Neural Mechanisms of Smooth Pursuit Eye Movements in Schizotypy

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Abstract: Patients with schizophrenia as well as individuals with high levels of schizotypy are known to have deficits in smooth pursuit eye movements (SPEM). Here, we investigated, for the first time, the neural mechanisms underlying SPEM performance in high schizotypy. Thirty-one healthy participants [$N = 19$ low schizotypes, $N = 12$ high schizotypes (HS)] underwent functional magnetic resonance imaging at 3T with concurrent oculographic recording while performing a SPEM task with sinusoidal stimuli at two velocities (0.2 and 0.4 Hz). Behaviorally, a significant interaction between schizotypy group and velocity was found for frequency of saccades during SPEM, indicating impairments in HS in the slow but not the fast condition. On the neural level, HS demonstrated lower brain activation in different regions of the occipital lobe known to be associated with early sensory and attentional processing and motion perception (V3A, middle occipital gyrus, and fusiform gyrus). This group difference in neural activation was independent of target velocity. Together, these findings replicate the observation of altered pursuit performance in highly schizotypal individuals and, for the first time, identify brain activation patterns accompanying these performance changes. These posterior activation differences are compatible with evidence of motion processing deficits from the schizophrenia literature and, therefore, suggest overlap between schizotypy and schizophrenia both on cognitive-perceptual and neurophysiological levels. However, deficits in frontal motor areas observed during pursuit in schizophrenia were not seen here, suggesting the operation of additional genetic and/or illness-related influences in the clinical disorder. *Hum Brain Mapp* 36:340–353, 2015. © 2014 Wiley Periodicals, Inc.

Key words: eye movements; smooth pursuit; personality; schizotypal; schizophrenia; fMRI

INTRODUCTION

Schizophrenia is a severe illness characterized by positive symptoms (e.g., delusions and hallucinations), negative symptoms (diminished emotional expression or

avolition) and disorganized speech and behavior [American Psychiatric Association, 2013]. Cognitive deficits are also found to be a substantial aspect of the schizophrenic psychopathology [Green et al., 2000; Palmer et al., 2009].

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An important milestone in the search for etiological factors has been the finding that such symptoms are not restricted to patients with schizophrenia or other psychotic disorders, but are also observed in healthy subjects in the general population. Specifically, Johns and Van Os [2001] distinguished between psychotic symptoms in the general population, which are similar to those seen in schizophrenic patients, and schizotypal signs, which represent a cluster of a subclinical form of those psychotic symptoms. Schizotypy is a multidimensional construct that can be subdivided into positive, negative, and disorganized factors [Nelson et al., 2013; Reynolds et al., 2000; Lin et al., 2013]. Positive schizotypy refers to psychotic-like cognitive and perceptual experiences [Mason et al., 1995; Raine et al., 1994]. Negative schizotypy includes physical and social anhedonia [Mason et al., 1995; Raine et al., 1994]. The disorganized dimension involves odd behavior, odd speech, and difficulties with concentration and attention [Mason et al., 1995; Raine et al., 1994].

Schizotypal traits appear related to schizophrenia on different levels of measurement: first, there is overlap on the descriptive phenomenological level, as results from factor analyses of schizotypal traits and schizophrenic symptoms, respectively, show a high degree of similarity [Claridge and Beech, 1995]. Second, a growing body of literature describes evidence for an overlap between schizotypy and schizophrenia with regard to genetics [Cannon et al., 2002; Fanous et al., 2007; Kendler et al., 1995; Kendler and Walsh, 1995; Tsuang et al., 1999], cognition [Giakoumaki, 2012] as well as neuroanatomical [Ettinger et al., 2012; Kühn et al., 2012; Modinos et al., 2010; Nelson et al., 2011], neurochemical [Chen et al., 2012], and neurophysiological [Aichert et al., 2012; Corlett et al., 2007; Corlett and Fletcher, 2012; Kumari et al., 2003, 2008] measures [for an overview, see Ettinger et al., 2014].

A time-honored approach in experimental research on schizophrenia and schizotypy is the study of smooth pursuit eye movements (SPEM) [Diefendorf and Dodge, 1908; Holzman et al., 1973; Klein and Ettinger, 2008; Levy et al., 2010]. SPEM are an example of a sensorimotor feedback system and can be characterized as a mechanism that allows subjects to track a moving object in extra-personal space with the eyes alone [Barnes, 2008]. Neural pathways of SPEM are well described [Ilg and Thier, 2008; Krauzlis, 2004; Leigh and Zee, 2006; Thier and Ilg, 2005] and include regions responsible for both motion processing and prediction, such as frontal eye fields (FEFs), parietal eye fields (PEFs), supplementary eye fields (SEFs), and the motion-sensitive area V5 [Lencer and Trillenber, 2008].

SPEM deficits in schizophrenia have been described both globally, using measures such as the root mean square error (RMSE) of eye position, as well as specifically, using measures such as the steady-state velocity gain [Hutton and Kennard, 1998; Levy et al., 1993, 1994, 2010; O'Driscoll and Callahan, 2008]. These deficits are relatively independent of the expression of schizophrenic symptom-

levels, supporting their trait-like nature [Hong et al., 2003; Lee et al., 2001; Nkam et al., 2001; Ross et al., 1996, 1997].

