PREDICTIVE PROCESSING IN THE RETINA THROUGH EVALUATION OF THE OMITTED-STIMULUS RESPONSE

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ABSTRACT OF THE THESIS

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While previous studies have demonstrated that individuals with schizophrenia demonstrate predictive coding abnormalities in high-level vision, it is unclear whether impairments exist in low-level predictive processing within the disorder. Evaluation of the omitted-stimulus response (OSR), i.e., activity following the omission of a light flash subsequent to a repetitive stimulus, has been examined previously to assess prediction within retinal activity. Given that little research has focused on the OSR in humans, the present study investigated if predictive processing could be detected at the retinal level within a healthy human sample, and whether this activity was associated with high-level predictive processing. Flash electroretinography (fERG) was recorded while eighteen healthy control participants viewed a series of consecutive light flashes within a 1.96 Hz single-flash condition with a flash luminance of 85 Td · s, as well as a 28.3 Hz flicker condition with a flash luminance of 16 Td · s. Participants also completed the Ebbinghaus

task, a context sensitivity task that assesses high-level predictive processing, and the Audio-Visual Abnormalities Questionnaire (AVAQ), which measures frequency of self-reported auditory and visual sensory distortions. For both conditions, within-group analyses were conducted to compare fERG amplitude and implicit time measurements following present-stimulus trials with those following omitted-stimulus trials. Additionally, mean omitted-stimulus waveforms reflecting averaged retinal responses across all subjects were examined for presence of an OSR. Results demonstrated the absence of an OSR within the 1.96 Hz condition and the presence of activity in response to omitted stimuli within the 28.3 Hz flicker condition that could represent an OSR. The amplitude of the OSR in the flicker condition was significantly correlated with the number of flicker repetitions prior to the first omission (r_s=.57, p=.02), supporting the conclusion that this activity was at least partially predictive in nature. Correlations were also run to analyze the relationships between fERG measurements and high-level predictive processing and sensory distortions. Results revealed that the flicker evoked response was not related to high-level predictive processing, as measured by Ebbinghaus illusion task performance, or self-reported sensory abnormalities, as measured by the AVAQ. However, stronger omitted-stimulus a-wave amplitude at 1.96 Hz was marginally related to greater top-down prediction. Additionally, findings indicated that earlier omitted-stimulus a-wave implicit time was associated with increased sensory distortions. While the mechanisms underlying the OSR remain unclear, data from previous studies suggest that this activity represents resonant activity elicited by ON bipolar cells, although additional studies are required to assess the OSR at different frequencies. Overall, findings indicate the presence of an OSR within retinal activity of a

healthy human sample following omissions embedded within a highly repetitive flicker train. Future studies should examine whether this activity is reduced in individuals with schizophrenia, as this could potentially be used as a visual biomarker for aspects of the disorder.

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Introduction

Schizophrenia is a chronic and debilitating syndrome with prevalence rates between 0.33% and 0.75% of the international population (Moreno-Küstner et al., 2018). Although the pathophysiology is still largely unclear, evidence suggests that the illness is characterized by a variety of sensory processing deficits (Javitt, 2009) and alterations in perception (Uhlhaas & Mishara, 2007). In particular, individuals with schizophrenia demonstrate visual processing impairments, including deficits in retinal function, contrast sensitivity, spatial frequency processing, backward masking, perceptual organization, and reduced or enhanced illusion and aftereffect perception, depending on the task (Silverstein, 2016). The investigation of visual perception in schizophrenia is essential, as evidence has shown about 65% of people with schizophrenia experience visual perceptual abnormalities (Keane et al., 2018), and visual perceptual dysfunction has been associated with poorer neuropsychological and social functioning (Butler & Javitt, 2005).

The predictive coding theory of psychosis (Sterzer et al., 2018) posits that abnormalities in the way in which individuals with schizophrenia generate predictions regarding sensory information, as well as process unexpected incoming stimuli, may contribute to psychosis. Mismatches between higher order predictions and incoming sensory signals may lead to reduced reliance on contextual cues and/or to over-reliance on internal states when generating mental representations about what is happening in the world, both of which could result in delusions and hallucinations. Evidence for predictive coding failures in schizophrenia comes from many sources (Corlett et al., 2016; Fletcher & Frith, 2009; Friston, 2010). However, predictive coding has never been investigated at the level of sensory processing in individuals with schizophrenia. Additionally, few

studies have focused on predictive processing within retinal activity in a healthy human sample (Gowrisankaran et al., 2013; McAnany et al., 2013; McAnany & Alexander, 2009). Therefore, the current study will determine, using two tests from electroretinography (ERG) that are suitable for use with people with schizophrenia, whether predictive processing occurs in retinal functioning in healthy people. These data provide the foundation and motivation for a future study comparing healthy controls to people with schizophrenia. The discussion below is presented in five sections. First, I will review the data on visual perceptual abnormalities in schizophrenia. Second, I will review the evidence on predictive coding impairments in the disorder. Next, I will discuss studies showing that people with schizophrenia demonstrate abnormalities in retinal structure and function. I will then review evidence from healthy human and animal studies, showing that predictive processing can be found in retinal signaling. Finally, the aims of the current study are discussed.

Visual distortions and perceptual anomalies in schizophrenia

Although visual hallucinations are less common than auditory hallucinations in people with schizophrenia, the majority of patients (~65%) report visual distortions and visual perceptual abnormalities (Phillipson & Harris, 1985). The visual distortions that people with schizophrenia experience are often thought of as a component of *basic symptoms*, which are subjectively experienced disturbances of the self and the world that are among the earliest signs of the illness, as well as ones that can persist for years regardless of the level of positive or negative symptoms (Huber, 1983). Studies have previously assessed these distortions with the Bonn Scale for the Assessment of Basic Symptoms (BSABS) (Gross et al., 1987), and the categories which assess visual

dysfunction in this scale are listed in Table 1. Evidence suggests that occurrence of these basic symptoms can predict onset of schizophrenia in a prodromal population (Klosterkötter et al., 2001). Additionally, Meng et al. (2009) demonstrated that a higher proportion of individuals with early onset psychosis endorsed at least one basic symptom, when compared to general adolescent and non-psychotic psychiatric disorder groups.

It is currently unclear, because it has never been investigated, to what extent retinal functioning contributes to visual distortions in schizophrenia. However, because a number of the visual distortions reported by people with schizophrenia are similar to those in people with known retinal impairment (Ffytche & Howard, 1999), and because schizophrenia patients have been shown to have abnormalities in retinal structure and function (Silverstein et al., 2020; Silverstein & Rosen, 2015), it is reasonable to investigate the extent to which reported visual distortions are associated with retinal changes. For the purposes of this study, visual distortions will be assessed with the Audio-Visual Abnormalities Questionnaire (AVAQ) (Nikitova et al., 2019), which was recently developed as part of a collaboration between the Division of Schizophrenia Research at Rutgers University and the Department of Psychology at the University of Glasgow. The AVAQ assesses anomalies in visual and auditory sensory processing that have been reported by people with schizophrenia, such as problems with light and sound sensitivity, perception/recognition of faces, and visual short-term memory. It is valid to study the AVAQ within a healthy human sample, as Nikitova et al. (2019) observed that heathy controls exhibited a range of scores within their validation study, and a significant proportion of people in the general population report experiencing visual distortions at times.

Studies have also consistently shown that people with schizophrenia demonstrate a variety of abnormalities in visual perceptual processing, from low- to high-level vision. Low-level impairments suggest the involvement of aberrant sensory processing, including retinal dysfunction in the disorder (Silverstein, 2016). For example, there is consistent evidence from behavioral and imaging studies demonstrating reduced contrast sensitivity (Butler et al., 2005; Calderone et al., 2013; Kelemen et al., 2013) and reduced low spatial frequency processing (Calderone et al., 2013; Kiss et al., 2006; Martinez et al., 2012) in schizophrenia, functions that have significant contributions from retinal ganglion cells owing to their center-surround (e.g., On center – Off surround) organization. In one study demonstrating dysfunctional contrast sensitivity in schizophrenia, Calderone et al. (2013) showed subjects a sensory grating (both low- and high-frequency) on either the left or right side of a screen. When subjects were asked to indicate which side of the screen they saw the grating, the schizophrenia group showed greater deficits in distinguishing the contrast than did controls. In an additional study, Martinez et al. (2012) found that people with schizophrenia were less able to distinguish low-frequency gratings than controls, and that P1 and N1 event-related potential (ERP) amplitudes were reduced in individuals with schizophrenia. The researchers also found reduced activity in the occipital cortex in schizophrenia when subjects attended to low spatial frequency items. While these studies could indicate a cortical and/or retinal origin for the impairments, multiple other studies have shown reduced strength (Butler et al., 2005) and increased latency (Malyszczak et al., 2004; Schechter et al., 2005) of the visual evoked potential in people with schizophrenia, indicating impairment in the signal prior to reaching the visual cortex. Taken together, these data suggest that visual processing is

impaired even prior to cortical processing in schizophrenia. Moreover, a number of studies of retinal function in schizophrenia indicate impairments in functioning. These studies will be considered in the section on retinal involvement in schizophrenia, below.

Predictive Coding in Schizophrenia

The ability to make predictions regarding external stimuli is essential to navigating one's environment. This view had its origins with Helmholtz's (1867) theory of unconscious inference, in which the brain uses predictions, based on prior experience, to actively make interpretations about the nature of incoming stimuli. Predictive coding generally refers to a computational modeling approach that represents this process. One view posits that errors occur when a higher level prediction does not match the incoming signal from the lower level, and error signals are sent as a result to the higher cortical level in order to dynamically update the predictive model of the world (Clark, 2013). Additionally, these models can be viewed within a Bayesian lens, in which probability distributions regarding incoming sensory information are formulated through the combination of prior knowledge and incoming sensory signals (Friston, 2005). Predictive processing is crucial in that it allows individuals to dynamically and efficiently adapt to changes they naturally encounter.

Anomalies in this processing of higher-order predictions regarding incoming sensory information may contribute to the development of delusions and hallucinations in schizophrenia. Some evidence suggests this may occur due to inaccurate predictions based on imprecise prior information (leading to faulty top-down signals) and/or abnormalities in processing low-level sensory information (leading to noisy signals that are difficult to map onto stored information) (Sterzer et al., 2018). In either scenario, top-

down prediction signals sent to earlier levels in the cortical hierarchy do not match as well to sensory input as occurs in healthy people. Fletcher and Frith (2009) suggested that as a result of an increased tendency to achieve a mismatch, unnecessary prediction errors may be generated, leading to inappropriate modifications of the predictive model (i.e., the model of the world), which can result in feelings that the self and world are changing, and eventually in delusional ideation. Some models posit that inaccurate predictions result from NMDA receptor hypofunction and aberrant dopaminergic functioning, which lead to abnormalities in post-synaptic gain following a prediction error (Adams et al., 2013). As a result of aberrant prediction errors, what would have previously been considered abnormal can start to be felt as normal, leading to entrenched false beliefs and perceptions.

Visual illusions provide compelling examples of the role of predictive coding, in that the illusory perception can often be understood as a mental representation based on what was expected to be seen based on prior experience with the perceptual context, as opposed to the actual sensory data (Notredame et al., 2014). Individuals with schizophrenia often demonstrate resistance to perceiving visual illusions, and will demonstrate greater accuracy in describing the nature of the external stimulus, compared to healthy controls. Researchers have shown this through use of the Ebbinghaus task, in which subjects are shown two target circles surrounded by circles of varying size (see Fig. 1). The participants are asked to indicate which circle they believe is larger. The illusion relies on contextual information, and the healthy subject typically perceives the circle as being larger when surrounded by small circles, and smaller when surrounded by large circles (Silverstein, 2016). The Ebbinghaus illusion can be viewed as an example of

predictive coding, as the perception of the size of the target circle is adjusted through a size constancy mechanism. This has been hypothesized to reflect the use of prior knowledge in judging size as a function of distance, with the surround circles providing the distance cues (see Fig. 2). The use of prior experience to evaluate distance in perceiving the size of the circle is further supported in studies demonstrating resistance to the illusion in young children (Doherty et al., 2010). In a condition that is typically misleading for healthy controls, individuals with schizophrenia are also able to more accurately distinguish the size of the target shape (Horton & Silverstein, 2011; Joseph et al., 2013; Uhlhaas et al., 2006; Yang et al., 2012). Interestingly, more accurate performance on the illusion task has been associated with disorganized symptoms, presumably due to weaker organization of the visual field leading to reduced size constancy (Horton & Silverstein, 2011; Silverstein et al., 2013) and the presence of active psychotic symptoms, especially after the first psychotic episode (Silverstein et al., 2013). I will discuss how this task will be used in this study as a measure of predictive coding in the sections describing the data analytic strategy and methods.

Surround suppression illusions (Chubb et al., 1989) represent an additional method to assess predictive processing in the visual domain, where the subject uses context cues to indicate how the contrast of the target shape (typically a circle) compares to the contrast of the surround (typically a thick ring around the target) (Sterzer et al., 2019). Healthy controls perceive the target shape as lower contrast than it truly is, when it is surrounded by a high-contrast background. Evidence has shown that people with chronic schizophrenia more accurately view the contrast of the target shape, and do not perceive the illusion to the same extent as do controls (Dakin et al., 2005; Tibber et al.,

2013). Seymour et al. (2013) measured abnormalities in neural responses to surround suppression with orientation surround stimuli through the use of fMRI. While controls showed a greater suppression in the V1 response when the surround and target shapes were parallel (as opposed to orthogonal), individuals with schizophrenia did not show a difference in neural suppression when context orientation conditions were compared. These findings are consistent with the hierarchical predictive coding hypothesis in that it is, in most circumstances, more adaptive to represent the sensory features of an image as a function of the surrounding context (e.g., to recover the 'true' color of an image viewed in semi-dark or rainy or foggy conditions), as opposed to processing the sensory data as if one's perception were a veridical representation of the stimulus taken out of context (Rao & Ballard, 1999).

Studies focused on depth inversion illusions, and the hollow mask illusion in particular, reveal similar findings, where schizophrenia groups demonstrate greater resistance to perceiving the illusion. Healthy controls' face perception typically relies heavily on top-down signals about the convexity of faces, in which previous beliefs of how a face should look (i.e., that they should always be convex) are used to inform the perception, even when the face image is concave (Gregory, 1997; Gregory, 1970). Further evidence indicating the involvement of top-down processes in perceiving concave faces was demonstrated in a study that found decreased accuracy in perceiving inverted concave faces in healthy controls (Papathomas & Bono, 2004). Previous studies have consistently shown that individuals with schizophrenia demonstrate greater accuracy when completing a hollow-mask illusion task (i.e., when judging whether a concave face is concave or convex) than healthy controls (Keane et al., 2013; Koethe et al., 2009;

Schneider et al., 2002), and performance on the task has been associated with positive symptoms (Keane et al., 2013) and acute psychosis (Schneider et al., 2002). In an effort to investigate the underlying neural mechanisms, Dima et al. (2009) used dynamic casual modeling to explore differences in connectivity between schizophrenia and control groups while viewing the illusion. The neural findings in controls were best explained by a model with backward connections from the intraparietal sulcus to the lateral occipital cortex, whereas the data from the schizophrenia group was best explained by a forward connection between V1 and lateral occipital cortex. Therefore, these results suggest that individuals with schizophrenia are characterized by reduced top-down influences (in the form of prior knowledge), to inform their perception when a prediction error should be occurring, relative to controls.

