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Long range frontal/posterior phase synchronization during remembered pursuit task is impaired in schizophrenia

Nithin Krishna *, Hugh O'Neill, Eva María Sánchez-Morla, Gunvant K. Thaker

Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD, United States

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ABSTRACT

Although smooth pursuit eye movement (SPEM) is a reliable endophenotype of schizophrenia, exact underlying cognitive and neural substrates remain unknown. A simple mechanistic model of SPEM assumes an efficient interaction in integrating sensory input from the medial temporal (MT)/medial superior temporal (MST) brain regions and subsequent motor response through the frontal eye field (FEF). Poor functional connectivity between these two regions could explain impaired motion perception and SPEM maintenance in schizophrenia. In the present study, we combined an eye tracking paradigm with electroencephalography (EEG) recordings to investigate the putative functional connectivity among frontal/posterior brain regions in mediating the modulation of SPEM. Twenty four schizophrenic (SZ) and 22 healthy control (HC) participants performed remembered pursuit tasks with EEG recordings. Behaviorally, HC subjects showed significant improvement in SPEM response on repeated presentations of target compared to SZ subjects. Neurophysiologically HC subjects showed higher frontal/posterior phase synchronization in the beta to low gamma range frequency bands during all target presentations. In addition there was a significant increase in phase synchronization in the beta-2 frequency band in HC subjects during late compared to early target presentation. In contrast, higher frontal/posterior phase synchronization in the beta-2 frequency predicted better performance during late target presentation and lower enduring psychosis in SZ subjects. These data suggest a pathologically perturbed connectivity between frontal and posterior cortical regions during SPEM in SZ. The integrative eye tracking-EEG approach used in this study to dissect the endophenotype may reveal novel targets for studying schizophrenia psychopathology.

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1. Introduction

The search for biomarkers of complex disorders such as schizophrenia has been difficult mostly because of their heterogeneity (Thaker and Carpenter, 2001). Measurable biomarkers that index stable and heritable physiological deficits which mark disease liability (i.e., endophenotypes) help reduce heterogeneity, and have value in genetic studies (Gottesman and Gould, 2003). Smooth pursuit eye movement (SPEM) abnormality, arguably the first biological marker identified in schizophrenia, is a well recognized and valid schizophrenia/psychosis endophenotype that is associated with cognitive dysfunction in schizophrenia including impairments in working memory and executive function (Diefendorf and Dodge, 1908; Holzman et al., 1974; Fukushima et al., 2013). However SPEM remains relatively complex and this inherent complexity remains an obstacle for its successful clinical application. Thus further characterization and continued refinement are a prerequisite for both a better understanding of the cognitive processes involved and a clearer understanding of the specific neurophysiological underpinnings; this remains an unmet need in schizophrenia research.

SPEM functions to maintain the image of a moving object of interest on the fovea, the most sensitive part of the retina. SPEM is a unique neurophysiological function present only in humans and primates, in that the eye movements do not occur in the absence of motion information (Thier and Ilg, 2005; Orban de Xivry and Lefevre, 2007). Initially, target motion (retinal motion) is relayed to the lateral geniculate nucleus, and then to primary visual cortex (V1), subsequently processed by V5 (mediotemporal cortex, MT). This then stimulates the initiation of SPEM (Born and Tootell, 1992); however, with a delay, when the eye catches up with the target, matching its speed, the motion of the target image on the retina is near zero. To maintain accurate pursuit, predictive eye velocity is generated using an internal representation of the target velocity, thought to be derived from the efference copy of the motor command, and/or a memory trace of the previous retinal motion (Newsome et al., 1988; Eskandar and Assad, 1999; Thier and Ilg, 2005; Orban de Xivry and Lefevre, 2007).

Frontal eye fields (FEF) are instrumental in anticipatory pursuit initiation and eye acceleration (Fukushima, 2003; Thier and Ilg, 2005;

* Corresponding author at: PO Box 21247, MPRC, Baltimore, MD 21228, United States. Tel.: +1 410 402 6820.
E-mail address: nkrishna@psych.umaryland.edu (N. Krishna).

