Individuals with schizophrenia may fail to appropriately use temporal context and apply past environmental regularities to the interpretation of incoming sensory information. Here we use the visual system as a test bed for investigating how prior experience shapes perception in individuals with schizophrenia. Specifically, we use visual aftereffects, illusory percepts resulting from prior exposure to visual input, to measure the influence of prior events on current processing. At a neural level, visual aftereffects arise due to attenuation in the responses of neurons that code the features of the prior stimulus (neuronal adaptation) and subsequent disinhibition of neurons signaling activity at the opposite end of the feature dimension. In the current study, we measured tilt aftereffects and negative afterimages, 2 types of aftereffects that reflect, respectively, adaptation of cortical orientation-coding neurons and adaptation of subcortical and retinal luminance-coding cells in persons with schizophrenia (PSZ; $n=36$) and demographically matched healthy controls (HC; $n=22$). We observed stronger tilt aftereffects in PSZ compared to HC, but no difference in negative afterimages. Stronger tilt aftereffects were related to more severe negative symptoms. These data suggest oversensitivity to recent regularities, in the form of stronger visual adaptation, at cortical, but not subcortical, levels in schizophrenia.

General Scientific Summary

Comprehensive and computational accounts of schizophrenia suggest that a subset of symptoms are characterized by an abnormality in using context to shape perception and guide behavior. Here, we focused specifically on temporal context—the influence of past history and stored regularities across time on the interpretation and response to current input. The current study sought to test whether such an abnormality would be present in the visual systems of individuals with schizophrenia by testing the strength of visual aftereffects—illusory perceptions caused by prior exposure to a visual stimulus. We found that one type of aftereffect was stronger in individuals with schizophrenia and related to the severity of negative symptoms, suggesting oversensitivity to recently presented information.

Keywords: schizophrenia, visual perception, aftereffects, Bayesian, adaptation

Supplemental materials: https://doi.org/10.1037/abn0000653.supp

Schizophrenia is often considered among the most debilitating of mental health conditions. Even with currently available interventions, individuals are often left with residual positive and negative symptoms, functional impairments, and decreased quality of life (Torres-González et al., 2014). Comprehensive, explanatory mechanistic frameworks for schizophrenia symptoms hold tremendous promise for guiding treatment development. At the core of several such explanations is a fundamental abnormality in how perception and action are shaped by context and stored regularities.
are guided by context—broadly defined to include past experience, current situational demands, and other simultaneous input (Fletcher & Frith, 2009; Gray et al., 1991; Hemsley, 2005; Phillips & Silverstein, 2003; Sterzer et al., 2018). Frameworks centered on the abnormal use of context unite several levels of explanation—linking diverse clinical phenomenology with cognitive and computational processes and neurobiological mechanisms. Here, we focus specifically on temporal context—the influence of past history and stored regularities across time on the interpretation of and response to current input; an abnormality in this inferential process is argued to lead to abnormal perceptions and beliefs (Fletcher & Frith, 2009; Sterzer et al., 2018).

The visual system can serve as a unique model system within which to understand the role of experience in how individuals perceive and interpret the world, as our constructed internal model of the world, formed by acquired knowledge, informs visual perception (Barlow, 1990; Clifford et al., 2000; Knîl & Richards, 1996). More specifically, visual aftereffects reflect, and provide a measure of, the role of prior experience in ongoing visual processing. Visual aftereffects occur after prolonged viewing of a stimulus and are the illusory perception of “the opposite” of this stimulus (e.g., opposite direction of motion, complementary color; demonstration in Figure 1). Aftereffects are caused by adaptation of neurons in the visual brain that are tuned to particular features. For example, the tilt aftereffect that appears after prolonged viewing of a grating of a particular orientation arises due to adaptation (i.e., attenuation of firing rate) of neurons responsive to the orientation of that adapter stimulus, and associated disinhibition of neurons that signal orientations away from those of the current stimulus (Figure 2). Neuronal adaptation reflects a fundamental assumption about temporal regularities in the environment: that one’s current experience is a reliable predictor of future experience (Kohn, 2007). Aftereffects can thus provide a clear metric of how temporal context contributes to perceptual inference and our constructed reality.

