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Manipulating visual scanpaths during facial emotion perception modulates functional brain
activation in schizophrenia patients and controls

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Abstract

Individuals with schizophrenia exhibit deficits in facial emotion processing, which have been associated with abnormalities in visual gaze behaviour and functional brain activation. However, the relationship between gaze behaviour and brain activation in schizophrenia remains unexamined. Studies in healthy individuals and other clinical samples indicate a relationship between gaze behaviour and functional activation in brain regions implicated in facial emotion processing deficits in schizophrenia (e.g., fusiform gyrus), prompting the question of whether a similar relationship exists in schizophrenia. This study examined whether manipulating visual scanpaths during facial emotion perception would modulate functional brain activation in a sample of 23 schizophrenia patients and 26 community controls. Participants underwent functional magnetic resonance imaging while viewing pictures of emotional faces. During the typical viewing condition, a fixation cue directed participants' gaze primarily to the eyes and mouth, whereas during the atypical viewing condition gaze was directed to peripheral features. Both viewing conditions elicited a robust response throughout face-processing regions. Typical viewing led to greater activation in visual association cortex including the right inferior occipital gyrus/occipital face area, whereas atypical viewing elicited greater activation in primary visual cortex and regions involved in attentional control. There were no between-group activation differences in response to faces or interaction between group and gaze manipulation. The results indicate that gaze behaviour modulates functional activation in early face-processing regions in individuals with and without schizophrenia, suggesting that abnormal gaze behaviour in schizophrenia may contribute to activation abnormalities during facial emotion perception.

Keywords: eye tracking, facial emotion perception, fMRI, OFA, psychosis

General Scientific Summary

Facial emotion recognition difficulties in schizophrenia have been linked to abnormalities in brain activation and in eye gaze behaviour while viewing emotional faces. Our study demonstrated an association between eye gaze patterns and activation in face perception brain regions in both schizophrenia patients and controls. These results suggest that gaze behaviour may contribute to the brain activation abnormalities reported in schizophrenia during facial emotion perception.

Manipulating visual scanpaths during facial emotion perception modulates functional brain activation in schizophrenia patients and controls

A characteristic feature of schizophrenia is the presence of deficits in social cognition, including in facial emotion processing (i.e., the ability to accurately perceive and recognize emotions from faces; Kohler, Walker, Martin, Healey, & Moberg, 2010). Facial emotion processing deficits are found across illness phases (prodromal, first-episode, chronic; Green et al., 2011) and to some extent in unaffected relatives of individuals with schizophrenia (Lavoie, Bédard Lacroix, Godmaire-Duhaime, Jackson, & Achim, 2013), suggesting these deficits may represent an endophenotype for the disorder. Moreover, facial emotion processing is a significant determinant of functional outcome in schizophrenia (Fett et al., 2011), suggesting these deficits are an important remediation target to promote patient outcomes.

Research into the neurobiological basis of facial emotion processing has delineated a distributed network of regions involved in the visual analysis of facial features (the occipital face area, OFA; fusiform face area, FFA; posterior superior temporal gyrus, STS) and more elaborate affective and semantic processing (e.g., amygdala, temporal pole, prefrontal cortex) (Duchaine & Yovel, 2015; Haxby, Hoffman, & Gobbini, 2000; Ishai, 2008). Meta-analyses of functional magnetic resonance imaging (fMRI) studies of facial emotion perception in schizophrenia indicate the presence of activation abnormalities, including hypoactivation in the regions described above (Li, Chan, McAlonan, & Gong, 2010; Taylor et al., 2012).

Other studies have used eye tracking to investigate visual attention to emotional faces and indicate that healthy individuals typically view faces using an “inverted triangle” or “T-shaped” gaze pattern, in which observers fixate predominantly the eyes, and also the nose and mouth (Henderson, Williams, & Falk, 2005; Luria & Strauss, 1978). Research examining gaze

behaviour during facial emotion perception in schizophrenia indicates that compared to controls, schizophrenia patients have a more restricted scanning strategy characterized by a smaller number of fixations with increased duration, shorter distances between fixations, and proportionally fewer fixations to salient facial features (Toh, Rossell, & Castle, 2011).

An outstanding question is whether there is a relationship between the reported functional activation patterns and eye gaze behaviour in schizophrenia during facial emotion perception. Evidence of a relationship between gaze behaviour and face-responsive activation in healthy controls was demonstrated in a study by Morris and colleagues (2006), who manipulated visual scanpaths to mimic “typical” or “atypical” face scanning. They reported greater activation for typical relative to atypical blocks in a face-responsive region of interest (ROI) comprising bilateral ventral occipito-temporal/fusiform cortex. Exploratory analyses revealed additional greater activation in regions involved in visual attention and oculomotor control (bilateral frontal eye fields and intraparietal sulcus), medial superior frontal gyrus, and right inferior frontal gyrus and superior colliculus. Of note, a similar association between gaze behaviour and functional activation has been documented in autism spectrum disorder (ASD) (Dalton et al., 2005; Perlman, Hudac, Pegors, Minshew, & Pelphrey, 2011; Tottenham et al., 2013), a disorder similarly marked by impaired social cognition, functional abnormalities in the FFA and amygdala, and restricted gaze behaviour during face perception (Pelphrey et al., 2002; Schulz, 2005). Demonstrating the presence of a comparable relationship between gaze behaviour and functional activation during facial emotion perception in schizophrenia would have important implications for understanding the nature and significance of activation abnormalities reported in previous facial emotion processing studies in schizophrenia, particularly in light of the accompanying gaze abnormalities in the disorder.

In the present study, we examined whether manipulating visual scanpaths during facial emotion perception modulates functional brain activation in face-processing regions in individuals with schizophrenia and community controls, with the goal of providing a causal test of the influence of gaze behaviour on functional activation in schizophrenia. We hypothesized that a condition in which participants make “typical” scanpaths with fixations primarily to salient facial features would elicit greater activation in the face-processing network compared to an “atypical” scanpath condition with fixations primarily to non-salient facial features.

