects or adaptation; and the requirement for common task paradigms across labs for reproducibility (Fox and Greicius, 2010). Besides its reliability (Shehzad et al., 2009), Rs-fMRI is shown to be sensitive to disease states and changes in physiological conditions (Greicius, 2008; van den Heuvel and Hulshoff Pol, 2010). Dysconnectivity in the frontal, temporal and parietal networks have been observed in many studies of schizophrenia (Woodward et al., 2011; Zhou et al., 2007) Graph theory analyses applied to the study of brain network topology have also found abnormalities in information processing properties in schizophrenia (Sheffield et al., 2016; Yu et al., 2011). Even within healthy individuals, a link between shorter path length of information transfer across the brain network (greater global efficiency) during rest and IQ has been demonstrated (van den Heuvel et al., 2009).

The sensitivity of Rs-fMRI over task-based fMRI to the effects of CR is demonstrated in the two recent Rs-fMRI studies of CR, both which examined a targeted working memory training programme in schizophrenia (Donohoe et al., 2018; Ramsay et al., 2017). One found regionalized rs-fMRI functional connectivity changes within the parietal lobe following CR, despite the lack of working memory task-based brain activation (Donohoe et al., 2018). The other showed a within-group before-and after-CR change in frontal-thalamic connectivity that correlated with working memory improvements, while no brain activation changes were detected using task-based fMRI (Ramsay et al., 2017).

While rs-fMRI approaches probe plasticity on a brain circuitry level, the study of epigenetic modifications allows for the capture of ongoing molecular-level regulation of gene expression, particularly the silencing or activation of genetic programs in response to environmental stimuli (Feil and Fraga, 2012; Latham et al., 2012). Compelling evidence of treatment-induced epigenetic reprogramming pertains, in particular, to two genes central to neuroplasticity: reelin (*RELN*) and brain-derived neurotrophic factor (*BDNF*).

Reelin is synthesized and secreted by γ-aminobutyric acid (GABA) ergic interneurons and highly expressed in the neuropil (Guidotti et al., 2000; Impagnatiello et al., 1998). Reelin alters synaptic structure and function, and modulates long-term potentiation (the cellular and molecular model of learning and memory) by modulating NMDA-type glutamate receptor activity (Levenson et al., 2008; Qiu et al., 2006; Rogers et al., 2011). *BDNF* plays a central role in neuronal growth, survival and differentiation, and also drives long-term potentiation (Huang and Reichardt, 2001; Lu et al., 2014). Altered gene expression and protein levels of *RELN* and *BDNF* have been reported in both postmortem brain tissues and peripheral tissues of schizophrenia (Costa et al., 2001; Eastwood and Harrison, 2003, 2006; Favalli et al., 2012; Fernandes et al., 2014; Guidotti et al., 2000; Hashimoto et al., 2005; Impagnatiello et al., 1998; Kordi-Tamandani et al., 2012; Weickert et al., 2003).

Epigenetic modification occurs in a few ways, of which DNA methylation is one of the most commonly studied and implicated in the etiology of schizophrenia (Castellani et al., 2015). Dynamic processes of DNA methylation and demethylation have been linked to cognitive function (Levenson et al., 2008; Marioni et al., 2018; Qiu et al., 2006). Furthermore, treatments such as valproaic acid, antidepressants and dialectical behavioral therapy are shown to modify DNA methylation of *RELN* and *BNDF* promoters (Chen et al., 2002; Grayson et al., 2005; Lopez et al., 2013; Perroud et al., 2013).

In the present study, we sought to understand from an integrated micro- and macro-level perspective how CR impacts neuroplasticity in schizophrenia, by examining epigenetic-neurocircuitry-behavioural outcome measures before and after a CR program targeting higher-cognitive functions. We pursued the following hypotheses. 1) At baseline, cognitive performance in schizophrenia is poorer compared with healthy individuals. There are differences in DNA methylation of CpG islands of *RELN* and *BDNF* promoters in peripheral tissues of schizophrenia compared with healthy individuals. There are also concomitant differences in the patterns of functional connectivity and efficiency of resting-state cortical networks in schizophrenia. 2) CR results in changes in the DNA methylation of candidate gene promoters, functional connectivity and global efficiency (i.e. more integrated information transfer across the network as a whole) (Bullmore and Sporns, 2012), as well as global cognitive improvements in schizophrenia. There is a relationship between changes in DNA methylation, global efficiency and cognitive performance in CR volunteers.

To mitigate the confounding effects from variability in outpatient environmental stimuli, we focused on a cohort of clinically stable inpatients who were referred to the rehabilitative ward for a course of psychosocial rehabilitation before discharge. We studied patient volunteers who opted for an hour of daily CR in addition to other rehabilitation activities (CR) and compared them with fellow patient volunteers who engaged in their own activities in the interim, such as reading or watching television programmes (non-CR). To detect illness-related differences at baseline and possible variability in methylation levels or Rs-fMRI fluctuations over time, healthy control volunteers (HC) were studied as an additional comparator group. Peripheral tissues permit the assessment of activity-dependent changes in DNA methylation that is not possible in postmortem brains. Here, buccal over blood samples were chosen as the surrogate tissue for brain genomic DNA because 1) collection of buccal swabs are less invasive, 2) buccal cells are more homogenous, with only two major cell types: buccal epithelial and leucocytes, 3) buccal epithelial has the same developmental ectodermic origins as the brain, and 4) buccal DNA methylome shows more interindividual epigenetic variation and is enriched with more disease-associated SNPs compared with blood methylome (Lowe et al., 2013; van Dongen et al., 2018).

## 2. Materials and methods

### 2.1. Subjects

The naturalistic, prospective study was carried out from 2015 to 2018, in accordance to the guidelines of the Institutional Review Board for the National Healthcare Group. Written informed consent was