On the brain functional level, schizophrenic patients present abnormal activation in areas that play an important role in both the processing and the prediction of the target's movement. Reduced blood oxygen level dependent (BOLD) signal was found for FEF or SEF [Hong et al., 2005; Keedy et al., 2006], and Nagel et al. [2012] showed that activation of SEF was correlated to target velocity in healthy controls but not in patients. However, when the target was blanked out for 1,000 ms in the middle of the ramp, there was an increase in BOLD signal in schizophrenics in bilateral FEFs [Nagel et al., 2007]. With reference to the perception and processing of motion, BOLD response in V5 correlated positively with mean eye velocity in controls but not in patients [Lencer et al., 2005], and activation was less strongly linked to target velocity in patients than in healthy controls [Nagel et al., 2012]. Furthermore, patients were found to show reduced BOLD during SPEM in V5 [Nagel et al., 2012] and in a subregion of the V5 complex in MST [Hong et al., 2005].

In agreement with the hypothesis of a neuro-behavioral continuum between schizophrenia and schizotypy [Ettinger et al., 2014; Nelson et al., 2013], healthy subjects with high levels of schizotypy show reduced velocity gain, a higher frequency of saccades and higher RMSE during SPEM [Gooding et al., 2000; Holahan and O'Driscoll, 2005; van Kampen and Deijen, 2009; Kattoulas et al., 2011; Kelly and Bakan, 1999; Kendler et al., 1991; Lenzenweger and O'Driscoll, 2006; Smyrnis et al., 2007]. These deficits are observed both in positive and negative schizotypals [Gooding et al., 2000; Holahan and O'Driscoll, 2005] as well as in subjects defined by overall schizotypy scores [van Kampen and Deijen, 2009].

However, no study has yet examined the neural correlates of SPEM deficits in schizotypy. This would be important to further investigate putative similarities in brain function between schizotypy and schizophrenia. The SPEM task is ideally suited to address this goal, as SPEM deficits have been proposed as schizophrenia endophenotypes [Calkins et al., 2008], with deficits being observed in patients, their relatives and in high schizotypals. Knowledge of the neural mechanisms of SPEM deficits in schizotypy would thus improve our understanding of the brain's functional changes observed across the schizophrenia spectrum. Importantly, the study of schizotypal individuals enables this knowledge to be gained in the absence of confounds such as possibly distracting clinical symptoms and pharmacological treatment.

Therefore, the current study used BOLD functional magnetic resonance imaging (fMRI) and concurrent oculography to examine the neural mechanisms of SPEM performance in high and low schizotypy subjects. Given the robustness of the SPEM deficit to different dimensions of schizotypy [Gooding et al., 2000; Holahan and O'Driscoll, 2005; Smyrnis et al., 2007] and symptoms of schizophrenia [O'Driscoll and Callahan, 2008], we recruited

individuals on the basis of their overall schizotypy score. On the basis of previous studies [Gooding et al., 2000; Holahan and O'Driscoll, 2005; Smyrnis et al., 2007], high schizotypals were hypothesized to show deficits in SPEM performance. With regards to fMRI, high schizotypals have been found to present reductions in BOLD signal qualitatively comparable to schizophrenic patients but less pronounced both in extent and intensity [Aichert et al., 2012; Corlett and Fletcher, 2012; Kumari et al., 2008]. Therefore, on the neural level, we expected the high schizotypy group to show reduced brain activation within the SPEM network that overlaps with the alterations seen in patients with schizophrenia (e.g., FEF, SEF, and V5).

METHODS

Participants

Healthy volunteers were recruited via flyers that were distributed on the Bonn University campus and in local bars, via circular emails, and via advertisements placed in a local newspaper. We also placed ads in internet forums that thematically deal with loneliness, esotericism and spirituality, to enrich the sample for highly schizotypal individuals. Participants were asked to complete an online version of the German translation of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE short) [Grant et al., 2013]. The O-LIFE short scales are a psychometrically constructed forced-choice questionnaire consisting of 43 "Yes/No" items measuring multiple dimensions of schizotypy [Grant et al., 2013; Mason et al., 2005].

The questionnaire was available online (<https://www.soscisurvey.de>; Leiner, 2013] between July and November 2012 and was completed by 1,261 subjects. The O-LIFE sum score of the three subscales Unusual Experiences (UnEx), Introverted Anhedonia (IntAn) and Cognitive Disorganization (CogDis) was chosen to establish a criterion for the selection of extreme groups, similar to previous studies using total schizotypy scores [van Kampen and Deijen, 2009]. Impulsive Nonconformity (ImpNon) was not considered for the sum score as it has been found to be an unstable factor [Lin et al., 2013] and has theoretically been questioned as a measure of schizotypy, given that most factor analyses result in a three factor solution [Raine et al., 1994] similar to the multidimensionality of schizophrenia [Liddle, 1987]. Internal consistencies (Cronbach's α) in the online sample were 0.73 (UnEx), 0.73 (CogDis) and 0.62 (IntAn) for the subscales and 0.79 for the sum score.

Low schizotypes (LS) were required to score at least 0.5 standard deviations (*SD*) below and high schizotypes (HS) 1.5 *SD* above the sample mean sum score [Mohanty et al., 2005]. Sample mean score was 12.04 (*SD* = 5.33). Exclusion criteria were any diagnoses of psychotic disorders among first-degree relatives, any prescription or over-the-counter medication (except for oral contraceptives and vitamins),

any personal history of head injuries with loss of consciousness, any eye surgery or impairment of vision (other than the use of corrective lenses), any reason for exclusion from MRI studies, any current Axis I disorder diagnosis and any current or history of psychotic disorders (as assessed with the MINI International Neuropsychiatric Interview; Ackenheil et al., 1999).

Approval of the local ethics committee was obtained and the study was conducted in agreement with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Participants provided written informed consent and were compensated with €50.