Predictive coding failures are not limited to vision in schizophrenia. Researchers have also reported dysfunction in auditory prediction processing in schizophrenia through the use of fMRI. Horga et al. (2014) found that patients with schizophrenia demonstrated reduced prediction error signals in the right auditory cortex. This suggests that deficits in prediction error signaling to higher level neural pathways may lead to the abnormal neural activity seen in the auditory cortex when an individual is experiencing an auditory hallucination. Deficits in auditory predictive processing in schizophrenia have also been shown in the laboratory with studies using electroencephalography (EEG) to measure the neural response to the occurrence of an unexpected stimulus. The mismatch negativity (MMN) event-related potential (ERP) is thought to represent the detection of a change in auditory stimuli when the presented stimulus does not match the higher order prediction, which was based on immediately preceding experiences (Näätänen et al., 2007). Studies

have consistently demonstrated reduction in the MMN difference waveform in schizophrenia, when compared to controls (Erickson et al., 2016; Umbricht & Krljes, 2005). From the predictive coding perspective, there was a weaker neural response to a stimulus that was incongruent with higher order predictions. Although most studies have displayed decreased MMN activity in the auditory modality, atypical MMN activity has been observed in visual studies as well. Reduced visual MMN activity in schizophrenia has been shown in response to unexpected changes in motion direction (Urban et al., 2008), emotional faces (Csukly et al., 2013), and changes in stimulus orientation (Farkas et al., 2015). The reviewed evidence suggests that predictive processing impairments are a general problem in schizophrenia, and that they are manifested in multiple sensory modalities and levels of processing, from sensory to cognitive functioning. In order to clarify the nature of the extent of these impairments and to have a brief and portable tool for use in patient monitoring, I propose to test the validity of a retinal marker of predictive coding.

Retinal Anomalies in Schizophrenia

Studies have consistently shown that, in addition to many visual changes suggestive of cortical functioning impairments in schizophrenia, changes can be found as early as the retina, including anomalies in retinal structure and retinal cell functioning (Silverstein & Rosen, 2015; Silverstein et al., 2020). The retina is part of the central nervous system (see Fig. 3 for illustration of retinal cells and layers), and therefore can be used as a proxy for assessing neural mechanisms. Many studies have indicated that individuals with schizophrenia demonstrate thinning of retinal layers, as revealed through optical coherence tomography (OCT). Initial studies showed peripapillary retinal nerve

fiber layer (RNFL) thinning, which represents a reduction in ganglion cell axons (Lee et al., 2013), as well as macula thinning (from the inner limiting membrane to the retinal pigment epithelium, or through all neural layers), in schizophrenia. While Ascaso et al. (2010) and Cabezon et. al (2012) found only RNFL thinning in schizophrenia, when compared to healthy controls, another study found both RNFL and macular volume (MV) reductions (Lee et al., 2013). Notably, Chu et al. (2012) did not find these reductions in retinal structure between groups, although this study used an older OCT technique with a weaker resolution. Consistent with previous findings, Ascaso et al. (2015) demonstrated reductions in peripapillary RNFL thickness, macular inner ring thickness, and MV in schizophrenia in a non-recent illness episode sample. Similarly, Yilmaz et al. (2016) reported reduced overall and nasal peripapillary RNFL thickness, and reduced macular thickness in outer nasal and outer inferior macular areas in schizophrenia. Some research groups have also chosen to investigate differences in ganglion cell layer (GCL) and inner plexiform layer (IPL) thickness anomalies in schizophrenia. One study (Celik et al., 2016) found decreased GCL and IPL parameters in schizophrenia, in addition to right eye RNFL thinning and right eye temporo-superior and temporo-inferior segment thinning. These parameters were associated with disease duration and symptom severity. To date, there have been few studies investigating outer nuclear layer (ONL) and inner segment layer (ISL) thinning in schizophrenia. Samani et al. (2018) focused on these retinal parameters and reported that individuals with schizophrenia demonstrated macular thinning, as well as ONL and ISL thinning. An additional study reported mixed results that indicated similar RNFL and subfoveal choroidal thickness (SFCT) values between schizophrenia and control groups, while also reporting reductions in macular values

within an acute sample (Topcu-Yilmaz et al., 2019). Similar to Ascaso et al. (2015), the patient group consisted of individuals on an inpatient unit, which the authors suggest may explain why reduction in RNFL was not found, as there may have been swelling (edema) of retinal tissue secondary to neuroinflammation associated with an acute psychotic episode. Notably, Silverstein et al. (2018) did not find differences in RNFL or macula parameters between schizophrenia and control groups. However, when participants were separated according to the presence of medical conditions highly prevalent in schizophrenia, such as diabetes and hypertension, researchers found thinning in these parameters in individuals with the conditions mentioned. However, the schizophrenia group did demonstrate greater optic cup volumes and cup-to-disc ratios than the control group. Taken together, studies have consistently demonstrated anomalies in retinal structure within schizophrenia, although the specific location of these abnormalities in the structure of the retina has differed somewhat across studies. At present, it is not known whether or to what extent these structural abnormalities cause problems in retinal function in people with schizophrenia, however, other literature, using flash electroretinography (fERG) indicates that retinal function is impaired in the disorder (Silverstein et al., 2020; Adams & Nasrallah, 2018; Silverstein & Rosen, 2015).

fERG involves recording electrical potentials produced from retinal cells in response to light stimuli. A resultant waveform is generated that includes an initial negative trough, or the a-wave, representing photoreceptor activity, and a positive peak, or the b-wave, representing bipolar-Müller cell activity. When fERG is recorded in a light-adapted or photopic condition, the a-wave measures cone activity, while a waveform generated in a dark-adapted condition represents rod or (with higher intensity

light stimuli) mixed rod-cone activity (Lavoie et al., 2014). Findings have indicated reduced cone a-wave (Balogh et al., 2008; Demmin et al., 2018; Hébert et al., 2015; Warner et al., 1999), and rod a- (Demmin et al., 2018) and b-wave activity (Demmin et al., 2018; Hébert et al., 2015; Warner et al., 1999) in schizophrenia. Additionally, studies have found mixed rod-cone a- (Warner et al., 1999) and b-wave amplitude reductions (Hébert et al., 2015; Warner et al., 1999) in schizophrenia. Demmin et al. (2018) also demonstrated a weaker photopic negative response (PhNR) among the schizophrenia group, which represented aberrant retinal ganglion cell activity. Overall, studies indicate deficits in retinal cell functioning, although the specific conditions under which patient-control group discrimination is maximal are still unclear.

Predictive Coding in the Retina

It is evident that individuals with schizophrenia demonstrate deficiencies in both low- and high-level visual processing. Although errors in predictive processing have been demonstrated multiple times in high level visual tasks (e.g., those involving illusions, see above), few studies have investigated this at the lower, sensory level, and no prior studies of schizophrenia have focused on predictive coding in retinal activity. The retina is believed to have the capability to adapt to the changes in one's environment through a dynamic process. Specifically, prior studies have shown that the ganglion cells, which transmit visual information from the retinal cells to the brain (specifically, to the lateral geniculate nuclei of the thalamus), signal predictions of upcoming sensory stimuli in the visual scene (Gollisch & Meister, 2010).

To assess predictive processing in the retina, previous studies have measured the omitted stimulus response (OSR), which represents the electrophysiological response of

the retina to a non-event when one is expected, typically after a series of similar or related (i.e., highly predictive of each other) stimulus presentations. An OSR has been observed in the electrophysiological response of salamander and mouse retinas, in which researchers found that retinal ganglion cells responded to the absence of an expected stimulus within a stimulus train (Schwartz et al., 2007; Schwartz & Berry, 2008). Studies have typically defined the OSR in terms of the constant delay between the time point of the expected but omitted-stimulus and the peak of the OSR (McAnany & Alexander, 2009). Schwartz and Berry (2008) found a variety of responses to omitted stimuli in ganglion cells studied (n=434), such as single peak, double peak, and ringing responses. Interestingly, cells that responded with a single peak following the first present flash did not show a response following the omitted-stimulus. Based on this, the authors hypothesized that the firing of a combination of particular ganglion cells in response to omitted stimuli signals to the brain that a violation in the prediction occurred. When the researchers blocked ON bipolar cell responses through a selective metabotropic glutamate receptor 6 agonist (mGluR6), the OSR response was eliminated. Therefore, the researchers suggested that the OSR may be a product of resonant ON bipolar cell activity. McAnany and Alexander (2009) demonstrated the presence of an OSR in human retinal data using a flicker paradigm. Following termination of the flicker train, an OSR was observed at a delayed latency from the time point of the expected stimulus. These researchers also reported an extra response following the omission of a light flash, when it was removed from the middle of a flicker train. Further evidence supports the conclusion of Schwartz and Berry (2008) that the OSR originates from resonant activity of ON bipolar cells. In particular, the absence of an OSR was observed in a subject with a

genetic mutation thought to inhibit the ON bipolar cell pathway (McAnany et al., 2013), and retinal activity following the termination of a flicker train has been fit to a resonance model in which omitted-stimulus responses are constant across stimuli of varying frequency (Gowrisankaran et al., 2013). Overall, the results of these studies suggest that the retina engages in predictive processing, as retinal cells generate electrical potentials when stimuli are not present.

Limitations of Current Literature

While there is evidence for pattern prediction at the cortical level, direct evidence for this processing at the primary sensory level of vision is limited to the few studies cited in the section above. Given that proposed models of the pathophysiology of schizophrenia postulate that abnormalities in predictive processing may contribute to psychosis, it would be useful to have a brief measure of predictive processing for clinical research. The advantages of this include: 1) it would demonstrate whether predictive processing is impaired at the level of the retina in schizophrenia; and 2) if it is impaired, such a measure could be used for routine monitoring of patients to determine if retinal predictive processing is a useful indicator of changes in clinical state such as impending relapse, or early response to treatment (as may be the case for measures of high-level vision, such as the depth inversion and Ebbinghaus illusions, noted above). However, prior to conducting such studies, it is necessary to determine if predictive processing in the retina can be detected in a healthy human population using the type of fERG procedure that is typically used in patient research.

Current Study

The current study investigates whether predictive processing exists at the level of retinal processing in a healthy control sample. The current study includes two specific aims: 1) to investigate if the OSR exists in the retinal response to an unexpected omitted light flash, and 2) to explore the relationship between predictive processing at the lower-level with that at the higher-level of visual perception. This is a foundational study to investigate if predictive processing exists at the primary sensory level of vision, which will inform future studies to explore how this process may go awry in schizophrenia.

Given that previous studies have observed an OSR in human retinal data following a highly repetitive stimulus train (Gowrisankaran et al., 2013; McAnany et al., 2013; McAnany & Alexander, 2009), it is hypothesized that an OSR will be present following omissions embedded within a 1.96 Hz single flash stimulus condition and a 28.3 Hz flicker condition. We also expect that OSR magnitude will be related to trial number and trial number of first omission, as predictive activity is expected to be related to the number of present-stimuli individuals have viewed consecutively. Lastly, it is hypothesized that low-level visual predictive processing, as measured by the strength of the OSR, will be associated with prediction in high-level vision, as measured by performance on the Ebbinghaus illusion.

Methods

Participants

The study sample consisted of healthy controls (*N*=18) recruited from a pool of subjects who participated in previous Division of Schizophrenia Research studies and who gave written consent to be contacted for future research studies. Subjects met inclusion criteria if they were between the ages of 18 and 60 and were able to speak and read English well enough to complete study tasks. Exclusion criteria included a lifetime diagnosis of schizophrenia or bipolar disorder, a first-degree relative with a psychotic or bipolar disorder, a diagnosis of a pervasive developmental disorder, a diagnosis of an intellectual disability, active substance-use disorder in the past 12 months, history of head injury with loss of consciousness greater than 10 minutes, diagnosis of a neurological condition or disorder, and history of seizures or epilepsy. Participants also met exclusion criteria if they had a history of ocular or neurological disease or condition (i.e. amblyopia), other diseases known to affect retinal functioning, history of eye injury, or history of ocular surgery in the past 6 months.

Procedure

First, participants reviewed and signed the informed consent form if they agreed to participate. Following the consenting process, subjects completed a demographic and history questionnaire, that inquired about the gender, age, race, ethnicity, handedness, educational attainment of self and parents, occupation, medical conditions, and current medications. Participants then completed the fERG protocol, including two separate light-adapted conditions, to measure the retinal response to a sequence of light flashes. The RETeval, an FDA-approved portable device that does not require corneal contact nor

pupil dilation (LKC Technologies, Gaithersburg, MD), was used to record the electrical potential produced by the retinal cells (see Fig. 4). Before testing began, subjects were light-adapted to the light in the study room for a minimum of 10 minutes. A sensor strip with positive, negative, and ground electrodes was placed on the skin 2 mm below the lower eyelid. Subjects were asked to focus on a fixation point and keep their eyes open as much as possible during the light stimulation. In order to account for pupil size, flash retinal luminance is measured in units of Trolands per second (Td · s), in which the flash luminance (cd · s/m^2) is multiplied by the area of the pupil (mm^2) (Davis et al., 2017). The first condition included an 85 Td · s light flash stimulus at a rate of approximately 1.96 Hz with 120 trials (see Fig. 5a). This condition also included an 848 Td white light background. The second condition involved a flicker paradigm with a 16 Td · s flash stimulus at a rate of approximately 28.31 Hz and the number of total trials ranged from 432 to 438 trials (see Fig. 5b). For both conditions, there was a 10% chance that each trial would be omitted. Data was collected at a sampling rate of 1953.13 Hz for both conditions.

After completing the fERG protocol, participants completed the Wechsler Test of Adult Reading (WTAR), which measures the estimated verbal IQ of the participant. Next, the participants completed the Audio-Visual Abnormalities Questionnaire (AVAQ), which measures abnormalities in sensory processing, as well as the Ebbinghaus illusion computer task, which assesses size constancy.

Measures

Demographics. Information was collected regarding the participant's sex, age, race, ethnicity, handedness, educational attainment of self and parents, occupation, medical conditions, and current medications.