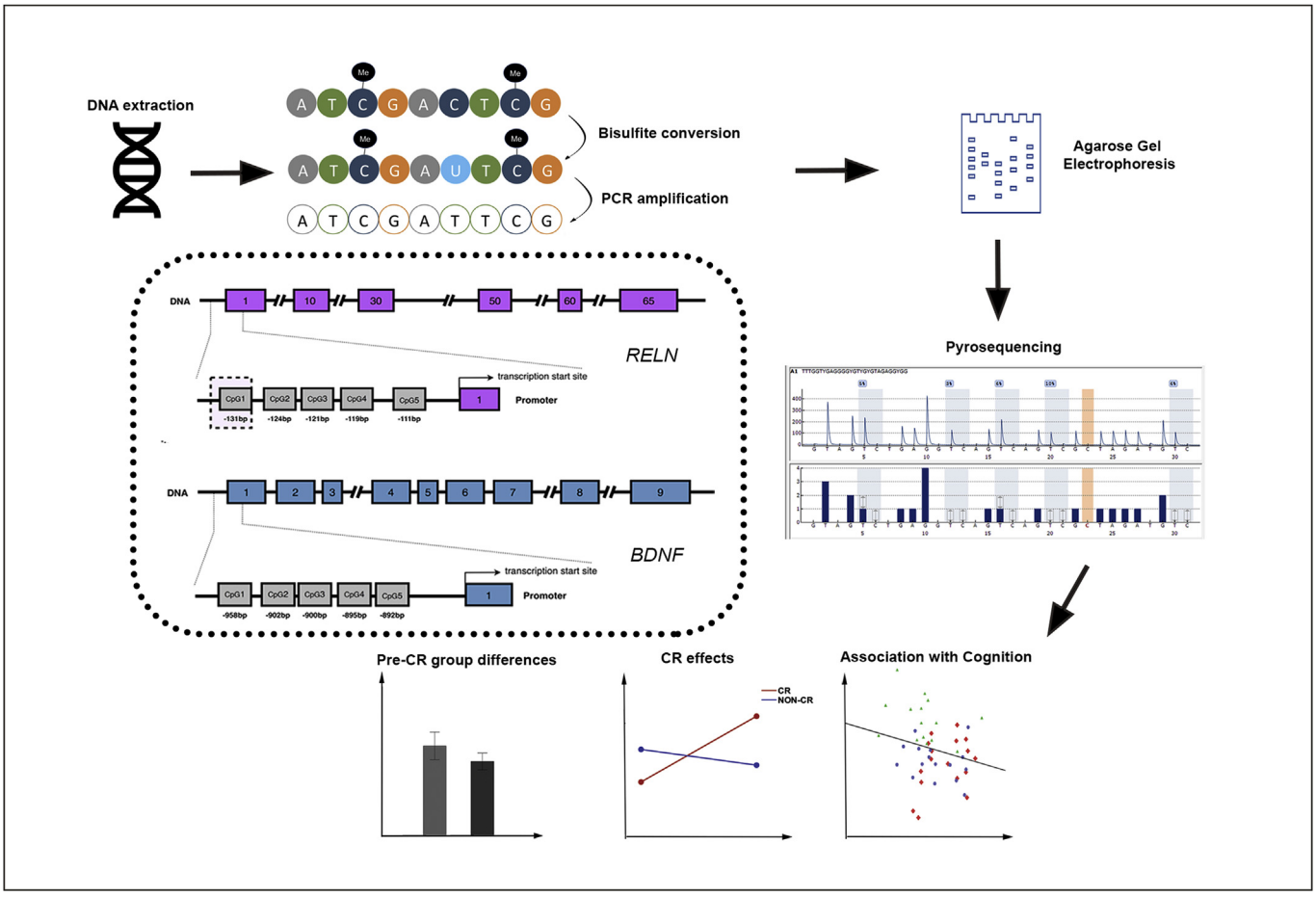


**Fig. 1. Study schematic. Quantifying DNA methylation of reelin and *BDNF* gene promoter cytosine phosphate guanine (CpG) islands before and after cognitive remediation (CR).** Genomic DNA was extracted from buccal samples of all participants. Bisulfite conversion was then carried out to convert unmethylated cytosine nucleotides into uracil, before polymerase chain reaction amplification of the promoter regions. Agarose gel electrophoresis was performed to ensure successful amplification of specific CpG islands embedding the reelin and *BDNF* gene promoter. The CpG islands upstream of the first RELN exon (out of 65) and first BDNF exon (out of 9) were amplified. Pyrosequencing was conducted to assess the levels of methylated and unmethylated cytosine residues (Supplementary methods). Baseline group differences between schizophrenia and healthy controls, effects of CR in schizophrenia and associations between DNA methylation and cognitive performance were evaluated.

obtained from all participants after they have understood the study procedures. CR was offered by the rehabilitative ward occupational therapists to all inpatients in the rehabilitation ward. A total of 50 subject volunteers were enrolled in three groups; 18 were inpatients who chose to participate (CR), 17 were those in same ward who chose to participate in their own activities instead (non-CR) and 15 were HC.

Inclusion criteria for all patients included diagnosis of schizophrenia based on existing medical records and confirmed by the Structured Clinical Interview for Diagnostic Statistical Manual-IV-Patient Version (SCID-I/P) (First et al., 2002b) and comprehension of English adequate for cognitive testing. Exclusion criteria for all patients included subjects older than 40 to prevent confounding effects of age on cognition, duration of hospital stay that is longer than eight months before referral; any form of prior CR in the form of scheduled training sessions, participation in studies involving the use of cognitive-enhancing drugs; and a history of attention deficit hyperactivity disorder. HC were recruited from the community and were screened using the SCID-Non-Patient Version (First et al., 2002a) to ensure no previous or existing, or first degree relatives with Axis I disorders.

Additional exclusion criteria for all participants included intellectual disability, impaired thyroid function, steroid use, history of alcohol and substance abuse within three months of the study, history of brain trauma or epilepsy, contraindications for MRI such as metal devices or claustrophobia.

Of the 50 subjects, three subjects from the non-CR group did not return for the follow-up visit, two subjects (1 CR, 1 non-CR) did not complete the MRI scan due to anxiety and three subjects (2 CR, 1 non-CR) were unwilling to participate in the follow-up scan.

### 2.2. CR

All patient subjects stayed in a ward with intensive rehabilitation programme comprising modules on medication management, symptom management and basic conversational skills, with CR as an optional module. See **Supplementary Methods** for details of the CR which was administered by Occupational Therapists trained to competency to provide a personalized and manualized programme called NEAR (Medalia et al., 2017) that targeted a range of higher cognitive skills using restorative and compensatory approaches. Participants needed to complete a total of 32 sessions of CR over a span of 5–7 weeks (M = 6.30, SD = 0.57).

There were no group differences in the number of weeks between baseline and follow-up visits (CR:6.76 ± 0 .60, non-CR:6.90 ± 0 .76, HC: 7.2 ± 0 .94).

### 2.3. Clinical and neuropsychological assessments

Research assistants blinded to the group assignments of patients

administered the following assessments: 1) Positive and Negative Syndrome Scale (PANSS), to measure severity of psychopathology (Kay et al., 1987), 2) Brief Assessment of Cognition in Schizophrenia (BACS), which provides a global score based on performance on measures of verbal memory, working memory, speed of processing, motor function, verbal fluency and executive function (Keefe et al., 2004), and 3) Wide Range Achievement Test 3 – Reading Test (WRAT-3), to estimate premorbid IQ (Wilkinson, 1993).

### 2.4. DNA methylation analysis

Buccal swabs were collected from all participants at both timepoints, except for the three subjects who did not return for the follow-up visit. Genomic DNA extraction, bisulphite conversion, PCR amplification and pyrosequencing to quantify DNA methylation at Cytosine-phosphate-Guanine rich (CpG) sites embedding *RELN* and *BDNF* promoters were performed at the Neuroepigenetics laboratory, National University of Singapore. Overall methylation values are quantified by averaging across the five CpG islands analysed.

The flowchart and description of methylation quantification procedure are provided in Fig. 1 and **Supplementary Methods**.

### 2.5. Image acquisition, preprocessing and quality control

Details of the image acquisition and preprocessing, including motion parameters, are provided in **Supplementary Methods**. Briefly, structure and resting-state fMRI scans were acquired on a 3-T MAGNETOM Prisma scanner (Siemens, Erlangen, Germany) at the Duke-National University of Singapore Medical School. Standard preprocessing of the structural images was performed with FreeSurfer 6.0 (Fischl, 2012). To reduce variability inherent to cross-sectional preprocessing at each time-point, the processed structural images for baseline and follow-up scans were further subjected to a specialized longitudinal processing pipeline (Reuter et al., 2012). The lowered variability and increased reliability after longitudinal processing permits sample size reduction (Reuter et al., 2012).