Procedure

First, following completion of the online questionnaire, participants were contacted regarding their availability for a telephone screening. If they agreed, they were screened for exclusion criteria via telephone. Suitable participants were then invited to the first laboratory session, where they were administered the Edinburgh Handedness Inventory (Oldfield, 1971) and a measure of verbal intelligence [Mehrfachwahl-Wortschatz-Intelligenztest, Version B, MWT-B; Lehrl, 2005].

The second session took place in the MRI-facilities of the Life & Brain Centre, Bonn. Participants were first screened for illegal drugs using a drug urine test (Drug-Screen Multi 5T, nal von minden GmbH). No participants had to be excluded due to a positive drug test. They were also strictly instructed not to drink alcohol the day before testing because of the known pursuit impairments that can be caused by alcohol consumption [Roche and King, 2010]. Volunteers first performed a Stroop and then a SPEM task while undergoing fMRI. The Stroop task and its results will be reported elsewhere.

SPEM Task

The fMRI SPEM task was presented in a block-design consisting of blocks of sinusoidal stimuli in two different velocities. A white circular target on a black background was used (width and height 15 pixels, no filling, stroke width 5). The target started in the center position (0°) in each block and then moved across the screen horizontally, subtending a visual angle of $\pm 5.8^\circ$. The target was presented either with 0.2 or 0.4 Hz sinusoidal velocity. Additionally, there were fixation blocks where the target remained stationary in the center of the screen. Each block lasted 30 s, and the order of the blocks was the same for each subject (SPEM.2 – FIX – SPEM.4 – FIX – SPEM.4 – FIX – SPEM.2 – FIX – SPEM.4 – FIX – SPEM.2 – FIX – SPEM.2 – FIX – SPEM.4 – FIX – SPEM.4 – FIX – SPEM.2 – FIX – SPEM.2). In total, 5 SPEM 0.2 Hz blocks, 5 SPEM 0.4 Hz blocks and 9 fixation blocks were presented. Subjects were instructed to follow the target as accurately as possible in trials where the target was moving and to fixate on the target

whenever it remained stationary at the center of the screen.

Eye Movement Measurement

Movements of the right eye were recorded using an MRI-compatible video-based combined pupil and corneal reflection tracker (EyeLink 1000, SR Research). The system had a minimal spatial resolution of 0.01° and an average accuracy of 0.25° to 0.5° . Centroid pupil-tracking algorithms were used to detect pupil and corneal reflection and a five-point calibration was performed before the scan. Sampling rate was 500 Hz.

Image Acquisition

Scanning was conducted using a Siemens 3 Tesla Trio Scanner. Volunteers wore headphones to reduce the impact of scanner noise. Foam paddings were used to minimize head movements.

First, a localizer scan for placing the volume of interest was acquired. Next, T2*-weighted MRI scans were collected with gradient-echo planar images sequences (TR = 2,500 ms; TE = 30 ms) that displayed the blood oxygenation level dependent (BOLD) response. For radio frequency transmission and reception, a standard eight-channel head coil was used. Slices were oriented parallel to the intercommissural plane (AC-PC line). Additional scan parameters were as follows: flip angle = 90° ; FoV = 192 mm; matrix size = 64×64 ; 37 slices; slice thickness = 3 mm; sequential slice order with interslice gap of 0.3 mm; voxel size = $3 \times 3 \times 3.3$. A total of 239 whole brain images were collected for each subject. Finally, a high-resolution structural scan (T1-weighted) for image coregistration was acquired. Scan parameters were as follows: TR = 1570 ms; TE = 3.42 ms; inversion time (TI) = 800 ms; flip angle = 15° ; FoV = 256 mm; matrix size = 256×256 ; 160 slices; slice thickness = 1 mm; sequential slice-order with no inter-slice gap; voxel size = $1 \times 1 \times 1$.

Data Processing and Statistical Analyses

SPEM Data

SPEM data were analyzed using Data Viewer software (SR Research) and purpose-written routines in LabVIEW (National Instruments Corporation, Austin, TX). The first half-ramp in each block was excluded from analysis and SPEM variables were calculated separately for 0.2 and 0.4 Hz velocities. Saccade frequencies (N/s) were computed using minimum amplitude 1° and velocity ($30^\circ/\text{s}$) criteria. Time-weighted average maintenance gain was calculated for sections of pursuit in the average 50% of each ramp by dividing mean eye velocity by mean target velocity. Saccades and blinks were excluded from such sections. RMSE

scores for sections of pursuit were computed for all ramps except the first half-ramp, excluding blinks.

Group differences for SPEM variables were analyzed using a mixed design ANOVA in SPSS Release 19.0 (IBM Corp., 2010) with velocity (0.2 and 0.4 Hz) as within-subjects factor and schizotypy (low, high) as between-subjects factor. For significant interactions post hoc comparisons were calculated using a Bonferroni-corrected alpha level ($\alpha = 0.0125$). Effect sizes were given using Cohen's *d* [Cohen, 1992] or partial eta squared [Cohen, 1973]. Gain, frequency of saccades and RMSE scores were screened for violation of normality-distribution and homogeneity of variances to ensure that assumptions for statistical analyses were met. To explore these assumptions, skewness scores, Shapiro-Wilk tests and Levene's statistics were used.

fMRI data analysis

fMRI data analysis was performed using Statistical Parametric Mapping 8 software (SPM 8; <http://www.fil.ion.ucl.ac.uk/spm/software/>) implemented in Matlab R2012a (The MathWorks, Natick, MA). Preprocessing included four steps: First, images for each subject were realigned along the mean image in the time series to correct for head motion using a least squares approach and a six-parameter rigid-body transformation. Functional scans were then coregistered to the T1-weighted anatomical image. To allow for standardization, in a third step, images were transformed into standard space (Montreal Neurological Institute, MNI template) using linear transformation (12-parameter affine). Voxel size was resampled to $2 \times 2 \times 2$ mm. This step also involved the segmentation of the structural image into grey matter, white matter and cerebrospinal fluid. Finally, an $8 \times 8 \times 8$ mm Gaussian full width at half maximum filter was used for smoothing.