Specifically, we hypothesized that the increased fMRI response during “typical” compared to “atypical” viewing would occur in the two key face-processing ROIs of the ventral visual pathway: the OFA and FFA (Haxby et al., 2000). We further examined whether modulation would occur in several exploratory ROIs: the STS and amygdala due to 1) their role in facial expression and emotion perception (Duchaine & Yovel, 2015; Haxby et al., 2000); 2) documented activation abnormalities in these regions during facial emotion perception in schizophrenia (Li et al., 2010; Taylor et al., 2012); and 3) the potential role of the amygdala in orienting attention to the eyes (Gamer & Buchel, 2009); as well as the frontal eye field (FEF) and intraparietal sulcus (IPS) due to their role in oculomotor control and visual attention (Müri, 2006).

Method

Participants

Participants were 26 community controls and 23 individuals with a DSM-5 diagnosis of schizophrenia or schizoaffective disorder (hereafter referred to as schizophrenia patients). Schizophrenia patients were recruited through outpatient clinics, community organizations, and from a database of individuals who participated in previous studies. Community controls were

recruited through advertisements posted online and in the community. Participant exclusion criteria were: age below 18 or above 60 years, estimated Intelligence Quotient (IQ) below 70, non-remitted current substance use disorder, history of head injury resulting in unconsciousness greater than 20 minutes or hospitalization, history of neurological disorder, history of electroconvulsive therapy, less than normal or corrected-to-normal vision, and MRI contraindications. Additional exclusion criteria for controls were personal or family history of psychotic or bipolar disorders, current major depressive episode, and lifetime use of antipsychotic medication. All schizophrenia patients were being treated with antipsychotic medication.

Diagnoses were assessed by the Structured Clinical Interview for DSM-5 (First, Williams, Karg, & Spitzer, 2015), and global functioning was rated via the Social and Occupational Functioning Assessment Scale (American Psychiatric Association, 2000). IQ was estimated using the Wechsler Abbreviated Scale of Intelligence – Second Edition two-subtest form (Wechsler, 2011). Symptom severity and social functioning in patients were assessed through the Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987) and Social Functioning Scale (Birchwood, Smith, Cochrane, Wetton, & Copestake, 1990), respectively. All participants provided written informed consent prior to participating. The University of Calgary Conjoint Health Research Ethics Board approved the study protocol.

Tasks and Stimuli

Participants first completed a “free viewing” facial emotion discrimination task in which gaze behavior was recorded to assess gaze patterns and recognition performance during unconstrained viewing, followed by two versions (practice and fMRI) of the “directed viewing” facial emotion perception task. Gaze behaviour was recorded during the practice task to ensure

that participants could successfully perform the task prior to the fMRI scan but was not recorded during the fMRI scan.

Free Viewing Facial Emotion Discrimination Task.

In this task, participants viewed photographs of faces while gaze behaviour was recorded with an eye tracker, and made a key-press indicating whether each face corresponded to a given target emotion category: anger, fear, or sadness. There were three target emotion blocks (one for each emotion category) presented in a randomized order. Each block included 23 trials comprised of six target emotion faces and 17 non-target emotion faces (four each of the other two emotion categories and nine neutral expression faces). Before each trial, participants viewed a fixation screen and were required to fixate to a circle randomly presented to a corner of the screen to verify the calibration accuracy of the eye tracker. Each face was presented for 5 s followed by a 2 s response screen. Participants were instructed to look at the face for the total duration of the trial and to wait until the response screen appeared before providing a response. The task was programmed with Experiment Builder (SR Research Ltd., Mississauga, ON, Canada) using grayscale stimuli from the Karolinska Directed Emotional Faces (KDEF) database (Lundqvist et al., 1998). Stimuli were centered on a gray background and subtended a visual angle of approximately 17.3° of width and 15.3° of height at a viewing distance of 76 cm.

Directed Viewing Facial Emotion Perception Task.

This task was modeled after the paradigm of Morris and colleagues (2006). Participants completed two versions of the task: a practice version outside the scanner in which eye gaze data were recorded, and the fMRI version. An illustration of the task design is presented in Figure 1.

Participants viewed photographs of faces while a small fixation cue appeared sequentially at different locations on the face, and participants were instructed to track the cue location and

only look at the area of the face directly behind and surrounding the cue. The fixation cue appeared primarily at the eyes and mouth for the typical viewing blocks or primarily at peripheral facial features for the atypical viewing blocks. Additionally, a visual control condition was included in which the cue appeared at random locations over a scrambled face image (shown in Figure 1). There was no facial emotion discrimination component to minimize conflicting task demands that would lead participants to attend to emotionally informative facial features rather than the cue locations. However, to encourage and assess participants' engagement throughout the task, participants had to make a key press following each block to indicate the side of the screen (i.e., left or right) where the last cue of the block was presented.

The task was programmed in Presentation (Neurobehavioral Systems, CA, USA), with cue parameters generated using custom code written in C# in Microsoft Visual Studio (Microsoft Corporation, Redmond, WA, USA). Stimuli were selected from fearful, neutral, and sad facial expressions from the KDEF database. Scrambled faces for the control condition were generated from KDEF images and similar to control stimuli used in previous neuroimaging studies of facial emotion perception in schizophrenia (e.g., Gur et al., 2007). Images were scaled to the scanner display and subtended a visual angle of approximately 19.3° in width and 22.2° in height.

The fixation cue was a white cross subtending approximately 0.5° visual angle and presented for an average duration of 1000 ms (range 600–1300 ms) per cue location. There were 11 discrete cue locations per face block, and each face was presented for 11 s. For typical viewing blocks, the cue landed 8 times on the eyes (73% of cue locations), twice on the mouth (18% of cue locations), and once elsewhere on the face. For atypical viewing blocks, the cue landed only once (9% of cue locations) on the eyes or mouth and 10 times on non-salient facial features (Figure 1). As in Morris et al. (2006), the percentages for the typical viewing scanpaths

were modeled on the face-viewing patterns of healthy control subjects (Pelphrey et al., 2002). Importantly, the average Euclidian distance between successive cue locations was equated across the three task conditions and approximately 5.8° . Please see the Supplementary Material for a detailed description of the generation of cue sequences.

