Clinical Neurophysiology 132 (2021) 1604–1611

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Altered interhemispheric signal propagation in schizophrenia and depression

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ARTICLE INFO

Article history:
Accepted 19 March 2021
Available online 26 April 2021

Keywords:
Depression
Electroencephalography
Prefrontal cortex
Schizophrenia
Transcranial magnetic stimulation

HIGHLIGHTS

- Interhemispheric signal propagation was elevated in schizophrenia and depression patients relative to healthy controls.
- Interhemispheric signal propagation did not differ between patient groups.
- There were no medication effects on interhemispheric signaling from inter-individual comparisons and no significant correlation with symptom severity.

ABSTRACT

Objective: Altered interhemispheric connectivity is implicated in the pathophysiology of schizophrenia (SCZ) and major depressive disorder (MDD) and may account for deficits in lateralized cognitive processes. We measured transcranial magnetic stimulation evoked interhemispheric signal propagation (ISP), a non-invasive measure of transcallosal connectivity, and hypothesized that the SCZ and MDD groups will have increased ISP compared to healthy controls.
Methods: We evaluated ISP over the dorsolateral prefrontal cortex in 34 patients with SCZ and 34 patients with MDD compared to 32 age and sex-matched healthy controls.
Results: ISP was significantly increased in patients with SCZ and patients with MDD compared to healthy controls but did not differ between patient groups. There were no effects of antidepressant, antipsychotic, and benzodiazepine medications on ISP and our results remained unchanged after re-analysis with a region of interest method.
Conclusion: Altered ISP was found in both SCZ and MDD patient groups. This indicates that disruptions of interhemispheric signaling processes can be indexed with ISP across psychiatric populations.
Significance: These findings enhance our knowledge of the physiological mechanisms of interhemispheric imbalances in SCZ and MDD, which may serve as potential treatment targets in future patients.

1. Introduction

Interhemispheric functional asymmetry is disrupted in psychiatric disorders such as schizophrenia (SCZ) and major depressive disorder (MDD) (Garcia-Toro et al., 2001; Ribolsi et al., 2009). In SCZ, deficits of lateralized sensorimotor and cognitive processes are linked to impaired cerebral specialization and interhemispheric communication (David, 1994; Whitford et al., 2010), in accordance with the disconnection hypothesis (Friston, 1999). Meanwhile, patients with MDD typically present with deficits in mood, emotion, and cognitive processing which also rely on hemispheric lateralization (Davidson, 2002). The corpus callosum is the largest white matter connective pathway in the brain and plays a critical

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https://doi.org/10.1016/j.clinph.2021.03.039
1388-2457/

role in interhemispheric connectivity, particularly for the lateralization of cognitive and perceptual processes (Gazzaniga, 2000). Transcallosal connectivity relies on a complex interplay of excitatory and inhibitory processes involving glutamate release from callosal axon terminals (Kawaguchi, 1992) and GABAergic neurotransmission initiated by local inhibitory interneurons in the contralateral hemisphere. Functional impairments of lateralized processes may reflect an underlying imbalance between excitatory and inhibitory signaling processes in the two hemispheres.

Various physiological markers of interhemispheric connectivity are disrupted in SCZ and MDD and thought to be closely related to disease symptomatology. In SCZ, resting electroencephalographic (EEG) analyses suggest higher levels of interhemispheric coherence compared to healthy controls (Kam et al., 2013; Merrin et al., 1989), in support of functional MRI evidence indicating altered interhemispheric effective connectivity between prefrontal cortices (Schlösser et al., 2003). These findings may be linked to impaired interhemispheric inhibition (Fitzgerald et al., 2002) and morphological abnormalities of the corpus callosum (Cheung et al., 2008; Friedman, et al., 2008; Woodruff et al., 1995), which tend to be localized towards anterior callosal regions and coincide with greater severity of positive and negative symptoms (Brambilla et al., 2005; Günther et al., 1991; Kubicki et al., 2008; Woodruff et al., 1997). In MDD, a number of studies also indicate impaired interhemispheric functional connectivity between prefrontal regions (Bruder et al., 1997; Debener et al., 2000; Guo et al., 2013; Yang et al., 2019), although the direction of this relationship has not been consistently established (Wang et al., 2013). Emerging evidence suggests that regional imbalances in cortical excitation-inhibition (Hinkley et al., 2012) may be a strong contributing factor to hemispheric deficits in depressed patients. When compared to healthy subjects, MDD patients demonstrate reduced density and size of GABAergic interneurons in the dorsolateral prefrontal cortex (DLPFC), a brain region that mediates cognition (Rajkowska et al., 2007). This may result in the loss of inhibitory control over excitatory input and consequently may affect working memory performance (Rao et al., 2000). Hence, deficits of interhemispheric signaling in SCZ and MDD may be caused by disturbances in cortical excitation and inhibition that affect interhemispheric neurotransmission.