At the first (single-subject) level, data were analyzed using a general linear model [Friston et al., 1995] based on a 30 s boxcar function as implemented in SPM 8. Experimental conditions were modulated parametrically to take into consideration that the velocity conditions are conceivably dependent on each other. Therefore, two vectors (SPEM = all SPEM blocks; VELOCITY = SPEM 0.2 Hz and SPEM 0.4 Hz) were implemented and contrasted with the implicit baseline, which consisted of fixation blocks. Motion parameters were considered as additional regressors. BOLD impulse response was modelled as a canonical hemodynamic response-function (hrf).

At the second level, random-effects analyses (two-sample *t*-tests) were performed to identify group differences in the SPEM and VELOCITY contrasts. Additionally, multiple regression analyses with behavioral variables as covariates were used to identify voxelwise correlations between BOLD signal and SPEM performance for the whole sample and separately for both schizotypy groups. Voxelwise correlations were also examined for BOLD signal and schizotypy score separately for the LS and the HS.

TABLE I. Descriptive statistics of demographic and personality variables by schizotypy group

Schizotypy group ($N = 31$)	Low ($n = 19$)	High ($n = 12$)	Statistical test
Mean age (SD)	22.84 (2.97)	24.83 (6.22)	$t(29) = -1.20$, $P = 0.24$, $d = -0.41$
N male (%)	11 (57.9)	2 (16.7)	Fisher's exact test, $P = 0.03$, $\phi = 0.41$
IQ (MWT-B) (SD)	26.16 (2.83)	28.08 (2.91)	$t(29) = -1.82$, $P = 0.08$, $d = -0.67$
O-LIFE sum-score (SD)	4.84 (2.29)	22.00 (1.54)	$t(29) = -22.8$, $P < 0.001$, $d = -8.79$

Results for the SPEM > baseline and VELOCITY > baseline contrasts are reported whole brain FWE-corrected ($P < 0.05$, voxel level). Further results are presented for clusters below a threshold of $P \leq 0.05$ (FWE) with an uncorrected threshold of $\alpha = 0.001$ at the voxel level. Analyses were conducted whole brain, not masked for any region of interest. Anatomical labels were obtained using the Anatomy Toolbox [Eickhoff et al., 2005]. Functional localizations were identified from the previous literature [Dieterich et al., 2009; Lencer et al., 2004, 2005; Nagel et al., 2012; Petit and Haxby, 1999].

RESULTS

Data Prescreening

A total of 36 subjects (13 high and 23 low) met all inclusion criteria and participated in the fMRI session. For four subjects no MRI data were obtained due to technical problems, and one subject had to be excluded from data analysis because the subject performed less than 50% of the task, resulting in a final sample of 19 LS and 12 HS. Average age in the low schizotypy group was 22.84 years ($SD = 2.97$), and 11 participants (57.9%) were males. Average age in the high schizotypy group was 24.83 years ($SD = 6.22$), and two volunteers (16.7%) were males. Handedness ($P = 0.02$) was significantly associated with schizotypy, indicating that ambidexterity (laterality quotient; Oldfield, 1971) was found more often in high schizotypes than in the low schizotypy group. Gender was significantly associated with schizotypy as the number of males was higher in the low schizotypy group ($P = 0.03$). No significant differences between groups were found for age or verbal intelligence quotient (IQ) (all $P > 0.08$) (Table I).

For gain and frequency of saccades skewness ranged between -1 and $+1$ and Shapiro–Wilk tests were non-significant ($P > 0.17$ for all conditions in both groups). RMSE scores were skewed and Shapiro–Wilk tests were significant in the 0.4 Hz condition ($P < 0.03$). To include RMSE scores into the mixed ANOVA, variables were log transformed and reached normality according to Shapiro–Wilk statistics ($P > 0.15$). Levene's statistics were all non-significant for both groups ($P > 0.06$).

SPEM Behavioral Data

For seven subjects (two high schizotypals and five low schizotypals) saccade frequencies, maintenance gain and

RMSE scores could not be analyzed due to poor data quality. Table II represents untransformed means and standard deviations of SPEM measures by group.

Maintenance gain

A significant main effect of velocity was observed, $F(1,22) = 35.75$, $P \leq 0.001$, $\eta_p^2 = 0.62$, indicating higher gain values for SPEM 0.2 Hz than for SPEM 0.4 Hz. No significant main effect of group was observed, $F(1,22) = 0.02$, $P = 0.89$, $\eta_p^2 = 0.001$. There was no significant velocity-by-group interaction, $F(1,22) = 0.80$, $P = 0.38$, $\eta_p^2 = 0.04$.

Frequency of saccades

A significant main effect of velocity was observed, $F(1,22) = 139.51$, $P \leq 0.001$, $\eta_p^2 = 0.86$, indicating higher frequency of saccades for SPEM 0.4 Hz than for SPEM 0.2 Hz. No significant main effect of group was observed, $F(1,22) = 0.21$, $P = 0.65$, $\eta_p^2 = 0.01$. As shown in Figure 1, there was a significant velocity-by-group interaction, $F(1,22) = 7.20$, $P = 0.01$, $\eta_p^2 = 0.25$, suggesting a pattern of worse performance in HS at the slow but not the fast velocity. However, follow up t -tests for group differences were both nonsignificant [SPEM 0.2 Hz: $t(22) = 1.58$, $P = 0.065$, $d = 0.66$; SPEM 0.4 Hz: $t(22) = -0.35$, $P = 0.37$, $d = -0.15$].