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Orban de Xivry and Lefevre, 2007; Fukushima et al., 2013). FEF interact with the MT during visual motion tasks (Zaksas and Pasternak, 2006). FEF are a likely source to relay the efference copy information to the two extrastriate visual areas (MT/MST), where it is integrated with the visual sensory input (i.e., corollary discharge) to form a motion perception (Nuding et al., 2008). Motion perception relies on the efference copy for adapting the visual receptive field in accordance with motion (Turano and Massof, 2001; Sommer and Wurtz, 2002; Hong et al., 2009). Converging lines of evidence suggest that schizophrenia probands and their relatives have impaired predictive pursuit (Thaker et al., 2003).

The current study aimed to examine the phase synchronization between frontal and posterior regions as a measure of efference copy utilization during a remembered pursuit task. Where performance is facilitated when a subject uses remembered target velocity from earlier trials to anticipate the next target velocity. Simultaneous electroencephalographic (EEG) recordings were obtained to study phase synchronization (PS) of oscillatory activity in narrow frequency bands between frontal and posterior electrodes. We tested the hypothesis that anticipatory or predictive improvement of SPEM relies on PS between the frontal and posterior regions. The hypothesis further posits that the remembered velocity information is integrated into the SPEM system, and impairment of the anticipatory SPEM in schizophrenia is associated with impaired frontal–posterior PS. Here, PS serves as a measure of functional connectivity between these regions. We also used power spectrum density in the frontal electrodes as a measure to estimate how well the efference copy is maintained in the underlying cortical tissue that includes FEF.

PS of a local network of neuronal ensembles in response to an event results in oscillatory activity that can be measured in the scalp EEG signal. Event-related oscillations are examined by deconstructing the EEG signal into different frequencies. Power in a specific frequency provides an estimate of the magnitude of synchronization within the local network and has been shown to index several cognitive processes such as perception and memory (Uhlhaas and Singer, 2010). Long-range PS across space, on the other hand, provides a method to examine communication between distal neuronal ensembles. Recent animal and human work suggests that phase coupling serves as a signature of ongoing oscillations that predict the perceptual detection of subsequent stimuli (Liebe et al., 2012; Ng et al., 2012). Investigators have used nonlinear dynamic tools to develop several novel methods that provide estimates of coupling between signals recorded from spatially-distributed networks (Gourevitch et al., 2006). Phase-locking or coupling has distinct advantages over traditional methods which measure linear covariance between two spectra that fail to distinguish amplitude covariance from phase covariance.

2. Methods

2.1. Subjects

All subjects gave written informed consent in accordance with the University of Maryland, Baltimore Institutional Review Board guidelines. Patients with SZ ($n = 24$) were recruited from our outpatient clinic. HC subjects had no Axis I diagnosis and no family history of psychosis ($n = 22$). The Structured Clinical Interview for DSM-IV (SCID) was administered to obtain diagnostic information. Clinical symptoms were assessed by the Brief Psychiatric Rating Scale (BPRS) (Table 1).

2.2. Remembered Pursuit Task (Fig. 1)

This task is described in detail in previous publications, being slightly modified to accommodate EEG measurements (Avila et al., 2006). Trials consisted of 3 identical, sinusoidal moving targets presented 1–2 s apart, each preceded by a 25 ms, 72 db audio cue (500 Hz; a sample trial). The targets had the same trajectory and velocity within each trial, enabling subjects to use target information from the preceding presentation to anticipate and facilitate SPEM in the next target presentation. The time between the onset of the auditory cue and the onset of target motion was a constant 330 ms. Trials (3 target presentations) were separated by a sequence of random left/right target steps and central fixation lasting 6–10 s. This procedure was added to remove effects from stored velocity memory. Target direction was varied across trials.