Wechsler Test of Adult Reading (WTAR). The WTAR (Wechsler, 2011) is used as an estimate of verbal IQ. Participants are asked to read a list of 50 words aloud and the accuracy of the pronunciation of each word is assessed. Raw scores range from 0 to 50 and are calculated by summing the amount of words participants pronounced correctly. Scaled scores range from 50 to 128 and are calculated using a participant's raw score and age. Data from two subjects were excluded from analyses because English was not their first language.

The Audio-Visual Abnormalities Questionnaire (AVAQ). The AVAQ (Nikitova et al., 2019) is an 85-item questionnaire that is used to assess dysfunction in auditory and visual processing. The items on this questionnaire represent domains of sensory experience in which abnormalities have been reported in people with schizophrenia. Participants are asked to indicate how often the perceptual experience occurred in the past year on a scale from zero to three. A response of zero indicates "never," a response of one indicates "sometimes," a response of two indicates "often," and a response of three indicates "nearly always." Total scores are calculated by summing the answers to each question. The questionnaire includes five catch questions to confirm accurate responses and these answers are not included in the total score. Data is typically excluded from analyses if the participant endorses greater than two catch questions.

Ebbinghaus Illusion. The Ebbinghaus illusion is displayed through a computerized task (Silverstein et al., 2013), in which participants view two target circles and are instructed to indicate which they believe is larger (see Fig. 1). They are given two seconds to provide an answer on each trial. Circles surrounding the target circle are either larger or smaller than the target circle, depending on the trial. The task involves no-context, misleading, and helpful conditions. In the no-context condition, the target circles are presented without surrounding stimuli. During the misleading condition, the larger of the inner circles is surrounded by eight large circles, and the smaller inner circle is surrounded by eight small circles. Here, the illusion leads the participant to perceive the smaller target as larger, and the larger target as smaller than they truly are. In the helpful condition, the larger of the inner circles is surrounded by eight small circles (making it appear larger than its actual size) while the smaller inner circle is surrounded by large circles (making it appear smaller than its actual size). The size difference between the target circles varies throughout the trial sequence. There are 192 trials in total. The first metric calculated is contextual facilitation, which is equivalent to the proportion correct in the no-context condition subtracted from the proportion correct in the helpful condition. Contextual impairment is equivalent to the proportion correct in the no-context condition subtracted from the proportion correct in the misleading condition. The final metric, context sensitivity, is calculated as the difference score between contextual facilitation and contextual impairment.

fERG Analysis

Single flash paradigm

Data was initially filtered using a 1 to 100 Hz bandpass filter and a 60—Hz notch filter. An artifact rejection routine was then conducted to reject epochs with greater than 1 millivolt change. Trials were then separated to distinguish between present-stimulus trials and omitted-stimulus trials.

To calculate the a-wave peak amplitude metric, a-wave amplitude was measured as the peak height of the negative a-wave trough after subtracting the baseline value. The negative trough of each trial was measured as the minimum value in microvolts (μV) that occurred between 8.19 ms and 17.92 ms following flash onset. B-wave amplitude was measured as the difference between the amplitude of the b-wave peak and the amplitude of the a-wave trough (Creel, 2015). The b-wave peak amplitude for each trial was measured as the maximum amplitude value between 24.07 ms and 34.81 ms following the flash onset. The minimum value calculated earlier was then subtracted from the maximum value in order to calculate the b-wave peak amplitude. The a- and b-wave implicit time measurements (i.e., latency) were calculated as the time elapsed from flash onset to a-wave trough or b-wave peak. The time windows chosen for the a-wave trough and b-wave peak were selected based on reference data collected by the manufacturer of the RETeval device. Separate a- and b-wave measurements were calculated for individual trials, and final a-wave and b-wave peak and implicit time measurements were determined by calculating the median of each measurement for all trials for each subject. Mean waveforms were also plotted by averaging the mean waveforms of all subjects across all timepoints.

Flicker paradigm

Data from the flicker paradigm was pre-processed offline using a 1 to 100 Hz bandpass filter and data was segmented into 60 ms epochs. Mean waveforms were calculated by averaging microvolt values across trials for all timepoints for each subject and the peak measurements were selected from the resultant waveform. Of note, this procedure differs from the procedure used to calculate the ERG measurements within the 2 Hz condition, in which the peak measurements were selected on each trial prior to plotting the mean waveform. The peak was measured as the maximum peak of the resultant waveform and the trough was measured as the minimum value prior to the identified peak. Peak-to-peak amplitude of the resultant waveform was measured as the height of the positive peak subtracted by the height of the trough. The flicker implicit time measurement was measured as the time elapsed from stimulus onset to the positive peak (McCulloch et al., 2015). Mean waveforms were plotted as the average of all individual subject mean waveforms across time.

Intraindividual Variability

The intraindividual variability metric for each subject within the single flash condition was measured by calculating the intraclass correlation coefficient (ICC; two-way random model) of ERG data across all trials. Here, the ICC measurement is equivalent to the variability of ERG activity across time points within a trial (collapsed across all trials) compared to the variability across trials at each time point. ICC was calculated using the Real Statistics Resource Pack software (Release 6.8). Copyright (2013 – 2020) Charles Zaiontz. www.real-statistics.com using the following equation:

$$\frac{var(\beta)}{var(\alpha) + var(\beta) + var(\varepsilon)}$$

(1)

Data was presented in a matrix with number of columns, or k, reflecting individual trials and with number of rows, or n, reflecting samples of data across individual trials across time. In the equation described above, Var(β) is equivalent to the variance due to differences in ERG activity across single trial duration and is calculated by $(MS_{Row} - MS_E)/k$. Var(α) is equivalent to $MS_{Col} - MS_E/n$. Var(ε) is equivalent to variance due to differences in microvolt values across timepoints, and is measured as MS_E. The ICC measurement ranges from 0, indicating greater variability among trials, to 1, indicating less variability, and greater consistency, across trials.

Baseline variability

For the 1.96 Hz condition, variability of baseline activity prior to stimulus onset for the single flash condition was measured as the median standard deviation of the mean of the baseline values across trials and subjects.

Data Analytic Strategy

The following analyses were conducted using SPSS Version 26. Shapiro-Wilk tests were first conducted to assess for normality among the variables. Non-parametric tests were used for all distributions that violated the normality assumption. Outliers were omitted from correlation analyses if they were present outside the whiskers on a box-and-whisker plot.

To investigate if predictive processing occurred at the level of the retina, differences in median a- and b-wave and mean peak-to-peak amplitude and implicit time measurements were compared between present-stimulus trials and omitted-stimulus trials using paired samples t-tests, Wilcoxon signed ranks tests, and sign tests, depending on

the normality of the distributions of the dependent variables. Mean waveforms across all subjects for each condition were also examined to assess if OSR activity was present.

To assess the second aim, the investigation of the relationship between lower- and higher-levels of predictive processing, correlations were conducted to examine the association between a-wave, b-wave, and flicker peak-to-peak amplitude, and context sensitivity scores from the Ebbinghaus Illusion task, representing degree of size constancy (a putative measure of predictive coding). These correlations were conducted between context sensitivity scores and ERG parameters following present-stimulus trials and omitted-stimulus trials for both ERG conditions. Non-parametric Spearman correlations were conducted for analyses that included distributions that violated the normality assumption and/or included outliers.

To investigate whether timepoint within the stimulus train where the omitted-stimulus occurred significantly predicted strength of the ERG response within the single flash condition, correlations were conducted between the omitted trial number and a- and b-wave amplitude for each subject. Correlation coefficients between omitted trial number and a- and b-wave amplitude were calculated for each subject and then averaged to calculate an averaged correlation coefficient for each ERG metric across all subjects. Similarly, correlations were run between a-wave, b-wave, and flicker peak-to-peak amplitude, and number of first omitted trial.

To assess the relationship between abnormalities in sensory processing and retinal activity, correlations were conducted between AVAQ scores and ERG parameters, including a-wave, b-wave, and peak-to-peak amplitude. These correlations were conducted for both conditions and for ERG parameters following both present-stimulus

and omitted-stimulus trials for both conditions. Three subjects' AVAQ scores were excluded from analyses due to excessive endorsement of catch questions. Data was included in analyses if subjects endorsed catch questions that were considered ambiguous.

To investigate differences in intra-individual variability in retinal activity between present-stimulus and omitted-stimulus trial waveforms, I conducted Wilcoxon signed-ranks tests, as the distributions of ICC values were not normal, between ICC indices for ERG data following present-stimulus trials and ICC indices following omitted-stimulus trials. In order to further assess relationships between variability and sensory processing, I conducted correlations between ICC indices following present-stimulus and omitted-stimulus trials, and Ebbinghaus and AVAQ scores.

In order to explore if activity following omitted trials was associated with variability in baseline activity, I conducted correlations between present-stimulus and omitted-stimulus a- and b-wave amplitude measurements and the median standard deviation of the averaged baseline data.

Results

Sample Descriptive Statistics

The study sample consisted of 18 subjects with ages that ranged from 18 to 57 years old and a mean age of 29.56 (*SD*=13.53). The sample consisted of six participants who identified as male (33.3%) and 12 subjects who identified as female (66.7%). Eight participants identified as Caucasian (44.4%), six participants identified as Asian (33.3%), and four participants identified as Black or African American (22.2%). The study sample consisted of 17 participants who identified as non-Hispanic (94.4%) and one participant who identified as Hispanic (5.6%). All demographic information for the study sample, including gender, race, ethnicity, and handedness is displayed in Table 2.

Single Flash Paradigm

Amplitude

The Shapiro-Wilk test was used to examine whether fERG amplitude distributions were normally distributed. Non-parametric tests were used for analyses that included variables that violated the normality assumption: a-wave present-stimulus (W=.87, p=.02), a-wave omitted-stimulus (W=.63, p<.001), and b-wave omitted-stimulus (W=.66, p<.001). The b-wave present-stimulus amplitude distribution was normally distributed (W=.96, p=.53).

Given that the distribution of a-wave values following omitted stimuli was not normally distributed, a one-sample Wilcoxon signed-ranks test was conducted to compare a-wave amplitude to zero. Results demonstrated that a-wave amplitude following omitted stimuli (*Mdn*=-3.72) was significantly different than zero, z=-3.72,

$p<.001$, r[1]$=-.62$. A one-sample Wilcoxon signed-ranks test was also conducted to compare b-wave amplitude following omitted stimuli and results indicated that b-wave amplitude following omitted stimuli (*Mdn*=5.91) was significantly different than zero, $z=3.72$, $p<.001$, $r=.62$.

In order to compare a- and b-wave amplitudes on present-stimulus trials with a- and b-wave amplitudes on omitted-stimulus trials, Wilcoxon signed-ranks tests were conducted. For the a-wave, present-stimulus amplitude (*Mdn*=-9.42) was significantly stronger (more negative) than omitted-stimulus a-wave amplitude (*Mdn*=-3.72), $z=-3.51$, $p<.001$, $r=.58$ (see Figs. 6 and 7). Of all 18 subjects, the a-wave present-stimulus amplitude was stronger (more negative) than omitted-stimulus a-wave amplitude for 17 subjects, whereas one subject demonstrated weaker a-wave present-stimulus amplitude when compared to omitted-stimulus a-wave amplitude. Results following a Wilcoxon signed-ranks test also showed that b-wave amplitude following present-stimulus trials (*Mdn*=32.59) was significantly greater than b-wave amplitude following omitted-stimulus trials (*Mdn*=5.91), $z=-3.72$, $p<.001$, $r=.62$ (see Figs. 6 and 7). All 18 subjects demonstrated stronger present-stimulus b-wave amplitude than omitted-stimulus b-wave amplitude.

Implicit time

The Shapiro-Wilk test was used to examine whether fERG implicit time distributions were normally distributed. For this condition, all implicit time variables

[1] For Wilcoxon Signed-Rank tests, effect sizes are expressed as *r*, which equals the value of the test output (Z statistic) divided by the square root of the total number of observations (i.e., number of cases * 2). Based on Cohen (1988), interpretation of *r* is as follows: .1 = small, .3 = medium, .5 = large.

were normally distributed, including present-stimulus a-wave implicit time (W=.94, p=.27), omitted-stimulus a-wave implicit time (W=.98, p=.90), present-stimulus b-wave implicit time (W=.91, p=.09) and omitted-stimulus b-wave implicit time (W=.94, p=.29).

A paired samples t-test comparing implicit time (i.e., latency) of the a-wave response following present-stimulus trials with the implicit time of the a-wave response following omitted-stimulus trials revealed that a-wave implicit time following present-stimulus trials (M=13.18) was not significantly different than the a-wave implicit time following omitted stimuli (M=12.67), $t(17)$=1.08, p=.30. A paired samples t-test also indicated that b-wave implicit time following present stimuli (M=30.28) was not significantly different than b-wave implicit time following omitted stimuli (M=29.77), $t(17)$=0.95, p=.36. These findings indicate that present-stimulus a- and b-wave occurred at a similar timepoint as omitted-stimulus a – and b-wave.

Averaged waveforms

Of note, the following waveforms were calculated as the average of individual subjects' mean waveforms averaged across time. Therefore, the ERG values may differ marginally from the values described above, which were selected as the median a- or b-wave amplitude or implicit time measurements from individual subjects' responses to each trial.

Fig. 6 represents the 1.96 Hz condition averaged waveform for ERG activity following present-stimulus trials averaged across all subjects within the study sample. This waveform reflects a typical ERG response to a single-flash stimulus. The initial trough displayed, which represents the a-wave, occurred at 13.31 ms and -7.36 μV, and the positive peak, which represents the b-wave, occurred at 30.21 ms and 20.04 μV.

Fig. 7 displays the plotted averaged waveform for retinal activity following omitted-stimulus trials across all subjects. As shown in this figure, the ERG activity displayed is weak and demonstrates the absence of an OSR response following omitted-stimulus trials.

Baseline variability

Correlations were conducted to examine whether baseline variability was associated with the strength of the retinal response following omitted trials. A Spearman correlation conducted between baseline variability (standard deviation of baseline activity) preceding omitted-stimulus trials and a-wave amplitude following omitted-stimulus trials revealed a non-significant relationship (r_s=-.38, p=.13) and this correlation remained non-significant after omitting one outlier (r_s=-.26, p=.32). Similarly, a non-significant Spearman correlation was found between baseline variability preceding omitted-stimulus trials and b-wave amplitude following omitted-stimulus trials (r_s=.43, p=.08) and this correlation remained non-significant after omitting three outliers (r_s=-.22, p=.46).

Correlations between fERG measurements and Ebbinghaus context sensitivity

Correlations were conducted to assess the relationship between low-level visual predictive processing, measured by a- and b-wave amplitude and implicit time measurements, and high-level visual processing, measured by the Ebbinghaus context sensitivity score. Non-parametric tests were used for correlations that involved non-normal distributions or outliers, including present-stimulus a-wave amplitude (W=.87, p=.02), omitted-stimulus a-wave amplitude (W=.63, p<.001), present-stimulus b-wave implicit time (one outlier) and omitted-stimulus b-wave amplitude (W=.66, p<.001).