Visual aftereffects can provide a computationally and biologically informed behavioral assay of temporal context processing abnormalities in schizophrenia for several reasons. First, aftereffects have been explained using formal mathematical models, which can frame the interpretation of behavioral findings (Bednar & Miikkulainen, 2000; Stocker & Simoncelli, 2005). Second, different aftereffects reflect neuronal adaptation at different levels of the visual processing hierarchy, from the retina up to higher-order integration areas, and thus can reveal at what level of a sensory hierarchy an abnormal influence of temporal context emerges. Third, neuronal adaptation has multiple mechanisms, including not only changes in the properties of single neurons and synaptic connectivity that alter the firing rate of neurons tuned to the features of the adapting stimulus (Kohn, 2007), but also changes in the strength of lateral inhibitory interactions between local processing units that alter the balance between differently tuned neurons in a local network (Bednar & Miikkulainen, 2000; Tolhurst & Thompson, 1975). In this way, visual aftereffects are sensitive to an imbalance between neuronal excitation and inhibition in local circuits. Finally, there are neuromodulatory influences on visual aftereffect strength: pharmacological manipulation of serotonin and dopamine influence visual aftereffect strength in healthy observers (Harris et al., 1986; Harris et al., 1983; Masini et al., 1990).

An older body of work is suggestive of stronger visual aftereffects related to tilt (Calvert et al., 1991) and motion (Abraham & McCallum, 1973; Barrett & Logue, 1974; Claridge, 1960) in schizophrenia. As we recently reviewed (Thakkar et al., 2019), however, significant sources of variability across studies, as well as methodological issues related to experimental design and clinical characterization, preclude conclusive interpretation of this older work. This work also did not address any association with symptom severity. Our goal in the current study was to use rigorous psychophysical paradigms and comprehensive and current clinical characterization to investigate putative differences in aftereffect strength in individuals in schizophrenia and to explore correlations with clinical symptom severity.

We measured two types of aftereffects: negative afterimages and tilt aftereffects. Negative afterimages occur after prolonged viewing of a stationary pattern (adapter stimulus). Subsequent presentation of a blank field (test stimulus) can result in the illusion of the ‘photo negative’ of the adapter stimulus in the retinal location that was exposed to that adapter pattern (Figure 1). Negative afterimages result from adaptation of luminance-coding retinal receptors (Brindley, 1962), retinal ganglion cells (Visu & Laurinen, 1977; Yeonan-Kim & Francis, 2019; Zaidi, 2012), and luminance-coding neurons in the lateral geniculate nucleus during exposure to the adapter (Li et al., 2017), although there is some evidence for an additional cortical contribution (Shimojo et al., 2001). Tilt aftereffects occur after prolonged viewing of, for instance, a slightly tilted grating pattern (adapter stimulus). A subsequently presented vertically oriented grating pattern (test stimulus) will appear tilted in the opposite direction. This so-called tilt aftereffect (Gibson & Radner, 1937; Wenderoth & Johnstone, 1987) is thought to arise from adaptation of orientation-selective neurons in early visual cortex based on the fact that
such neurons can be found in primary visual cortex but not subcortically or in the retina (Clifford, 2002).

Aside from forming a measure of the influence of temporal context, tilt aftereffects can also provide an index of orientation tuning width (defined below). Put another way, in interpreting tilt aftereffect strength in terms of temporal context, one has to rule out explanations in terms of orientation tuning width. This is relevant because previous studies suggest broader orientation tuning in schizophrenia (Robol et al., 2013; Rokem et al., 2011; Schallmo et al., 2015; Silverstein et al., 2017). The reasoning that ties tuning curve widths to tilt aftereffects is as follows. The measured strength of tilt aftereffects is dependent on the difference in tilt between the adapter and test stimulus. The more similar the tilt is to the adapter, the stronger the measured tilt aftereffect. This is because of orientation tuning properties of visually responsive neurons, which respond most vigorously to a particular orientation and increasingly less to stimuli oriented further from that preferred orientation. More neuronal adaptation accumulates for neurons that are sensitive to orientations nearer to that of the adapter, whereas neurons that are tuned to an orientation that is far removed will adapt weakly if at all (Schwartz et al., 2007). The implication here is that broader orientation tuning in schizophrenia could conceivably lead to a different aftereffect strength, depending on the orientation difference between adapter and test. We thus manipulated this parameter in our paradigm in order to distinguish whether putative altered tilt aftereffects would be best explained by broader orientation tuning curves or by altered neuronal adaptation based on previous regularities. Hypothesized outcomes under these two potential scenarios are detailed in Figure 3.