The combination of transcranial magnetic stimulation (TMS) with EEG (TMS-EEG) provides a reliable cause-and-effect approach to probe cortical circuits in non-motor regions, such as the DLPFC (Hui et al., 2019; Lioumis et al., 2009). TMS-evoked interhemispheric signal propagation (ISP) measures the transmission of cortical evoked activity from the area of stimulation to the homologous region in the contralateral hemisphere through EEG recordings (Voineskos et al., 2010). DLPFC ISP is related to the structural integrity of the genu sub-region of the corpus callosum and demonstrates high reproducibility among participants (Hui et al., 2020; Casula et al., 2020; Voineskos et al., 2010). Recently, ISP was shown to be modulated by the GABA-B receptor agonist baclofen (Hui et al., 2020) and correlate linearly with interhemispheric inhibition (Casula et al., 2020), a GABAergic TMS marker of transcallosal-mediated inhibition. Hence, ISP offers a valuable tool to investigate the pathophysiology of interhemispheric connectivity that occurs in psychiatric disorders due to abnormal transcallosal circuitry.

Here, we evaluated and compared ISP in the DLPFC between patients with SCZ, patients with MDD, and healthy subjects. Part of our dataset contains a re-analysis of data from a previously published paper (Radhu et al., 2015), which indicated the presence of inhibitory deficits in the DLPFC of SCZ patients. As dysfunctional inhibitory neurotransmission is related to hemispheric deficits and has been implicated in both disorders, we hypothesized that individuals with SCZ and MDD will have increased ISP compared to healthy controls. Additionally, as there is stronger evidence for altered transcallosal connectivity in SCZ, we hypothesized that SCZ patients would demonstrate larger deficits in ISP compared to MDD patients. Correlation with clinical severity, medication effects, and other regions of interest (ROI) were analyzed on an exploratory basis.

2. Methods and materials

2.1. Participants

The study included 34 patients with a Diagnostic and Statistical Manual of Mental Disorders Structured Clinical Interview (DSM-IV SCID) confirmed diagnosis of SCZ or schizoaffective disorder, 34 patients with a Mini-International Neuropsychiatric Interview (MINI) confirmed diagnosis of MDD, and 32 healthy subjects matched for age and sex. All MDD patients participated in a larger clinical trial receiving repetitive TMS treatment at the Centre for Addiction and Mental Health (ClinicalTrials.gov Identifier: NCT02729792) who underwent TMS-EEG recordings as part of baseline assessments prior to receiving treatment. Psychopathology was ruled out in healthy subjects using the DSM-IV SCID. All participants were right-handed. Exclusion criteria for all participants included: concurrent cognitive disorder secondary to a neurological or other medical disorder affecting the central nervous system; concomitant major unstable medical illness; MINI-confirmed diagnosis of substance dependence or abuse within the last 3 months; diagnosis of bipolar disorder; pregnancy; and any material or condition that would cause contraindication to the MRI or TMS-EEG measures (Rossi et al., 2009). All participants provided written informed consent in accordance with the Declaration of Helsinki. This study was approved by the ethics committee at the Centre for Addiction and Mental Health.

In patients with SCZ, the Brief Psychiatric Rating Scale (BPRS-24) (Overall and Gorham, 1962) was used to index the severity of psychopathology (Table 1). The summed factor BPRS score for 1) "affective symptoms" (including low mood, anxiety, guilt, somatic concern, hostility, tension), 2) "psychotic symptoms" (including unusual thought content, hallucinations, conceptual disorganization, suspiciousness, grandiosity, bizarre behaviour, disorientation), and 3) "negative symptoms" (including blunted affect, motor retardation, emotional withdrawal, uncooperativeness, mannerisms and posturing, disorientation, self-neglect) was also calculated (Velligan et al., 2005; Zhu et al., 2019). In patients with MDD, the Hamilton Rating Scale for Depression (HRSD-17) was used to assess symptom severity (Table 1) and a score of > 20 confirmed an active major depressive episode (Hamilton, 1960). Concomitant medications are provided in Table 2.

