

INTRODUCTION

- ❖ Individuals with schizophrenia have abnormal performance across tasks of motor inhibitory control (Ettinger et al., 2018).
- ❖ Motor excitatory/inhibitory balance can be indexed using paired-pulse transcranial magnetic stimulation (TMS) by obtaining measures such as the short-interval intracortical inhibition (SICI).
- ❖ Higher SICI (indicating reduced inhibition) is readily replicated in schizophrenia (Bunse et al., 2014; Rogasch et al., 2014).
- ❖ Yet the neural mechanisms underlying reduced intracortical inhibition in schizophrenia remain elusive.
- ❖ Primary Aim: map local and long-distance connectivity measures associated with SICI in a sample of 52 human participants (23 patients with schizophrenia, 29 controls). We hypothesized that strength of local connectivity at the motor cortex stimulation site would be associated with SICI score.

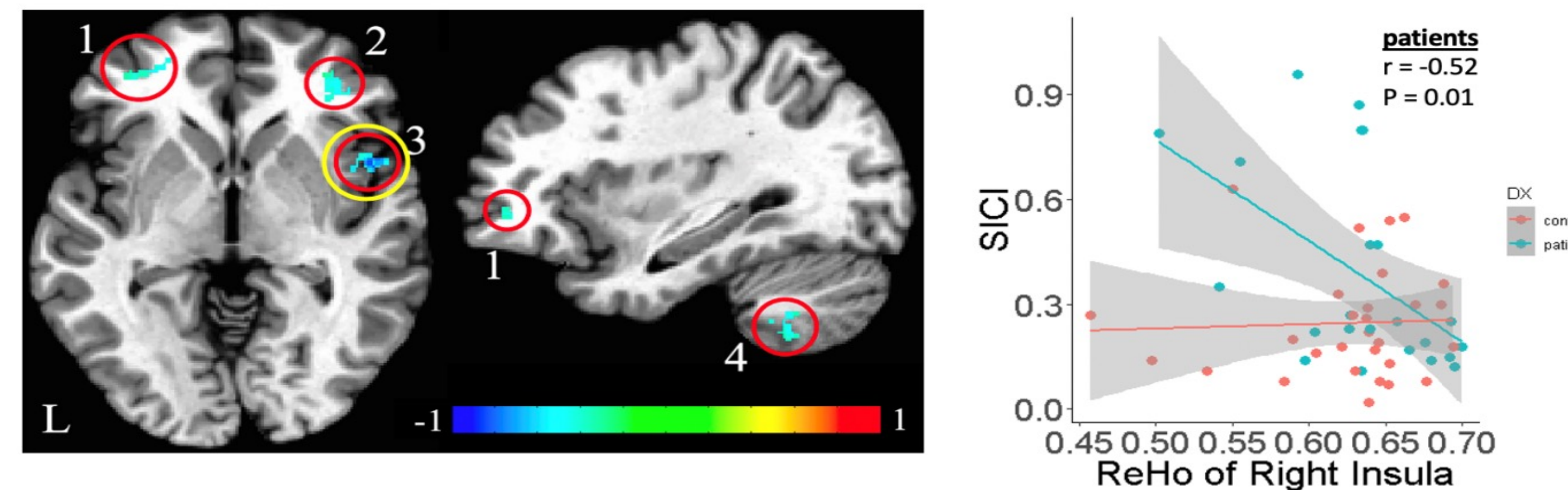
Table 1. Demographic and Clinical Information
Mean (std. deviation), and frequencies reported below

	SZ (n = 23)	Controls (n = 29)	Statistic (t, F, χ^2)	P-value
Age	37.0 (13.5)	41.6 (13.5)	1.23	0.23
Male/Female	16/7	15/14	1.72	0.15
Symptoms (BPRS Total)	40.2 (10.6)	–	–	–
Duration of Illness	14.9 (15.6)	–	–	–
RMT	47.4 (8.5)	47.4 (6.5)	0.02	0.99
SICI	0.38 (0.28)	0.25 (0.16)	-2.1	0.04

METHODS

- ❖ Exclusion criteria (all participants): history of head injury with loss of consciousness, any major illnesses, intellectual disability, substance abuse/dependence in past 6 months (except nicotine).
- ❖ Controls were also excluded if they had a current Axis I diagnosis or family history of psychosis in two generations. Patients taking clozapine more than 400 mg/day were excluded; no patients took benzodiazepines at the time of scanning.
- ❖ Written informed consent was obtained from all participants as approved by the University of Maryland IRB.
- ❖ Resting fMRI data were collected using a Siemens 3T TRIO MRI (Erlangen, Germany) system.
- ❖ Standard preprocessing steps were performed using the Analysis of Functional NeuroImages (AFNI) software (Cox, 1996).