Pre-processing for resting-state fMRI in individual native space was conducted using the CONN toolbox, version 17f (Whitfield-Gabrieli and Nieto-Castanon, 2012). Co-registration of functional and anatomical images were conducted in individual subject native space. The analysis of subject native space, as opposed to a standard volume space (e.g. Talairach or MNI atlas space) accounts for the unique neuroanatomy of individuals and any possible disease- or age-related structural changes (Seibert and Brewer, 2011).

Based on existing literature on abnormal *RELN* and *BDNF* expression, as well as task-based and resting-state functional connectivity findings of regions commonly associated with cognitive deficits in schizophrenia (Donohoe et al., 2018; Eack et al., 2016; Fan et al., 2017; Garrity et al., 2007; Guidotti et al., 2000; Impagnatiello et al., 1998; Lawrie et al., 2002; Subramaniam et al., 2014; Weickert et al., 2003), 40 regions-of-interest (ROIs) that spanned the entire frontal, temporal and parietal cortices from the Desikan-Killiany atlas incorporated into FreeSurfer (Desikan et al., 2006) were examined. BOLD time-courses for each ROI were computed by averaging the timeseries for all voxels within the ROI. Functional connectivity between two ROIs was computed as the Fisher-transformed bivariate correlation coefficients of their time series, generating a functional connectivity matrix of all the ROIs was generated. Graph adjacency matrices (global and local efficiency) were then generated by thresholding the ROI-ROI correlation matrix at various cost thresholds that ranged from 0.15 to 0.35 (Qian et al., 2018). Analyses were conducted at 5% increments of cost to ensure stability of results over thresholds, and graph metrics reported here are the average values of all costs (Cohen and D'Esposito, 2016).

The flowchart for the Rs-fMRI analysis procedure is shown in Fig. 2.

### 2.6. Statistical analysis

All statistical analyses were conducted in SPSS (Version 24, IBM). Before primary statistical testing, normality and homogeneity of variances of all outcome measures were ensured by conducting Shapiro-Wilk tests and Levene's test. BACS scores were standardised to normative data from a local community-based cohort (Lam et al., 2014). Group differences in demographics were tested using either $\chi 2$ tests or *F/t*-tests. Years of education was added as a covariate/regressor in subsequent analyses because this variable was significantly different between HC and patients, and also influences cognitive performance (Wilson et al., 2009).

To test Hypothesis 1 of baseline group differences in outcome measures of global BACS scores, DNA methylation levels of *RELN* and *BDNF* promoter CpG sites, functional connectivity and efficiency (local and global), analyses-of-covariance (ANCOVA) was conducted. Linear regression was conducted to determine the relationship between biological variables and cognitive performance.

To test Hypothesis 2 of whether CR led to changes in outcome measures in schizophrenia, mixed ANCOVA was applied to test for group-by-time effects. Posthoc within-group paired t-tests was conducted to confirm the direction of change. Also, to determine whether there was a relationship between changes in DNA methylation, efficiency and cognitive improvements in CR participants, linear regression was conducted. Change scores were calculated by subtracting post-intervention scores from baseline performance.

Multiple comparisons for methylation levels were corrected using Bonferroni and for imaging measures using false discovery rates (FDR), which was inbuilt with the CONN toolbox. Partial eta squared, $\eta_p^2$, was used as the measure of effect size; 0.01, 0.06 and 0.14 were considered to be small, medium and large effects, respectively (Cohen, 1988).

Secondary analyses were conducted using similar ANCOVA and regression models to ascertain that significant findings were not confounded by duration of illness or antipsychotic doses.

## 3. Results

### 3.1. Baseline findings

#### 3.1.1. Demographic, cognitive, clinical measures

With the exception of years of education between healthy controls and schizophrenia, no group differences were found in premorbid IQ, gender, handedness, age or ethnicity (Table 1A). No clinical differences between the patient groups in symptom severity, age onset, baseline global BACS, duration of illness and antipsychotic loads were observed.

As expected, global BACS scores were significantly lower in schizophrenia compared with HC (Fig. 3A).

#### 3.1.2. DNA methylation measures

At baseline, levels of DNA methylation in *RELN* and *BDNF* CpG islands were not significantly different between patients and HC. Table 1B shows the between-group statistics.

Short- and long-range functional connectivity abnormalities in patients.

Functional connectivity differences between HC and patients were evident at baseline (Fig. 3B). Regionalized hyperconnectivity between right dorsolateral and ventrolateral frontal regions: inferior frontal gyrus (pars triangularis) and middle frontal gyrus (caudal) ($F_{1,45}$ = 14.12,*p-FDR* = .017,$\eta_p^2$ = 0.24) and regions around the right intraparietal sulcus i.e. between superior parietal cortex and inferior parietal cortex ($F_{1,45}$ = 13.15,*p-FDR* = .026,$\eta_p^2$ = 0.23) were found in patients compared with HC. Longer-range frontotemporal and frontoparietal hyperconnectivity in patients compared with HC were also found, namely between the right middle frontal gyrus (caudal) and left superior temporal gyrus ($F_{1,45}$ = 10.29,*p-FDR* = .043,$\eta_p^2$ = 0.19), left anterior cingulate cortex (rostral) and left inferior temporal gyrus