Each task run had an alternating structure beginning with a 13 s central fixation screen, followed by a typical, control, and atypical block (11 s each), with a 2 s response screen appearing at the end of each block (Figure 1). This structure was repeated six times per run, with an additional central fixation screen at the end of the run. The order of the alternations between typical and atypical blocks was reversed (i.e., atypical, control, typical) for half of the task runs. The typical and atypical conditions each contained two blocks of fearful, neutral, and sad faces randomly distributed within a run, and each face in the task was unique. Participants completed six task runs presented in randomized order, for a total of 36 typical viewing, 36 atypical viewing, 36 control blocks, and 42 rest blocks per participant.

Participants also completed 3 practice runs of the task with eye tracking outside the scanner prior to the fMRI session. Stimuli were scaled for the computer display, with images subtending a visual angle of 17.3° in width and 15.3° in height, and with an average Euclidian distance between successive cue locations in each condition of 5.4° .

Data Acquisition and Analysis

Demographic and accuracy data analysis.

Demographic data were analyzed using independent t-tests and Pearson's chi-squared tests. Facial emotion discrimination accuracy for the Free Viewing task was analyzed using two separate analyses of variance (ANOVA): a 2×4 (Group [controls, patients] $\times$ Stimulus Expression Condition [anger, fear, neutral, sadness]) ANOVA and a 2×3 (Group [controls,

patients] $\times$ Target Emotion Condition [anger, fear, sadness]) mixed-design ANOVA. These analyses permitted examining bottom-up (stimulus-driven) and top-down (task context) effects of emotion, respectively. However, since the main effect of group and group by condition interaction results were similar between the two approaches, only the group by stimulus expression condition ANOVA results are reported here, and the group by target emotion condition ANOVA results are reported in the Supplementary Material. Accuracy on the left-right judgment for the Directed Viewing task was analyzed using independent t-tests. For all ANOVA analyses (including those described below), statistically significant ($p < .05$, two-tailed) findings were followed up by planned pairwise comparisons when relevant, and independent t-tests were used instead of pairwise comparisons when the homogeneity of variance assumption was violated. Greenhouse-Geisser adjustments to degrees of freedom were made when the assumption of sphericity was violated. Reported significance values were corrected for multiple comparisons using the Bonferroni correction. Effect sizes are reported as partial eta squared. All behavioural analyses were performed using IBM SPSS Statistics (IBM Corp., Armonk, NY).

Eye gaze recording, data reduction, and analysis.

Gaze recording for the behavioural tasks was performed with an EyeLink 1000 eye tracking system (SR Research Ltd., Mississauga, ON, Canada), with a sampling rate of 1000 Hz and an average gaze recording error of less than 0.5° visual angle. Recording accuracy was ensured using a calibration and validation procedure prior to each task block, with calibration drift assessed throughout each task. Data reduction was performed using the EyeLink Data Viewer software package (SR Research Ltd., Mississauga, ON, Canada). Individual trials were inspected for data quality, and gaze drift correction and data exclusion were performed when necessary. Additional details of the eye gaze recording and data reduction are provided in the

Supplementary Material. The resulting sample sizes for the eye gaze analyses were 26 controls and 21 patients for the Free Viewing task and 25 controls and 22 patients for the Directed Viewing practice task.

Free Viewing task.

The dependent variables for this task were the percentage of fixations (%Fixations) and dwell time percentage (%DwellTime) to salient facial features (eyes, nose, and mouth, combined). The salient facial feature regions were defined for each stimulus image, as described in the Supplementary Material. Dependent variables were analyzed using a 2×4 (Group [controls, patients] $\times$ Stimulus Expression [anger, fear, neutral, sadness]) mixed-design ANOVA and a 2×3 (Group [controls, patients] $\times$ Target Emotion [anger, fear, sadness]) mixed-design ANOVA. Similar to the analysis of emotion discrimination accuracy, only the group by stimulus expression ANOVA results are reported here, and the group by target emotion results are reported in the Supplementary Material.

Directed Viewing task (practice version).

Two metrics were evaluated to verify that participants successfully fixated to the cues: 1) the percentage of cues in a block to which the participant made at least one fixation ($\%CoincidenceCount = \text{number of successfully fixated cues} / 11 \text{ cues in a block} \times 100$); 2) the duration of fixations to a given cue, converted to percentage ($\%CoincidenceDuration = \text{duration of coincidences between fixations and cues} / \text{total block fixation time} \times 100$).

Fixation data for each participant were produced in EyeLink Data Viewer and the above metrics were calculated using custom software written in C# in Microsoft Visual Studio. In order to count as coinciding with the cue, a fixation was required to have temporal overlap with a given cue presentation and meet at least one of two spatial overlap criteria: 1) have a Euclidean

distance of no more than 45 pixels (approximately 1.5° visual angle) from the cue location, or 2) be located within the same facial feature as the cue if the cue was displayed on a salient facial feature (eyes and mouth). The two coincidence metrics were analyzed using separate 2×3 (Group [patients, controls] $\times$ Viewing Condition [typical, atypical, control]) mixed-design ANOVAs.

fMRI data.

Image acquisition.