Our primary question in the current study was whether there are alterations in aftereffect strength in individuals with schizophrenia, and, if so, whether the putative underlying alterations in neural adaptation are primarily cortical or subcortical in nature, or both. Given prior work (reviewed in Thakkar et al., 2019), we hypothesized that aftereffects of cortical origin (i.e., tilt aftereffects) would be stronger in persons with schizophrenia; investigation of negative afterimages was exploratory. We additionally hypothesized that putative alterations in visual aftereffect strength would be related to severity of clinical symptoms, given altered context processing as a purported mechanism of symptom genesis, broadly. Our secondary exploratory question was whether putative alterations in tilt aftereffect strength could be explained by differences in tuning curve width. As visual aftereffects are a manifestation of the visual system incorporating information about past events into its current processing, findings from the current study have the potential to shed further light on the nature of temporal context processing abnormalities in schizophrenia.

Method and Materials

Participants

36 persons with schizophrenia or schizoaffective disorder (PSZ) and 22 healthy controls (HC) were recruited from outpatient mental health facilities and via community advertisements. Demographic characteristics are presented in Table 1. Diagnoses were based on results of an electronic version of the Structured Clinical

Figure 2
Schematic of Neuron Implementing a Tilt Aftereffect

Note. The response of a neuron that responds to the adapter stimulus (leftward grating) is depicted as a function of stimulus presentation. Upon presentation of a left-orientated grating, the neuron responds vigorously, but with repeated presentation firing rate is attenuated (i.e., it adapts). Upon the onset of a blank screen, the neuron returns to a below-baseline level of firing. Because orientation perception depends on the aggregation of responses across neurons with many orientation preferences, reduced firing of the adapted neurons results in the perceptual phenomenon of a rightward bias in the perception of stimulus orientation (i.e., aftereffect). From “A Review of Visual Aftereffects in Schizophrenia,” by K. N. Thakkar, S. M. Silverstein, and J. M. Brascamp, 2019, Neuroscience and Biobehavioral Reviews, 101, p. 69. Copyright [2019] by Elsevier. Reprinted with permission.

Figure 3
Hypothesized Tilt Aftereffect Findings in PSZ (Orange Lines) and HC (Gray Lines)

Note. Adaptation is stronger in neurons that are sensitive to orientations nearer to that of the adapter (labeled near on the x-axis), and neurons that are tuned to an orientation that is far removed from the adapter orientation will adapt weakly if at all (labeled far on the x-axis). Accordingly, when the orientation of the adapter and nuller are similar, aftereffects will be strong, in contrast to when they are far apart. Thus, we expect that in both groups, tilt aftereffects will be stronger in the near compared to far condition. Aftereffect strength also depends on tuning curve widths (i.e., how selective orientation-tuned neurons are to a particular orientation). If putatively stronger tilt aftereffects in PSZ are due to true amplitude differences, then we would expect that PSZ would show stronger tilt aftereffects in the near condition, but make no prediction about the far condition (A). However, if stronger tilt aftereffects in PSZ were due to wider tuning curves, we would expect that tilt aftereffects would be stronger in PSZ than HC in the far condition, but expect weaker or equal aftereffect strength in PSZ in the near condition (B). See the online article for the color version of this figure.
Interview for DSM–5 Axis I disorders (American Psychiatric Association, 2013; Brodey et al., 2016), material from medical records, and collateral informants. Final diagnosis was reached at a consensus conference. 31 PSZ were taking antipsychotic medication, and many PSZ were medicated with additional psychotropic medication (Supplemental Table 1). Chlorpromazine (CPZ) equivalent dosages of antipsychotic medication were calculated in PSZ (Andreasen et al., 2010).

Clinical symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), and Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). IQ was measured with the Weschler Test for Adult Reading (WTAR; Wechsler, 2001). Handedness was assessed using the Modified Edinburgh Handedness Inventory (Oldfield, 1971). Exclusion criteria included meeting DSM–5 criteria for moderate or severe substance use disorder within the previous six months, history of neurological disorders, history of head injury with loss of consciousness >10 min, and vision that was not normal or corrected-to-normal. HC were excluded if they had a personal history of DSM–5 Axis-I disorders or family history of schizophrenia spectrum disorders or bipolar disorder. Groups were matched for age, gender, and handedness. All subjects gave written informed consent approved by the Michigan State University Institutional Review Board and were paid.