2.3. Data collection

Testing was performed in an enclosed, sound-attenuated (background noise between 61 and 63 db), and darkened room (background luminance of 0.01 foot candle at the level of subject's eyes). The target display and eye movement data were recorded and processed using the same procedures previously reported (Avila et al., 2006). EEG recordings were performed on a 64-channel Neuroscan Acquire and Synamp2 system, using sintered Ag/AgCl electrodes (impedance less than 5 K; Quik-Cap). EEG recordings (DC coupled) were amplified (12,500×), digitized (1000 Hz) and bandpass-filtered from 0.1 to 200 Hz using Neuroscan version 4.3. For off-line data processing, we used spatial regression (Semlitsch et al., 1986) based mathematical corrections to remove eye blink related potentials, done on continuous recordings. We applied a threshold filter (±75 uV) on corrected data and verified by visual inspection to be certain about eye movement artifact processing (Light et al., 2006). Subjects were instructed to refrain from smoking 30 min prior to testing.

2.4. Eye movement and EEG data processing

2.4.1. Pursuit data

Algorithms were written in MatLab and Igor Pro environments. Methods have been extensively published previously (Avila et al., 2006).

2.4.2. Phase synchronization (PS)

We used calculation of Hilbert entropy method for analyzing PS between two oscillators because it showed low variability in our preliminary studies and has been successfully applied previously(Wendling et al., 2009).

EEG data were subjected to current density interpolation using a current source density (CSD) toolbox to interpolate scalp potentials and estimates of scalp current densities using spherical splines to enhance the spatial precision and avoid confounding (Kayser and Tenke, 2006; Kayser, 2014). EEG data were processed on the three prestimulus 500-ms epochs in the pursuit task: pre-cue 1, pre-cue 2 and pre-cue 3. Specifically we used this sequence because we hypothesized

Table 1
Subjects.

	Schizophrenia ($n = 24$)	Healthy control ($n = 22$)	Statistics
Age (mean and SD)	40 ± 12 yrs	43 ± 9 yrs	NS
Sex (% female)	20%	30%	NS
Race (%Caucasian: African American: other)	62:38:0	66:28:6	NS
Antipsychotic medications	1 on 1st generation, 20 on 2nd generation, and 3 on both		
Other medications	1 on lithium, 1 on benztropine, and 5 on selective serotonin reuptake inhibitors		

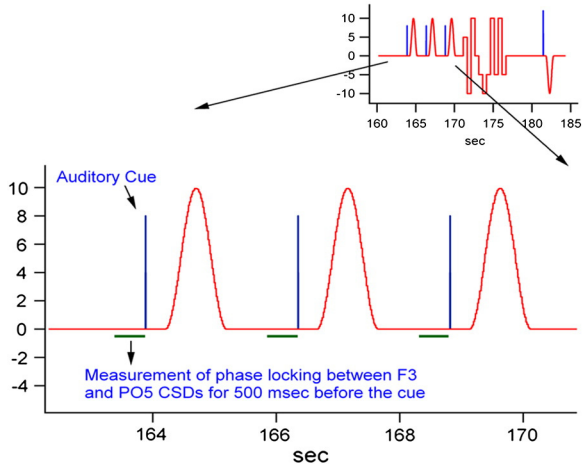

Fig. 1. Remembered Pursuit Task presented the same target motion three times in a rapid succession. Within a trial, the target motion had the same speed and direction. Each time an auditory cue signaled the upcoming target motion in 333 ms. PS was measured in 500-ms epochs before each cue (pre-cue 1, pre-cue 2 and pre-cue 3). Each pursuit trial was followed by a saccadic task and fixation lasting for 6–10 min (see insert).