Scanning was performed using a 3 T General Electric Discovery MR750 scanner (General Electric Healthcare, Waukesha, Wisconsin, USA) equipped with an 8-channel head coil at the Seaman Family Magnetic Resonance Research Centre, University of Calgary. For each of the six functional runs, 131 (plus 4 discarded dummy volumes) T2*-weighted gradient echoplanar images (EPI) were acquired using the following parameters: 46 oblique slices with descending acquisition and whole-brain coverage, slice thickness = 3.5 mm, echo time (TE) = 30 ms, repetition time (TR) = 2500 ms, flip angle = 70° , field of view (FOV) = 22 cm, matrix = 64×64 , voxel size = $3.4 \times 3.4 \times 3.5$ mm. Additionally, a whole-brain T1-weighted MP-RAGE scan was acquired to anatomically register the functional data (TE = 3.1 ms, TR = 7.4 ms, inversion time = 650 ms, FOV = 25.6 cm, 236 1 mm slices). High-order shimming was employed to reduce EPI magnetic field inhomogeneities, and a B_0 map was acquired to perform offline EPI geometric distortion correction.

fMRI preprocessing.

Imaging preprocessing and analyses were performed using tools from the FMRIB Software Library (FSL) (www.fmrib.ox.ac.uk/fsl) version 5.0.10. Preprocessing included image realignment, EPI geometric distortion correction, non-brain tissue removal, grand-mean intensity

normalization, spatial smoothing using a 7 mm full-width-half-maximum (FWHM) Gaussian kernel, and highpass temporal filtering ($\sigma = 45$ s). Functional images were first registered to the participant's structural image using rigid body transformations and a boundary-based registration cost function, and then to the Montreal Neurological Institute (MNI) Avg152 standard-space template using affine transformations of the structural image and further refinement with nonlinear transformations.

EPI volumes with extreme intensity values associated with large head motion (metric values exceeding the 75th percentile + 1.5 times the interquartile range) were identified using FSL Motion Outliers and de-weighted in the fMRI analysis during subject-level modeling. There were no group differences in head motion assessed by average absolute displacement, $t(40.79) = 0.87, p = .388$; however, the patient group ($M = 0.08$ mm, $SD = 0.05$) had significantly higher average relative (i.e., frame-to-frame) displacement than the control group ($M = 0.06$ mm, $SD = 0.02$), $t(26.19) = -2.32, p = .028$. Therefore, participant average relative displacement was included as a nuisance covariate in the group-level analyses.

fMRI artifact removal and additional data exclusion.

Two controls and two patients included in the sample were scanned prior to the replacement of a malfunctioning scanner head coil. These data underwent quality control inspection to identify images contaminated by coil-related artifact, followed by data-cleaning using an independent component analysis (ICA)-based temporal filtering procedure. All scans for these participants either did not contain coil-related artifact originally or were successfully denoised (i.e., coil artifact was no longer present on ICA maps). Details of this process are documented in the Supplementary Material.

To ensure data quality, functional runs were excluded from the analysis if participants made more than three incorrect responses and/or had more than two timed-out responses on the left-right judgments (controls: one run; patients: three runs across two participants). One additional participant from each group had one missing functional run due to equipment malfunction.

fMRI analysis.

Subject-level analyses were conducted with FSL's FEAT. Model fitting was performed using time-series regression with local autocorrelation correction. Boxcar functions representing each block type were convolved with a double gamma hemodynamic response function to create model regressors. The six head motion correction parameters and each regressor's temporal derivative were included as nuisance regressors to improve model fit, and timepoints identified as motion outliers (described above) were de-weighted using individual regressors. The following subject-level contrasts were conducted: 1) Faces (Typical + Atypical) > Control; 2) Typical > Atypical; and 3) an Atypical > Typical. Second-level fixed-effects analyses were then performed to average intra-subject statistics images from the contrasts above across scanner runs prior to group-level analysis.

Group-level analyses were performed for *a priori* ROIs, followed by an exploratory whole-brain analysis. ROIs of primary interest (i.e., with directional hypotheses) were the right and left inferior occipital cortex (encompassing the anatomical location of OFA) and temporal-occipital fusiform gyrus (encompassing the anatomical location of FFA). These ROIs are referred to as the OFA and FFA hereafter for clarity. ROIs of secondary interest (i.e., exploratory ROIs) were the right and left STS, amygdala, FEF, and IPS. Please see the Supplementary Material for details of the creation of the ROI masks. Group-level analyses included participants'

average framewise displacement as a nuisance covariate, and were performed using nonparametric permutation tests using FSL's Randomise (Winkler, Ridgway, Webster, Smith, & Nichols, 2014), with 5000 permutations per statistical test. Statistical inference was conducted using Threshold-Free Cluster Enhancement (TFCE), thresholded at $p < .05$, familywise error (FWE)-corrected. For the ROI analysis, each ROI served as a separate input mask, and the FWE-corrected results were then evaluated for significance using a Bonferroni-corrected α level to account for the number of primary and secondary ROIs being evaluated. Thus, $\alpha = 0.0125$ ($0.05/4$ regions) was used for the primary ROIs and $\alpha = 0.00625$ ($0.05/8$ regions) for the secondary ROIs.

Group-level analyses were also performed excluding the two control and two patient participants scanned prior to the scanner coil replacement. As the differences between the two sets of results were minor, with no differences in the results of group comparisons, the full sample results are reported here and the reduced sample results are reported in the Supplementary Material.

Results

Participant Characteristics

Participant characteristics and statistical comparisons are reported in Table 1. Controls had higher years of completed education than patients, and greater estimated IQ, Matrix Reasoning, and Vocabulary subtest scores. As expected, controls had greater social and occupational functioning scores than patients, and patients had a greater percentage of lifetime diagnosis of depressive or substance use disorders than controls. No other demographic variables were statistically different between the two groups.

Free Viewing Task

Facial emotion discrimination accuracy.