Interestingly, a marginal relationship was found between Ebbinghaus context sensitivity score and omitted-stimulus a-wave amplitude (r_s=-.45, p=.06) and this relationship remained unchanged after omitting one outlier (r_s=-.55, p=.06). That is, greater context sensitivity on the Ebbinghaus illusion task was associated with stronger (more negative) omitted-stimulus trial a-wave activity, suggesting that individuals who made greater use of prior knowledge when generating perceptual representations in high-level tasks were more likely to generate a stronger photoreceptor response to an expected (but absent) stimulus.

We did not find evidence that Ebbinghaus context sensitivity was related to magnitude or implicit time of the other fERG variables tested. In particular, no significant Spearman correlations were found between Ebbinghaus context sensitivity score and present-stimulus a-wave amplitude (r_s=.00, p=.95), present-stimulus a-wave implicit time (r=.24, p=.34), omitted-stimulus a-wave implicit time (r_s=.-.08, p=.76), present-stimulus b-wave amplitude (r=-.04, p=.90), present-stimulus b-wave implicit time (r_s=.19, p=.45), omitted-stimulus b-wave amplitude (r_s=-.02, p=.96), or omitted-stimulus b-wave implicit time (r=.30, p=.22). After removing outliers in several of these analyses, findings remained non-significant: present-stimulus a-wave amplitude (one outlier; r_s=-.28, p=.31), present-stimulus b-wave implicit time (one outlier; r_s=.21, p=.42), and omitted-stimulus b-wave amplitude (four outliers; r_s=-.02, p=.96).

Correlations between fERG measurements and WTAR

Correlations were also conducted to examine the association between WTAR scores, or estimated verbal IQ, and fERG measurements. The WTAR distribution was normal (W=.91, p=.11), and therefore non-parametric tests were only used for

correlations that included non-normal fERG distributions and/or outliers, as described earlier. Non-significant correlations were found between WTAR and present-stimulus a-wave amplitude (r_s=-.30, p=.27), present-stimulus a-wave implicit time (r=-.17, p=.54), omitted-stimulus a-wave amplitude (r_s=-.02, p=.93), omitted-stimulus a-wave implicit time (r=-.01, p=.88), present-stimulus b-wave amplitude (r=.34, p=.20), present-stimulus b-wave implicit time (r_s=-.38, p=.15), omitted-stimulus b-wave amplitude (r_s=.25, p=.34), and omitted-stimulus b-wave implicit time (r=-.01, p=.98). These results remained non-significant after omitting outliers for correlations between WTAR and present-stimulus a-wave amplitude (one outlier; r_s=-.31, p=.26), omitted-stimulus a-wave amplitude (one outlier; r_s=.21, p=.45), present-stimulus b-wave implicit time (one outlier; r_s=-.38, p=.15), and omitted-stimulus b-wave amplitude (four outliers; r_s=.38, p=.22). These results indicate that there was no relationship between estimated verbal IQ and retinal activity during stimulus present and omitted-stimulus trials for the 1.96 Hz condition.

Correlations between fERG measurements and AVAQ

Given that the AVAQ distribution violated the normality assumption (W=.70, p<001), Spearman correlations were run to determine the relationship between sensory distortions and amplitude and implicit time of a- and b-wave activity. Results demonstrated a significant negative correlation between AVAQ score and omitted-stimulus a-wave implicit time (r_s=-.62, p=.01) and this remained significant after removing two outliers (r_s=-.72, p=.005). This indicated that greater frequency of sensory distortions was associated with earlier, or faster, occurrence of the retinal response to omitted stimuli.

Additional analyses demonstrated non-significant Spearman correlations between AVAQ score and present-stimulus a-wave implicit time (r_s=.07, p=.82), omitted-stimulus a-wave amplitude (r_s=-.12, p=.67), present-stimulus b-wave amplitude (r_s=.36, p=.19), present-stimulus b-wave implicit time (r_s=-.16, p=.56), omitted-stimulus b-wave amplitude (r_s=.07, p=.80), and omitted-stimulus b-wave implicit time (r_s=-.10, p=.72). While the correlation between AVAQ score and present-stimulus a-wave amplitude was originally significant (r_s=-.62, p=.01), this result became non-significant after omitting three outliers (r_s=.-.31, p=.33). The remaining correlations remained non-significant after omitting outliers for correlations between AVAQ score and present-stimulus a-wave implicit time (two outliers; r_s=-.03, p=.93), omitted-stimulus a-wave amplitude (three outliers; r_s=-.07, p=.83), present-stimulus b-wave amplitude (two outliers; r_s=.35, p=.24), present-stimulus b-wave implicit time (three outliers; r_s=-.10, p=.77), omitted-stimulus b-wave amplitude (five outliers; r_s=-.21, p=.55), and omitted-stimulus b-wave implicit time (three outliers; r_s=.03, p=.91). These findings indicated no relationship between sensory anomalies and magnitude of the retinal response, and latency of the present-stimulus response.

Correlations between omitted-stimulus trial number and ERG magnitude

Correlations were conducted between omitted-stimulus trial number and a- and b-wave values for each subject. Correlation coefficients were then averaged across all subjects. The average Pearson correlation coefficient for the correlation between omitted-stimulus trial number and omitted-stimulus a-wave was 0.11 and the average Spearman correlation coefficient was 0.13. The average Pearson correlation coefficient for the correlation between omitted-stimulus trial number and omitted-stimulus b-wave was

-0.02 and the Spearman correlation coefficient was -0.01. These data indicate essentially no relationship between omitted-stimulus trial number and neural responses during the a- and b-wave time windows on omitted-stimulus trials, and provide further support for the conclusion that the 1.96 Hz condition was not associated with an OSR.

Correlation between first omitted trial and ERG magnitude

Correlations were conducted between first omitted trial and a- and b-wave amplitude in order to examine whether buildup of expected upcoming stimuli was associated with the magnitude of the omitted-stimulus response. One outlier was omitted from the omitted-stimulus a-wave distribution and three outliers were omitted from the omitted-stimulus b-wave distribution. Given that the first omitted trial number distribution was not normally distributed (W=.89, p=.03), Spearman correlations were conducted to assess the relationship between trial number of the first omitted trial and omitted-stimulus a- and b-wave amplitudes. Results indicated a non-significant correlation between number of first omitted trial and omitted-stimulus a-wave amplitude (r_s=-.15, p=.56). A Spearman correlation also revealed a non-significant relationship between number of first omitted trial and omitted-stimulus b-wave amplitude (r_s=-.16, p=.57). These findings support the non-significant correlations between omitted-stimulus condition activity and omitted trial number (see preceding paragraph), in suggesting that any activity on omitted trials in this condition was not a function of prediction.

Intra-individual variability of retinal response

A Wilcoxon signed-ranks test was conducted to compare ICC of present-stimulus trials to ICC of omitted-stimulus trials. Results demonstrated that present-stimulus ICC (Mdn=.22) was significantly greater than omitted-stimulus ICC (Mdn=.02), z=-3.59,

$p<.001$ which is further evidence of a lack of consistent activation in response to omitted stimuli.

For the following analyses, three outliers were omitted from the distribution of ICC of omitted-stimulus trials and two outliers were omitted from the AVAQ distribution. A non-significant relationship was found between present-stimulus ICC and Ebbinghaus context sensitivity ($r=12$, $p=.63$). As the omitted-stimulus ICC distribution was not normally distributed ($W=.63$, $p<.001$), Spearman correlations were conducted between omitted-stimulus ICC and Ebbinghaus context sensitivity scores and results indicated a non-significant correlation ($r_s=.08$, p=.74) and this remained non-significant after omitting three outliers ($r_s=-.20$, $p=.48$). Spearman correlations also demonstrated non-significant relationships between AVAQ scores and present-stimulus ICC ($r_s=.04$, $p=.90$) and omitted-stimulus ICC ($r_s=-.19$, $p=.51$), and these results remained non-significant after omitting outliers for present-stimulus ICC (two outliers; $r_s=.30$, $p=.32$) and omitted-stimulus ICC (five outliers; $r_s=-.06$, $p=.87$). These results suggest that trial-by-trial variability, for present and omitted-stimulus trials, was not related to high-level predictive processing, through measurement of performance on a context sensitivity task, and frequency of sensory distortions.

Flicker paradigm

Amplitude

A paired samples *t*-test was conducted to compare peak-to-peak amplitude following omitted-stimulus trials to zero. Analyses revealed that peak-to-peak amplitude following omitted-stimulus trials ($M=9.26$) was greater than zero, $t(17)=14.25$, $p<.001$, $r=.96$. Additionally, a paired samples *t*-test indicated that peak-to-peak amplitude

following present stimuli (M=16.37) was greater than peak-to-peak amplitude following omitted stimuli (M=9.26), $t(17)$=7.59, p<.001, r=.88. These results indicate that present-stimulus trial retinal activity was stronger than omitted-stimulus trial activity.

A paired samples t-test was conducted to compare omitted-stimulus peak-to-peak amplitude with that from a random sample of present-stimulus trials that was equivalent in number to the amount of omitted-stimulus trials, ranging from 38 to 44 trials, for individual subjects. This was done to determine whether any differences between stimulus present and omitted stimuli might be due to the smaller number of trials overall in the omitted condition (and thus to lower reliability of the findings). Similar to analyses with present-stimulus trials, results showed that the peak-to-peak amplitude of the random subset of present-stimulus trials (M=16.68) was significantly greater than peak-to-peak amplitude following omitted-stimulus trials (M=9.26), $t(17)$=-8.49, p<.001. Additionally, peak-to-peak amplitude of the randomly selected subset of present trials (M=16.68, SD=5.45) was not significantly different than peak-to-peak amplitude of the full set of present trials (M=16.37, SD=5.27), $t(17)$=-0.81, p=.43. Additionally, the subset of present-stimulus trials demonstrated a similar standard deviation as the full set of present-stimulus trials. Taken together, these findings indicate that analysis of fewer trials does not lead to increased variability.

Implicit Time

An exact sign test was conducted to compare present-stimulus implicit time and omitted-stimulus implicit time, as the distribution of omitted-stimulus peak-to-peak implicit time was not normally distributed (W=.80, p<.001) and the shapes of differences between present-stimulus implicit time and omitted-stimulus implicit time was not

symmetrical, as indicated by visual inspection of the histogram. Of the 18 subjects, the omitted-stimulus implicit time occurred later than the stimulus-present implicit time for 14 subjects, whereas the omitted-stimulus implicit time occurred earlier than the stimulus-present implicit time in 4 subjects. The exact sign test indicated that the earlier peak times on present-stimulus trials (*Mdn*=29.70) compared to omitted trials (*Mdn*=37.89) was a significant effect, z=2.12, exact p=.031. That is, omitted-stimulus peak implicit time was delayed when compared to present-stimulus implicit time.

In order to further test if increases in variability accounted for differences between present-stimulus and omitted-stimulus activity, a Wilcoxon signed-ranks test was run to compare omitted-stimulus peak-to-peak implicit time to that from a random sample of present-stimulus trials that was equivalent in number to the amount of omitted stimuli for each subject, ranging from 38 to 44 trials, as this was not normally distributed. Results demonstrated that peak implicit time of the omitted-stimulus trials (*Mdn*=37.89) was greater than the peak implicit time of the subset of present-stimulus trials (*Mdn*=29.70), z=-3.68, p<.001. Additionally, the present-stimulus subset implicit time (*M*=29.90, *SD*=1.47) was not significantly different from full set present-stimulus implicit time (*M*=29.81, *SD*=1.26), $t(17)$=-0.42, p=.68. Taken together, these results further indicate that the differences observed between present-stimulus and omitted-stimulus responses were not due to reduced reliability within a smaller amount of trials.

Averaged Waveforms

Due to differences in calculations, the overall mean waveform values may differ slightly from the measurements used for statistical analyses. The peak-to-peak values used in the analyses were measured according to individual subjects' mean waveforms.

The mean waveforms below represent the averaged waveforms for each trial condition across all subjects.

Fig. 8 illustrates the mean waveform for the ERG response to present-stimulus trials averaged across all subjects. The initial trough occurred at 12.8 ms and reflected -4.74 μV of activity and the positive peak occurred at 29.70 ms and reflected 10.47 μV of activity, with a peak-to-peak amplitude of 15.22 μV. The figure also displays a second negative deflection at 47.62 ms and -4.99 μV that occurred following the end of the sample period of 35.33 ms.

As shown in Fig. 9, for omitted stimuli, an initial negative deflection was observed at 9.73 ms that is weaker than expected (-3.66 μV), when compared to the flicker response to present stimuli (-4.74 μV). Following the first negative deflection, there is an initial positive peak at 28.67 ms, reflecting 3.06 μV of activity, that occurs at a similar timepoint as the present-stimulus peak (29.70 ms), but is reduced in magnitude (10.47 μV). A second and maximal positive peak is delayed in relation to the present-stimulus peak and occurs at 38.91 ms, reflecting 4.18 μV of activity. The peak-to-peak amplitude of the omitted-stimulus trials (7.84 μV) is diminished compared to the peak-to-peak amplitude of present-stimulus trials (15.22 μV). After these positive peaks, an expected secondary negative trough, reflecting -5.69 μV of activity, occurs at 53.25 ms following the end of the sample period and subsequent to the next trial's light flash.

Fig. 10 demonstrates the mean ERG waveform for the flicker 28.3 Hz condition from a random sample of present-stimulus trials equivalent in number to the amount of omitted-stimulus trials, determined for each subject, across all subjects. This waveform follows the expected pattern of a response to a flicker stimulus. An expected negative

deflection occurs at 12.29 ms, reflecting -4.92 μV of activity, and the positive peak occurs at 30.21 ms, reflecting 10.68 μV of activity. The peak-to-peak amplitude is 15.6 μV. An expected secondary negative deflection occurs at 47.62 ms that reflects -5.10 μV of activity. The mean waveform for the subset of present-stimulus trials follows the expected shape, including similar amplitude and implicit time values, as the mean waveform for the full set of present-stimulus trials, suggesting that differences between present-stimulus and omitted-stimulus responses were not due to less reliability within a smaller amount of trials.

Correlations between fERG measurements and Ebbinghaus context sensitivity, WTAR and AVAQ scores

Non-significant correlations were found between Ebbinghaus context sensitivity score and present-stimulus peak-to-peak amplitude (r=.03, p=.90), stimulus present peak implicit time (r=.17, p=.50), omitted-stimulus peak-to-peak amplitude (r=.37, p=.13), and omitted-stimulus peak implicit time (r_s=-.26, p=.29). That is, context sensitivity performance was found to be independent of retinal response strength to present and omitted stimuli within the flicker condition.

