Inter-Hemispheric Transfer Time and White Matter Integrity in Schizophrenia: a Combined ERP and DTI Study

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Introduction

- Abnormal inter-hemispheric communication has been argued to underlie the symptoms of schizophrenia[1]. While structural damage to the corpus callosum (CC) has been proposed as a potential cause of this aberrant communication[2], no previous studies have directly investigated the relationship between CC integrity and interhemispheric transfer in patients with schizophrenia.
- At least two previous Event-Related Potential (ERP) studies have reported abnormally long inter-hemispheric transmission times (IHTTs) to unilaterally-presented visual stimuli in patients with schizophrenia[3,4].
- While several Diffusion-Tensor Imaging (DTI) studies have reported structural abnormalities in the corpus callosum (CC) in patients with schizophrenia[5], the structural integrity of the visual CC fibers have not been directly investigated.
- The present study aimed to investigate the relationship between IHTT (calculated from ERP latencies) and the structural integrity of the visual CC fibers (measured with the complementary DTI metrics of FA and Mode[6]) in schizophrenia patients and healthy controls.

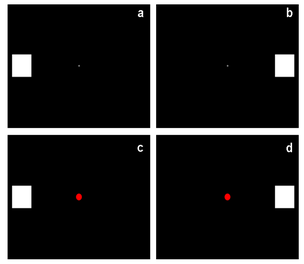
Methods

Participants

• 30 schizophrenia patients (SZ) and 22 matched healthy controls (HC) underwent ERP recording. Of these participants,19 patients and 16 controls also underwent DTI scanning.

Stimuli and Task

• Unilateral visual stimuli (squares, 2x2 degrees visual angle) were presented for 82ms on the horizontal meridian, 6 degrees lateral to a central fixation cross. On target trials, the central fixation cross transformed into a red circle. There were 4 experimental blocks, each consisting of 60 non-target and 15 target trials, randomly presented. Target trials were subsequently removed from the analysis.



Visual Stimuli. (a) LVF non-target, (b) RVF non-target, (c) LVF target, (d) RVF target

ERP Acquisition and Analysis

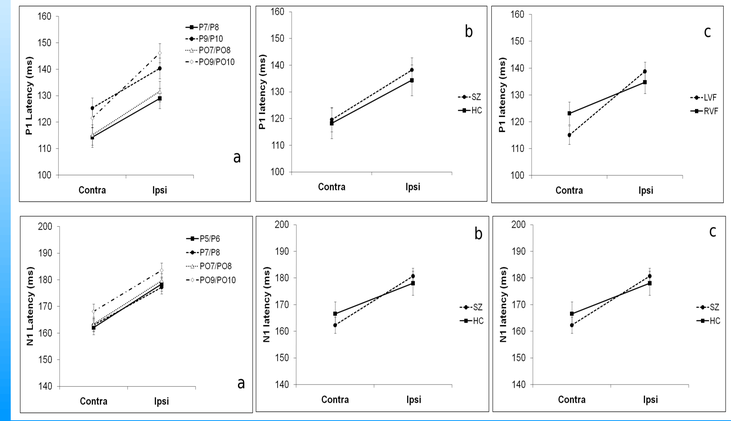
- 512 Hz sampling rate, DC-100 Hz filter.
- 68 channels, re-referenced offline to average reference.
- ICA for ocular artifact correction.
- ERPs transformed from voltage to Current Source Density (CSD) waveforms.
- P1 and N1 components measured with a custom made peak-picking algorithm
- IHTTs calculated as the peak latency at the ipsilateral electrode minus the peak latency at the homologous contralateral electrode.

DTI Acquisition and Analysis

- Diffusion-Weighted Images were acquired on a 3T GE system (51 gradient directions, b=900 s/mm^2, 8 b0 images, TR 17000 ms, TE 78 ms, 1.7 x 1.7 x 1.7 mm^3 voxels) and converted to DTIs.
- Splenium manually defined on migsagittal slice. Defined voxels used as seeds for deterministic (streamline) tractography. Fibers were excluded if they passed through an axial ROI at the dorsal midbody or if they failed to pass through a coronal ROI at the parieto-occipital sulcus.
- Mean FA and Mode were calculated for the extracted visual CC fibers. FA is an index of the asphericity of diffusion, and is sensitive to disruptions in fiber integrity. Mode is an index of the shape of diffusion: specifically, whether diffusion is prolate (i.e., shaped like a cigar) or oblate (i.e., shaped like a pancake).