There was a significant main effect of group, $F(1,47) = 5.05, p = .029, \eta_p^2 = 0.10$, 90% CI [.01, .24], with lower discrimination accuracy for patients ($M = 82.96\%$, $SD = 9.86$) than controls ($M = 87.82\%$, $SD = 7.25$) (Figure 2). There was also a main effect of stimulus expression condition, $F(3,141) = 8.60, p < .001, \eta_p^2 = 0.16$, 90% CI [.06, .23], such that sad expressions ($M = 78.54\%$, $SD = 12.84$) were significantly more difficult to accurately evaluate than all other expressions (anger: $M = 88.28\%$, $SD = 13.29$; fear: $M = 84.87\%$, $SD = 11.34$; neutral: $M = 88.10\%$, $SD = 13.40$; all p 's $< .011$). The group by condition interaction was not significant, $F(3,141) = 0.40, p = .756, \eta_p^2 = 0.01$, 90% CI [.00, .03].

%Fixations.

There was a significant main effect of group, $F(1,45) = 5.04, p = .03, \eta_p^2 = 0.10$, 90% CI [.005, .25], and a significant main effect of stimulus expression condition, $F(3,135) = 32.34, p < .001, \eta_p^2 = 0.42$, 90% CI [.30, .50], while the Group $\times$ Stimulus Expression interaction was not significant, $F(3,135) = 2.19, p = .092, \eta_p^2 = 0.05$, 90% CI [.00, .10]. Compared to controls ($M = 83.73\%$, $SD = 3.96$), patients ($M = 80.48\%$, $SD = 5.71$) on average made a smaller percentage of fixations to salient features (Figure 2). Participants also had a greater percentage of fixations to salient features when viewing fearful faces ($M = 85.14\%$, $SD = 5.42$) compared to all other expressions (anger: $M = 78.91\%$, $SD = 6.17, p < .001$; neutral: $M = 81.71\%$, $SD = 5.16, p < .001$; sadness: $M = 83.01\%$, $SD = 5.96, p = .023$). Additionally, participants made a smaller percentage of fixations to salient features when viewing angry faces compared to all other stimulus expressions (all p 's $\leq .001$).

%DwellTime.

There was a main effect of stimulus expression condition, $F(3,135) = 27.71, p < .001, \eta_p^2 = 0.38$, 90% CI [.27, .46], while the main effect of group, $F(1,45) = 2.51, p = .120, \eta_p^2 = 0.05$, , 90% CI [.00, .18], and the group by stimulus expression interaction, $F(3,135) = 1.68, p = .175, \eta_p^2 = 0.04$, , 90% CI [.00, .08] were not significant, Participants had smaller %DwellTime to salient features when viewing angry faces ($M = 81.29\%$, $SD = 6.92$) compared to all other stimulus expressions (fear: $M = 87.21\%$, $SD = 6.08$; neutral: $M = 84.24\%$, $SD = 5.85$; sad: $M = 85.60\%$, $SD = 6.43$; all p 's $\leq .002$). Participants also had greater %DwellTime to salient features when viewing fearful expressions relative to neutral expressions ($p < .001$).

Directed Viewing Task**Accuracy data.**

Both groups had near-perfect responses on the left-right judgment task; however, accuracy was significantly higher for the control group (practice task: $M = 98.72$, $SD = 1.64$; fMRI task: $M = 98.57$, $SD = 2.24$) than the patient group (practice task: $M = 97.38$, $SD = 2.66$; fMRI task: $M = 96.66$, $SD = 3.13$); practice task: $t(35.71) = 2.08, p = .044$; fMRI task: $t(39.36) = 2.44, p = .019$.

Eye movement data (practice task).

Both groups made fixations to the cues with high accuracy across viewing conditions. However, there was a significant main effect of viewing condition, $F(2,90) = 4.83, p = .010, \eta_p^2 = 0.10$, 90% CI [.01, .19], such that %CoincidenceCount was significantly higher for typical viewing ($M = 97.35$, $SD = 3.34$) than atypical viewing ($M = 95.78$, $SD = 4.65, p = .009$). The main effect of group, $F(1,45) = 0.29, p = .866, \eta_p^2 = 0.00$, 90% CI [.00, .09] and Group $\times$

Viewing Condition interaction, $F(2,90) = 0.48, p = .558, \eta_p^2 = 0.01$, 90% CI [.00, .05] were not significant.

Participants successfully maintained their gaze to the location of the cues while the cues were present (%CoincidenceDuration). However, as expected, these scores were lower than for %CoincidenceCount due to the time required to make saccades from one cue location to the next. There was a significant main effect of viewing condition, $F(2,90) = 17.16, p < .001, \eta_p^2 = 0.28$, 90% CI [.14, .38], while the main effect of group, $F(1,45) = 0.75, p = .391, \eta_p^2 = 0.02$, 90% CI [.00, .12] and Group $\times$ Viewing Condition interaction, $F(2,90) = 1.23, p = .298, \eta_p^2 = 0.03$, 90% CI [.00, .09] were not significant. Participants had greater %CoincidenceDuration for typical viewing ($M = 71.93, SD = 6.35$) than atypical viewing ($M = 68.66, SD = 7.58, p < .001$) and control ($M = 69.61, SD = 7.66, p = .002$) conditions.

ROI fMRI Analysis

The number and percentage of significant voxels in each ROI mask, and peak nonparametric t -statistic values for significant ROIs are reported in Table 2. Averaging across the entire sample, the ROI analysis for the Faces > Control contrast indicated significant activation in bilateral OFA and FFA, right STS, and bilateral amygdala. The Typical > Atypical contrast showed a significant response in the right OFA, and in a small number of voxels in left OFA. In contrast, Atypical > Typical viewing returned significant voxels in bilateral FEF and IPS. There were no significant group differences in any of the ROIs for any contrast.

Whole-Brain fMRI Analysis

Individual group results for the contrasts below are reported in the Supplementary Material.

Faces > Control.

Averaging across the full participant sample, the directed viewing of facial expressions elicited a distributed pattern of activation in bilateral visual cortex, key visual face-processing regions (bilateral OFA and FFA, right STS), adjacent regions in parietal and temporal cortex, and regions of the distributed face-processing network (right amygdala and anterior temporal fusiform cortex/temporal pole) (Table 3; Figure 3). No group differences were found for this contrast.

