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

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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;

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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		