2.2. Localization of DLPFC

The DLPFC stimulation site for SCZ patients and healthy subjects was localized through neuronavigation techniques with the mini-BIRD system (Ascension Technology Group) and MRI co-registration software using a T1-weighted anatomical MRI scan for each subject with seven fiducial markers (Radhu et al., 2015). Stimulation of the left DLPFC was targeted at Talairach coordinates $(x, y, z) = (-50, 30, 36)$, corresponding to the overlapping regions of posterior Brodmann area (BA) 9 with the superior sections of BA 46. This region was selected based on a meta-analysis of functional imaging studies of working memory and the DLPFC (Glahn et al., 2005). For MDD patients, the DLPFC was targeted using a modified Beam F3 approach. A previous study has shown that Beam F3 provides a reasonable approximation for MRI-guided neuronavigation

Table 1
Subject demographics.

	Controls (*n* = 32)	Schizophrenia (*n* = 34)	Depression (*n* = 34)
Age (years)	36.2 ± 1.8	37.7 ± 1.9	35.8 ± 1.4
Sex (male:female)	16:16	17:17	17:17
Age of Illness Onset (years)	NA	22.1 ± 0.9	18.8 ± 1.3
Illness Duration (years)	NA	11.6 ± 1.6	NA
Length of Episodes	NA	NA	26.0 ± 4.6
BPRS-24 Score	NA	40.9 ± 1.8	NA
HRSD-17 Score	NA	NA	22.7 ± 0.7

Data are given as mean ± standard error of the mean.
Legend: BPRS, Brief Psychiatric Rating Scale; HRSD, Hamilton Rating Scale for Depression; NA, not applicable.

Table 2
Psychotropic medications taken by the schizophrenia and major depressive disorder patients.

	Schizophrenia (*n* = 34)	Depression (*n* = 34)
Antidepressants, *n*		
SSRI	10	12
SNRI	0	12
NDRI	0	7
TCA	0	8
Antipsychotics, *n*		
First generation	3	0
Second generation	31	5
Third generation	3	6
Benzodiazepines, *n*	8	10
Mood Stabilizers, *n*	4	2
Stimulants, *n*	0	3

Legend: SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; TCA, tricyclic antidepressant.

in localizing the left DLPFC, with an average discrepancy of only 0.70 cm (Mir-Moghtadaei et al., 2015).

2.3. TMS-EEG in the DLPFC

Monophasic single TMS pulses were administered to the left DLPFC using a 70 mm figure-of-eight coil and a Magstim 200 stimulator (Magstim Company Ltd., Carmarthenshire, Wales). When establishing each participant's resting motor threshold (RMT), the TMS coil was placed at an optimal location to elicit motor-evoked potentials (MEPs) in the right abductor pollicis brevis (APB) (Rossini et al., 1994). The stimulus intensity was then adjusted to produce a mean MEP amplitude of 1 mV over 20 trials. This intensity was used to deliver 100 single pulses at 0.2 Hz to the left DLPFC while the handle of the TMS coil was oriented 45° to the midsagittal line. There were no significant between-group differences for the 1 mV peak-to-peak TMS intensity [$F(2,97) = 2.09$, $p = 0.129$] (mean ± standard deviation: HCL = 69.12% ± 13.14%, SCZ = 73.59% ± 14.32%, MDD = 75.44% ± 10.87%). TMS technicians monitored the participants for visible signs of drowsiness and intermittently prompted them to remain awake and keep their eyes open during recording sessions.

EEG data was acquired through a 64-channel Neuroscan Synamps 2 EEG system (Compumedics, Charlotte, North Carolina) with Ag/AgCl ring electrodes on a 64-channel EEG cap. All electrodes were re-referenced to an electrode on the vertex posterior to the CZ electrode and the impedance was lowered to ≤ 5 kΩ. To monitor for eye movement artifacts, four electrodes were placed on the outer side of each eye, as well as above and below the left eye. EEG signals were recorded with DC amplifiers using a lowpass filter of 100 Hz and anti-aliasing filter of 200 Hz at a sampling rate of 20 kHz, which was shown to avoid amplifier saturation and minimize the TMS-related artifact (Rajji et al., 2013).