Typical > Atypical.

Across the entire sample, the whole-brain analysis for the Typical > Atypical contrast indicated greater activation in left and right hemisphere clusters including the occipital pole and inferior lateral occipital cortex, which extended to the right OFA (Table 3; Figure 4). There were no significant group differences for this contrast.

Atypical > Typical.

Across the full sample, the Atypical > Typical contrast revealed a bilateral cluster spanning early visual cortex and parietal cortex (including the IPS), as well as the right supramarginal gyrus and inferior lateral occipital cortex. There was an additional right-hemisphere cluster in the region of the FEF, and a cluster in the left cerebellum (Table 3; Figure 4). There were no significant group differences for this contrast.

Discussion

The purpose of the present study was to examine whether manipulating visual scanpaths during facial emotion perception would modulate functional activation patterns in a sample of schizophrenia patients and controls. During the unconstrained Free Viewing facial emotion discrimination task, patients had lower discrimination accuracy and made a reduced percentage

of fixations to salient facial features compared to controls, consistent with previous research (Kohler et al., 2010; Toh et al., 2011). For the Directed Viewing facial emotion perception task, fMRI results indicated robust recruitment of face-processing regions during the face-viewing conditions (Faces > Control). Typical scanpaths were associated with greater activation compared to atypical scanpaths (Typical > Atypical) in occipital clusters within bilateral visual association cortex, which included the right OFA. In contrast, atypical scanpaths (Atypical > Typical) were associated with greater activation in primary visual cortex and regions involved in visual attention (IPS and FEF). There were no group differences in brain activation for any task condition, contrary to previous findings of functional activation abnormalities during facial emotion perception in schizophrenia (Li et al., 2010; Taylor et al., 2012).

Despite the unique elements of the Directed Viewing facial emotion perception task, which featured a moving visual cue that directed participant gaze to various face locations, the faces in this task nonetheless elicited the characteristic response across key regions of the facial emotion processing network (Haxby et al., 2000). These included face-selective regions involved in face perception (OFA, FFA, STS), and regions supporting emotional face processing (right amygdala and anterior temporal lobe).

Collapsing across participant groups, the visual scanpath manipulation significantly modulated brain activation patterns during facial emotion perception. Compared to the atypical viewing condition, the typical viewing condition elicited greater activation in the right OFA ROI, supporting the predicted greater activation in ventral visual regions of the face perception network when increasing fixations to salient facial features. However, this effect was weak in the left OFA, which may reflect the established right-hemisphere dominance of the face-processing network (Zhen et al., 2015), and consistent with our results of right- but not left-hemisphere STS

activation when contrasting faces and control stimuli. The whole-brain analysis revealed that the OFA finding was part of a more posterior and medial area of activation spanning occipital pole and inferior lateral occipital cortex bilaterally. Notably, this cluster had close correspondence with occipital clusters from a recent meta-analysis of face-processing studies (Müller, Höhner, & Eickhoff, 2018). Additionally, the Typical > Atypical cluster overlapped with a reported area of hypoactivation in schizophrenia patients from a meta-analysis of fMRI studies of emotion perception in schizophrenia (Taylor et al., 2012). Therefore, the present results indicate that the manipulation of visual scanpaths modulated brain activation in face-processing regions that have been associated with activation abnormalities in schizophrenia.

In contrast to the significant OFA finding, manipulating visual scanpaths was not associated with activation changes in the FFA, failing to replicate the central result by Morris et al. (2006). The lack of significant FFA results is also at variance with the relationship between FFA activation and visual attention to the eyes suggested by several studies of individuals with ASD (Dalton et al., 2005; Perlman et al., 2011). Nonetheless, the significant effect of the visual scanpath manipulation in OFA but not FFA is consistent with previous research on face and object processing in visual cortex. OFA is predominantly sensitive to facial features, while FFA is sensitive to both facial features and face configurations (i.e., the T-shaped placement of the eyes above the nose and mouth) but with potentially greater preference for face configurations (D. F. Nichols, Betts, & Wilson, 2010; Zhang, Li, Song, & Liu, 2012). Thus, the significant response modulation in OFA may reflect the sensitivity of OFA to differences in whether salient features were attended to in the two viewing conditions (i.e., maximal or minimal fixations to the eyes and mouth in the typical and atypical conditions, respectively). In contrast, the lack of significant modulation in FFA may reflect the sensitivity of this region to the presence of a face

configuration, which changed with each new face presentation but was not systematically manipulated between the two viewing conditions. Additionally, the documented hierarchical increase in neuronal population receptive field size (i.e., the extent of the represented visual field) from posterior (i.e., OFA) to anterior (i.e., FFA) face-sensitive regions (Kay et al., 2015), and the hierarchical gradient from local to global object representations along the posterior to anterior ventral visual stream (Lerner, Hendler, Ben-Bashat, Harel, & Malach, 2001) may further account for the sensitivity of the OFA cluster to the visual scanpath manipulation and the lack of modulation for the FFA.

The Atypical > Typical contrast led to a more widespread pattern of findings, including visual cortex regions involved in low-level visual processing, and bilateral IPS and FEF. The significant IPS and FEF findings support the hypothesis that the visual scanpath manipulation would modulate functional activation in regions involved in visual attention; however, these findings were in the opposite direction of those of Morris et al. (2006). The typical scanpaths, in which the majority of cues landed on the eyes, were more predictable than the atypical scanpaths, which also required participants to override the preference for fixating to salient facial features (Eisenbarth & Alpers, 2011). Previous research using concurrent fMRI and eye tracking indicates a significant positive correlation between eye movements and functional activation in regions including low-level visual cortex, IPS, and FEF (Lu, Hung, Wen, Marussich, & Liu, 2016). Therefore, the greater response in these regions during the atypical scanpaths may reflect the greater attentional control requirements of this viewing condition.