that this period is critical for processing and modulation of the remembered velocity needed to facilitate repeated SPEM response. Subsequently these specific epochs were used for phase and power analysis as described below. Phases of these narrow-band signals were calculated using the Hilbert transform (Kayser and Tenke, 2006; Ng et al., 2012) and, are summarized in Fig. 2. The power in the frontal CSD was calculated using fast Fourier transform (with Hanning window to avoid spectral leakage) to determine the top 8 dominant frequencies within the traditional frequency bands (theta, alpha, beta, and gamma) (Fig. 2a). These frequency bands were further processed using a finite impulse response (FIR) narrow (+1 Hz) band pass filter to extract oscillatory activity around dominant frequencies. FIR filters were used to assure zero phase shift, and frequency response in the reject band of less than −55 dB. We examined Hilbert transform separately for each of four electrodes of interest (F3, F4, PO5 and PO6) and instantaneous phase for each of the frequency bands at each electrode of interest (Fig. 2b). F3 or F4 approximately corresponds to the site above posterior middle frontal gyrus/precentral gyrus junction area of the Brodman's Area 6 where human frontal eye fields reside. PO5 or PO6 corresponds to the medial temporal areas where human MT resides. Subsequently, PS between a pair of electrodes (i.e., F3 and PO5, or F4 and PO6) was evaluated based on the mod 2pi phase difference (Fig. 2c), calculating Shannon entropy S based on its frequency distribution (Fig. 2d) and normalizing (Fig. 2e) to obtain Hilbert entropy, which ranges from 0 (no synchronization) to 1 (perfect synchronization). Simulation studies with embedded signals that were perfectly in synch showed *p* values of ~0.4 for perfectly synched oscillations, and near zero (~0.01) for non-synched oscillations.

2.5. Statistical analyses

We used repeated measures analysis of variance to examine the effects of repeated target presentation over 500 ms in 50-ms time bins (i.e., two within subject factors) on eye velocity across the two groups (a between subject factor). Similar analyses were carried out to examine the effects of repeated target over eight frequency bands and group on the phase synchrony measure. In these analyses we used Greenhouse–Geisser corrections. With degrees of freedom associated with this correction. Post hoc comparisons used Tukey's tests in SigmaPlot 11.

3. Results

3.1. Smooth pursuit eye movements (SPEM)

On repeated presentation of the target motion, SPEM response improved in both groups, more so in the HC subjects and particularly for the 3rd target presentation (Fig. 3). This was confirmed by a repeated measures ANOVA that showed a significant diagnosis by repeat target presentation by time interaction [$F_{(18,168)} = 3.1$, $p < 0.02$]. There was no significant diagnosis, or diagnosis by time interaction effects for the