### Table 1

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>HC (n = 22) M (SD)</th>
<th>PSZ (n = 36) M (SD)</th>
<th>Statistic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36.4 (10.3)</td>
<td>37.8 (10.2)</td>
<td>t = .51</td>
<td>.61</td>
</tr>
<tr>
<td>Gender</td>
<td>11 F / 11 M</td>
<td>16 F / 20 M</td>
<td>ϕ = .17</td>
<td>.79</td>
</tr>
<tr>
<td>IQ</td>
<td>109.2 (7.8)</td>
<td>99.6 (11.9)</td>
<td>t = 3.21</td>
<td>.002</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>17.1 (2.4)</td>
<td>15.6 (2.2)</td>
<td>t = 5.69</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Handedness</td>
<td>69.5 (37.3)</td>
<td>49.3 (53.9)</td>
<td>t = 1.54</td>
<td>.14</td>
</tr>
<tr>
<td>Years of Illness</td>
<td>12.7 (9.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPZ Equivalent</td>
<td>349.9 (360.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS</td>
<td>46.3 (12.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS</td>
<td>22.1 (16.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SANS</td>
<td>34.4 (21.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Participants were seated in a dimly lit room, their head stabilized 59 cm away from a computer screen. Stimuli were presented on a 20” CRT monitor (spatial resolution: 1280x1024 pixels, vertical refresh rate: 85 Hz). Eye position was recorded to ensure fixation using an Eyelink 1000 (SR Research, Canada). Manual responses were recorded with a keyboard. Stimulus presentation and response collection were controlled with Python using PsychoPy (Peirce et al., 2019).

### Experimental Paradigms and Procedure

Participants completed a negative afterimage and tilt aftereffect paradigm (order counterbalanced across participants). Participants were instructed to keep their gaze fixated at the center of the display throughout each trial. Both experiments were preceded by a practice session, which was repeated until it was clear that the participant understood the task.

**Negative Afterimage**

The negative afterimage task is illustrated in Figure 4A (see Supplemental Methods for full details). On each trial the subject was presented with a blurry disk with one bright half and one dark half for 1.5 s (adapter stimulus). We used a so-called nulling method to measure the strength of the negative afterimage. The nuller stimulus was a “photo negative” of the afterimage (in other words, a low-contrast version of the adapter stimulus) that was presented for 0.5 s immediately following the adapter stimulus. Participants were asked to indicate which part of the nuller appeared brightest, with perception of this nuller being formed by the illusory negative afterimage superimposed on the physically present nuller stimulus. If the nuller is strong enough to overpower the afterimage, then the participant typically experiences a pattern that is consistent with the nuller stimulus—light where the nuller is light, and dark where it is dark. Alternatively, if the nuller is not strong enough to counteract the afterimage, then the participant will see a pattern that is of opposite contrast polarity: light and dark where the afterimage is light and dark.

### Figure 4

Negative Afterimage (A) and Tilt Aftereffect (B) Paradigms

Note. See the online article for the color version of this figure.
This nuller strength provides an index of afterimage strength (Brascamp et al., 2010; Georgeson & Turner, 1985; Leguire & Blake, 1982). Practically, this is quantified as the 50% point on the psychometric curve fitted to responses plotted against nuller strength (see Quantifying Aftereffects section below). A third image followed the nuller and masked any lingering afterimage; it remained on screen until the response. Participants were instructed to select the area in which the nuller image appeared brightest using a mouse click. Their response was followed by a 1-s pause, a gaze drift correction procedure, and another 3-s intertrial interval.

**Tilt Aftereffect Paradigm**

The tilt adaptation task is illustrated in Figure 4B (see Supplemental Methods for full details). On each trial a flashing grating tilted at 20 degrees from vertical—the adapter stimulus—was presented for 2 s. Like negative afterimage strength, tilt aftereffect strength was quantified using a nulling procedure. Here the nuller stimulus was a second grating tilted at various degrees from vertical from trial to trial. Participants indicated whether the nuller appeared tilted leftward or rightward from vertical. Tilt aftereffect strength was then quantified as the degree of physical tilt away from vertical, in the direction of the adapter’s tilt, that is required to reach a subjective sense of vertical, again corresponding to the 50% point of the psychometric curve plotting responses against nuller strength (here, tilt; see Quantifying Aftereffects section below). The nuller lasted 0.4 s and was separated from the adapter by a 0.3 s blank. Then, a circle with two lines originating from the center, one oriented rightward and the other oriented leftward, was presented, and the participant was instructed to indicate whether the nuller appeared to be oriented leftward or rightward by making a mouse click on the corresponding line. Their response was followed by a 0.5 s pause, a gaze drift correction procedure, and a 4 s intertrial interval.