The results discussed above collapsed across the community control and schizophrenia patient groups as no group activation differences were found for any of the task conditions. This lack of group differences is in contrast to a number of studies with comparable sample sizes and

using a variety of facial emotion processing paradigms (e.g., explicit, implicit, passive viewing) documenting functional activation abnormalities in face and emotion processing regions in schizophrenia (Li et al., 2010; Taylor et al., 2012). However, a key difference between the present task and those of previous studies is that the Directed Viewing task equated visual scanpaths between the groups; therefore, eliminating a potentially important behavioural group difference that may have influenced the fMRI response to faces. Indeed, the schizophrenia patients in the present sample had lower facial emotion discrimination accuracy and made a significantly smaller percentage of fixations to salient facial features than controls during the Free Viewing task, consistent with prior literature.

The present study demonstrated a relationship between visual scanpaths and brain activation in face-responsive regions in schizophrenia, similar to controls. Given the documented eye gaze abnormalities during facial emotion perception in schizophrenia, an important next step is to examine the extent to which this relationship accounts for activation differences between schizophrenia patients and controls. Such studies will require in-scanner recording of gaze behaviour and sufficiently large sample samples to examine correlations with functional activation. Depending on the results, interpretations of previous fMRI findings may need to be revisited: for example, rather than representing neurobiological dysfunction contributing to facial emotion recognition deficits, hypoactivation in face-processing regions in schizophrenia may instead reflect group differences in gaze behaviour, which might subsequently contribute to recognition deficits. However, it should be mentioned that the fMRI response modulation resulting from increasing fixations to salient features was restricted to OFA and visual association areas putatively lower in the visual-processing hierarchy. Therefore, any direct contribution of gaze abnormalities in schizophrenia to functional activation differences may be

limited to visual cortex areas involved in early face processing, and with the potential for downstream effects at later processing stages due to the interconnectivity of the face-processing network (Gschwind, Pourtois, Schwartz, Van De Ville, & Vuilleumier, 2012).

The visual scanpath-related modulation of face-responsive fMRI activation in the present study was demonstrated using a Directed Viewing task that did not assess facial emotion recognition accuracy. Therefore, the present study cannot speak to whether modulating fMRI activation influences the ability to perceive and *recognize* faces. Given that a positive association has been found between face recognition ability and the magnitude and extent of face-selective functional activation in the face processing network (Elbich & Scherf, 2017), an important area for future research is to examine the functional consequences of visual scanpath-related response modulation for various aspects of face recognition (e.g., emotion, identity). There is evidence that training schizophrenia patients to attend to salient facial features leads to improvements in facial emotion recognition (e.g., Combs et al., 2008). Similarly, an outstanding question is whether gaze behaviour influences functional activation related to later stages of facial emotion processing; for example, the medial prefrontal cortex hypoactivation in schizophrenia when evaluating faces (Spilka & Goghari, 2017).

The current study had several limitations. Sample size limitations prevented subgroup (schizophrenia vs. schizoaffective disorder) and moderator (e.g., illness duration, symptom severity) analyses in the patient group that may be relevant to facial emotion processing variables (e.g., Green, Williams, & Davidson, 2003). Additionally, the lack of an MR-compatible eye tracker prevented recording gaze behaviour during the fMRI session, making it impossible to confirm with certainty that all participants were following the cue sequences when performing the Directed Viewing task in the scanner. However, participants' ability to perform the task was

verified by recording eye movements during a practice task outside the scanner. Furthermore, although patients were statistically less accurate than controls on the attentional control aspect of the task, all participants provided near-perfect responses. Finally, due to the duration of the Directed Viewing task and scanning time constraints, we could not include an unconstrained or “free viewing” facial emotion perception task in the scanner, which prevented confirming that the present sample of schizophrenia patients would have demonstrated brain activation abnormalities similar to those reported in comparable samples during traditional facial emotion perception tasks.

Notwithstanding these limitations, the present study is the first, to our knowledge, to examine the relationship between two important variables associated with facial emotion processing deficits in schizophrenia: eye gaze behaviour and functional brain activation. We demonstrated that the experimental manipulation of visual scanpaths during facial emotion perception led to corresponding changes in brain activation, with greater activation in visual association areas involved in face perception when increasing fixations toward salient facial features. Given the documented gaze abnormalities in schizophrenia, our findings suggest that gaze behaviour represents a potential confounding variable for neuroimaging studies of facial emotion perception in this disorder. The current results indicate the need for future studies to investigate the extent to which the relationship between gaze and functional activation in schizophrenia contributes to the documented functional activation abnormalities. Our findings may also be relevant for between-group studies of other clinical populations where differences visual attention may impact functional activation patterns.

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Table 1.

Participant Characteristics

	Schizophrenia Patients	Controls	Statistic
<i>N</i>	23	26	
Age	40.00 (12.41)	39.46 (11.93)	$t(47) = -0.16, p = .878$
Gender (male/female)	16/7	17/9	$\chi^2(1, N = 49) = 0.10, p = .755$
Handedness (right/left)	20/3	24/2	$\chi^2(1, N = 49) = 0.38, p = .537$
Education (years)	13.17 (3.42)	15.54 (2.25)	$t(47) = 2.90, p = .006$
Mother's Education (years)	13.67 (2.25)	12.74 (3.32)	$t(38) = -1.10, p = .280$
Father's Education (years)	15.22 (2.58)	13.36 (3.71)	$t(37) = -1.70, p = .098$
Diagnosis (schizophrenia/schizoaffective disorder)	15/8	—	
Years since diagnosis	13.05 (10.93)	—	
Positive and Negative Syndrome Scale (PANSS)	53.22 (11.02)	—	
Total			
PANSS Negative	14.00 (5.50)	—	
PANSS Positive	13.30 (3.35)	—	
PANSS General	25.48 (5.53)	—	
Social Functioning Scale Mean of Scaled Scores	113.71 (10.22)	—	
Social and Occupational Functioning Assessment Scale (SOFAS)	60.04 (11.53)	87.65 (4.94)	$t(29.03) = 10.66, p < .001$
IQ	98.35 (7.47)	111.12 (11.73)	$t(42.93) = 4.60, p < .001$
Matrix Reasoning Scaled Score	10.30 (1.92)	12.04 (1.73)	$t(47) = 3.33, p = .002$
Vocabulary Scaled Score	9.26 (1.86)	12.08 (3.22)	$t(47) = 3.68, p = .001$
Lifetime diagnosis of depressive or substance use disorders (%)	52.17	11.54	$\chi^2(1, N = 49) = 13.11, p < .001$

Note. Means and standard deviations (in parentheses) are presented where appropriate.