Root mean square error

A significant main effect of velocity was observed, $F(1,22) = 33.60$, $P \leq 0.001$, $\eta_p^2 = 0.60$, indicating higher

TABLE II. Descriptive statistics of SPEM variables by schizotypy group

Schizotypy group ($N = 24$)	Low ($n = 14$)	High ($n = 10$)
SPEM 0.2 Hz		
Maintenance gain (%)	94.45 (4.97)	94.88 (6.75)
Saccade frequency (N/s)	0.80 (0.38)	1.05 (0.38)
RMSE	51.43 (24.61)	47.65 (15.59)
SPEM 0.4 Hz		
Maintenance gain (%)	89.90 (6.00)	88.72 (10.01)
Saccade frequency (N/s)	1.69 (0.57)	1.61 (0.51)
RMSE	66.12 (25.96)	58.23 (19.25)

SPEM = smooth pursuit eye movements; RMSE = root mean square error. Data represent untransformed means (standard deviations).

Figure 1.

Velocity-by-group interaction for frequency of saccades. $N = 14$ LS; $N = 10$ HS.

RMSE-scores for SPEM 0.4 Hz than for SPEM 0.2 Hz. No significant main effect of group was observed, $F(1,22) = 0.21$, $P = 0.65$, $\eta_p^2 = 0.009$. There was no significant velocity-by-group interaction, $F(1,22) = 1.05$, $P = 0.32$, $\eta_p^2 = 0.05$.

SPEM fMRI Data

Table III displays areas with significant BOLD response during SPEM compared to baseline. Activation was found across groups in left V3A, left V5, bilateral lingual gyri, bilateral calcarine gyri (extending to right V3A and right V5), bilateral FEFs, left SEF, bilateral middle cingulate cortices, bilateral PEFs, left inferior parietal lobule, bilateral

thalamus, and left cerebellum (Fig. 2, areas in blue). There was no significant brain activation during baseline compared to SPEM.

For the VELOCITY contrast (SPEM 0.4 Hz compared to SPEM 0.2 Hz, Supporting Information Fig. 1), BOLD signal was higher in a cluster (3544 voxels) that incorporates the bilateral cuneus (right: $x = 8$, $y = -84$, $z = 22$, $T = 6.10$; left: $x = -10$, $y = -92$, $z = 30$, $T = 9.41$), bilateral lingual gyri (right: $x = 6$, $y = -78$, $z = -6$, $T = 7.39$; left: $x = -10$, $y = -80$, $z = -2$, $T = 8.19$), bilateral superior occipital gyri (right: $x = 18$, $y = -86$, $z = 20$, $T = 5.68$; left: $x = -14$, $y = -92$, $z = 2$, $T = 7.62$), bilateral calcarine gyri (right: $x = 6$, $y = -84$, $z = 8$, $T = 7.81$; left: $x = -10$, $y = -76$, $z = 8$, $T = 7.39$), and left inferior occipital gyrus ($x = -22$, $y = -88$, $z = -6$, $T = 6.31$). No brain regions were significantly activated in the baseline > VELOCITY contrast.

Table IV shows differences between the low and high schizotypy groups for SPEM compared to baseline. HS were found to present significantly lower BOLD signal in bilateral middle occipital gyri, left fusiform gyrus, and right V3A (Fig. 2, areas in red). There were no areas that showed significantly higher BOLD for HS than for LS. No brain regions differed between groups in the baseline > SPEM contrast. There were no group differences in the VELOCITY contrast.

Figures 3 and 4 present the results for the multiple regression analyses. Associations between brain activation and SPEM dependent variables were only found in the high schizotypy group. RMSE in the 0.2 Hz condition correlated positively with BOLD signal in clusters in left fusiform gyrus (cluster size: 251 voxels; $x = -24$, $y = -72$, $z = -8$, $T = 8.12$)

TABLE III. BOLD response during SPEM vs. baseline across all subjects^a

Anatomical label <i>Functional label</i>	Hemisphere	Cluster size (<i>k</i>)	MNI coordinates			<i>T</i> -value
			<i>x</i>	<i>y</i>	<i>z</i>	
Superior occipital gyrus <i>Area V3A</i>	Left	14,426	-16	-86	12	17.83
Middle occipital gyrus <i>Area V5</i>	Left		-44	-74	2	17.00
Lingual gyrus	Right		8	-74	0	16.49
Calcarine gyrus extending into <i>Area V3A</i>	Right		10	-78	8	15.49
Calcarine gyrus	Left		-4	-78	10	13.93
Calcarine gyrus extending into <i>Area V5</i>	Right		20	-80	16	12.86
Lingual gyrus	Left		-18	-82	-4	12.66
Cerebellum	Left		-10	-70	-18	12.28
Precentral gyrus <i>Frontal eye field</i>	Left	4,444	-46	-8	46	11.81
Precentral gyrus <i>Frontal eye field</i>	Right		48	-8	52	11.66
Supplementary motor area <i>Supplementary eye field</i>	Left		0	-8	58	9.84
Middle cingulate cortex	Left	153	-12	-22	42	10.62
Superior parietal lobule <i>Parietal eye field</i>	Left	530	-26	-62	62	7.89
Inferior parietal lobule	Left		-30	-46	54	7.85
Thalamus	Left	43	-20	-28	-2	7.52
Thalamus	Right	50	22	-28	-2	7.43
Middle cingulate cortex	Right	47	12	-24	44	7.27
Superior parietal lobule <i>Parietal eye field</i>	Right	222	20	-60	58	7.03

MNI = Montreal Neurological Institute.