To investigate whether putatively altered tilt aftereffects in schizophrenia are secondary to wider orientation tuning curves (rationale outlined in Figure 3), the trials described above—which we refer to as ‘near’ trials—were interleaved with ‘far’ trials. During far trials the adapter stimulus was tilted at a much steeper angle (65 degrees from vertical). In healthy individuals, adaptation during far trials the adapter stimulus was tilted at a much steeper angle (65 degrees from vertical). In healthy individuals, adaptation to gaze deviation more than 2.5 degrees of visual angle from central fixation during the adapter stimulus (Knapen et al., 2010) or in which more than 25% of the samples were missing (i.e., due to blinks, head movements, recording errors, etc.). Of those participants with usable behavioral data, eye movement data were either partially or completely missing from 3 PSZ and 2 HC in the negative afterimage paradigm and from 4 PSZ and 3 HC in the tilt aftereffects paradigm. Differences in clinical and demographic variables between those PSZ that were and were not excluded from either of the two tasks are presented in Supplemental Methods and Supplemental Table 2.

**Eye Movements**

As aftereffects have some degree of spatial selectivity, breaks in fixation could cause weaker aftereffects. Thus, for participants for whom we had usable eye data for that particular task, we repeated the quantification of aftereffect strength after removing trials in which gaze deviated more than 2.5 degrees of visual angle from central fixation during the adapter stimulus (Knapen et al., 2010) or in which more than 25% of the samples were missing (i.e., due to blinks, head movements, recording errors, etc.). Of those participants with usable behavioral data, eye movement data were either partially or completely missing from 3 PSZ and 2 HC in the negative afterimage paradigm and from 4 PSZ and 3 HC in the tilt aftereffects paradigm. Differences in clinical and demographic variables between those PSZ that were and were not excluded from analyses controlling for eye movements are presented in Supplemental Methods and Supplemental Table 3.

**Statistical Analyses**

First, to test for the presence of significant aftereffects, the magnitude of negative afterimages and tilt aftereffects (in both the near and far conditions) were compared to 0 using a one sample t test. Negative afterimage strength was compared between PSZ and HC using independent samples t tests. Mixed model ANOVAs were used to examine tilt aftereffect strength, with group included as a between-subjects factor and condition (near, far) included as a within-subjects factor. The above analyses were repeated after removing trials based on eye gaze data. We also evaluated the two other parameters from the cumulative Gaussian function fitting response data to nuller strength: standard deviation and lapse rate, to examine potential differences in sensitivity to the strength of the nuller stimulus. Group differences in lapse rate and standard deviation were tested using the same methods as were used to assess differences in mean. Spearman’s rho (r_s) was computed to evaluate correlations between negative afterimage strength, tilt aftereffect strength in both conditions and both positive and negative symptoms and CPZ equivalent antipsychotic doses. The alpha level for correlations between aftereffect strength and symptoms was Bonferroni-corrected to 0.05/6 = 0.008. Finally, Pearson correlation coefficient (r) was used to correlate tilt aftereffect strength with negative afterimage strength.
Results

Negative Afterimages

Results are depicted in Figure 5. Robust negative afterimages were observed in both HC, $t(20) = 20.6, p < .0001, d = 4.5$ (95% CI [3.0 5.9]) and PSZ, $t(32) = 14.8, p < .0001, d = 2.6$ (95% CI [1.9 3.3]). There was no difference in negative afterimage strength between groups, $t(52) = 1.0, p = .32, d = 0.3$ (95% CI [−0.3 0.8]), nor any difference in standard deviation and lapse rate (see Supplementary Results).

Tilt Aftereffects

Results are depicted in Figure 6. Robust tilt aftereffects were observed in both HC, $t(20) = 6.6, p < .0001, d = 1.4$ (95% CI [0.8 2.1]) and PSZ, $t(29) = 12.1, p < .0001, d = 2.2$ (95% CI [1.5 2.9]) in the near condition. Neither group showed a significant tilt aftereffect in the far condition (HC, $t(20) = 1.3, p = .22, d = −0.3$ (95% CI [−0.7 0.2]); PSZ: $t(29) = 1.3, p = .20, d = 0.2$ (95% CI [−0.1 0.6])), consistent with prior reports (Schwartz et al., 2007). A mixed model ANOVA on tilt aftereffect strength revealed significant main effects of both condition ($F(1, 49) = 102.7, p < .0001, \eta^2 = 0.7$ (95% CI [0.5 0.8])) and group $F(1, 49) = 10.5, p = .002, \eta^2 = 0.2$ (95% CI [0.0 0.4]). Tilt aftereffects were larger in the near condition, and PSZ had significantly stronger tilt aftereffects than HC. There was no significant group-by-condition interaction ($F(1, 49) = 1.0, p = .32, \eta^2 = 0.02$ (95% CI [0.0 0.1])). We take this lack of a significant interaction as evidence that differences in tilt aftereffect strength cannot be explained by broader tuning curves; otherwise, we would have specifically expected larger aftereffects in PSZ compared to HC in the far condition and perhaps even the opposite difference in the near condition (see Figure 3B), resulting in a significant group-by-condition interaction. On the other hand, a lack of group-by-condition interaction indicates that differences in tilt aftereffect strength between PSZ and HC are not significantly larger in the near compared with the far condition, thus suggesting that stronger tilt aftereffects occur alongside marginally broader orientation tuning curves.