2.4. EEG data processing

EEG data were preprocessed offline with Neuroscan (Compumedics, Charlotte, North Carolina) and resampled from 20 kHz to 1 kHz. Analysis was performed using the EEGLAB toolbox and a custom-made script developed in MATLAB (The MathWorks, Natick, MA, USA). Data were segmented into epochs (-2000 ms to 2000 ms) around the TMS pulse, adjusted to baseline using the mean of the TMS artifact-free time period (-500 to −10 ms), and data around the TMS pulse (-2 to 10 ms) were removed and interpolated (Voineskos et al., 2019). Trials were visually scrutinized and those containing excessive artifacts were removed from further analysis (Rogasch et al., 2013). Before re-referencing the EEG data, contaminated or missing channels were interpolated using the spherical spline interpolation procedure as implemented in the EEGLAB toolbox. EEG data were digitally filtered using a second-order, Butterworth, notch filter (58–62 Hz) to remove any line noise, followed by a fourth-order, Butterworth, zero-phase shift band pass filter (1–55 Hz) (Voineskos et al., 2019). Next, two rounds of independent component analysis (ICA) were applied to the data to remove high amplitude muscle artifacts, eye movements, or electrode movements (Rogasch et al., 2014).

2.5. TMS-Induced ISP

ISP was calculated using the ratio of TMS-evoked potentials (TEPs) in the right DLPFC (F6 electrode) over the left DLPFC (F5 electrode) using the rectified TEP curve averaged across trials (Voineskos et al., 2010). F5 was selected based on the closest electrode to the area of stimulation (F3) that was uncontaminated with excessive TMS and muscle artifacts and F6 was chosen as the corresponding electrode in the contralateral hemisphere. We previously showed that ISP calculated over the F5 and F6 electrodes provided a reproducible measure of interhemispheric activity in the prefrontal cortices over time (Hui et al., 2020). For the left DLPFC, the area under the curve was measured between 50 to 150 ms post-stimulus, corresponding to the earliest onset of artifact-free data (Voineskos et al., 2010). The interhemispheric transfer time was set to 10 ms (Ferbert et al., 1992; Meyer et al., 1995) to account for the latency of signal transmission between contralateral hemispheres. For the right DLPFC, the area under the curve was obtained for 60 to 160 ms post-TMS pulse, in accordance with previous studies (Hui et al., 2020; Voineskos et al., 2010).

2.6. Statistical analyses

Data were first checked for normality using the Kolmogorov-Smirnov test ($p > 0.05$). All TMS-EEG data underwent logarithmic transformation to meet the assumption for homogeneity of variances required for parametric statistics. A one-way analysis of variance (ANOVA) was used to compare ISP differences between the groups. Post-hoc pair-wise comparisons were two-tailed and *p*-values underwent Bonferroni adjustment. Medication effects were determined with two-tailed *t*-tests. Pearson's correlation analyses were conducted to determine the relationship between ISP and clinical severity scores (BPRS-24 or HRSD-17 scores) in SCZ and MDD groups. Group means are reported in the form of mean ± standard error mean (SEM) unless stated otherwise, and a *p*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 16.0 (SPSS, Chicago, Illinois).

3. Results

3.1. ISP

The ANOVA yielded a significant effect of group on ISP ($F(2,97) = 7.24$, $p = 0.001$). Post-hoc t-test comparisons revealed increased ISP in SCZ patients than in healthy controls ($t(64) = -3.642$, $p = 0.002$; Bonferroni corrected $p < 0.05$; $d' = 0.90$) and in MDD patients compared to healthy controls ($t(64) = -3.311$, $p = 0.01$; Bonferroni corrected $p < 0.05$; $d' = 0.82$) (Fig. 1). We found no differences in ISP between SCZ patients and MDD patients ($t(66) = -0.545$, $p = 1.00$, $d' = 0.13$) (Fig. 1). The group mean topoplots and rectified TEPs are shown in Fig. 2. To evaluate whether elevated ISP was also extended to remote regions, we measured ISP in the T7 and T8 regions and found no significant differences between groups ($F(2,97) = 0.20$, $p = 0.82$).