^aWhole brain FWE (family-wise error) corrected, $P < 0.05$.

Figure 2.

Activation pattern during SPEN compared to baseline across all subjects (blue) and differences between groups (low schizotypy > high schizotypy, red). Whole brain FWE-corrected ($P < 0.05$) for SPEN > baseline across all subjects, FWE-corrected with cluster threshold $k = 306$ for group differences (peak voxel threshold $P < 0.001$, uncorrected). $N = 19$ LS, $N = 12$ HS.

and right cuneus (cluster size: 222 voxels; $x = 10$, $y = -98$, $z = 10$, $T = 7.12$). For frequency of saccades in the 0.2 Hz condition positive correlations were found in right middle occipital gyrus (cluster size: 158 voxels; $x = 34$, $y = -90$, $z = 6$, $T = 7.74$). Gain scores in both velocity conditions were negatively associated with brain activity in clusters in middle occipital gyrus (cluster size: 521 voxels; $x = -22$, $y = -98$, $z = 14$, $T = 10.98$) extending to right cuneus ($x = 14$, $y = -100$, $z = 10$, $T = 10.50$) (0.2 Hz condition) and in left superior occipital gyrus (cluster size: 145 voxels; $x = -14$, $y = -98$, $z = 10$, $T = 7.92$) (0.4 Hz condition).

Schizotypy score was negatively correlated to BOLD signal in the high schizotypy group in clusters in bilateral

putamen and globus pallidus (right cluster size: 193 voxels; right putamen: $x = 30$, $y = 0$, $z = 8$, $T = 5.70$; right globus pallidus: $x = 20$, $y = -8$, $z = 2$, $T = 8.48$; left cluster size: 191 voxels; left putamen: $x = -26$, $y = 4$, $z = 8$, $T = 5.19$; left globus pallidus: $x = -20$, $y = -2$, $z = 6$, $T = 6.62$) in the 0.4 Hz condition. There were no significant associations for the low schizotypy group.

DISCUSSION

The aim of the present study was to investigate, for the first time, the neural correlates of SPEN performance in individuals with high levels of schizotypy. A significant interaction between schizotypy group and target velocity indicated that, at the level of SPEN performance, differences between HS and LS were present for saccade frequency in the 0.2 Hz but not in the 0.4 Hz condition. However, the groups did not differ in gain or RMSE scores in either condition. At the neural level, the high schizotypy group showed lower brain activation in different regions in the occipital lobe, an effect that was independent of target velocity.

A first finding of the present study was that the performance of pursuit eye movements was associated with brain activation in pursuit-related pathways consistent with the previous literature [Ilg and Thier, 2008; Krauzlis, 2004; Leigh and Zee, 2006; Thier and Ilg, 2005]. Specifically, there was activation in left V3A, left V5, bilateral lingual gyri, bilateral calcarine gyri (extending to right V3A and right V5), bilateral FEFs, left SEF, bilateral middle cingulate cortices, bilateral PEFs, left inferior parietal lobule, bilateral thalami, and left cerebellum. This initial finding underlines the validity of the task that was used.

Differences in brain activation related to an increase in target velocity were observed in bilateral cuneus, bilateral lingual lingual gyri, bilateral superior occipital gyri, bilateral calcarine gyri, and left inferior occipital gyrus. These findings agree with the results of Culham et al. (2001b), who emphasized the role of visual areas (e.g., area V3A and lingual gyrus) in motion processing. Our findings thus indicate that such visual areas are taxed more strongly with increasing target (and eye) velocity. Furthermore, the findings are comparable to those of Nagel et al. [2008], who examined pursuit eye movements during continuous and target blanking conditions using a step-ramp paradigm with different velocities. Similar to us, for the main effect of velocity, these authors also found increased activation in the cuneus.

The main finding of the present study, however, concerns differences between high and low schizotypy groups on the neural level. These were found to be located in occipital regions: BOLD signal during SPEN compared to baseline was lower in the high schizotypy group compared to the low schizotypy group in a part of the middle occipital gyri close to visual area V5, left fusiform gyrus and right V3A. These areas have been found to play an important role in

TABLE IV. BOLD response during SPEM versus baseline group differences (low > high)^a

Anatomical label <i>Functional label</i>	Hemisphere	Cluster size (<i>k</i>)	MNI coordinates			<i>T</i> -value	FWE _c -corrected <i>P</i>
			<i>x</i>	<i>y</i>	<i>z</i>		
Middle occipital gyrus	Left	406	-44	-88	0	5.55	0.01
Fusiform gyrus	Left		-32	-80	-18	5.24	
Superior occipital gyrus	Right	306	24	-88	28	4.69	0.04
Area V3A							
Middle occipital gyrus	Right		40	-78	20	4.49	

MNI = Montreal Neurological Institute.

^aCluster threshold was set at $k = 306$ (peak voxel threshold $P < 0.001$, uncorrected).

Figure 3.

Voxelwise correlation between BOLD signal in occipital lobe and behavioral performance variables. FWE_c-corrected with cluster threshold $k = 251$ (a), $k = 222$ (b), $k = 521$ (c), $k = 145$ (d), $k = 158$ (e) (peak voxel threshold $P < 0.001$, uncorrected). R^2 refers to high schizotypy group. $N = 14$ LS, $N = 10$ HS.

Figure 4.

Voxelwise correlation between BOLD signal in globus pallidus and putamen and schizotypy score. FWE_c-corrected with cluster threshold $k = 193$ (a), $k = 191$ (b) (peak voxel threshold $P < 0.001$, uncorrected). R^2 refers to high schizotypy group. $N = 19$ LS, $N = 12$ HS.

perceiving motion [Braddick et al., 2001; Culham et al., 2001b; Sinaert et al., 1999; Tootell et al., 1995, 1997].