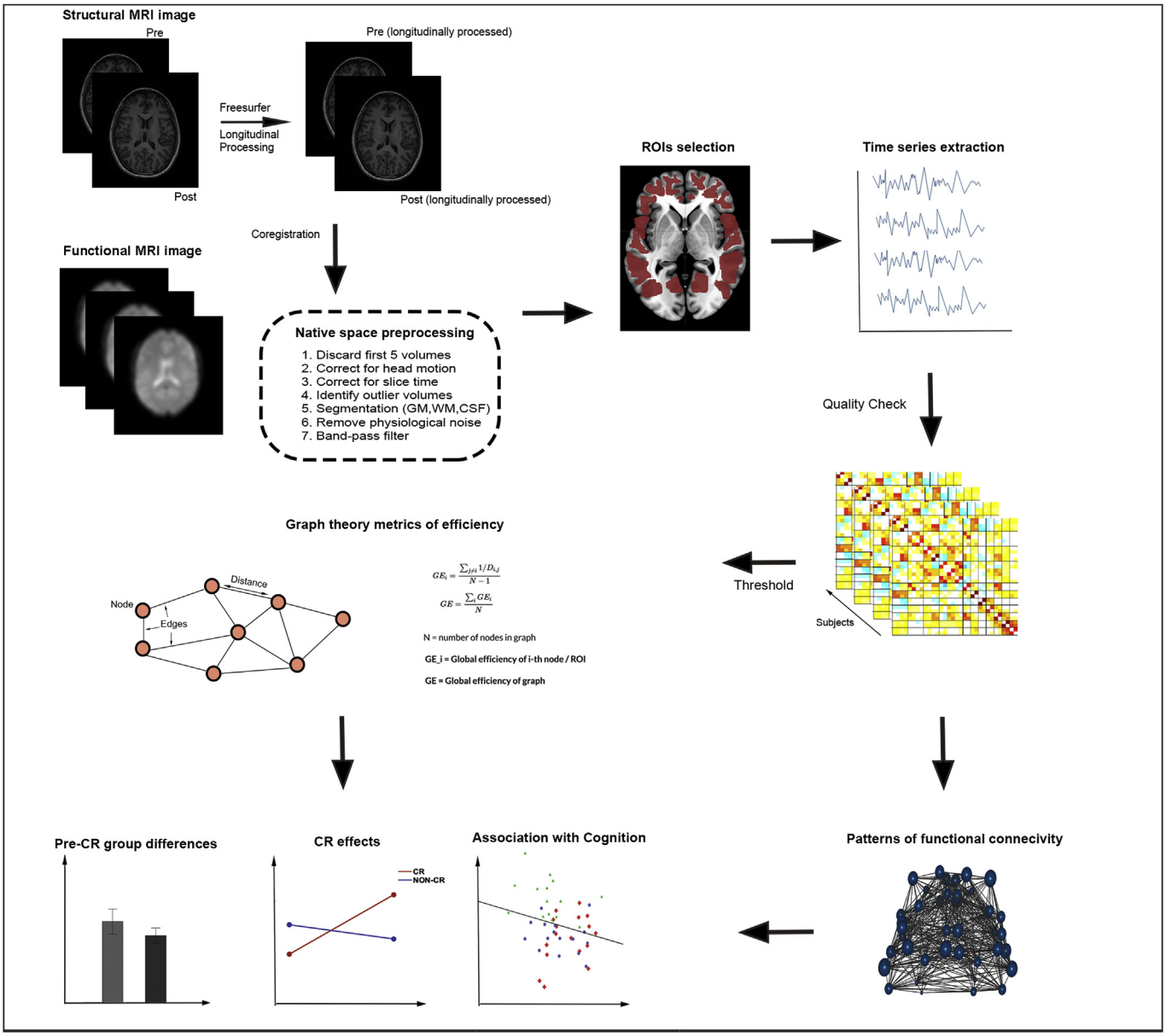


**Fig. 2. Study schematic. Examination of resting-state functional connectivity and efficiency of the fronto-temporal-parietal network before and after CR.** Preprocessing of resting-state fMRI T2*weighted images included removal of first five volumes, correction for head motion, correction for slice timing, identification of outlier volumes, segmentation into grey matter, white matter and cerebrospinal fluid, removal of physiological noise and band-pass filtering (0.01–0.08 Hz). The resting-state images were co-registered to the higher-resolution T1-weighted structural images in individual subject native space. The structural scans had been additionally processed using a specialized longitudinal pipeline to eliminate cross-sectional variability across the baseline and follow-up scans. Regions-of-interests (ROIs) across the fronto-temporal-parietal cortex were selected from the Desikan-Killiany atlas, namely the superior frontal gyrus, middle frontal gyrus (rostral and caudal), inferior frontal gyrus (subdivided into pars opercularis, pars triangularis and pars orbitalis), orbitofrontal cortex (lateral and medial divisions), anterior cingulate cortex (rostral and caudal), superior temporal gyrus, middle temporal gyrus, entorhinal cortex, parahippocampal gyrus, inferior temporal gyrus, transverse temporal cortex, superior parietal cortex, inferior parietal cortex, precuneus and posterior cingulate cortex. The time series within each ROI was extracted and a ROI-ROI functional connectivity matrix constructed for each subject. The mean functional connectivity (z-score) between two ROIs at a group level can be calculated from the matrices. Global and local efficiency of information transfer can also be calculated from the matrices by modelling the brain network as a graph. Nodes (the network science term for ROIs) are connected by edges. The path length is defined the number of edges between nodes and represents the number of processing steps along the routes of information transfer. Efficiency refers to the ability to exchange information throughout the network, and is a function of minimum path length. Global efficiency refers to how densely connected all the nodes in the network are to one another. Local efficiency refers to the extent to which the network is organized into smaller sub-networks (Achard and Bullmore, 2007). Here, the following functional connectivity metrices: strength of functional connectivity between brain regions, global efficiency and local efficiency of the brain network were examined for baseline group differences between schizophrenia and healthy controls, effects of CR in schizophrenia and brain-behaviour associations.

($F_{1,45}$ = 10.06,*p-FDR* = .057,$\eta_p^2$ = 0.18), right inferior frontal gyrus (pars triangularis) and right inferior parietal cortex ($F_{1,45}$ = 11.9,*p-FDR* = .021,$\eta_p^2$ = 0.21), right anterior cingulate cortex (rostral) and left superior parietal cortex ($F_{1,45}$ = 12.32,*p-FDR* = .036,$\eta_p^2$ = 0.22).

Secondary analyses revealed that significant results remained after adjusting for illness duration or antipsychotic medication doses across the CR and non-CR volunteers. Secondary tests also found no baseline differences in functional connectivity between CR and non-CR.

**Table 1**
**Between-group comparisons of participant characteristics. Data are presented as means ± standard deviation.** A) Baseline demographics, clinical and cognitive measures. B) Percentage of DNA methylation in CpG islands of *RELN* and *BDNF* promoter regions.