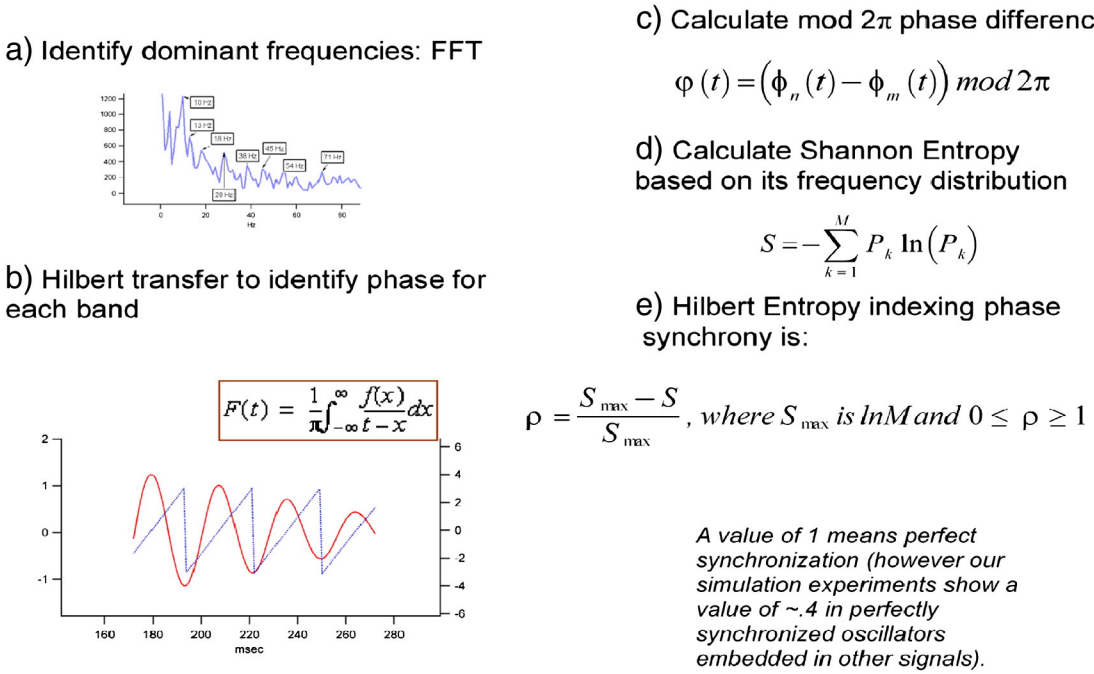

Fig. 2. Fast Fourier transfer (with Hanning window to avoid spectral leakage) was used to determine the top 8 dominant frequencies within the traditional frequency bands (theta, alpha, beta, and gamma) in the frontal CSD (Fig. 2a). We used FIR narrow (±1 Hz) band pass filter to extract oscillatory activity around dominant frequencies. Subsequently, instantaneous phase for each of the frequency bands at each electrode of interest were calculated using Hilbert transfer function (Fig. 2b). PS between a pair of electrodes (e.g., F3 and PO5) was evaluated based on the mod 2pi phase difference (Fig. 2c), calculating Shannon entropy S based on its frequency distribution (Fig. 2d) and normalizing (Fig. 2e) to obtain Hilbert entropy.

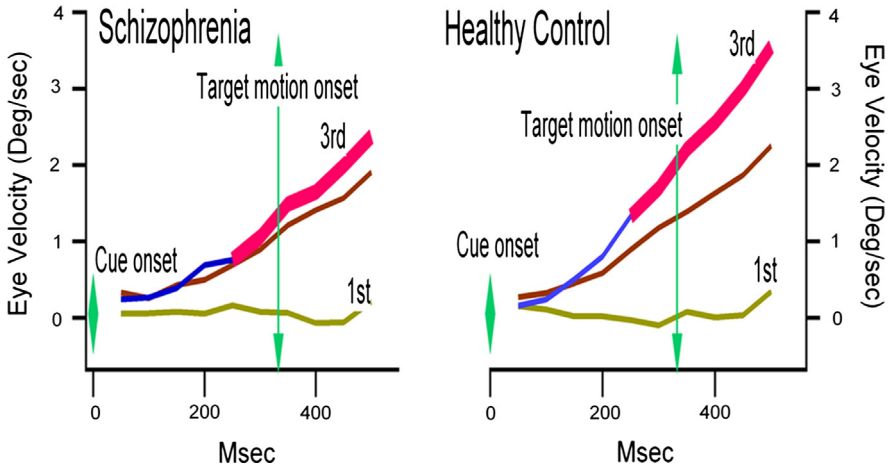

Fig. 3. Smooth pursuit response to repeated target motion in schizophrenia (left panel) and healthy control subjects (right panel). Eye velocity data are in 50 ms bins. Both groups made predictive pursuit responses on repeated presentation of target motion with healthy control subjects showing significantly higher eye velocity than schizophrenia subjects during the 3rd target presentation between 250 and 500 ms (shown with a red thick line).

first two target presentations ($p > 0.1$). For the 3rd target, there was a significant diagnosis by time interaction [$F_{(9,128)} = 6.7$, $p < 0.005$]; post hoc comparisons showed significant between group differences for mean eye velocities 250 ms after the cue ($p < 0.01$; Fig. 3).

Responses to repeated motion were predictive since the eye started moving immediately after the cue (see Fig. 3). There was no significant improvement in response to the 1st target presentation across trials.