Analyses of standard deviation and lapse rate are presented in Supplementary Results. Briefly, standard deviation, but not lapse rate, was significantly larger in PSZ. This indicates reduced sensitivity to the orientation of the nuller stimulus, consistent with previous reports of reduced orientation discrimination in individuals with schizophrenia (Robol et al., 2013). The effect of group on tilt aftereffect strength remained, even after controlling for standard deviation.

Correlational Analyses

Correlations between symptoms and aftereffect strength are presented in Figure 7. Stronger tilt aftereffects in the near condition (where significant tilt aftereffects were observed) were related to more severe negative symptoms ($r = 0.50, p = .005$), even after Bonferroni-correction for the number of correlational analyses. There were no other relationships between clinical symptoms and aftereffect strength, nor any relationships with normalized medication dose (all $r$’s < 0.34, all uncorrected-$p$’s > 0.13). Negative afterimage strength correlated positively with tilt aftereffect strength in the near condition in HC, $r = .53, p = .006$, and at a trend level in PSZ, $r = .34, p = .07$. There were no significant correlations between tilt aftereffect strength in the far condition and negative afterimage strength.

Controlling for Eye Movements

Group differences in aftereffect strength remained when using gaze deviation criteria to exclude individual trials (see Supplementary Results).

Discussion

We observed stronger tilt aftereffects, but no difference in negative afterimages, in individuals with schizophrenia. Although our data were suggestive of broader orientation tuning curves in individuals with schizophrenia, consistent with previous studies (Qian et al., 2020; Rokem et al., 2011; Schallmo et al., 2015), differences in tuning curve width did not explain group differences in tilt aftereffect strength. Attesting to their clinical relevance, stronger tilt aftereffects were related to more severe negative symptoms. These data corroborate findings that hinted at stronger aftereffects of primarily cortical origin (i.e., orientation and motion) in schizophrenia (reviewed in Thakkar, Silverstein, et al., 2019), and circumvent methodological confounds present in those
changes in neural connection strengths (Quiroga et al., 2016). This recurrent connectivity within networks even in the absence of any interactions between these neurons (Bednar & Miikkulainen, 2000). In addition, adaptation can also be an emergent property of short-term changes in the strength of lateral inhibitory connections (Z. Li, 1998), and aftereffects arguably arise from short-term changes in the selectivity to visual input. Tilt aftereffects emerge primarily from adaptation of orientation-tuned neurons in visual cortex (Clifford, 2002), while negative afterimages are based largely in adaptation of retinal and subcortical neurons (Craik, 1940; H. Li et al., 2017; Zaidi, 2012). Thus, one mechanistic interpretation of our findings is that individuals with schizophrenia have altered cortical, but not retinal or subcortical, neuronal adaptation. At apparent odds with this idea is our finding that tilt aftereffects and negative afterimages correlate with each other (see also Brascamp et al., 2018). One likely resolution is that neuronal adaptation reflects multiple separate processes. One such process at the single-cell level is synaptic plasticity (Kohn, 2007), which may operate similarly across cortical and subcortical regions. However, there are also interactions at the network level that give rise to aftereffects, and these may differ across regions. By way of background, single neurons that are tuned to particular dimensions of visual input interact through both excitatory and inhibitory connections (Z. Li, 1998), and aftereffects arguably arise from short-term changes in the strength of lateral inhibitory interactions between these neurons (Bednar & Miikkulainen, 2000). In addition, adaptation can also be an emergent property of recurrent connectivity within networks even in the absence of any changes in neural connection strengths (Quiroga et al., 2016). This work points to stronger excitatory connections and broadly tuned inhibitory connections within visual cortex as causing stronger aftereffects, providing clues as to how network architecture may be altered in schizophrenia.