| | | CR ($n$ = 18) | Non-CR ($n$ = 17) | HC ($n$ = 15) | $\chi^2$ or $t$ or $F$ (d.f) | $p$ |
|---|---|---|---|---|---|---|
| A) | **Demographics** | | | | | |
| | Gender (M/F) | 9/9 | 14/3 | 9/6 | 4.12 | .13 |
| | Handedness (R/L) | 16/2 | 15/2 | 14/1 | .27 | .87 |
| | Age (years) | 33.96 ± 5.2 | 32.04 ± 5.6 | 33.34 ± 4.6 | .62 (2, 47) | .54 |
| | Education (years) | 13.36 ± 4.1 | 11.03 ± 2.4 | 15.50 ± 3.3 | 6.94 (2, 47) | .002[a] |
| | Ethnicity (C/M/I) | 12/2/4 | 15/1/1 | 13/1/1 | 3.43 | .49 |
| | **Clinical Measures** | | | | | |
| | Age onset of illness | 24.06 ± 5.68 | 23.24 ± 4.59 | – | .22 (1,33) | .64 |
| | Duration of illness (years) | 9.42 ± 4.99 | 8.27 ± 4.04 | – | .55 (1, 33) | .46 |
| | Antipsychotic dosage (daily CPZ equivalent; mg) | 763.54 ± 420.53 | 626.26 ± 398.87 | – | .98 (1, 33) | .33 |
| | PANSS Positive | 15.28 ± 4.61 | 14.41 ± 4.80 | – | .30 (1, 33) | .59 |
| | PANSS Negative | 16.83 ± 5.40 | 15.53 ± 4.82 | – | .57 (1, 33) | .46 |
| | PANSS General | 32.39 ± 6.20 | 33.35 ± 10.74 | – | .11 (1, 33) | .75 |
| | **Cognitive Measures** | | | | | |
| | Premorbid IQ[b] | 44.83 ± 6.90 | 44.53 ± 5.14 | 47.27 ± 7.8 | .79 (2, 47) | .46 |
| | BACS (Composite)[c] | −1.32 ± 0.18 | −1.07 ± 0.20 | .15 ± .22 | 14.09 (2. 46) | < .001[d] |
| B) | **DNA methylation** | | | | | |
| | *RELN* | | | | | |
| | Overall[e] | 5.98 ± .25 | 6.44 ± .29 | 6.13 ± .29 | .75 (2, 44) | .48 |
| | CpG1 (−131 bp) | 5.18 ± .17 | 5.49 ± .20 | 5.14 ± .20 | .89 (2, 44) | .42 |
| | CpG2 (−124 bp) | 4.27 ± .17 | 4.34 ± .20 | 4.00 ± .19 | .81 (2, 44) | .46 |
| | CpG3 (−121 bp) | 5.92 ± .28 | 6.62 ± .33 | 6.18 ± .33 | 1.30 (2, 44) | .28 |
| | CpG4 (−119 bp) | 7.69 ± .40 | 8.43 ± .47 | 8.36 ± .47 | .98 (2, 44) | .39 |
| | CpG5 (−111 bp) | 6.82 ± .38 | 7.32 ± .45 | 6.96 ± .45 | .37 (2, 44) | .70 |
| | *BDNF* | | | | | |
| | Overall[e] | 6.26 ± 1.71 | 6.15 ± 1.85 | 6.34 ± 1.97 | .04 (2, 44) | .96 |
| | CpG1 (−958 bp) | 6.90 ± 1.68 | 6.62 ± 1.65 | 6.67 ± 1.71 | .12 (2, 44) | .89 |
| | CpG2 (−902 bp) | 6.87 ± 1.72 | 6.77 ± 2.00 | 7.14 ± 2.15 | .15 (2, 44) | .87 |
| | CpG3 (−900 bp) | 5.46 ± 1.65 | 5.46 ± 1.78 | 5.55 ± 1.90 | .01 (2, 44) | .99 |
| | CpG4 (−895 bp) | 6.40 ± 1.87 | 6.34 ± 2.03 | 6.55 ± 2.11 | .04 (2, 44) | .96 |
| | CpG5 (−892 bp) | 5.70 ± 1.71 | 5.58 ± 1.88 | 5.78 ± 2.06 | .04 (2, 44) | .96 |

Abbreviations: Brief Assessment of Cognition in Schizophrenia, BACS; brain derived neurotrophic factor gene, *BNDF*; Chinese, C; Cognitive Remediation, CR; 5′ cytosine-phosphoguanine, CpG; Females, F; Healthy Controls, HC; Indian, I; Left, L; Malay, M; Males, M; Positive and Negative Syndrome Scale, PANSS; reelin gene, *RELN*; Right, R; UPSA, University of California San Diego Performance-Based Skills Assessment; Wide Range Achievement Test 3, WRAT-3.

[a] HC received more years of education compared with non-CR subjects.

[b] Premorbid IQ was estimated using WRAT-3.

[c] Raw scores were standardised to normative data; composite score was derived from the mean of the sub-tests (Lam et al., 2014). An analysis of covariance was performed to test for group differences at baseline, with years of education as a covariate.

[d] HC performed better than CR and Non-CR, and no patient group differences was observed.

[e] Overall methylation patterns refer to the average of DNA methylation across all five CpG islands.

#### 3.1.3. Efficiency of brain network

Marginal decreases in global efficiency in patients compared with HC ($F_{1,45}$ = 3.26,$p$ = .078,$\eta_p^2$ = 0.07) were found but there were no group differences in local efficiency (Fig. 3C).

Association of functional brain connectivity and global efficiency with cognitive performance.

There was a significant association between frontal hyperconnectivity between right middle frontal gyrus (caudal) and right inferior frontal gyrus (pars triangularis) and poorer global BACS performance ($r$ = −0.38,$p$ < .01) across all participants, patients and healthy controls alike (Fig. 3D). A similar association between frontotemporal hyperconnectivity, specifically the left anterior cingulate cortex (rostral) and left inferior temporal gyrus, and poorer global BACS performance ($r$ = −0.34,$p$ = .021) was found in both patients and healthy controls (Fig. 3E).

A positive correlation between global efficiency and global cognitive performance ($r$ = −0.46,$p$ = .01) was also seen across groups (Fig. 3F).

### 3.2. CR effects

#### 3.2.1. Cognitive and symptomatic improvements

Group-by-time comparisons between the patient groups revealed large effect size improvements in BACS global scores in CR compared with non-CR ($F_{1,29}$ = 4.50,$p$ = .043,$\eta_p^2$ = 0.13, Fig. 4A). Significant group-by-time effects for negative symptoms ($F_{1,29}$ = 4.75,$p$ = .038,$\eta_p^2$ = 0.14) were seen, driven by increasing severity of negative symptoms in non-CR participants. Group-by-time effects were not seen in positive or general psychopathology symptoms. Supplementary Table S3 shows the within-group pre-and post-CR findings for cognitive performance and symptoms.

#### 3.2.2. Changes in DNA methylation of reelin promoter

Significant group-by-time effects in *BDNF* were absent between CR and non-CR patients., but were found in overall *RELN* promoter methylation ($F_{1,29}$ = 6.46,$p$ = .017,$\eta_p^2$ = 0.18) and in specific CpG islands (CpG3: $F_{1,29}$ = 9.82,$p$ < .01,$\eta_p^2$ = 0.25; CpG4: $F_{1,29}$ = 9.55,$p$ < .01,$\eta_p^2$ = 0.25) (Fig. 4B). The group-by-time effects remained when HC was taken into account (overall: $F_{2,43}$ = 4.24,$p$ = .021,$\eta_p^2$ = 0.17; CpG3: $F_{2,43}$ = 5.84,$p$ < .01,$\eta_p^2$ = 0.21; CpG4: $F_{2,43}$ = 5.41,$p$ < .01,$\eta_p^2$ = 0.20). Within-group comparisons showed significant methylation increases in CR and decreases in non-CR (Table S3). The effects were neither associated with duration of illness nor antipsychotic dosages (overall: $F_{1,27}$ = 7.40,$p$ = .011,$\eta_p^2$ = 0.22; CpG3: $F_{1,27}$ = 11.00,$p$ = .003,$\eta_p^2$ = 0.29; CpG4: $F_{1,27}$ = 11.24,$p$ = .002,$\eta_p^2$ = 0.29).