3.2. Functional connectivity between frontal and posterior electrodes: phase synchronization (PS)

Findings from F3-PO5 electrodes with analyses of PS customized based on dominant frequencies in individual subjects are given below. Similar findings were observed for F4-PO6. The PS was significantly higher in HC subjects in beta to gamma range under all target conditions compared to SZ subjects (Fig. 4). In HC subjects, there was an increase in phase locking in high beta range frequencies with repetition of the target presentation. No such change was observed in SZ subjects (Fig. 4). These observations were confirmed by a repeated measures ANOVA (repeat presentations of target and frequency as within subjects factor, diagnosis as between subjects factor, and age as covariate) that showed a significant diagnosis by repeated presentation by frequency interaction [$F_{(14,297)} = 2.32$, $p < 0.03$). Subsequent analyses at each level of frequency showed significant main effects of diagnosis on phase locking at ~12 Hz, ~21 Hz and ~40 Hz ($p < 0.05$; Fig. 4). For ~30 Hz, there was a significant diagnosis by repeated presentation interaction [$F_{(2,73)} = 6.9$, $p < 0.003$]. A significant effect of repeated presentation of target in HC subjects but not in SZ subjects was observed. PS in ~30 Hz was significantly higher for the 3rd target presentation compared to the 2nd ($p < 0.02$) and 1st ($p < 0.01$) presentations in HC subjects; these were significantly higher than in SZ subjects under all target conditions.

3.3. Comparison of power spectrum density (PSD)

No significant effects of diagnosis or interactions involving diagnosis on PSD.

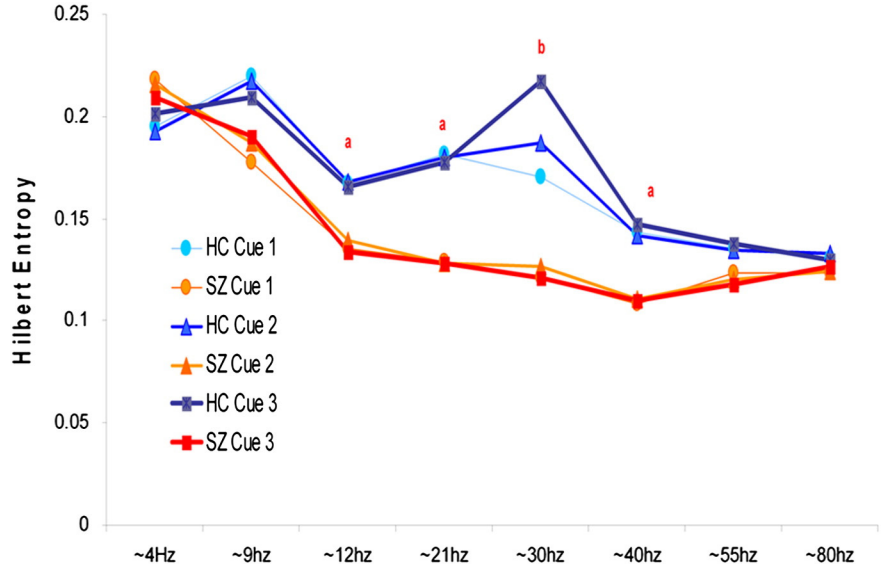

Fig. 4. Healthy control subjects showed higher PS in beta to gamma range under all target conditions than schizophrenia subjects (A, $p < 0.05$). There additional increase in the F3-PO5 phase locking of ~30 Hz frequency band with repeated presentation of the target motion. At this frequency, phase locking just before the 3rd target presentation was significantly higher than for the 1st and 2nd presentation (B, $P < 0.02$).