We also found non-significant correlations between WTAR score and present-stimulus peak-to-peak amplitude (r=.21, p=.43), present-stimulus peak implicit time (r=.19, p=.48), omitted-stimulus peak-to-peak amplitude (r=.18, p=.50), and omitted-stimulus peak implicit time (r_s=.27, p=.32). These results suggest that estimated verbal IQ was not related to present-stimulus and omitted-stimulus retinal activity.

As the AVAQ distribution was not normally distributed (W=.70, p<.001), Spearman correlations were conducted to assess the relationship between AVAQ scores

and peak-to-peak amplitude and peak implicit time within the flicker condition. There were no significant correlations found between AVAQ score and present-stimulus amplitude (r_s=.31, p=.26), present-stimulus peak implicit time (r_s=.17, p=.55), omitted-stimulus peak-to-peak amplitude (r_s=-.03, p=.90) or omitted-stimulus implicit time (r_s=.17, p=.56). These results remained non-significant after omitting two outliers from the AVAQ distribution for correlations with present-stimulus amplitude (r_s=.27, p=.37), present-stimulus peak implicit time (r_s=.10, p=.77), omitted-stimulus peak-to-peak amplitude (r_s=-.10, p=.75) and omitted-stimulus implicit time (r_s=-.45, p=.13). These results indicated that retinal activity in response to a flicker stimulus was unrelated to extent of self-reported sensory distortions.

Correlation between first omitted trial and ERG peak-to-peak magnitude

Spearman correlations were conducted between trial number of first omitted trial and peak-to-peak amplitude, as the distribution of first omitted trials violated the normality assumption (W=.83, p=.01). Results demonstrated a significant correlation between trial number of the first omitted trial and omitted-stimulus peak-to-peak amplitude, r_s=.56, p=.02 and this remained significant after omitting two outliers, r_s=.57, p=.02 (see Fig. 11). This indicated that the later in the series the first omission occurred (allowing for the regularity of the pattern to be more strongly established before the first omission), the stronger was the overall neural response on omitted trials.

Discussion

The present study investigated whether predictive processing could be detected at the sensory level of vision in human subjects. This was tested by examining the retinal response to omitted flash stimuli embedded within a series of consecutive light flashes within a single flash 1.96 Hz condition and a 28.3 Hz flicker condition. Previous studies have observed an OSR in human retinal activity (McAnany et al., 2013; McAnany & Alexander, 2009), and mouse and salamander retinal activity (Schwartz et al., 2007; Schwartz & Berry, 2008). Therefore, it was hypothesized that an OSR would be present following omitted-stimulus trials in both conditions tested. The study also sought to examine if predictive processing in low-level vision was associated with predictive processing in high-level vision. Given that the Ebbinghaus illusion involves the use of prior knowledge and contextual clues to inform predictions (Doherty et al., 2010), it was hypothesized that the magnitude of predictive activity at the sensory level would be related to top-down prediction at the higher level.

Hypothesis 1: Presence of Predictive Processing within Retinal Activity

Single flash 1.96 Hz condition

Contrary to hypotheses, results demonstrated the absence of an OSR following omitted-stimulus trials within the single flash 1.96 Hz condition. Fig. 7 illustrates the plotted mean waveform of ERG responses to omitted-stimulus trials within this condition. The waveform appears to flatline after stimulus onset at the zero timepoint. The absence of an OSR within this condition is further supported by a comparison of this response to the present-stimulus mean waveform that reflects a typical ERG response to a single light flash (see Fig. 6). While results of the statistical analyses demonstrated weak

a- and b-wave values that were not equivalent to zero, suggesting that an OSR may have been present, the analytic strategy likely biased the analyses towards finding a significant difference between the ERG metric and zero. The strategy to determine the a- and b-wave selected the minimum point relative to the baseline average and the maximum point relative to the baseline average, respectively, during typical a- and b-wave time windows (based on reference data reported by the manufacturer using this condition). Thus, the a- and b-wave values that were selected for each omitted-stimulus trial were always in the predicted direction (i.e., the a-wave value selected was always negative and the b-wave value was always positive). Although an OSR was observed in previous human and animal studies (McAnany et al., 2013; McAnany & Alexander, 2009; Schwartz et al., 2007; Schwartz & Berry, 2008), it is possible that the absence of an OSR within this condition was due to differences in stimuli between studies. For instance, trials in the present study task included single flashes that occurred at a frequency of 1.96 Hz. In contrast, McAnany and Alexander (2009) observed an ERG response in human subjects using a flicker train with stimulus frequencies between 38.5 and 100 Hz, with the strongest OSR effects occurring between 38.5 and 62.5 Hz. Animal studies observed activity representative of an OSR in conditions with flashes that occurred at a frequency between 6 and 20 Hz, with the strongest OSR effects occurring at the highest temporal frequencies within this range (Schwartz et al., 2007; Schwartz & Berry, 2008). Therefore, it is possible that the absence of ERG activity reflecting an OSR response within the 1.96 Hz single flash condition may be due to the slow frequency of the light flashes, and the lack of establishment of strong expectations or neural entrainment within this condition. This suggests that at this frequency, retinal cells do not fire in expectation of an

upcoming stimulus after a series of consecutive light flashes (at least within the range of 101 to 112 trials used in the 1.96 Hz condition in this study).

The absence of an OSR within this condition is further supported by the finding of a non-significant relationship between the trial number of the first omitted trial and magnitude of the a- and b-wave response. This suggests that a strong representation of the temporal pattern of light flashes was not established in this condition, and/or that a violation of this pattern was not recognized as a significant event – even when the first violation occurred late in the stimulus train - due to the overall slow presentation rate. Additionally, weak, mostly non-significant correlations were found between trial number of omitted-stimulus trials and a- and b-wave magnitude on those trials, suggesting that the observed activity does not reflect a predictive response that depends on a consistent number of present stimuli in order to elicit a response. Moreover, findings demonstrated less trial by trial consistency in the omitted-stimulus response compared to stimulus-present trials and this is further indication that any omitted-stimulus activity observed was likely not elicited in response to an expected stimulus. Results also demonstrated a non-significant relationship between baseline variability preceding omitted-stimulus trials and amplitude of the a- and b-wave response. This suggests that for the 1.96 Hz conditions, omitted-stimulus retinal responses were not simply driven by the variability in background retinal activity, even though these responses did not constitute meaningful levels of activation.

Flicker 28.3 Hz condition

Consistent with hypotheses, a retinal response suggestive of an OSR was observed following omitted-stimulus trials embedded within the 28.3 Hz flicker condition

(see Fig. 9). Results demonstrated that present-stimulus peak-to-peak amplitude was stronger than omitted-stimulus peak-to-peak amplitude and that omitted-stimulus peak implicit time was delayed when compared to present-stimulus peak implicit time. The plotted mean waveforms provide further support that the OSR was diminished and delayed (see Fig. 9) when compared to typical stimulus-driven activity in response to present-stimulus trials (see Fig. 8).

Importantly, current analyses support that activity observed was representative of a retinal response and does not reflect an increase in noise associated with a small number of omitted-stimulus trials. I examined the retinal response to a random number of present-stimulus trials that was equivalent to the number of omitted-stimulus trials, which ranged from 38 to 44 trials. Similar to total present-stimulus activity, with a total of 432 to 438 trials, the evoked peak-to-peak activity to a subset of present-stimulus trials was greater than omitted-stimulus peak-to-peak activity (see Fig. 10). This suggests that differences found between present-stimulus peak-to-peak amplitude and omitted-stimulus peak-to-peak amplitude were not due to increased variability (or reduced reliability) within a smaller amount of trials, as the subset of present-stimulus and omitted-stimulus responses included the same number of trials. Moreover, Fig. 9b suggests that this activity reflects an evoked response, as the noise visualization (displayed as 1 standard error of measurement) is small and does not reach zero.

It is important to consider whether activity occurring during omitted trials reflects a true response to the unexpected omission versus simply late activity in response to the previous light stimulus that is unmasked when not followed closely in time by an additional light stimulus. Examination of the omitted-stimulus response demonstrates that

the peak activation occurs after all expected activity from the previous stimulus. The initial positive peak occurred at a similar timepoint as in present-stimulus trials (e.g., ~ 29 ms post-stimulus onset) and the delayed maximal positive peak occurred 38.91 ms following omitted-stimulus onset (see Fig. 9). Our data also differs from that of a 27.8 Hz condition from a previous study, in which peak activity following omitted stimuli represented the upward portion of the waveform (after the second trough) from the previous present-stimulus trial (see Fig. 12; from McAnany & Alexander, 2009). Within that study, the positive peak from the previous trial occurred prior to the end of the stimulus period, whereas the maximal positive peak within the current study (38.91 ms) occurred after the end of the stimulus period of 35.33 ms. Therefore, the current study's delay between the last present-stimulus peak and the OSR peak is longer than what McAnany and Alexander (2009) observed. This difference in the delay across the two studies suggests that the peak activation observed in the current study occurred after completion of all expected activation from the prior trial. Moreover, the waveform depicting activity from the prior trial in McAnany and Alexander (2009) appears to return to baseline subsequent to the end of the stimulus period, whereas the current study demonstrated a waveform that follows the typical pattern of an evoked retinal response, including negative troughs before and after a positive peak. Overall, the weight of evidence suggests that the activation observed following stimulus omissions is not late-activity from the prior trial.

In fact, the timing of the current study OSR relative to the timing of the present- and omitted-stimulus appears to be similar to previous OSR studies. In particular, the delay between omitted-stimulus *onset* and OSR peak within the current study (38.91 ms;

see Fig. 9) appears to be similar to the constant delay between omitted-stimulus *peak* and OSR peak for frequencies between 38.5 and 62.5 Hz (from McAnany & Alexander (2009); see Figs. 13 and 14). Additionally, the current study OSR peak occurred about 74.24 ms following the *onset* of the last present-stimulus. Interestingly, McAnany and Alexander (2009) found that the amount of time elapsed between the last present-stimulus *peak* and the OSR peak decreased consistently as stimulus frequency increased, and, consistent with this, the delay found in the current study is increased when compared to that of higher frequencies (see Figs. 13 and 14). Thus, consistent findings of the delays observed between timing of the OSR peak and omitted and present stimuli provide additional support for the presence of an OSR in this study.

Of note, the current study present-stimulus and OSR amplitudes were lower than those reported in McAnany and Alexander (2009). However, this is likely due to differences in flicker stimuli and electrode type between the two studies. For example, the current study used a white-light flicker stimulus (16 td · s) with no background which equated to an average brightness of 450 Td. In contrast, McAnany and Alexander (2009) used a half green and half red light (10,053 Td with an estimated dilated pupil diameter of 8 mm) with a blue background of 620 Td, leading to an average brightness of approximately 5300 Td. Therefore, the current study's average luminance was about twelve times weaker than the flicker condition in McAnany and Alexander (2009). McAnany and Alexander (2009) also used corneal contact electrodes, which elicit stronger retinal responses than the sensor strip electrodes used in the current study. The current study results are also consistent with healthy control data from a study that examined differences in 16 Td · s flicker responses between controls, and subjects with

diabetes without retinopathy (Zeng et al., 2019). In particular, this study found a mean peak-to-peak amplitude of 20.09 μV within controls, compared to the current study's mean peak-to-peak amplitude of 16.37 μV. Therefore, differences in amplitude of the flicker responses between the current study and McAnany and Alexander (2009) may have been due to differences in luminance of the flicker stimuli.

While the current results suggest activity representative of an OSR, McAnany and Alexander (2009) found an absence of an OSR within a 27.8 Hz flicker condition, which is similar to the stimulus frequency (28.3 Hz) used in the current study. The reasons for this discrepancy are likely to be varied, and not simply due to the difference in stimulus frequency of .05 Hz. For instance, the current study's flicker train was presented for about 15 seconds and the amplitude and implicit time measurements were calculated as the mean of 432 to 438 present-stimulus responses or the mean of 38 to 44 omitted-stimulus responses. In contrast, in McAnany and Alexander (2009), there was only about one second of flicker stimuli presented before the flicker train ended and the OSR was measured. For omitted trials embedded within the middle of the flicker train, flicker stimuli were presented for 400 ms before and after one or two consecutive omissions. Therefore, it is possible that a greater number of consecutive present-stimulus trials are required for retinal cells to entrain to stimuli at lower frequencies such as 28.3 Hz. Additionally, in McAnany and Alexander (2009), ERG responses were calculated as the mean of the three responses with the least amount of noise and artifacts, whereas the OSR in the present study was calculated based on approximately 40 trials per subject, which should be associated with an even higher signal-to-noise ratio.

As the source of the OSR remains largely unknown, it is unclear whether the activity observed within the current study represents a predictive response or resonance in response to a highly repetitive stimulus. In support of a predictive response, findings from the current study indicated that the later the first omitted trial occurred, the greater the magnitude of the peak-to-peak omitted-stimulus amplitude was. Additionally, the initial positive peak of the omitted-stimulus waveform occurred around the timepoint expected if a stimulus was present. On the other hand, evidence from previous studies suggest that responses following omitted-stimulus trials may represent resonant activity. In particular, at certain frequencies, OSR peaks occur at a constant delay following the peak of omitted stimuli, and therefore the activity is considered independent of stimulus frequency (McAnany & Alexander, 2009). Gowrisankaran et al. (2013) studied three consecutive ERG responses subsequent to the termination of a flicker train and found that the inter-response intervals were constant across stimulus frequencies studied and that the peak amplitudes decreased over time. Moreover, this data fit well with a mathematical model of a resonant system (Gowrisankaran et al., 2013). This suggests that the OSR is generated by a resonant response, because a true predicted response elicited to an omitted-stimulus would be expected to be linked to the specific stimulus frequency of the flicker. I was unable to test this theory with data from the present study, as only one flicker frequency was tested and multiple consecutive omissions were not included within the flicker train.

Data from previous studies suggests that the resonant activity is elicited by ON bipolar cells. One study observed the absence of an OSR within the retinal activity of a participant with a NYX gene mutation and congenital stationary night blindness (CSNB)

that is thought to be associated with abnormalities in the ON bipolar cell pathway. In particular, this participant did not demonstrate an OSR in response to stimuli elicited at frequencies that ranged from 31.25 to 62.50 Hz, while healthy controls did exhibit an OSR. When studying the resonant response within the salamander retina, Schwartz and Berry (2008) blocked ON bipolar cell activity by administering the selective metabotropic glutamate receptor 6 (mGluR6) agonist APB. As a result, ganglion cell activity did not demonstrate an OSR. The authors proposed that the OSR observed in previous studies reflected resonance of ON bipolar cell activity, transmitted to ganglion cells to facilitate the processing of subsequent trial(s). Additionally, Schwartz and Berry (2008) posit that this activity may reflect a reduction or absence of OFF bipolar cell activity, due to possible desensitization as a result of excessive ON firing to prior stimuli. These results suggest that ERG peaks following omitted stimuli, that are proceeded by consecutive flicker stimuli, reflect resonant oscillations elicited by ON bipolar cells.