3.2. Correlation with symptom severity

There was a trending correlation between ISP values and the HRSD scores for patients with MDD ($r = 0.334$, $p = 0.054$), suggesting that increased depression severity may be related to higher levels of signal transmission to the unstimulated hemisphere. For patients with SCZ, the total BPRS score and summed factor BPRS were used to determine the relationship between clinical severity with ISP. There was no correlation between ISP values with the total BPRS score ($r = -0.005$, $p = 0.979$), affective symptoms ($r = 0.255$, $p = 0.145$), psychotic symptoms ($r = 0.113$, $p = 0.524$), or negative symptoms ($r = -0.140$, $p = 0.429$).

3.3. Effect of medications on ISP

The individuals in our SCZ and MDD groups were taking several different classes of medications which may have occluded the group differences in ISP. In the MDD cohort, we compared ISP among the 12 patients who were taking selective serotonin reuptake inhibitors with the 21 who were not, 12 patients taking serotonin norepinephrine reuptake inhibitors with the 21 who were not, 10 patients taking benzodiazepines with the 23 who were not, and 11 patients taking antipsychotics with the 22 who were not and found no significant differences in ISP ($p > 0.05$, Table 3). In the SCZ cohort, we compared the 8 patients who were taking selective serotonin reuptake inhibitors with the 25 who were not, 6 patients taking benzodiazepines with the 27 who were not and did not find any differences in ISP ($p > 0.05$, Table 3).

3.4. ROI analysis

To minimize the technical limitation of using different DLPFC localization methods between datasets, an electrode clustering method for ISP data analysis was also applied. The left DLPFC ROI (AF3, F1, and F5 electrodes) was selected based on the nearest uncontaminated electrodes to the area of stimulation and the right DLPFC ROI (AF4, F2, and F6 electrodes) contained corresponding electrodes from the right hemisphere. F3 and F4 were excluded from our analyses due to contamination. Our ISP results remained unchanged when averaging the response from several electrodes with an ROI approach ($F(2,97) = 4.71$, $p = 0.011$) and elevations in ISP differences were still present in SCZ patients ($t(64) = -3.026$, $p = 0.018$; $d' = 0.75$) and MDD patients ($t(64) = -2.791$, $p = 0.042$; $d' = 0.68$) compared to healthy controls.

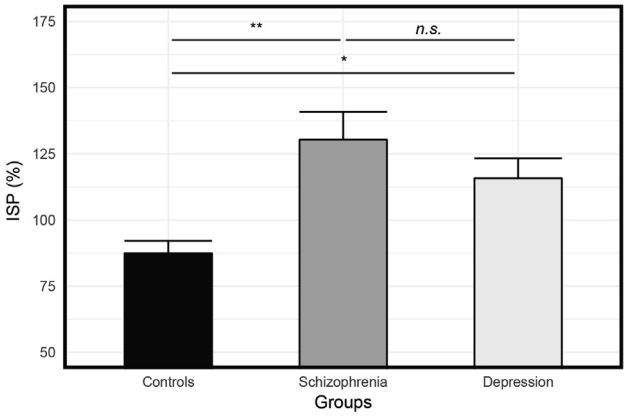

Fig. 1. Interhemispheric signal propagation across psychiatric conditions. Interhemispheric signal propagation (ISP) is represented as a ratio of the cortical evoked activity from the right dorsolateral prefrontal cortex (DLPFC) region of interest (ROI) to the left DLPFC ROI. The ANOVA and post-hoc analysis indicated a significant increase in ISP across patients with schizophrenia (**$p < 0.01$) and depression (*$p < 0.05$) compared to healthy controls. Error bars indicate 1 standard error above the mean.

4. Discussion

Our results provide evidence for DLPFC abnormalities of interhemispheric connectivity in SCZ and MDD. Specifically, ISP was increased in these two patient groups when compared against healthy participants but did not differ between groups. We found no significant relationship of ISP with the severity of depressive and psychotic symptoms. We found no effect from various antidepressant, antipsychotic, and benzodiazepine medications on ISP from inter-individual analyses.