#### 3.2.3. Short- and long-range functional connectivity changes

Large group-by-time effects between the right transverse temporal

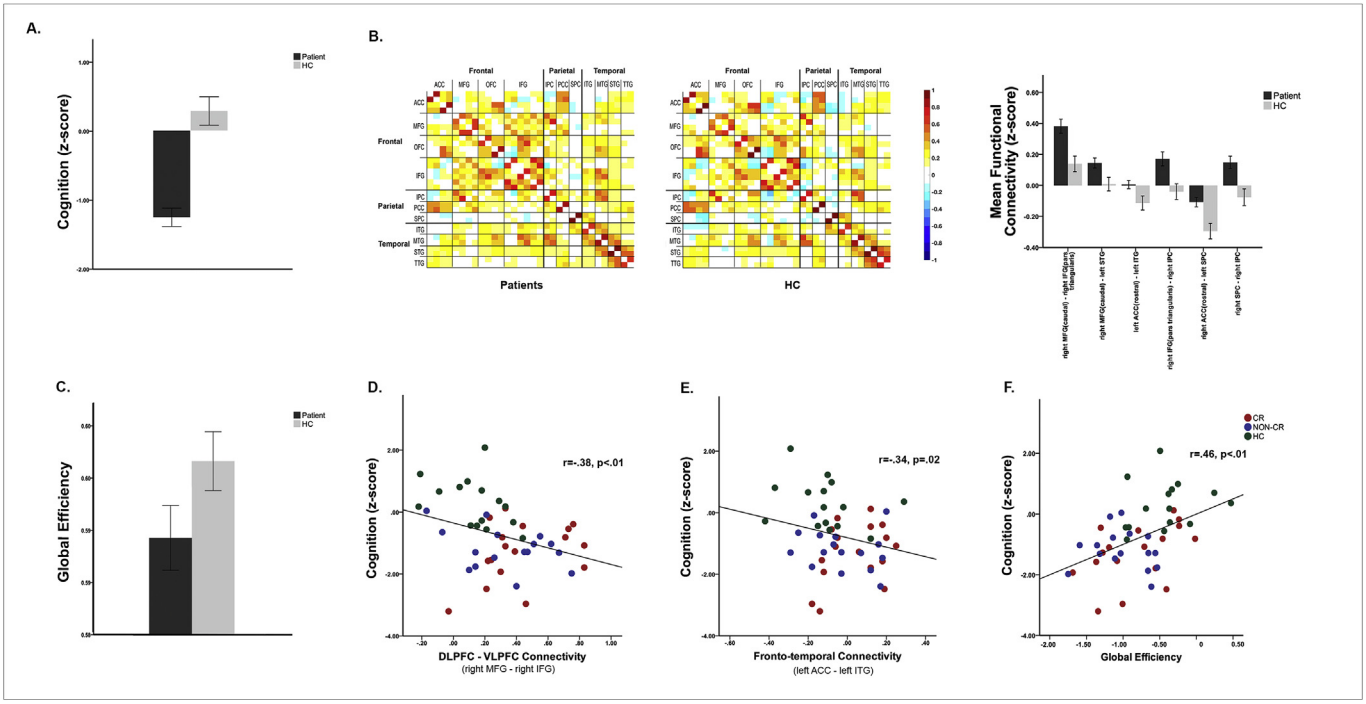


**Fig. 3. Comparison of schizophrenia and healthy controls at baseline.** (A) Despite having similar pre-illness IQ, schizophrenia patients performed worse than healthy individuals (HC) in the composite of a cognitive battery (BACS), which is standardized to local population normative data. (B) Functional connectivity matrix of fronto-temporal-parietal regions in schizophrenia and HC; warmer/cooler colours indicate greater/less functional connectivity. The bar chart indicates the mean functional connectivity strengths (z-scores) between the brain regions showing significant group differences. (C) Patient subjects had marginally decreased global efficiency values when compared with healthy individuals. Error bars indicate standard errors. Across, all subjects, hyperconnectivity within the frontal lobes (D) and between frontotemporal regions (E) were associated with poorer overall BACS performance, patients and HC alike. (F) Higher global efficiency values were also associated with better cognitive performance in all subjects.

Abbreviations: anterior cingulate cortex, ACC; functional connectivity, FC; healthy controls, HC; inferior frontal gyrus, IFG; inferior parietal cortex, IPC; inferior temporal gyrus, ITG; middle frontal gyrus, MFG; middle temporal gyrus, MTG; orbitofrontal cortex, OFC; posterior cingulate cortex, PCC; superior parietal cortex, SPC; superior temporal gyrus, STG; transverse temporal gyrus, TTG.

gyrus and left middle temporal gyrus ($F_{1,24}$ = 11.99,*p-FDR* = .035,$\eta_p^2$ = 0.33), left orbitofrontal cortex (medial) and right transverse temporal gyrus ($F_{1,24}$ = 13.89,*p-FDR* = .037,$\eta_p^2$ = 0.37), left orbitofrontal cortex (lateral) and left middle temporal gyrus ($F_{1,24}$ = 12.09,p-FDR = .035,$\eta_p^2$ = 0.34), right inferior frontal gyrus (pars orbitalis) and right transverse temporal gyrus ($F_{1,24}$ = 10.18,*p-FDR* = .046,$\eta_p^2$ = 0.30) in CR versus non-CR, driven by decreasing connectivity in the CR group over time (Fig. 4C), which is the reverse trend of hyperconnectivity found in patients relative to HC at baseline.

To corroborate that the group-by-time effects were related to the intervening effects of CR, group comparisons between non-CR and HC were conducted; no slope differences were seen.

### 3.2.4. Efficiency changes

Large group-by-time effects in global efficiency were seen ($F_{1,24}$ = 7.35,*p* = .012,$\eta_p^2$ = 0.23), driven by increases in CR compared with non-CR (Fig. 4D). Conversely, group-by-time effects in local efficiency were seen, driven by decreases in CR compared with non-CR ($F_{1,24}$ = 10.17,*p* = .004,$\eta_p^2$ = 0.30). The large group-by-time effects remained when HC was taken into account ($F_{2,43}$ = 6.26,*p* = .004,$\eta_p^2$ = 0.25). The effects were also not associated with duration of illness or antipsychotic dosages ($F_{1,22}$ = 7.73,*p* = .011,$\eta_p^2$ = 0.26).

### 3.2.5. Association between changes in RELN methylation, global efficiency and cognitive improvement in patients with CR

Post-hoc within-group correlation analyses of the significant outcome measures revealed positive associations between the changes in *RELN* CpG3 and global efficiency ($r$ = 0.63, $p$ = 0.01) (Fig. 4E), *RELN* CpG3 and BACS global scores ($r$ = 0.51, $p$ = 0.03) (Fig. 4F) and global efficiency and BACS global scores ($r$ = 0.67, $p$ = 0.006) (Fig. 4G).

## 4. Discussion

To our knowledge, this study is first to report concomitant modifications in Reelin promoter DNA methylation, functional brain connectivity and efficiency that are accompanied by global cognitive improvements in schizophrenia inpatients who participated in a CR program that targeted a broad range of higher-order cognitive functions.

### 4.1. CR associated with differential DNA methylation of RELN

Previous studies have found a significant association between hypermethylation of the RELN promoter and downregulation of RELN expression in mouse cortical neurons *in vitro* (Dong et al., 2005; Noh et al., 2005), neuroprogenitor NT2 cells (Chen et al., 2002; Mitchell et al., 2005) and postmortem dorsolateral prefrontal cortical tissue of patients with schizophrenia (Abdolmaleky et al., 2005). However, the evidence for RELN hypermethylation in schizophrenia is still mixed; while some studies have found hypermethylation in postmortem brain white matter (Eastwood and Harrison, 2003), grey matter (Abdolmaleky et al., 2005), and peripheral blood samples (Nabil Fikri et al., 2017), others report a lack of case-control difference in both grey and white matter (Tochigi et al., 2008) as well as in blood samples (Bönsch et al., 2012; Ikegame et al., 2013).