Table 2.

Region of Interest (ROI) Analysis Results

ROI	Faces > Control								
	Full Sample			Controls			Schizophrenia Patients		
	Voxels	%	t_{Max}	Voxels	%	t_{Max}	Voxels	%	t_{Max}
rOFA	692	87.59%	14.8	534	67.59%	10.1	615	77.85%	10.1
lOFA	211	100.00%	11	153	72.51%	8.32	183	86.73%	8.14
rFFA	794	77.92%	14.3	504	49.46%	10.4	456	44.75%	9.05
lFFA	464	87.38%	12.5	290	54.61%	10.2	340	64.03%	7.39
rSTS	525	20.96%	6.07						
rAmygdala	223	79.64%	5.63				77	27.50%	5.97
lAmygdala	183	76.25%	5.63						
ROI	Typical > Atypical								
	Full Sample			Controls			Schizophrenia Patients		
	Voxels	%	t_{Max}	Voxels	%	t_{Max}	Voxels	%	t_{Max}
rOFA	164	20.76%	10.4	48	6.08%	6.99	68	8.61%	8.33
lOFA	15	7.11%	4.5						
ROI	Atypical > Typical								
	Full Sample			Controls			Schizophrenia Patients		
	Voxels	%	t_{Max}	Voxels	%	t_{Max}	Voxels	%	t_{Max}
rFEF	162	93.10%	6.84	4	2.30%	4.56	76	43.68%	5.67
lFEF	59	23.32%	4.2						
rIPS	306	98.64%	9.27	100	22.68%	7.19	235	64.40%	6
	129		8.98				49		8.22
lIPS	258	60.32%	7.99	1	0.23%	5.3	122	28.31%	5.68
	1		4.93						
	1		5.3						

Note. Voxels = number of significant voxels within a given cluster. % = percentage of suprathresholded voxels within ROI mask. t_{Max} = nonparametric t -statistic value of the maximum significant voxel. r = right; l = left; OFA = occipital face area; FFA = fusiform face area; STS = posterior superior temporal sulcus; FEF = frontal eye field; IPS = intraparietal sulcus. Primary ROIs (left and right OFA and FFA) were evaluated for significance at $p < .0125$, FWE-corrected. Secondary ROIs (left and right STS, Amygdala, FEF, and IPS) were evaluated for significance at $p < .00625$, FWE-corrected.

Table 3.

Whole-Brain Analysis Results Across the Full Participant Sample

Contrast and Regions Within Each Cluster	Voxels	t_{Max}	Peak Coordinates		
			x	y	z
<u>Faces > Control</u>					
R/L inferior lateral occipital cortex (OFA), occipital and temporal fusiform gyrus (FFA), occipital pole, calcarine cortex, lingual gyrus, temporo-occipital part of the middle temporal gyrus, angular gyrus; R STS, supramarginal gyrus, cuneus	18357	14.8	38	-80	-8
R anterior temporal fusiform cortex	83	6.29	34	2	-40
R amygdala	73	5.63	26	-4	-22
R temporal pole	4	5.09	34	12	-22
<u>Typical > Atypical</u>					
R occipital pole, inferior lateral occipital cortex (including OFA)	1905	16.9	30	-90	-10
L occipital pole, inferior lateral occipital cortex	1598	13.6	-24	-94	-10
<u>Atypical > Typical</u>					
R/L lingual gyrus, calcarine cortex, occipital pole, cuneus, precuneus, marginal sulcus, superior lateral occipital cortex (including IPS), superior parietal lobule; R supramarginal gyrus, inferior lateral occipital cortex	28660	12.2	-8	-78	-6
R superior frontal and precentral sulcus (FEF)	648	6.98	28	-4	56
L cerebellum (VIIIb/IX)	23	6.46	-16	-52	-48

Note. Voxels = number of significant voxels within a given cluster. t_{Max} = nonparametric t -statistic value of the maximum voxel within the cluster. R = right; L = left. OFA = occipital face area; FFA = fusiform face area; STS = posterior superior temporal sulcus; FEF = frontal eye field; IPS = intraparietal sulcus. Coordinates are in MNI space.

Figure 1. Experimental design for the Directed Viewing Facial Emotion Perception task. The top panel shows examples of the cue sequences for the three viewing conditions. The allocation of cues to different face areas were the following: Typical: 73% eyes, 18% mouth, 9% other; Atypical: 9% eyes/mouth, 91% other; Control: random. The bottom panel illustrates the structure of the task. The order of typical and atypical blocks was counterbalanced across scans.

Figure 2. Discrimination accuracy, %Fixations, and %DwellTime group comparisons for the Free Viewing Facial Emotion Discrimination Task. $*p < .05$

Figure 3. Whole-brain activation map for the Faces > Control contrast averaged across the full sample of participants. Results are thresholded at a TFCE t -score equivalent to $p < .05$, FWE-corrected. Images are displayed in neurological convention (i.e., the right hemisphere is on the viewer's right).

Figure 4. Whole-brain activation maps of the sample-level results for the Typical > Atypical (red-yellow) and Atypical > Typical (blue-green) contrasts. Results are thresholded at a TFCE t -score equivalent to $p < .05$, FWE-corrected. Images are displayed in neurological convention.