This was the first TMS-EEG study to investigate interhemispheric connectivity in both SCZ and MDD patients. We demonstrated increased ISP levels in the DLPFC across these two patient groups compared to healthy participants. These deficits are in line with previous physiological evidence indicating altered interhemispheric connectivity in SCZ (Merrin et al., 1989) and MDD (Guo et al., 2013). Excessive excitatory activation of the contralateral hemisphere may be caused by an excitatory-inhibitory imbalance relating to decreases in inhibitory neurotransmission and/or structural deficits of the corpus callosum (Daskalakis et al., 2002; Wahl et al., 2007). Evidence for this imbalanced circuitry has been provided by several studies. For example, reduced levels of GABA inhibitory interneurons have been demonstrated in the DLPFC region for both SCZ (Akbarian et al., 1995; Benes et al., 1991) and MDD (Rajkowska et al., 2007), which may lead to excessive disinhibition of excitatory input (Rao et al., 2000). The morphology of the genu has also been shown to be impaired in MDD (Xu et al., 2013; Yuan et al., 2010) and SCZ (Brambilla et al., 2005; Kubicki et al., 2008) and is related to the extent of cortical activation in the contralateral hemisphere. Deficits of transcallosal inhibition are thought to cause inferior performance during lateralized cognitive tasks (Putnam et al., 2008), particularly relating to working memory (Walter et al., 2003) and language (Bleich-Cohen et al., 2012). Hence, the finding of impaired ISP in the DLPFC provides additional electrophysiological evidence to support these anatomical and behavioral results of dysfunctional interhemispheric connectivity in SCZ and MDD.

In contrast to our second hypothesis, ISP deficits were not statistically greater in SCZ patients compared to MDD patients. As higher ISP levels are linked to lower structural integrity of callosal fibres (Voineskos et al., 2010), our finding suggests that structural genu deficits may have been present in both of our cohorts of

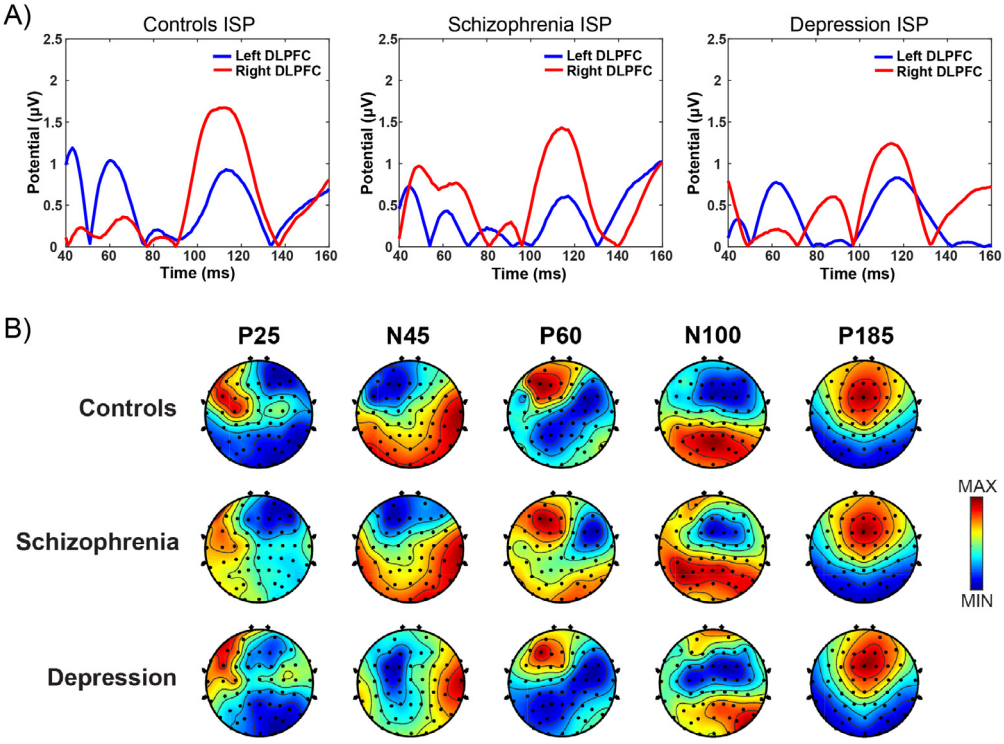

Fig. 2. Temporal representation of cortical evoked potentials. A) Mean rectified waveforms following application of transcranial magnetic stimulation (TMS) to the left dorsolateral prefrontal cortex (DLPFC). Cortical evoked potentials are measured in the ipsilateral DLPFC (blue line) and contralateral DLPFC (red line) of healthy controls, schizophrenia patients and depression patients. **B)** Mean amplitudes of cortical evoked potentials are represented topographically across 64 electrodes at different timepoints, according to the main deflections of the TMS-evoked potential.