Altered connectivity in visual cortex is consistent with a prominent pathophysiological account of schizophrenia, which proposes a central imbalance in cortical excitation and inhibition (E/I imbalance) as a result of NMDA receptor hypofunction (Anticevic & Lisman, 2017). Altered excitatory and inhibitory dynamics in visual cortex of individuals with schizophrenia is supported by behavioral work indicating an abnormal use of spatial context in visual perception (Dakin et al., 2005; Schallmo et al., 2015; Serrano-Pedraza et al., 2014; Tadin et al., 2006; Tibber et al., 2013; Yang et al., 2013; Yoon et al., 2009), magnetic resonance spectroscopy showing altered concentrations of GABA and glutamate in visual cortex (Thakkar et al., 2017; Yoon et al., 2010), and animal (Hamm et al., 2017) and computational models (Silverstein et al., 2017). Findings from the current study are furthermore consistent with data suggesting a predominantly cortical origin of contextual processing in schizophrenia and in visual dysfunction more generally (reviewed in Silverstein, 2016). Future studies investigating relationships between aftereffect strength and other behavioral or physiological measures of E/I balance would be illuminating.

Differences in aftereffect strength can also be interpreted at the level of neuromodulators, given findings that reduced serotonergic and increased dopaminergic activity are associated with stronger tilt aftereffects (Calvert et al., 1991; Dickson et al., 2009; Harris et al., 1983; Harris et al., 1986; Harris et al., 1983; Masini et al., 1990; Murray et al., 2012). These effects may be due to the influence of serotonin in plasticity of the visual cortex (Gu, 2007) and to dopamine’s effect on retinal activity (Brandies & Yehuda, 2008) and/or its role in regulating cortical excitability (Nitsche et al., 2010). Alterations of dopaminergic (Tost et al., 2010) and serotonergic (Bleich et al.,
systems have been posited in schizophrenia and may relate to stronger tilt aftereffects.

Bayesian observer accounts of tilt aftereffects provide potential computational explanations for stronger tilt aftereffects in individuals with schizophrenia. According to one such account (Stocker & Simoncelli, 2005), exposure to a tilted grating may have two simultaneous and opposite effects. On the one hand, prolonged exposure to a stimulus leads to an interpretation of the sensory data (in Bayesian terms, a likelihood function) that is shifted away from those adapting features via a sharpening of tuning curves of neurons responsive to the adapter orientation: the repulsive tilt aftereffect. This tendency would relate to the posited functional role of neuronal adaptation, to adjust sensory systems’ limited resources to optimally process prevalent inputs—in this case the use of gain control to see best what one sees most (Thompson & Burr, 2009). The same Bayesian account, stipulates a second effect of the adapting stimulus, namely a shift in the system’s prior expectations toward the adapting features: a growing expectation that newly encountered stimuli will have those features, too. This shift in expectation (in Bayesian terms, the prior) would act against the repulsive effect that is observed in the tilt aftereffect and diminish its strength. Although both these posited effects of the adapting stimulus constitute adjustments of neural processing in response to prior input, an interpretation of our data in terms of these two effects would lead to an opposite conclusion in each case. Specifically, increased tilt aftereffect strength is consistent with an increased readiness to bias sensory processing, but also with a reduced readiness to adjust expectations. This idea of two oppositely acting components to history-dependent updating may also be helpful in framing the wider literature investigating the influence of history and knowledge on visual processing in schizophrenia, which is rife with mixed findings (Corlett et al., 2019;
Keane et al., 2013; Schmack et al., 2017; Schneider et al., 2002; Teufel et al., 2015). The Bayesian account discussed above (Stocker & Simoncelli, 2005) hints at potential reconciliations that center on a distinction between changes in sensory processing (related to the likelihood function) and changes in expectation (related to the prior).