Overall, current findings indicate that a weak OSR is present in human retinal data in response to omissions embedded within a 16 td · s 28.3 Hz flicker train. The initial positive peak occurred at the timepoint that would be expected given a predictive response, while the maximal peak occurred at a delayed timepoint, suggesting that the response represents resonant activity. However, it cannot be determined whether the current study OSR reflects predictive or resonant activity, as only one stimulus frequency was examined. Therefore, future studies testing additional stimulus frequencies are needed to determine whether the OSR is reflective of resonant oscillatory activity or prediction of an expected stimulus.

Hypothesis 2: Relationship between low-level predictive processing and high-level predictive processing

The second aim of the study was to investigate if predictive activity at the retinal level was related to predictive coding in high level vision. Consistent with hypotheses, a-wave omitted-stimulus amplitude was marginally related to Ebbinghaus context sensitivity performance. In particular, results showed that greater performance on the Ebbinghaus task was marginally related to stronger (more negative) photoreceptor activity in omitted-stimulus trials. Perception of the Ebbinghaus illusion within a healthy population requires use of prior knowledge regarding context (distance cues and distance perception in particular) in order to inform top-down predictions about the size of the target circle (Doherty et al., 2010). Thus, this finding suggests that people who perceive what is expected, based on prior knowledge, are also more likely to elicit a larger photoreceptor response in expectation of an upcoming stimulus. However, contrary to hypotheses, a significant relationship was not found between single flash b-wave amplitude, flicker peak-to-peak amplitude and Ebbinghaus context sensitivity performance, suggesting that predictive activity, or oscillatory resonance, within retinal cell activity is distinct from top-down processes employed during the Ebbinghaus task. Given that b-wave and flicker peak-to-peak amplitude were not associated with top-down predictive processing, further studies with larger sample sizes and analyses of data from both eyes are required to test whether the relationship between a-wave magnitude and Ebbinghaus context sensitivity can be replicated. Based on the data from this study, however, it appears that predictive activity in the retina is independent of predictive activity at the cortical level.

Correlations between retinal activity, estimated verbal IQ and sensory distortions

Results showed non-significant relationships between estimated verbal IQ and strength and implicit time of retinal responses to present-stimulus trials and omitted-stimulus trials in both the conditions studied. Although a significant association was not observed within this sample of healthy controls, investigation of the relationship between estimated verbal IQ and magnitude of predictive activity will be important to include in future studies that focus on retinal changes in people with schizophrenia, as this population typically has lower IQ scores, which may be indicative of neural dysfunction more generally.

When investigating the relationship between sensory distortions and retinal activity, I found that increased sensory distortions were associated with faster a-wave omitted-stimulus responses, within the 1.96 Hz condition. While this may indicate that abnormal sensory processing is associated with earlier photoreceptor activity in response to an expected but omitted-stimulus, to the best of my knowledge, there have been no studies demonstrating that earlier responses to predicted stimuli are associated with sensory abnormalities. Additionally, significant associations were not found between sensory distortions and omitted-stimulus b-wave implicit time, or flicker omitted-stimulus implicit time variables. However, due to the small sample size included in this analysis (n=15), the restricted range of the AVAQ distribution (5 to 23 excluding outliers), and the lack of correction for multiple correlations, the significance of this finding remains unclear until replication with a greater sample is attempted. It will also be important to study whether this relationship exists in a sample of people with schizophrenia, given that people with schizophrenia demonstrate abnormalities in retinal

function and the AVAQ includes sensory distortions often endorsed by people with schizophrenia (Nikitova et al., 2019; Silverstein et al., 2020). Future studies should investigate whether sensory abnormalities are also related to earlier latency of retinal responses to an expected stimulus within a patient population.

Lastly, correlations were conducted between trial-by-trial variability in activation across the trial period, measured by ICC, and high-level visual processing performance, measured by the Ebbinghaus context sensitivity score, and abnormalities in sensory processing (AVAQ scores). Although no overall OSR effect was found within the 1.96 Hz condition, these analyses were conducted to detect whether individual differences in activation in the condition might be related to scores on these measures (and whether the subjects with the most pronounced responses after omitted stimuli might be demonstrating a small OSR). Results showed non-significant relationships between variability within present-stimulus and omitted-stimulus trials, measured by ICC, and context sensitivity performance within the single flash condition. Thus, I found that individual differences in variability of retinal activation were not associated with performance on a task that requires high-level visual predictive processing within this sample. Additionally, variability within present-stimulus and omitted-stimulus trials was not related to self-reported visual and auditory sensory distortions within the single flash condition. This suggests that individual differences in consistency of retinal activity were not related to abnormalities in sensory processing within the 1.96 Hz condition. A parallel analysis was not conducted on the flicker condition data because only averaged waveforms (across all trials) were used for each subject.

Limitations

This study included several limitations. First, for both conditions, the number of omitted trials was not consistent across subjects. Additionally, most omitted trials were followed by a present trial and this did not allow for the investigation of response peaks following the first (or the maximal, and second) omitted-stimulus peak. The inclusion of two or three consecutive omissions would allow for further exploration of the possibility of a resonant response or another delayed response that was nevertheless related to stimulus frequency. This would also allow for more definitively ruling out the possibility that the activity observed on omitted trials was part of the response to the previous present-stimulus trial. Additionally, this would reduce the potential effect of the light stimulus from the subsequent trial, which is particularly important for a complete understanding of the activity observed after the end of the stimulus period. The present study is also limited due to the small sample size. However, the number of participants was greater than that of initial studies focused on retinal activity in response to omitted stimuli within a flicker train (Gowrisankaran et al., 2013; McAnany & Alexander, 2009) and a retinal response following omitted-stimulus trials was still observed, despite the small sample. Lastly, the current study only examined retinal activity from one eye. Consistent results between retinal activity from both eyes would increase confidence in the OSR effect within the flicker condition and the lack of an OSR effect within the 1.96 Hz condition.

Summary and Future Directions

The present study investigated whether the human retina engages in predictive processing that could be measured by the response to an omission violation embedded

within a train of consecutive stimuli. In particular, this process was studied within a single flash 1.96 Hz condition that assessed photoreceptor and bipolar-Müller cell activity, as well as a 28.3 Hz flicker condition that assessed isolated cone activity. Only three studies to date have investigated the post-stimulus retinal response in human subjects to an omission following a predicted pattern of consecutive light flashes (Gowrisankaran et al., 2013; McAnany et al., 2013; McAnany & Alexander, 2009). Given that an OSR has been observed in animal (Schwartz et al., 2007; Schwartz & Berry, 2008) and human studies (Gowrisankaran et al., 2013; McAnany et al., 2013; McAnany & Alexander, 2009), it was hypothesized that an OSR would be observed following omitted-stimulus trials within both conditions. Results demonstrated no response following omitted-stimulus trials within the 1.96 Hz condition that measured photoreceptor and bipolar-Müller cell activity. This represents a novel finding, given that previous published studies have only looked at retinal prediction within flicker paradigms that assessed isolated cone activity. Additionally, evidence of a retinal response following omitted trials was found within a flicker condition. While future studies assessing conditions with different stimulus frequencies are needed to distinguish whether this activity reflects a prediction of an upcoming stimulus or the presence of resonant activity, the current literature suggests that this activity is representative of resonant oscillations elicited by ON bipolar cells. The second aim of the study was to determine if predictive processing within the retina was related to top-down predictions measured by performance on a context sensitivity task. While I did not find evidence that low-level visual predictive processing was associated with high-level predictions within a flicker condition, I found that stronger omitted-stimulus photoreceptor activity was marginally

related to greater predictive processing on the Ebbinghaus. Given that this was a marginal finding in a small sample, and that all other correlations between fERG variables and context sensitivity on the Ebbinghaus illusion tests were not significant, additional studies are required to determine whether this finding remains consistent within a larger sample that analyzes retinal data from both eyes.

Future studies should use these findings to further investigate whether retinal activity in response to an omission embedded within a flicker train represents a prediction or resonant response. Data from previous studies suggest that the activity observed reflects a resonant response elicited by ON bipolar cells. In particular, this is supported by a study that demonstrated OSR responses inconsistent with stimulus frequency (Gowrisankaran et al., 2013). In order to further test whether this activity is representative of a predictive response or resonant oscillatory activity, additional studies are needed to compare responses between flicker conditions at different stimulus frequencies and to distinguish whether the observed activity reflects a constant delay. Additional studies with greater sample sizes and analyses of data from both eyes are also needed to test the relationship between low- and high-level visual predictive processing.

The current findings provide the foundation to study whether people with schizophrenia demonstrate abnormalities in activity following omitted stimuli. It will be important to study the retinal response to unexpected omissions following a highly repetitive stimulus within schizophrenia, whether the response is representative of predictive or resonant activity. In addition to clarifying the type of activity that the OSR represents, the meaning of a reduced OSR (if one is observed) in schizophrenia will need to be clarified. For example, if resonant activity is a necessary condition for predictive

responses to be generated, but not a sufficient condition (i.e., not generative of the predictions themselves), then a reduced OSR might be reflective more of an impairment in gain or gain control (i.e., sensitivity to environmental changes, or a process that optimizes other aspects of perception, both of which are impaired in schizophrenia on tests of cortical function (Silverstein, 2016), rather than an aspect of predictive coding. If future studies observe a reduction in this activity in a sample of people with schizophrenia, the data could be tested for its use as a biomarker for diagnosis and changes in clinical state, as performance on visual illusion tasks has been previously shown to be related to changes in clinical state in people with schizophrenia (Silverstein et al., 2013). Of note, the portable and noninvasive handheld device and flash paradigms used in the present study have been used in previous studies that demonstrated differences in retinal activity between individuals with schizophrenia and healthy controls (Demmin et al., 2018).

Overall, our findings demonstrate that the human retina generates a response following an omitted-stimulus subsequent to a series of consecutive light flashes within a flicker condition, but not to a stimulus that repeats at 1.96 Hz. While it is unclear whether this activity reflects predictive activity or resonant oscillatory activity, findings from previous studies suggest that this response reflects resonant oscillations elicited by ON bipolar cells in response to a highly repetitive stimulus. These results provide the basis to study whether these processes are impaired in schizophrenia with a cost-effective and noninvasive portable device that has been used in previous studies focused on retinal changes in schizophrenia.

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Table 1

Categories and selected questions from BSABS assessing visual basic symptoms

Category	Selected questions
Blurred vision	Is your vision sometimes, either shortly or for a longer time, blurred and turbid, unclear or imprecise?
Transitory blindness	Have you experienced being blind for a while?
Partial seeing	Can you sometimes see only parts of an object?
Hypersensitivity to light or certain optic stimuli	Have you become sensitive to light?
Photopsias	Do you sometimes for moments see flashes of light or other very bright figures like sparks, stars, dots, or flames?
Other optic perception disturbances	Have any unusual things happened to your vision?
Porropsia	Do objects seem to be farther away, to come closer or to move?
Micropsia, macropsia	Do you sometimes see things bigger or smaller than they really are?
Metamorphosia (dysmorphobsia)	Do every day things ever look distorted, warped, or deformed?
Changes in color vision (metachromopsia)	Do colors ever change? Become more intense? Less intense?
Changes in the perception of the face and/or body of others	Does the face or body of others appear different or changed?
Pseudomovement of objects	Does it ever seem like stationary objects are moving?
Double, oblique, slanting (sloping) and reversed vision	Do you sometimes see things two- or threefold, lopsided or crooked?

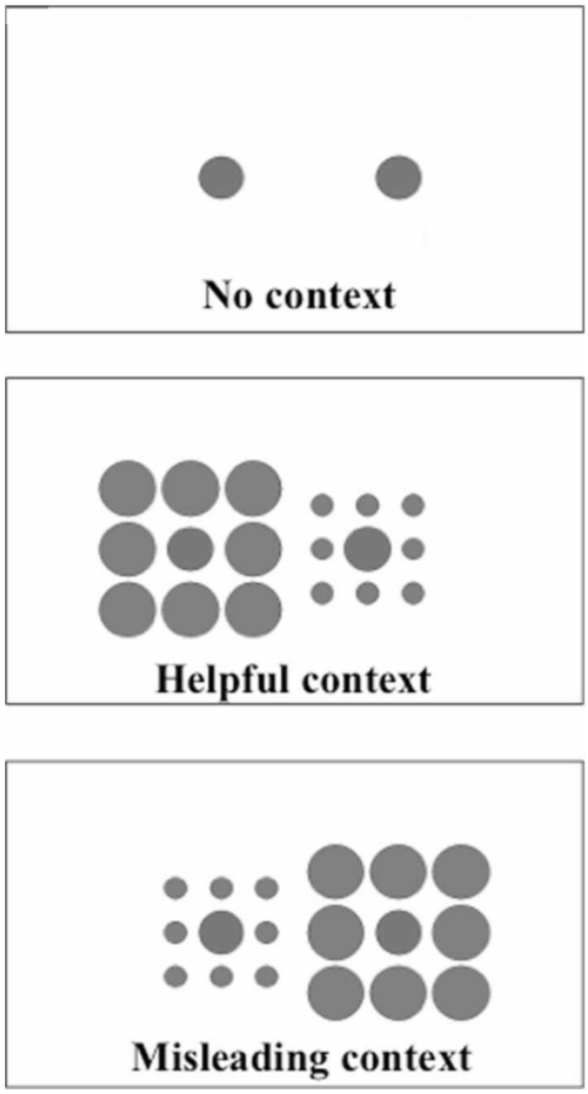
Category	Selected questions
Disturbances of the estimation of distances	Is it difficult to estimate how far away or close something is?
Disintegration of the linearity of (objective) contours of objects	Do objects ever seem broken up, bending or curved?
Dysmegalopsia	Does it ever seem like an object is bigger on one side and smaller on the other?
Abnormally long–lasting persistence of optic stimuli	Does it ever seem like you are seeing abstract patterns that are not really there? As if they are stuck in your vision and no matter where you look they are in the same spot in your visual field?