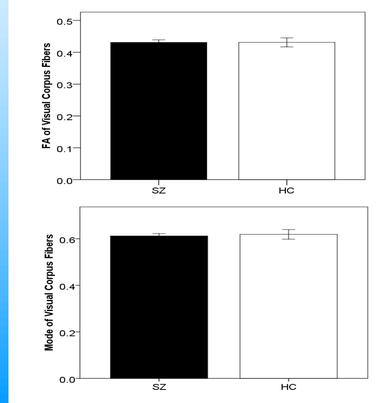
ERP Results

- Highly significant (p<0.001) IHTTs were observed in both the SZ patients and HC for both P1 and N1.
- There were no between-group differences in IHTT in either P1 (p=0.68) or N1 (p=0.09).
- IHTT was asymmetric for P1 (p=0.03). Specifically, IHTT from the left-to-the-right hemisphere was shorter than from the right-to-the-left hemisphere in both groups.



DTI Results

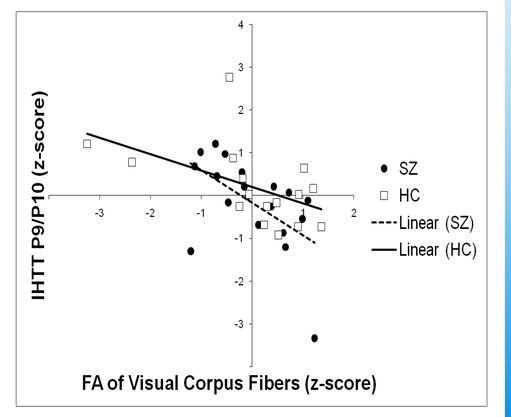
No between group differences were observed in either the FA (p=0.99) or Mode (p=0.75) of the visual fibers of the corpus callosum.

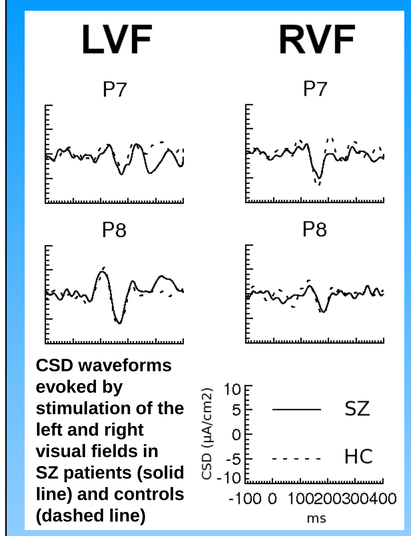


ERP / DTI Relationship

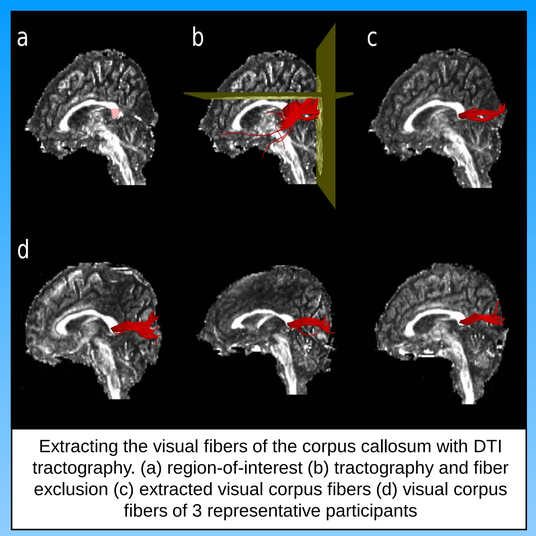
Linear regression revealed a highly predictable relationship (p<0.005) between participants' IHTT and their FA and Mode in the visual CC fibers.

$IHTT_{P1:p9/p10}$ = -283.FA + 72.Mode + 93, r^2=0.285





CSD waveforms evoked by stimulation of the left and right visual fields in SZ patients (solid line) and controls (dashed line)



Extracting the visual fibers of the corpus callosum with DTI tractography. (a) region-of-interest (b) tractography and fiber exclusion (c) extracted visual corpus fibers (d) visual corpus fibers of 3 representative participants

Conclusions

- IHTT was predicted by DTI measures of visual CC fiber integrity.
- No evidence that the schizophrenia patients showed abnormalities in either their IHTTs to unilaterally-presented visual stimuli or in the structural integrity of their visual corpus fibers.
- However, structural abnormalities have consistently been reported in patients with schizophrenia in several fasciculi, including the uncinate, arcuate and cingulum bundle[7].
- These frontally-projecting fasciculi are among the latest to mature, with myelination typically continuing through adolescence and into early adulthood[8]: the primary age of onset for schizophrenia.
- If the observed relationship between transmission time and fiber integrity holds in these fasciculi, then schizophrenia patients would be expected to show marked conduction delays in signals transmitted along these fibers.
- Such delays could feasibly underlie the functional disconnectivity and cognitive disorganization that has repeatedly been argued to underlie the symptoms of schizophrenia[9,10].

References

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