Motion perception is hypothesized to represent a key component of pursuit eye movements [Levy et al., 2010], and abnormal motion perception has been found to be related to pursuit deficits in patients with schizophrenia (Chen et al., 1999a, 1999b; Stuve et al., 1997). Lencer et al. [2011] compared the neural activation pattern of untreated first-episode schizophrenic patients, psychotic bipolar disorder patients and healthy controls during a passive motion task and a pursuit task in which subjects actively tracked target motion. During the passive motion task, both patient groups were found to display lower BOLD signal in the posterior parietal projection fields of area V5. During the pursuit task, both patient groups showed greater activation in anterior intraparietal sulcus and insula, and schizophrenics, additionally, showed greater BOLD signal in the dorsolateral prefrontal cortex and dorsomedial thalamus. The authors suggested that lower brain function in the passive motion task might reflect reduced bottom-up transfer of visual motion information

to the parietal association cortex. Thus, greater activation during pursuit might be the result of an increase in extra-retinal input to compensate for reduced input of visual motion information about target speed and tracking error to parietal areas that are responsible for sensorimotor transformations [Lencer et al., 2011].

Furthermore, there is evidence that BOLD correlated significantly with mean eye velocity in controls but not in patients [Lencer et al., 2005] and that neural activation in V5 was less strongly related to target velocity in patients than in controls [Nagel et al., 2012]. To summarize, these findings imply that motion perception is impaired in patients that suffer from schizophrenia. Our data similarly suggest hypofunction in visual areas in subjects with highly schizotypal traits. However, schizophrenia patients also presented increased brain activation in further posterior retinal motion regions in the medial occipitotemporal cortex [Hong et al., 2005], which were not seen to differ between groups here.

It should be noted that occipitotemporal areas (including area V3A) have been found to play a role not only in

motion processing but also in load-dependent attention responses during tracking of moving stimuli [Culham et al., 2001a; Jahn et al., 2012]. Attention represents an important factor in pursuing a moving target [Barnes, 2008] and when enhancing attention, pursuit performance has been found to be improved in patients that suffer from schizophrenia [Cegalis and Sweeney, 1981; Schlenker et al., 1994; Yee et al., 1998] and their unaffected offspring [Rosenberg et al., 1997]. Therefore, our findings are not necessarily indicative of a motion processing deficit but may also stem from attentional dysfunctions.

Interestingly, reduced activation in visual areas in schizophrenia patients and schizotypal individuals have also been observed in saccadic eye movement tasks. Camchong et al. [2008] found that both schizophrenia patients and their first-degree relatives demonstrated decreased BOLD signal in the middle occipital gyrus, insula, and cuneus during volitional saccades. The authors hypothesized that abnormal activation of these areas might be associated with poor early sensory and attention processing after stimulus presentation [Camchong et al., 2008]. Compatible with these findings, Aichert et al. [2012] demonstrated that decreased activation of the visual cortex (calcarine sulcus) was the strongest predictor of schizotypy in an fMRI study of prosaccade and antisaccade eye movements. Together, these findings suggest that deficits in visual areas are observable not only when the visual system is taxed through motion-sensitive pursuit tasks but also during volitional and automatic saccade tasks.

In addition to reduced BOLD signal in visual motion areas, patients who suffer from schizophrenia have also been found to present lower brain activation in sensorimotor system, for example, FEF or SEF [Hong et al., 2005; Keedy et al., 2006]. Here, the high schizotypy group was not found to differ from low schizotypals in frontal regions suggesting the operation of additional genetic and/or illness-related influences in the clinical disorder.

Consistent with the results of previous studies [Lenzenweger and O'Driscoll, 2006; Smyrnis et al., 2007], we also found high and low schizotypy groups to differ in total saccade frequency, though the differences were not present in both conditions. An interaction indicated that group differences were found in the lower but not the higher target speed condition. This pattern may at first seem unexpected, as greater group differences may have been hypothesized to emerge with greater target velocity (and higher demands on the pursuit system). In fact, there is evidence in the literature of greater pursuit impairments with increasing target velocity in patients with schizophrenia [Haraldsson et al., 2008]. However, in line with the current findings, a study by Ettinger et al. [2004], who compared schizophrenia patients, their siblings, and healthy controls, found differences between the sibling group and the control group for SPEM gain and anticipatory saccade rate in the low (10°/s) but not in the high (24°/s) speed condition.

An unexpected finding was that there were no differences between high and low schizotypy groups regarding

maintenance gain and RMSE. Deficits in these parameters had previously been shown for highly schizotypal subjects [Gooding et al., 2000; Holahan and O'Driscoll, 2005; van Kampen and Deijen, 2009; Kattoulas et al., 2011; Lenzenweger and O'Driscoll, 2006; Smyrnis et al., 2007] and schizophrenic patients [O'Driscoll and Callahan, 2008]. Other studies, however, failed to replicate SPEM differences between highly and low schizotypal subjects. Simons and Katkin [1985] found no differences in the mean quality of pursuit, but high schizotypes showed a higher variability in pursuit quality. No differences in SPEM tracking performance were found by Blackwood et al. [1994] for adult subjects diagnosed as "schizoid" in childhood. Gooding et al. [2000] compared two negative and one positive schizotypy group to healthy controls and found differences in RMSE and gain but not in total or anticipatory saccade rates. In a study by Lenzenweger and O'Driscoll [2006], catch-up saccade rate was only linked to disorganized schizotypy but not to the total Schizotypal Personality Questionnaire (SPQ) score [Raine, 1991].