Table 2
Demographic information

Variable	Healthy controls (*N*=18)
Age *M* (*SD*)	29.56 (13.53)
Gender N (%)	
Females	12 (66.7%)
Males	6 (33.3%)
Race N (%)	
White	8 (44.4%)
Asian	6 (33.3%)
Black/African American	4 (22.2%)
Ethnicity N (%)	
Non-Hispanic	17 (94.4%)
Hispanic	1 (5.6%)
Handedness N (%)	
Right-handed	16 (88.9%)
Left-handed	2 (11.1%)

Figure 1

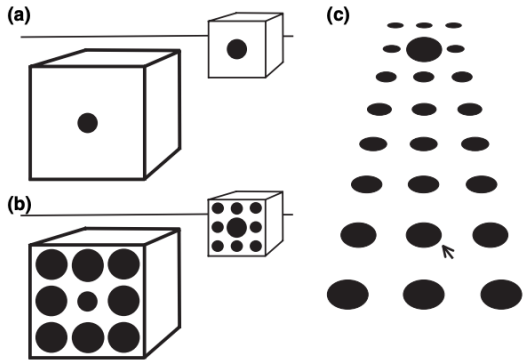
Ebbinghaus Illusion Task



Note. Three conditions from the Ebbinghaus task, which asks participants to choose which target circle they perceive is larger. From "The Ebbinghaus illusion deceives adults but not young children," by M. J. Doherty, N. M. Campbell, H. Tsuji and W. M. Phillips, *Developmental Science, 13*(5), p. 719. Copyright 2009 by Blackwell Publishing Ltd.

Figure 2

Distance Cues in Ebbinghaus Illusion Task

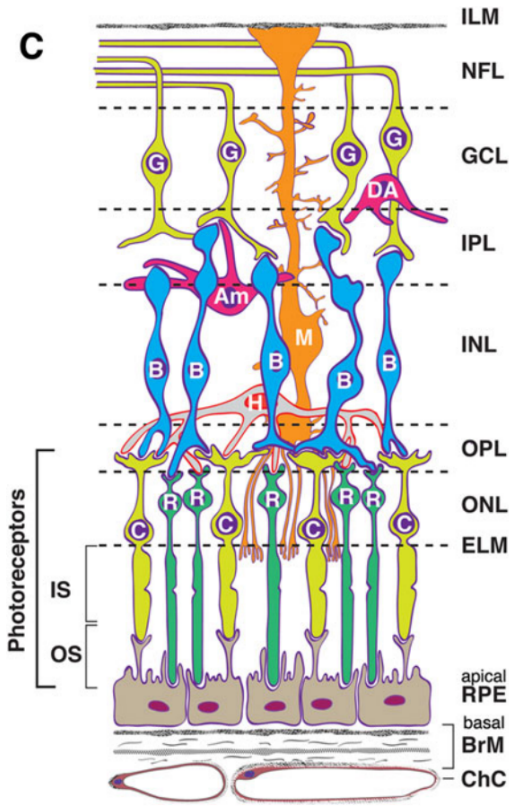


Note. (a) Most people see the further circle as being larger than the nearer one, though they are equal. They would also judge the 'real' size of the further circle within the pictured space to be much larger than the nearer circle. This shows that pictorial cues to depth and size influence perception of the markings on the picture surface. (b) Adding surrounds, as in the Ebbinghaus illusion, increases the perceived size difference between the two circles. This suggests that surround size adds to the other pictorial depth cues. (c) In texture gradients the mean size and separation of elements decreases with depth. The size of the elements on the picture surface is seen as decreasing with depth, but their 'real' size within the pictured space would be judged to be approximately constant. The large element in the center of the second row from the top may be seen as being larger than that arrowed below, but they are equal. Its 'real' size within the pictured space would be judged to be much larger. The bottom and top three rows are versions of the Ebbinghaus illusion. Therefore, this suggests that the illusion may in part be due to the visual system learning to use such pictorial cues. Figure and caption reprinted from "The Ebbinghaus illusion deceives adults but not young children," by M. J. Doherty, N. M.

Campbell, H. Tsuji and W. M. Phillips, *Developmental Science, 13*(5)*,* p. 719. Copyright 2009 by Blackwell Publishing Ltd.

Figure 3

Cells and Layers of the Retina



Note. Representation of cells and layers of the retina are shown above. Cells: RPE, retinal pigment epithelium; C, cone photoreceptor, R, rod photoreceptor; B, bipolar cell; M, Müller cell, Am, amacrine cell; DA, displaced amacrine cell; G, ganglion cell. Layers: ChC, choriocapillaris; BrM, Bruch's membrane; ELM, external limiting membrane; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer; NFL, nerve fiber layer; ILM, inner limiting membrane. Image and majority of figure caption reprinted from Fig. 2c in: Zheng W, Reem RE, Omarova S, Huang S, DiPatre PL, et al. (2012) Spatial Distribution

of the Pathways of Cholesterol Homeostasis in Human Retina. PLOS ONE 7(5): e37926 via a Creative Commons Attribution (CC BY) license.

Figure 4

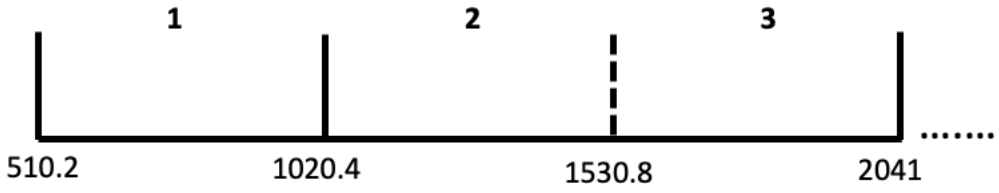
RETeval Device

Note. This figure shows how flash electroretinography (fERG) is measured using the FDA-approved RETeval device (LKC Technologies, Gaithersburg, MD). A sensor strip with positive, negative and ground electrodes is placed 2 mm under the subject's lower eyelid and the dome of the RETeval is placed over the subject's eye. The device emits flash stimuli and records the retinal electrical response to flash stimuli.

Figure 5

Diagram of Sample Flash Stimuli within 1.96 Hz and 28.3 Hz Conditions

(A)

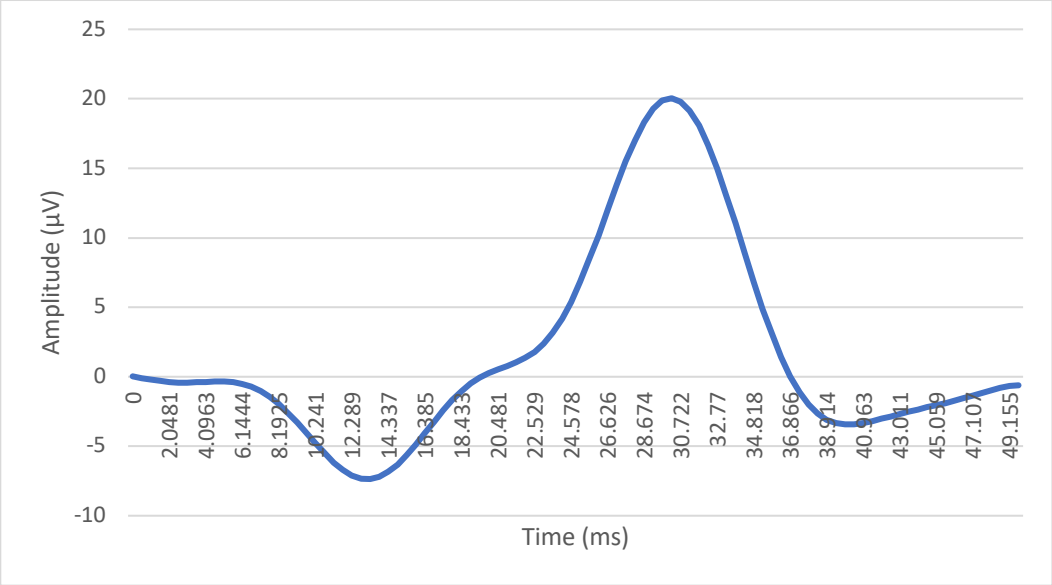


(B)

Note. These figures represent examples of present-stimulus and omitted-stimulus trials for a 1.96 Hz condition (A) and 28.3 Hz condition (B). Time elapsed from condition onset is measured in milliseconds at the bottom of each figure. The solid lines represent flash onset and the dashed lines represents an omitted stimulus. There was a 10% chance on each trial that the stimulus would be omitted. The trial number is represented by the number at the top of each stimulus period. The 1.96 Hz condition included 120 total trials and the 28.3 Hz condition included approximately 435 trials.

Figure 6

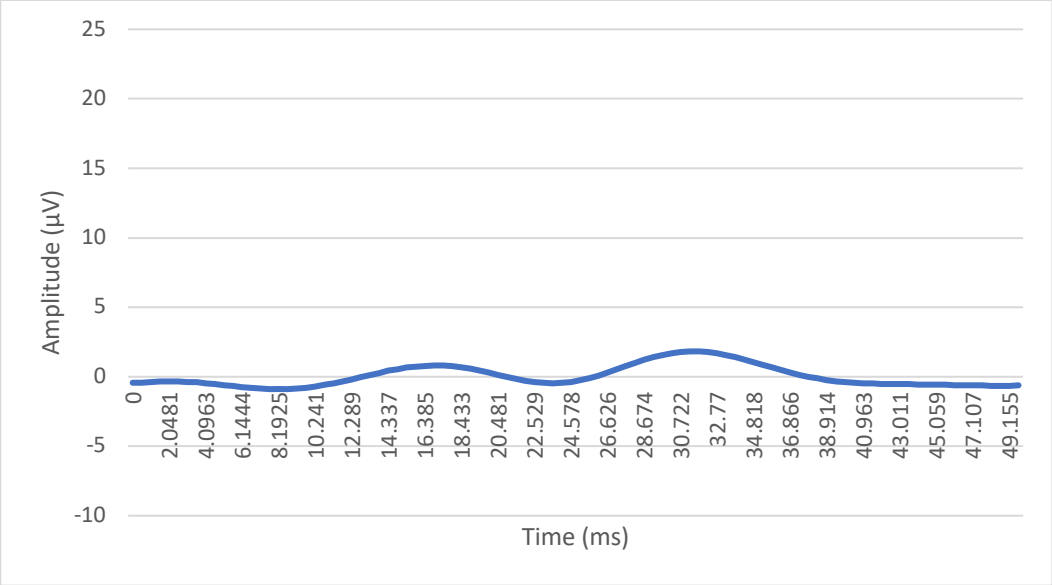
2 Hz Single Flash Present-Stimulus Mean Waveform



Note. This figure demonstrates the 2 Hz single flash condition ERG waveform averaged across all responses following present-stimulus trials averaged across all subjects. Amplitude is measured in microvolts on the y-axis and the x-axis reflects time from stimulus onset that occurred at timepoint zero. The initial negative deflection represents the a-wave and the positive deflection represents the b-wave.

Figure 7

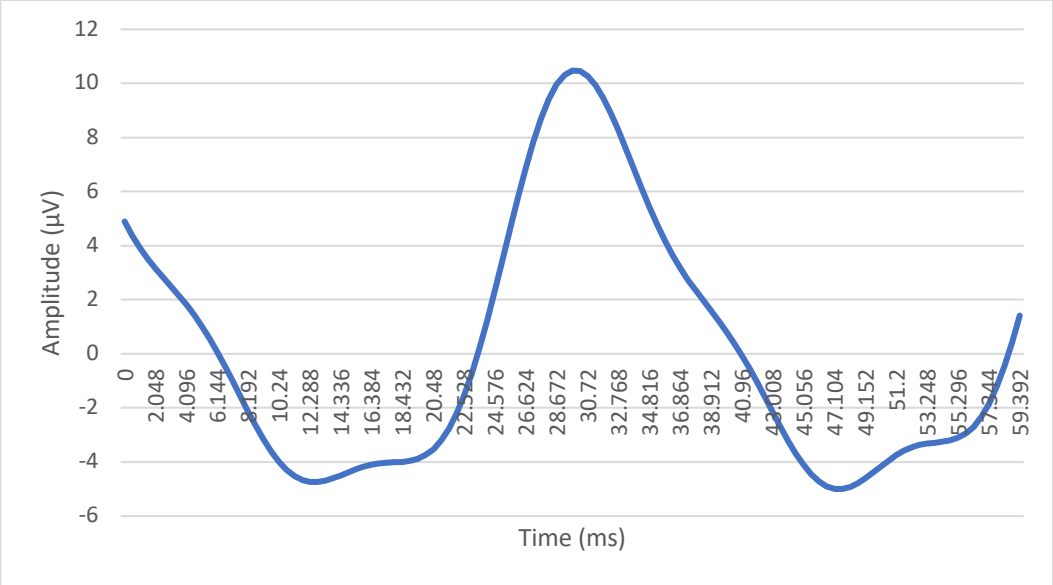
2 Hz Single Flash Omitted-Stimulus Mean Waveform



Note. This graph displays the 2 Hz single flash condition ERG waveform averaged across all responses following omitted-stimulus trials averaged across all subjects. Amplitude is measured in microvolts on the y-axis and time is measured in milliseconds on the x-axis from stimulus onset at timepoint zero. A clear ERG response was not observed.

Figure 8

28.3 Hz Flicker Present-Stimulus Mean Waveform

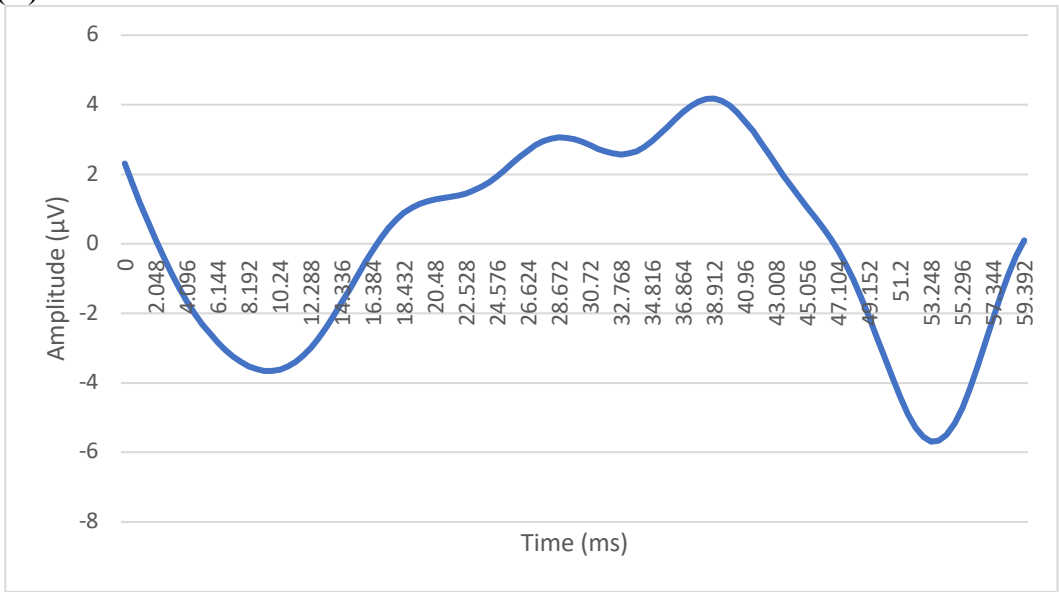


Note. This graph represents the 28.3 Hz flicker condition ERG waveform averaged across all responses following present-stimulus trials averaged across all subjects. Amplitude is measured in microvolts on the y-axis and time is measured in milliseconds on the x-axis from stimulus onset at timepoint zero.