In interpreting these findings, we must consider potential confounds—the most obvious being medication. It is unlikely that the dopaminergic activity of antipsychotic medication is driving our findings for two reasons. First, typical antipsychotics reduce the strength of tilt aftereffects (Harris et al., 1986; Harris et al., 1983); we observed the opposite. Second, antipsychotic dose did not correlate with aftereffect strength in our sample. However, atypical antipsychotic medications also block serotonin receptors (Meltzer et al., 2011), and less serotonergic activity relates to stronger antipsychotic medications also block serotonin receptors (Meltzer et al., 2011), and less serotonergic activity relates to stronger antipsychotic medications, many of which increase levels of synaptic serotonin, which may be expected to decrease aftereffect strength (Bachatene et al., 2013; Maya Vetencourt et al., 2008). Findings in nonclinical samples may provide further insights into a potential role of medication. In an undergraduate sample, we found that the strength of tilt aftereffects, but not negative afterimages, was related to schizotypal traits (Thakkar et al., 2019). However, the direction of that relationship was opposite to what the current findings would predict; increased schizophrenia-like traits were associated with weaker tilt aftereffects. Although these findings in healthy individuals may seem at odds with the current findings, we must consider the restricted range and minimal levels of schizotypal traits in that sample as well as the compensatory and homeostatic neural processes that likely occur in response to core disturbances associated with schizophrenia—all of which muddy a direct comparison. A further potential confound is perceived stimulus contrast. Individuals in the chronic stage of schizophrenia, which would characterize the majority of our sample, have reduced contrast sensitivity (e.g., Butler et al., 2005; e.g., Slaghuis, 1998).

In healthy individuals, both negative afterimages and tilt aftereffects become weaker as the physical contrast of the adapter stimulus decreases (Georgeson & Turner, 1985; Parker, 1972) raising the question of whether group differences in contrast sensitivity might be related to the current findings. Our pattern of results and previous findings in the literature would suggest that stronger tilt aftereffects are not secondary to altered contrast sensitivity (see Supplemental Discussion). It may well be, however, that common properties of early visual processing in schizophrenia produce both altered contrast sensitivity and altered tilt aftereffect strength, but more work is needed to understand the nature of these properties.

The observed correlation between tilt aftereffect strength and negative symptoms attests to the clinical relevance of these findings. This correlation is consistent with contextual processing deficits, broadly, as a potential mechanism of the heterogeneous symptoms of schizophrenia and, relatedly, findings that the strength of context in the spatial domain (i.e., surround suppression) is associated with negative symptoms (Robel et al., 2013; Tadin et al., 2006; Yang et al., 2013). Nonetheless, accounts of schizophrenia that specifically center on temporal context have typically described relationships with positive symptoms (Fletcher & Frith, 2009; Sterzer et al., 2018). In considering why we observed a relationship with negative, but not positive symptoms, we highlight the aforementioned mixed evidence for how past experience shapes current input in schizophrenia, noting that the story cannot be as simple as more or less history dependence in schizophrenia. There are likely a multitude of task-related factors that bear on experimental findings and that might yield different relationships with different symptom dimensions. As an example, group differences in the degree to which perception is shaped by a particular past event may depend on the duration of that past experience. Very recent past history may be overweighted at the expense of more distal experiences in schizophrenia such that the influence of recent history may be amplified (Salzinger, 1984), and the effect of more remote history may be attenuated. This can be tested in the context of aftereffect paradigms by varying the adapter duration, as aftereffects become stronger with longer adapter durations in healthy observers (Harris & Calvert, 1989). Testable predictions include the possibility that individuals with schizophrenia would have stronger tilt aftereffects at short adapter durations, but comparatively weaker tilt aftereffects at longer adapter durations, and that aftereffect strength at different timescales might relate differently to clinical symptoms. Finally, it is possible that the relationship between extent of tilt aftereffect and negative symptoms is based in altered gain control in schizophrenia. That is, to the extent that visual aftereffects are a form of gain control, in the sense of reducing neural activity to prevent saturation of neuronal responses (Thompson & Burr, 2009), then this is consistent with one view of negative symptoms which states that these reflect compensatory diminishment of functioning as a response to excessive excitation, neural disorganization, cognitive errors, and resultant instrumental and social failure experiences (e.g., Lee et al., 2003; Rector et al., 2005; Venables & Wing, 1962).

The association between tilt aftereffect strength and negative symptoms also highlights the inherent heterogeneity of schizophrenia. It is possible that stronger tilt aftereffects are only present in chronically ill individuals with predominant negative symptom presentation. Indeed, the observed overreliance on past history in shaping current perception in schizophrenia may develop over time and in response to disruptions present earlier in the illness or during acute psychosis. Research in individuals across illness stages and with more diverse symptom severities will be an important area of future study.

To conclude, a wealth of findings suggest that the processing of information is tuned differently to context in schizophrenia, which may provide a compelling cognitive and mechanistic explanation for clinical phenomenology. Visual aftereffects provide a unique opportunity for understanding the role of temporal context, thereby fostering a deeper computational and physiological understanding of how past experience sculpts our reality and how precisely this inferential process may differ in individuals with schizophrenia. Our present findings form a promising first step toward exploiting this potential of visual aftereffects in furthering the understanding of the disease.


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