Figure 1. Strong Negative Association Between Local Connectivity of Right Insula and SICI Score in Schizophrenia Patients



METHODS

- ❖ TMS was delivered using Magstim 200 BiStim stimulators.
- ❖ Surface muscle electromyographic (EMG) was recorded from right first dorsal interosseous (FDI) muscle of right finger.
- ❖ Resting motor threshold (RMT) = minimum intensity to elicit a motor evoked potential (MEP) of .50 mV in 5 of 10 consecutive stimuli (Du et al., 2014).
- ❖ Brainsight™ software was used to allow individualized positioning of the coil at left motor cortex target
- ❖ For SICI, a subthreshold conditioning stimulus (80% RMT) was followed by a suprathreshold stimulation (120% RMT) separated by a brief interval (1ms and 3ms ISI trials were merged).
- ❖ SICI ratio = Peak-to-peak EMG response to paired-pulse TMS / EMG to a single suprathreshold test pulse of 120% RMT.
- ❖ To estimate local connectivity, we calculated regional homogeneity (ReHo) within five clusters, guided by our prior work (Du et al., 2019), including the left motor cortex and four additional clusters (see Fig1). ReHo was defined as the Kendall's coefficient of concordance score with the resting fMRI time series of neighboring voxels (Zang et al., 2004). Clusters in which ReHo was significantly associated with SICI were included as regions of interest in a follow-up analysis of resting state functional connectivity (rsFC).

RESULTS

- ❖ In patients, higher SICI (indicating reduced inhibition) was significantly associated with lower ReHo in the right insula ($r = -0.52, p=0.01$) (Fig 1), but not with ReHo in the other clusters; regression validation (Harrell, 2015) suggested the association between insula ReHo and SICI was reliable.
- ❖ No significant associations were observed in healthy controls.
- ❖ Using the right insula as a seed, higher SICI (indicating reduced inhibition) was associated with lower insula rsFC with left sensorimotor cortex and left basal ganglia (Fig 2).
- ❖ In patients, long-distance rsFC between right insula and left sensorimotor cortex significantly mediated the association between resting right insula ReHo and SICI (Fig 3).