Reasons for our failure to replicate RMSE and gain deficits may include the instrument that was chosen to measure schizotypy. However, associations between schizotypy and SPEM deficits have been demonstrated with different schizotypy scales, for example, Chapman Scales [Chapman et al., 1976, 1978; Eckblad and Chapman, 1983; see Gooding et al., 2000; Holahan and O'Driscoll, 2005; O'Driscoll et al., 1998; Smyrnis et al., 2007], SPQ [Raine, 1991; see Kattoulas et al., 2011; Lenzenweger and O'Driscoll, 2006; Smyrnis et al., 2007] or Schizotypic Syndrome Questionnaire (SSQ) [van Kampen, 2006; see van Kampen and Deijen, 2009]. Furthermore, O-LIFE and SPQ sum scales are highly correlated ($r = 0.81$), which suggests that both measure nearly the same concept of schizotypy [Asai et al., 2011]. As the items of the O-LIFE are, however, easier to be endorsed by members of the general population [Grant et al., 2013] and not, as in the SPQ, based on clinical criteria for schizotypal personality disorder [Raine, 1991], we would assume differences in schizotypal traits between our high and low groups to be less pronounced than had, for example, the SPQ been used. This reduced schizotypal variance between groups may, thus, explain why we could not replicate the deficits in RMSE and gain in highly schizotypal participants. This conjecture, at the same time, underlines the importance of those deficits that we were able to significantly detect.

We did not find any associations between BOLD signal and the SPEM behavioral performance measures or the schizotypy score in the low schizotypal subjects or, for SPEM performance, in the whole sample. However, in the high schizotypy group, there were significant correlations of BOLD with both behavioral performance and schizotypy level.

Regarding the behavioral level, higher brain activation was associated with worse performance in different occipital regions. This finding may at first seem at odds with the observation of reduced occipital BOLD and slightly worse performance in the high schizotypy group. However, this

result may be in agreement with the hypothesis that there might be compensatory or protective factors in highly schizotypal subjects [Ettinger et al., 2014; Siever and Davis, 2004]. Although schizotypy and schizophrenia are closely linked on different levels of measurement there might be protective factors such as higher prefrontal cortical sickness [Kühn et al., 2012] or higher global and focal gray-matter volume in posterior cingulate cortex and medial precuneus [Modinos et al., 2010] that reduces the vulnerability to transition into schizophrenia. The association of higher BOLD with worse performance in our sample of HS might be compatible with these findings, as it indicates that within this group at risk for schizophrenia [Gooding et al., 2005] subjects tend to show only one of two deficits, that is, reduced BOLD or impaired pursuit, but not both. Given the association between worse performance and reduced BOLD in schizophrenia [Lencer et al., 2005] it is tempting to speculate that individuals without protective or compensatory influences on one of these mechanisms are most likely to attain a clinical diagnosis.

Furthermore, we found in the high schizotypy group that BOLD signal in bilateral putamen and globus pallidus was negatively associated to schizotypy score. BOLD signal in the basal ganglia has previously been described in the control of pursuit eye movements in healthy subjects and non-human primates [Kimmig et al., 2008; Krauzlis, 2004; Lencer et al., 2004; O'Driscoll et al., 2000; Yoshida and Tanaka, 2009]. Activation of globus pallidus was shown to play a role in the velocity of movement [Turner et al., 1998] and Nagel et al. [2012] found that activation of right putamen during a SPEM task with different velocities was lower in schizophrenic patients compared to healthy controls.

There are some limitations to our study that should be noted. First, as community samples and samples from relatives of schizophrenic patients have been found to differ qualitatively in their schizotypal characteristics [Thaker et al., 1993, 1996], our findings are not directly comparable to findings from studies that examined schizotypal traits in relatives of patients.

Second, the gender distribution in our sample differed between the low and high schizotypy groups. We therefore analyzed the BOLD data for gender effects (data not shown). There were no differences in BOLD signal between males and females, indicating that differences in brain activation between low and high schizotypy groups are unlikely to be driven by gender differences.

Furthermore, sample sizes in previous studies that found behavioral SPEM differences between low and high schizotypy groups [Gooding et al., 2000; Holahan and O'Driscoll, 2005] were larger than the sample size of the present study. Therefore, the present sample may have been insufficient to detect small effects and a replication of our design using larger samples would help to validate the current results. Conversely, significant results from small samples are even more compelling and suggest that the actual effect sizes in the population may be even larger [Friston, 2012].

Participants were strictly instructed not to drink alcohol the day before testing, but there was no breathalyzer test to measure the concentration of alcohol during the second study session.

Another limitation is that we did not discriminate between the different dimensions of schizotypy. Although positive, negative, and disorganized schizotypes have all been found to show deficits in pursuit eye movements, differences have also been reported [Holahan and O'Driscoll, 2005; Smyrnis et al., 2007]. Thus, it would be of interest to examine whether those subtypes also differ on the brain-functional level.

Finally, as we are not able to resolve whether neural group differences in the SPEM contrast are the result of deficits in motion processing or in attentional control, further studies are needed to clarify the role of motion processing and attention in the SPEM network of high schizotypal subjects.

To conclude, the present study suggests that subjects with highly schizotypal traits show a higher frequency of saccades in the low speed condition, as indicated by the significant velocity-by-group interaction. Furthermore, high schizotypes had lower brain activation in areas that are associated with motion perception and early sensory and attentional processing, compatible with evidence of impaired motion perception in schizophrenia. Therefore, our findings suggest overlap between schizotypy and schizophrenia on cognitive and neurophysiological levels.

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