3.4. Correlations

BPRS illness duration symptom severity was obtained in 19 patients. We examined correlations between the phase locking in ~30 Hz and the mean eye velocity during the first 500 ms of the cue were 0.19 (NS) following cue 1, 0.24 (NS) following cue 2 and 0.34 ($p < 0.03$, $n = 44$, Fig. 5) following cue 3. In addition we examined correlation between phase locking and total BPRS, psychosis, hallucinations, and negative symptom scores. Significant positive correlations of phase locking with eye velocities after the 3rd cue ($r = 0.32$–0.50, $p < 0.05$) and negative correlations with hallucination ratings ($r = -0.48$, $p < 0.04$) and psychosis ratings ($r = -0.44$, $p < 0.05$). No significant correlations with negative symptom scores ($r = 0.05$) or total BPRS scores ($r = -0.19$) were observed.

4. Discussion

The aim of the study was to examine functional connectivity between frontal and posterior cortical regions during a remembered pursuit task, which posits that efference copy utilization related improvement of SPEM relies on PS between the frontal and posterior regions. Predictive component acts as a proxy for cognitive function, specifically working memory (Fukushima et al., 2013). Consistent with previous findings (Avila et al., 2006), all subjects showed improvement in SPEM response on repeated presentation with significantly more improvement in HC subjects. Poor response in schizophrenia on repeated target presentation could be because patients were not able to adequately use efference velocity or were not able to integrate the efference copy with the MT/MST corollaries for the pursuit response. We examined both the power spectrum density and long-range PS to test our hypothesis.

SZ subjects showed poor frontal/posterior PSs in beta to low gamma frequencies compared to HC subjects during all target conditions. Coincident with improvement in pursuit response, HC subjects showed increased PS in ~30 Hz from 1st to 3rd target presentation. In contrast such increases were not observed in SZ subjects. There were no differences in energy in these frequency bands across groups. Together, these findings suggest that SZ subjects have normal activation in the frontal cortical region while holding eye motion (i.e., efference copy) information on-line. However, during the pursuit response to repeated target motion, patients showed significantly poorer frontal/posterior functional connectivity. High long-range frontal/posterior synchronization in ~30 Hz was associated with faster eye velocity during the 3rd presentation of the target velocity.

Information processing involves many cognitive functions across physically distant neuronal systems. In order to integrate activities and to achieve a coherent representational state, communication among these regions is critical. Animal studies demonstrate that synchronization serves this purpose locally and across widely separated cortical regions (Roelfsema et al., 1997; Womelsdorf et al., 2007). Similar findings have been observed in human EEG studies (Melloni et al., 2007). The magnitude of synchronization ranges from 15 to 35% (higher values noted are from animal studies with intracortical recordings). A similar magnitude was observed in our study. Additionally we find that communications between cortical regions are aberrant in schizophrenia and this may lead to an incoherent representational state, which may explain some of the cognitive impairments and core schizophrenia symptoms. Specifically several researchers (Frith, 1987; Feinberg and Guazzelli, 1999) have argued that psychosis is secondary to an impaired processing of efference copy or corollary discharge. Recently, Ford et al. have provided experimental data showing abnormal processing of corollary discharge in the auditory system that explains auditory perception dysfunction in schizophrenia patients (Ford et al., 2005; Ford and Mathalon, 2012). Monkey experiments suggest that disruption of the corollary discharge leads to distorted representation of the external world (Sommer and Wurtz, 2006). We hypothesized on this basis that frontal-posterior synchronization mediates corollary discharge that would predict perceptual distortions and psychosis. Since the SPEM abnormality is a stable trait, we rated psychosis and hallucinations based on a long time window. Poor frontal-posterior phase locking in ~30 Hz was associated with more stable psychotic symptoms and hallucinations.