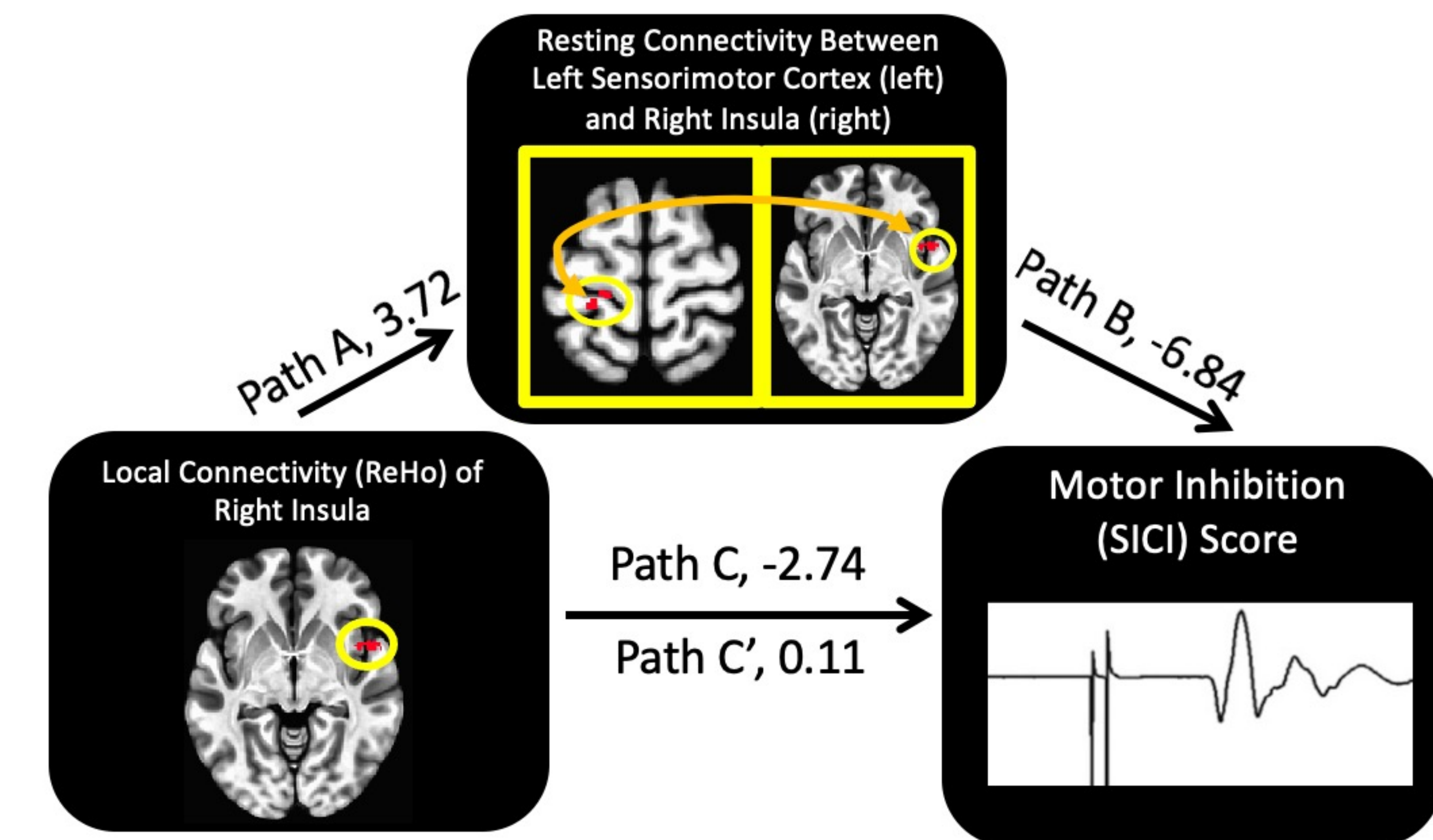
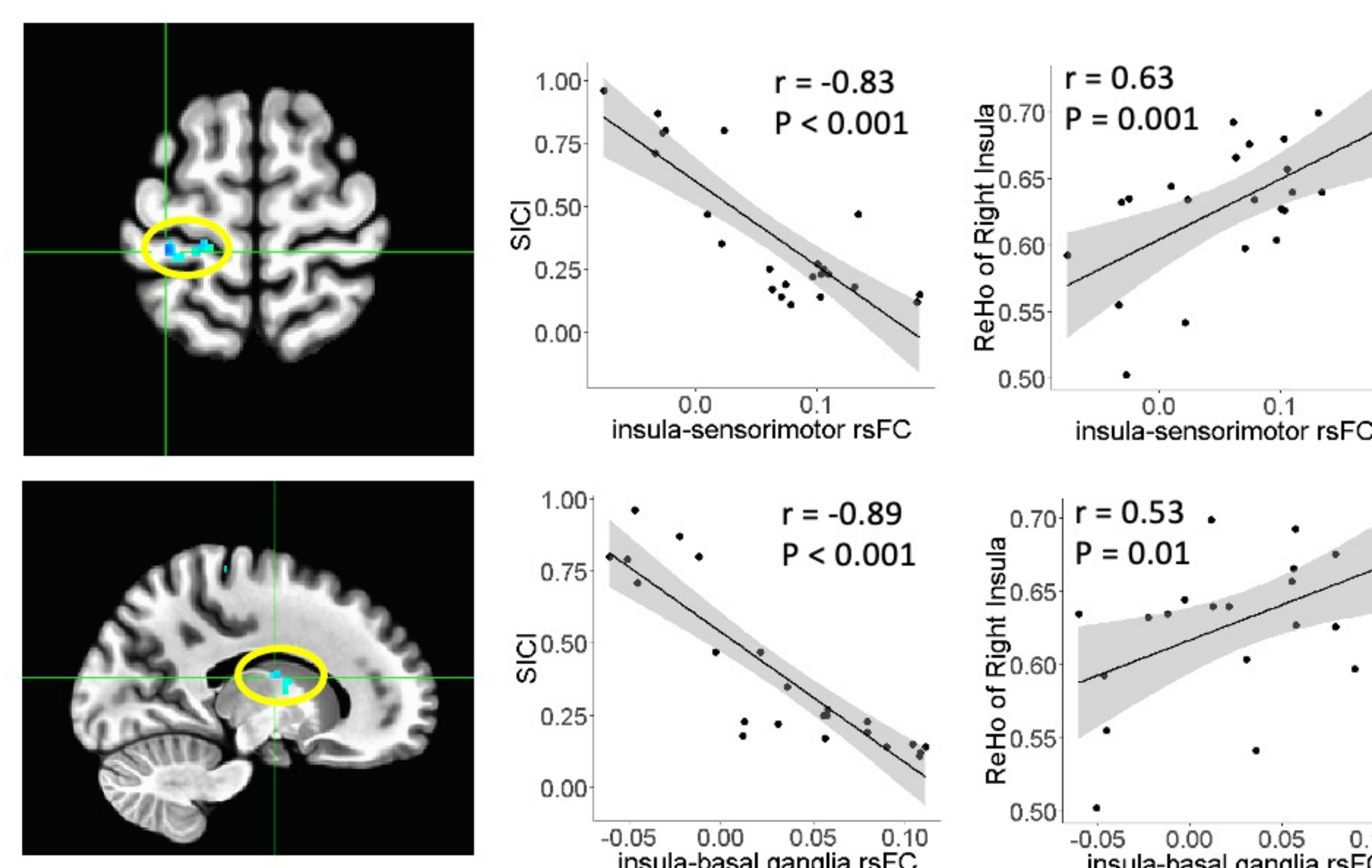


Figure 3. Significant result of mediation analyses
*t-values for individual paths are shown.

Figure 2. Results of rsFC analysis with right insula seed



CONCLUSIONS

The right insula – a region that is not traditionally studied in the context of motor inhibitory control – may contribute to abnormal intracortical inhibition in schizophrenia. Local connectivity within this region may indirectly affect SICI through its long-distance resting functional connections with contralateral hubs of the motor corticospinal pathway. Novel interventions designed to improve connectivity strength with the right insula may strengthen inhibition in schizophrenia. Future research is needed to replicate the current pattern of findings in an independent sample and address important remaining questions pertinent to improving our understanding of motor inhibitory control and impact of abnormal signaling in motor-inhibitory pathways in schizophrenia and other clinical samples.