By using buccal samples, which has not been previously studied, we did not find case-control differences in CpGs of *a priori* neuroplastic

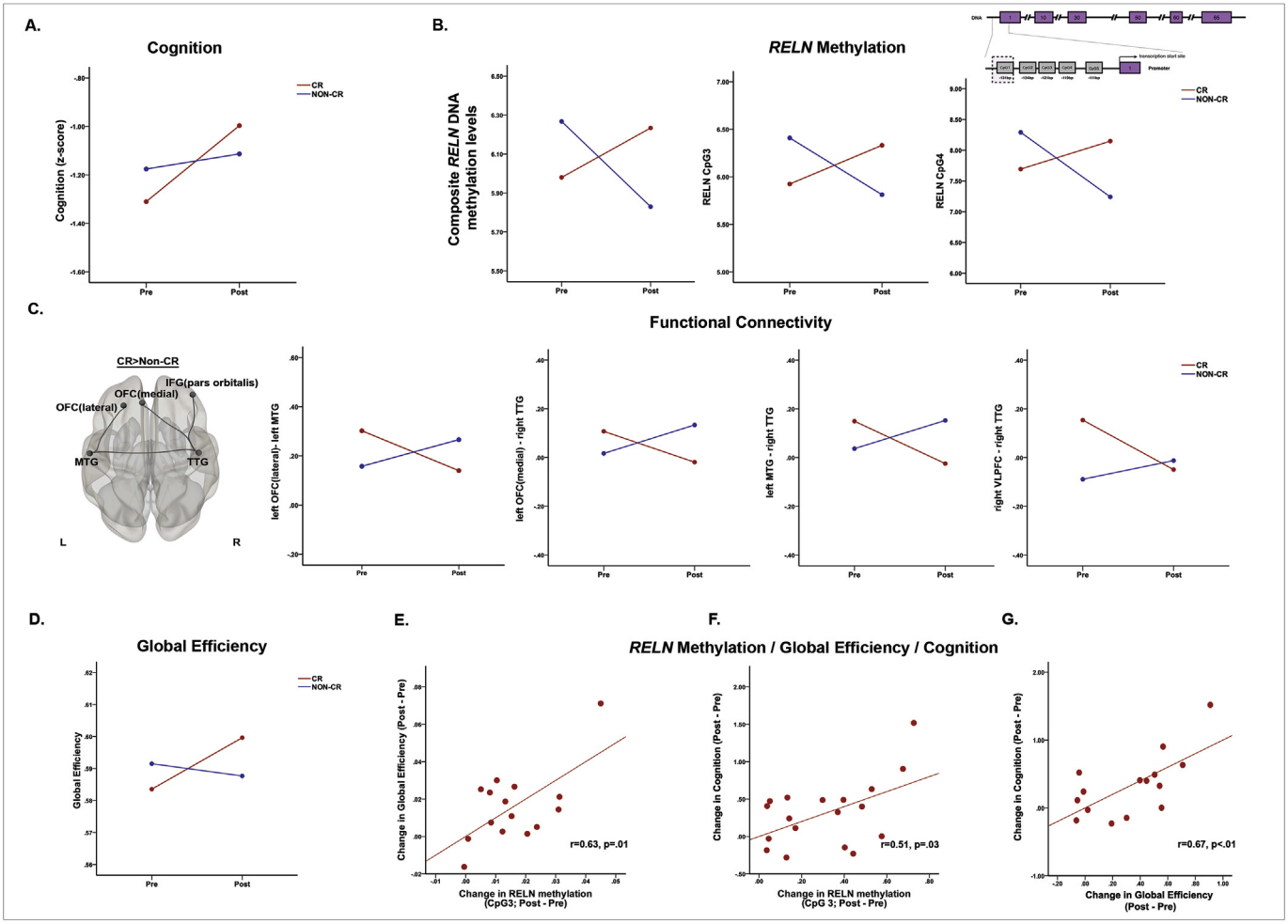


**Fig. 4. Cognitive remediation (CR) effects in schizophrenia.** Comparison of patient groups show significant group-by-time effects in (A) overall cognitive performance (BACS) due to improvements in CR; (B) composite DNA methylation levels, CpG islands 3 and 4 of reelin gene promoter due to increasing methylation in CR; (C) functional coupling in the frontotemporal (OFC-MTG, OFC-TTG, IFG-TTG) and within the temporal regions (MTG-TTG), driven by decreasing functional connectivity in CR; (D) global efficiency (an indicator of network integration), due to increasing global efficiency in CR. Across CR subjects, (E) changes in CpG3 *RELN* methylation level were significantly associated with changes in global efficiency and (F) cognitive performance. (G) Changes in global efficiency were significantly associated with improvements in cognitive performance across CR subjects.
Abbreviations: inferior frontal gyrus; IFG; middle temporal gyrus, MTG; orbitofrontal cortex, OFC; transverse temporal gyrus, TTG.

genes *RELN* and *BDNF* at baseline. The levels of methylation observed in discrete CpG islands in the present study are low (ranging from 4 to 10) but are comparable to what had been previously reported (Ferrer et al., 2019; Grayson et al., 2006; Ikegame et al., 2013; Nabil Fikri et al., 2017; Tochigi et al., 2008).

Also, we did not see any changes in BDNF methylation over the course of CR. The lack of findings runs counter to our hypothesis, which was based on the widely recognized role of BDNF in activity-dependent increase in synaptic strength i.e. long-term potentiation. Variability in the following factors could contribute to the lack of findings, for instance, variability in 1) cell-type sampled (e.g. blood, different parts of brain tissue), 2) methods used in conducting methylation analyses (e.g. methylation specific real-time PCR, bisulphite conversion and pyrosequencing) and 3) medication. Antipsychotics in general except for haloperidol are associated with global hypomethylation in schizophrenia leucocyte samples (Melas et al., 2012), whereas antidepressants are associated with decreased histone methylation (Lopez et al., 2013).

Nonetheless, over the course of CR, differential CpG DNA methylation changes in *RELN* promoter are seen. Importantly, increasing levels in *RELN* CpG3 is associated with improving cognitive performance in CR patients, who have matched years of education to non-CR patients. The positive correlation supports a recent observation of increasing *RELN* promoter methylation in blood samples of schizophrenia patients and their general cognitive performance (Alfimova et al., 2018).

While mechanistic evidence between the differential effects of site-specific CpG islands and RELN promoter regulation is currently lacking, we postulate two plausible mechanisms by which hypermethylation of CpG3 and CpG4 may regulate gene expression. One, the site-specific hypermethylation may block repressors from binding to the promoter region, thus permitting enhancers and other transcription factors to exert their positive effect on gene expression. Two, differential methylation of CpG islands upstream of Reelin promoter may influence alternative splicing of Reelin mRNA and consequent localization and functionality of the mature protein (Jia et al., 2017). Whereas these hypotheses necessitate validation by cell and animal models, there is emerging evidence in the field of learning and memory to suggest that dynamic hypermethylation can drive activity-dependent expression in certain genes (Marshall and Bredy, 2016). Regardless, present findings suggest that *RELN* methylation is a dynamic process even in patients with severe mental illnesses, and suggest that certain epigenetic marks from surrogate tissues may be sensitive to the effects of CR.