The relationships between the eye movement and frontal/posterior synchronization are consistent with strong reciprocal connectivity between the MT/MST and FEF. The MT/MST region processes retinal information (Born and Tootell, 1992), which is fed forward to FEF (Stanton et al., 2005). FEF plays a key role in pursuit initiation and predictive pursuit (MacAvoy et al., 1991; Shi et al., 1998; Fukushima, 2003). It is likely that FEF incorporates eye movement related projections from the central thalamus, and acts as a relay station to feedback efference copy to

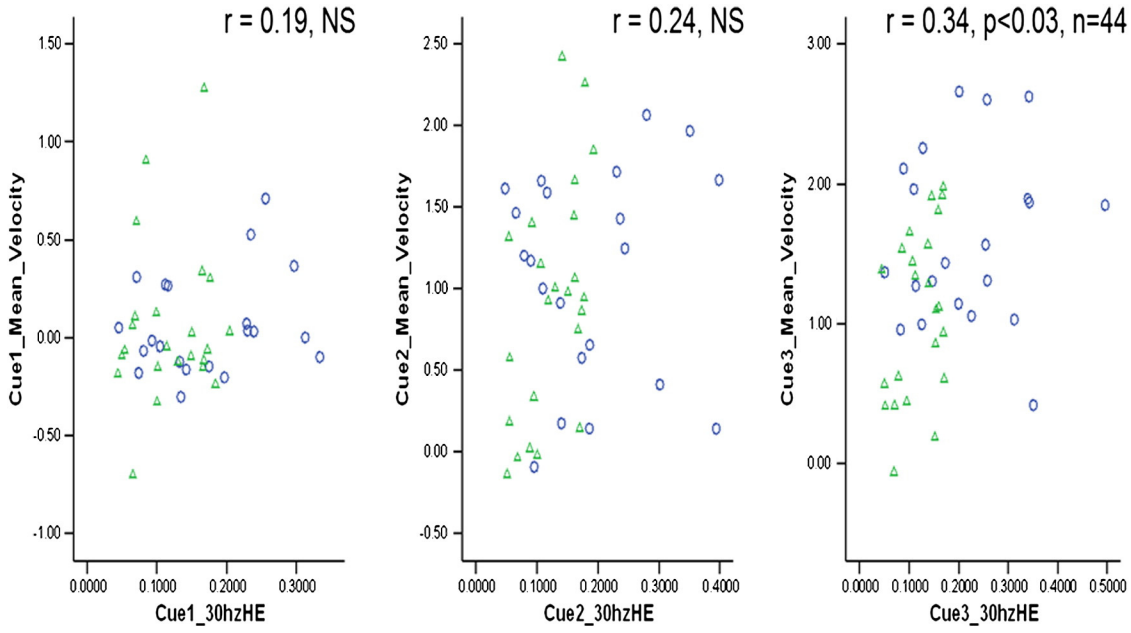

Fig. 5. Correlations between the Hilbert entropy and the mean eye velocity (1st 500 ms) following Cue 1 (left panel), Cue 2 (middle panel) and Cue 3 (right panel). Circles are healthy control subjects and triangles are patients.

MST (Tanaka, 2005; Nuding et al., 2008). Synchronization across regions depends on the integrity of connection between regions (Munk et al., 1995; Arrondo et al., 2009). Findings from our study raise the possibility that the structural integrity of pathways connecting FEF and the MT/MST region is compromised in schizophrenia. Our data do not rule out the possibility that reduced synchronization in patients was a medication effect. It is still unclear to what extent this abnormality accounts for the variation in the smooth pursuit endophenotype. Additional studies in relatives of schizophrenia and medication-free patients are needed to address these issues. However based on findings reported here along with findings from other studies, it is clear that SPEM is a complex phenotype with impairments in ability to use efference function are associated with psychosis (Ford et al., 2005; Nkam et al., 2010; Ford and Mathalon, 2012; Spering et al., 2013). In the present study, we used EEG recording during a repeated pursuit task, and utilized the framework of information theory (IT) (Shannon, 1948) to assess PS between frontal and posterior brain regions.

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Contributors

G.T. came up with the hypothesis, designed the experimental strategy, and wrote the manuscript.

N.K performed the experiments, interpreted the results, wrote the manuscript and generated the figures/tables.

HON analyzed the data and edited the manuscript.

ES performed the experiments, analyzed the data, helped generate the figures/tables and edited the manuscript.

Conflict of interest

Authors report no conflict of interest.

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