Table 3
Summary of results for medication analyses.

t value of ISP (p)		
Medications	*Schizophrenia*	*Major Depressive Disorder*
+/- SSRIs	0.809 (0.425)	0.510 (0.613)
+/- SNRIs	–	−0.129 (0.898)
+/- Benzodiazepines	0.132 (0.896)	1.345 (0.188)
+/- Antipsychotics	–	−0.001 (0.999)

(–) represents tests not performed.
Legend: ISP, interhemispheric signal propagation; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

patients. Excessive signal transmission to the unstimulated DLPFC may have been further augmented by impairments of inhibitory GABAergic transmission in the DLPFC (Rajkowska et al., 2007; (Voineskos et al., 2019), although demonstration of these relationships is beyond the scope of this paper. In addressing a potential medication effect on transcallosal transmission, we found no statistically significant differences in ISP for participants treated with antidepressants, antipsychotics, and benzodiazepines with those who were not. Lastly, we verified that our results were unchanged when applying an ROI analysis method for calculating ISP, to account for different DLPFC localization methods used between datasets.

In the neurotypical brain, previous studies have provided evidence for a balanced excitatory/inhibitory relationship involving GABAergic inhibition and glutamate receptor-mediated excitation (Yizhar et al., 2011). Impairments of this balance in the genu are linked to deficits of cognition and social behaviour in SCZ (Rowland et al., 2016; Yizhar et al., 2011) and of cognition and emotion in MDD (Bermpohl et al., 2006; Killgore et al., 2007). Interestingly, there are a number of overlapping phenotypic features also related to impaired GABAergic inhibitory neurotransmission, such as bilateral motor incoordination and disorganized thought in SCZ (McCormick et al., 2012) and anhedonia and cognitive deficits in MDD (Crestani et al., 1999; Shen et al., 2010). These features are thought to arise from impaired synchronization of neural responses due to excessive excitability of the cortex (Uhlhaas et al., 2006). Many of the described processes are typically lateralized to a specific hemisphere and rely on transcallosal pathways to mediate interhemispheric signal transfer and inhibition (Gazzaniga, 2000). Therefore, dysfunctional interhemispheric signal transmission in the DLPFC due to imbalances in glutamatergic and/or GABAergic signaling may potentially underlie cognitive impairments in MDD and SCZ.

In comparison to the first paper describing the properties of ISP from our group (Voineskos et al., 2010), there are several methodological differences in the present study that should be acknowledged and discussed. We previously measured ISP over the AF3 (left hemisphere) and AF4 (right hemisphere) electrodes as this was thought to optimally represent the overlap of Brodmann's areas 9 and 46 of the DLPFC. In the present study, we verified the location of the DLPFC for individual subjects with neuronavigation and Beam F3 methods prior to stimulation. The recording electrodes of interest were F5 and F6, as F5 represented the closest electrode uncontaminated with excessive TMS and muscle artifacts to the area of stimulation (F3). We verified that our results were unchanged when applying a ROI analysis containing an average of surrounding electrodes (AF3, F1, F5). Additionally, we used ICA to detect and remove artifacts, which is superior over automated eye movement correction algorithms for data correction (Hoffmann et al., 2008) but presents with its own caveats that may affect the amplitude and latency of TEPs (Rogasch et al., 2014). In general, ICA accurately identifies and removes artifacts

with minimal impact on TMS-evoked neural activity and is widely used in TMS-EEG research (Rogasch et al., 2014).