### 4.2. CR changes functional connectivity in schizophrenia

Baseline abnormalities in patterns of functional connectivity in schizophrenia are distributed across the frontal, temporal and parietal lobes. The shorter-range connectivity abnormalities are localized within ventrolateral-dorsolateral prefrontal cortices and around the intra-parietal sulcus (superior-inferior parietal cortices), regions found in task-based fMRI to be associated with deficits in attention and episodic memory in schizophrenia (Barch and Ceaser, 2012; Ragland et al., 2015). Longer-range connectivity abnormalities in fronto-temporal and fronto-parietal regions are also regions shown to be implicated in cognitive impairments in schizophrenia (Barch and Ceaser, 2012). Whereas the present study patterns of frontal and fronto-temporal-parietal hyperconnectivity in schizophrenia are consistent with some extant literature (Anticevic et al., 2015; Guo et al., 2015), other studies have instead reported patterns of hypoconnectivity (Cole et al., 2011; Rotarska-Jagiela et al., 2010; Woodward et al., 2011). The phenomenon of mixed resting-state findings in schizophrenia has been discussed at length (Cole et al., 2010; Ho, 2019; Sheffield and Barch, 2016; Sheffield et al., 2015), and may relate to the diverse Rs-fMRI analysis methodology, and mixed application of global brain signal removal, variability in delineation of seed regions due to differing brain atlases, and in patient heterogeneity. In this regard, functional hyperconnectivity in schizophrenia has been postulated to reflect elevated cortical excitability or disinhibition of excitatory signals owing to dysfunction in NMDA or GABA receptor neurotransmission (Anticevic et al., 2015; Moghaddam and Javitt, 2012; Schobel et al., 2013; Uhlhaas and Singer, 2010).

The ventrolateral-dorsolateral prefrontal and medial prefrontal–inferior temporal hyperconnectivity negatively correlated with cognitive performances across all individuals. Task-based studies have shown the roles of prefrontal and inferior temporal cortices in broad cognitive functions of executive functioning and visual working memory (Ranganath and D'Esposito, 2005). Germane to the two existing seed/ROI-based studies of cognitive function in the cortical regions of schizophrenia (Cole et al., 2011; Unschuld et al., 2014), the trend of present findings is consistent with an earlier study which found associations between medial prefrontal-temporal hyperconnectivity and composite scores of working memory and attention (Unschuld et al., 2014).

A positive relationship between global efficiency and global cognitive performance at baseline across all groups is also observed. Our data support recent findings of a consortium Rs-fMRI study of psychotic spectrum disorders that showed a lack of strong group differences in whole-brain global efficiency (Sheffield et al., 2017), and directly corresponded with a pseudo-resting state study of schizophrenia and HC which found a positive correlation between whole-brain global efficiency and global cognition, with only subtle group differences in global efficiency (Sheffield et al., 2015). One possible reason for the lack of robust group differences could be that the premorbid IQ levels of patients did not significantly differ from HC in the current and previous studies (Sheffield et al., 2015).

A main aim of the present study is to address whether CR leads to changes in functional brain connectivity and efficiency in schizophrenia. Because the patients were engaged in a CR program that targeted a range of higher cognitive functions, we did not expect to see changes in specific neurocircuitries subserving specialized cognitive processes. The two key findings are that CR resulted in 1) decreasing connectivity within the temporal and fronto-temporal regions (VLPFC-temporal and orbitofrontal-temporal), a reversal of the patterns of hyperconnectivity seen at pre-intervention; and 2) decreasing local efficiency and increasing global efficiency—also a reversal of the trend seen at baseline—that is associated with improving global cognitive performance. High global efficiency indicates the brain network is highly integrated, while high local efficiency indicates segregation of brain networks (Bullmore and Sporns, 2012).

Importantly, the positive relationships between the various CR-led outcome measures, i.e. changes in reelin DNA methylation, increases in global efficiency and improved cognitive performance, provides an integrated micro- and macroscopic perspective of the neuroplastic mechanisms of the present CR program.

### 4.3. Limitations and future directions

Present findings, nonetheless, are by no means definitive and there are several limitations to note. First, we did not examine gene expression or protein levels of reelin and *BDNF*, so it is hard to conclude whether CR-related DNA methylation changes can map onto intermediary changes in cellular expression of neural connectivity. Second, all inpatients were medicated with antipsychotics and some were on antidepressants and/or anxiolytics. Previous studies have shown a link between psychotropics and DNA methylation or resting-state functional connectivity (Guidotti and Grayson, 2014; Hadley et al., 2014). Although we did not find any statistically significant medication-biological associations in our study sample, present findings warrant corroboration with independent samples with unchanging, non-complex drug regimen. Finally, although comparable with extant CR imaging studies (Donohoe et al., 2018; Keshavan et al., 2017; Ramsay et al., 2017), the present study cohort size is modest. Larger randomized controlled trials with an additional prolonged follow-up interval post-CR could build on the findings of this study.

In conclusion, the study suggests that the neuroplastic effects of CR across the spectrum of molecular to behavioural manifestations— epigenetic modification, brain connectivity re-configuration and network efficiency, and amelioration of cognitive deficits— can be concomitantly quantified, and provides promising proof-of-concept data that future studies of CR response monitoring can be approached from a neuroscience-informed standpoint.

## CRediT authorship contribution statement

**New Fei Ho:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Jordon Xin Jie Tng:** Data curation, Formal analysis, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Mingyuan Wang:** Data curation, Formal analysis, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Guoyang Chen:** Data curation, Formal analysis, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Vigneshwaran Subbaraju:** Formal analysis, Visualization, Writing - review & editing. **Suhailah Shukor:** Data curation, Writing - review & editing. **Desiree Si Xian Ng:** Data curation, Writing - review & editing. **Bhing-Leet Tan:** Data curation, Writing - review & editing. **Shu Juan Puang:** Formal analysis, Visualization, Writing - review & editing. **Sok-Hong Kho:** Formal analysis, Visualization, Writing - review & editing. **Rachel Wan En Siew:** Formal analysis, Visualization, Writing - review & editing. **Gwen Li Sin:** Data curation, Writing - review & editing. **Pui Wai Eu:** Data curation, Writing - review & editing. **Juan Zhou:** Conceptualization, Data curation, Formal analysis, Methodology, Writing - review & editing. **Judy Chia Ghee Sng:** Conceptualization, Data curation, Formal analysis, Methodology, Writing - review & editing. **Kang Sim:** Conceptualization, Data curation, Formal analysis, Methodology, Writing - review & editing. **Alice Medalia:** Conceptualization, Data curation, Formal analysis, Methodology, Writing - review & editing.

## Declaration of competing interest

Dr. Medalia discloses a royalty from Oxford University Press. All the other authors report no financial conflict of interest.

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## Appendix A. Supplementary data

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