There are some limitations in our study. First, TMS-EEG procedures were performed without auditory noise masking to minimize the impact of the TMS auditory "click" on late TEP potentials (Conde et al., 2019; Gordon et al., 2018). However, all participants underwent the same TMS-EEG paradigm, reducing the contribution of the auditory click on between-group comparisons. We also controlled for auditory and somatosensory-evoked artifacts by calculating ISP as a ratio of right over left hemisphere cortical evoked activation (Hui et al., 2020) and removing the associated components during offline data processing with ICA (Rogasch et al., 2014). Additionally, we discuss the connectivity between the left and right DLPFC vis-à-vis EEG approximations, in accordance with previous ISP papers (Hoppenbrouwers et al., 2014; Hui et al., 2020; Jarczok et al., 2016; Voineskos et al., 2010; Zipser et al., 2018). It is well-accepted in the literature that signal propagation induced by TMS travels to the contralateral homotopic region via immediate connectivity, i.e. the corpus callosum (Voineskos et al., 2010; Zibman et al., 2019), and we attempted to probe this circuitry by ensuring that the left DLPFC was directly targeted with TMS for each participant. We did not assess the relationship between ISP with the structural integrity of the corpus callosum, as we were limited by the imaging methods used in the originally published data (Radhu et al., 2015). However, this analysis would have been of great interest to examine how the ISP and corpus callosum relationship may contribute to the neurophysiological transcallosal abnormalities in SCZ and MDD patients. Finally, this study did not include cognitive measures. Cognitive symptoms are regarded as one of the strongest predictors of functional disability in SCZ (van Os and Kapur, 2009), and has been increasingly recognized as an important mediator of response in MDD (Pimontel et al., 2016). Comparing dimensions of cognitive performance that are mediated by frontal brain regions with the degree of ISP can help elucidate the complex role of interhemispheric pathways in higher-order cognitive processing.

In summary, this study shows that ISP in the DLPFC is impaired in patients with SCZ and MDD. Future work is needed to explore the precise mechanisms underlying facilitatory transcallosal signal transmission to the contralateral DLPFC and whether deficits of interhemispheric connectivity are specific to MDD and SCZ or can be generalized as a neurophysiological endophenotype across other psychiatric disorders. Additionally, it would be of great interest to further evaluate the potential effects of psychotropic medications on ISP through intra-individual analyses. Overall, these results are promising and suggest that disruptions of interhemispheric signal processes can be indexed with ISP across psychiatric populations.

CRediT authorship contribution statement

Jeanette Hui: Formal analysis, Investigation, Data Curation, Writing - original draft, Visualization. **Reza Zomorrodi:** Formal analysis, Investigation, Data Curation, Writing - review & editing, Visualization. **Pantelis Lioumis:** Investigation, Writing - review & editing. **Elnaz Ensafi:** Formal analysis, Writing - review & editing. **Daphne Voineskos:** Writing - review & editing. **Aristotle Voineskos:** Writing - review & editing. **Itay Hadas:** Writing - review & editing. **Tarek K. Rajji:** Supervision, Writing - review & editing. **Daniel M. Blumberger:** Supervision, Writing - review & editing. **Zafiris J. Daskalakis:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. None of the authors have potential conflicts of interest to be disclosed.

Acknowledgements

TKR has received research support from Brain Canada, Brain and Behavior Research Foundation, BrightFocus Foundation, Canada Foundation for Innovation, Canada Research Chair, Canadian Institutes of Health Research, Centre for Aging and Brain Health Innovation, National Institutes of Health, Ontario Ministry of Health and Long-Term Care, Ontario Ministry of Research and Innovation, and the Weston Brain Institute. TKR also received in-kind equipment support for an investigator-initiated study from Magstim. DMB has received research support from CIHR, NIH, Brain Canada and the Temerty Family through the CAMH Foundation and the Campbell Research Institute. He receives research support and in-kind equipment support for an investigator-initiated study from Brainsway Ltd. and he is the site principal investigator for three sponsor-initiated studies for Brainsway Ltd. He also receives in-kind equipment support from Magventure for an investigator-initiated study. He receives medication supplies for an investigator-initiated trial from Indivior. In the last 5 years, ZJD has received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc and Magventure Inc. His work was supported by the Ontario Mental Health Foundation (OMHF), the Canadian Institutes of Health Research (CIHR), the National Institutes of Mental Health (NIMH) and the Temerty Family and Grant Family and through the Centre for Addiction and Mental Health (CAMH) Foundation and the Campbell Institute.

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