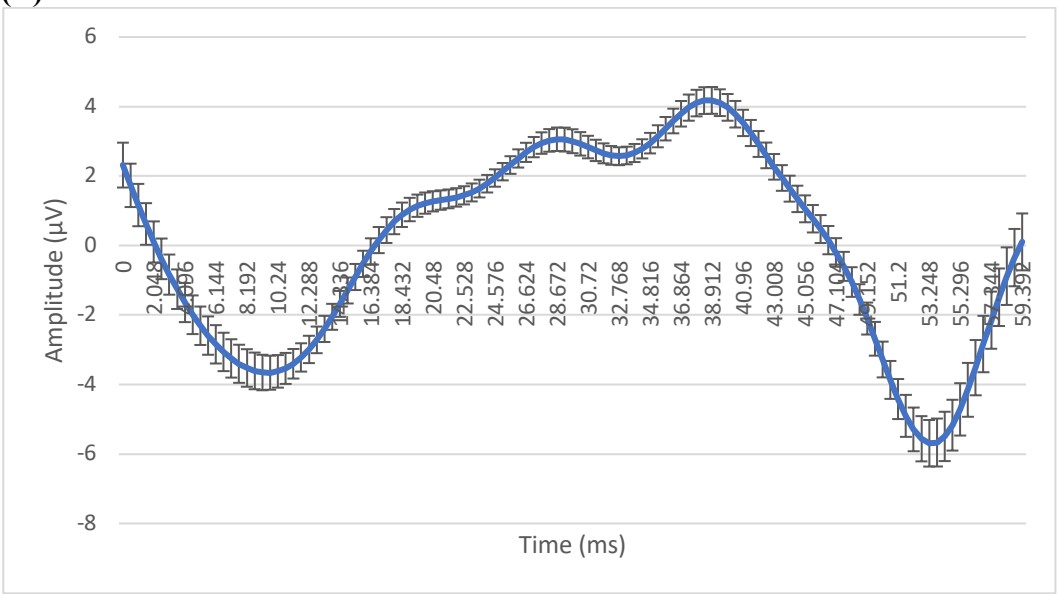
Figure 9

28.3 Hz Flicker Omitted-Stimulus Mean Waveform

(A)



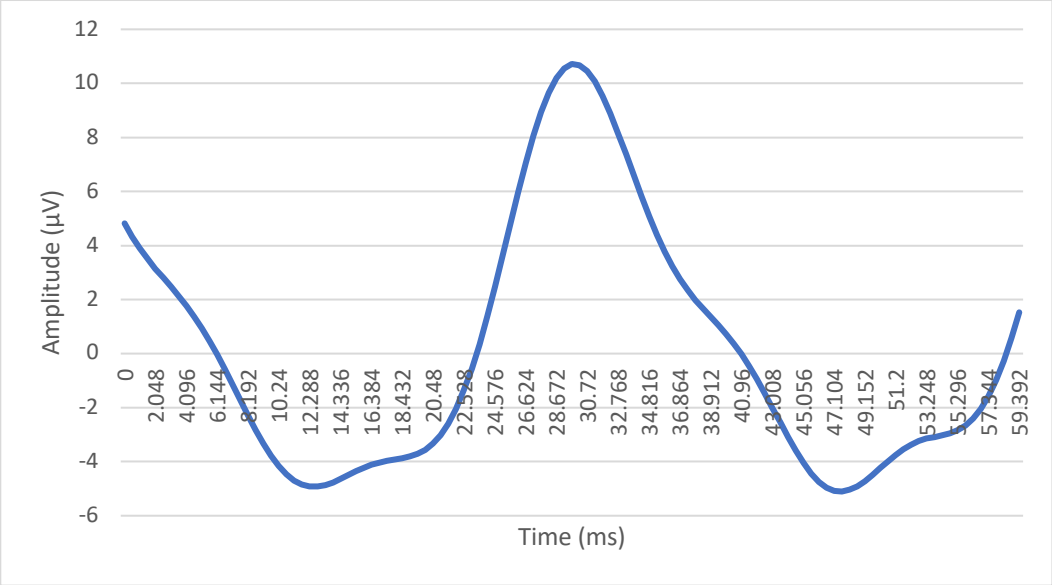
(B)



Note. These graphs represent the 28.3 Hz flicker condition ERG waveform averaged across all omitted-stimulus responses across all subjects. Error bars reflect +/- 1 standard error of the mean (Fig. 9b).

Figure 10

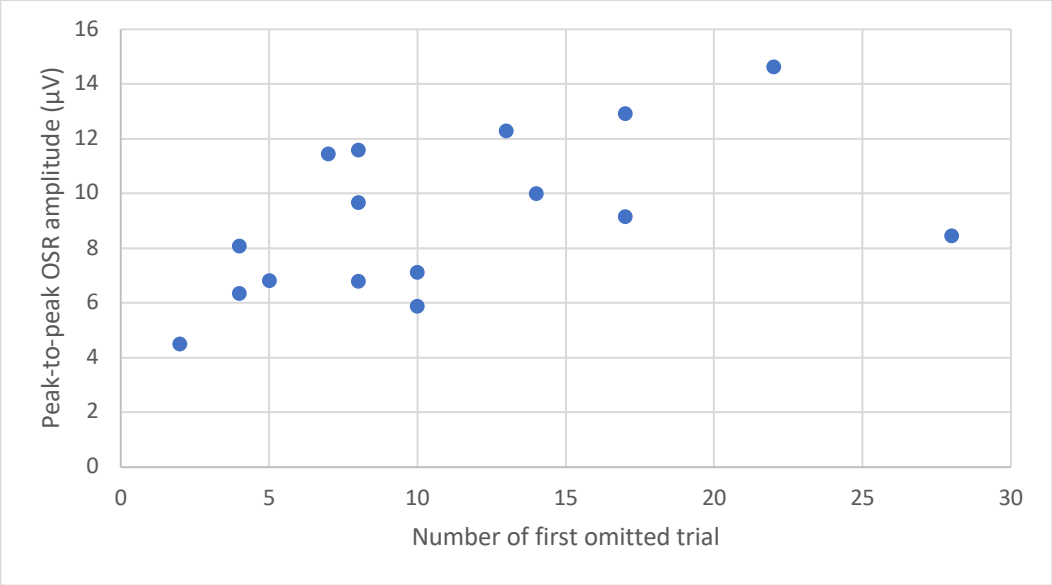
28.3 Hz Flicker Subset of Present-Stimulus Trials Mean Waveform



Note. This waveform reflects the mean waveform of a subset of present-stimulus trials equivalent to the number of omitted-stimulus trials across all subjects. This waveform followed the same pattern as the mean waveform of the full set of present-stimulus trial responses.

Figure 11

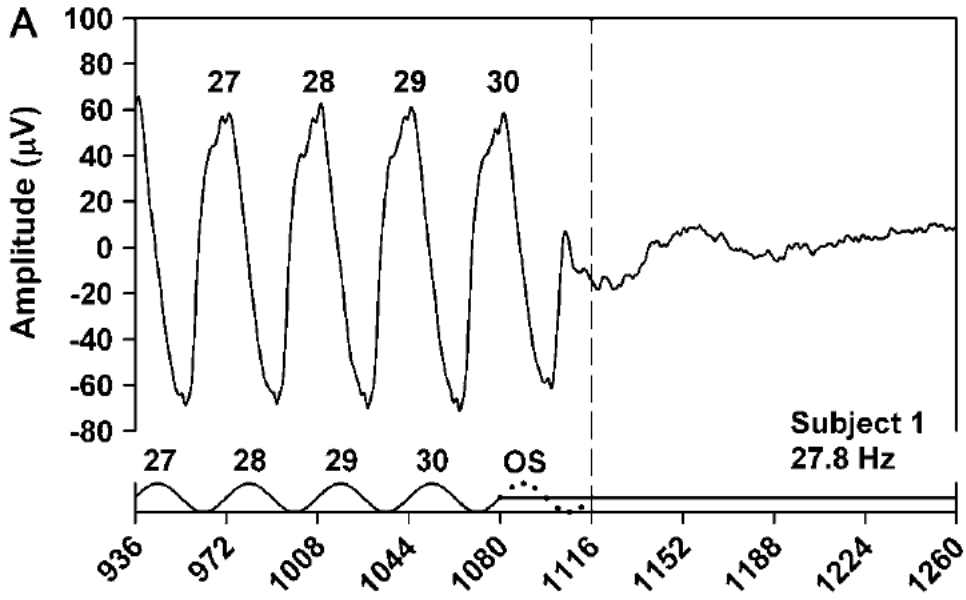
First Omission and Peak-to-Peak Omitted-Stimulus Amplitude



Note. The number of first omitted trial was highly correlated with peak-to-peak omitted-stimulus amplitude (r_s=.57, p=.02). Amplitude of the OSR peak response is measured in microvolts (μV) on the y-axis and the trial number of the first omitted trial is displayed on the x-axis.

Figure 12

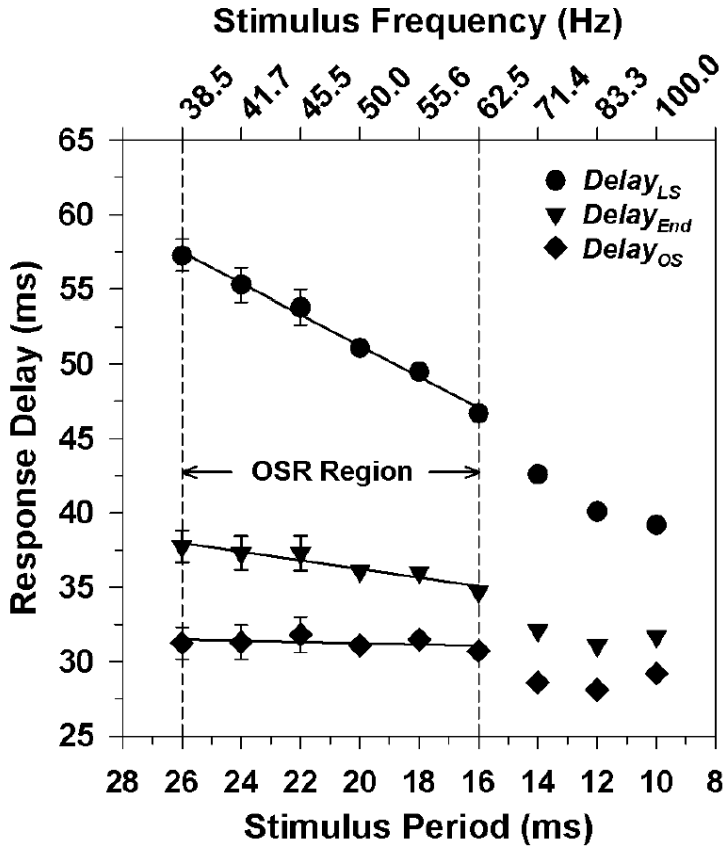
Absence of Omitted-Stimulus Response in 27.8 Hz Condition



Note. Representation of activity from a prior flash stimulus that is present after an omitted-stimulus within a 27.8 Hz flicker condition. Figure adapted from "Is there an omitted-stimulus response in the human cone flicker electroretinogram?" by J. J. and K. R. Alexander, 2009, *Visual Neuroscience, 26,* p. 189-194. Copyright 2009 by Cambridge University Press.

Figure 13

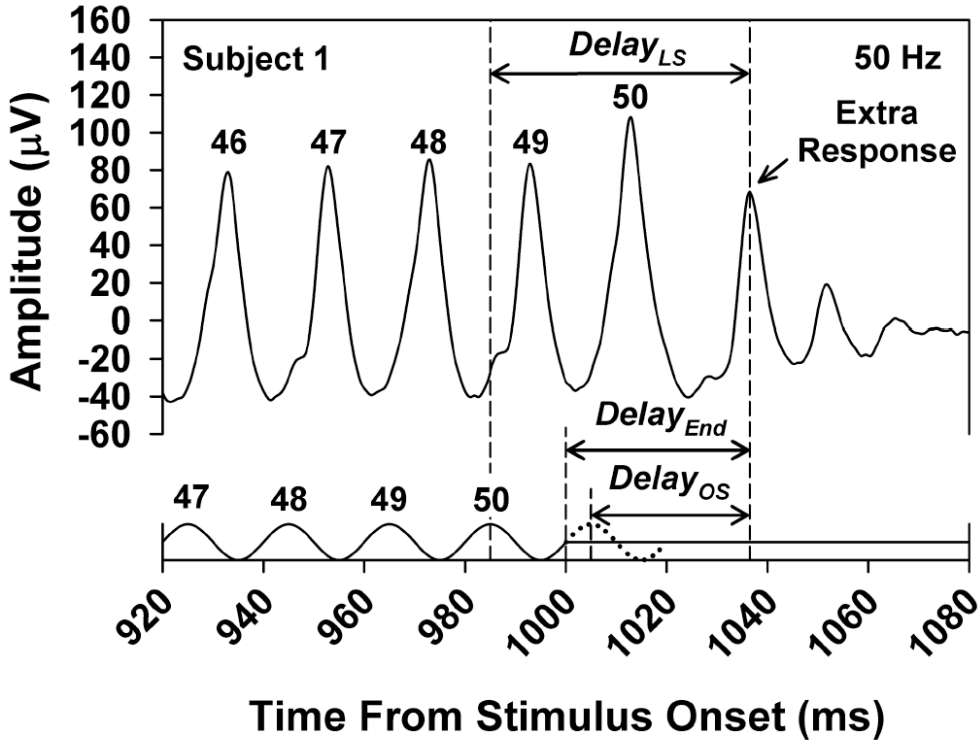
Omitted-Stimulus Response Peak Delay Across Various Stimulus Frequencies



Note. Representation of response delays of the OSR peak for stimulus frequencies between 38.5 and 100 Hz. $Delay_{LS}$ is equivalent to the delay from the peak of the last present-stimulus to the peak of the OSR. $Delay_{END}$ is measured from the end of the previous stimulus to the OSR peak. $Delay_{OS}$ is equivalent to the time elapsed between the peak of the omitted-stimulus and the OSR peak. From "Is there an omitted-stimulus response in the human cone flicker electroretinogram?" by J. J. and K. R. Alexander, 2009, *Visual Neuroscience, 26,* p. 189-194. Copyright 2009 by Cambridge University Press.

Figure 14

Omitted-Stimulus Response in 50 Hz Condition



Note. Representation of activity following a flicker train within a condition with a 50 Hz stimulus frequency. From "Is there an omitted-stimulus response in the human cone flicker electroretinogram?" by J. J. and K. R. Alexander, 2009, *Visual Neuroscience, 26,* p. 189-194. Copyright 2009 by Cambridge University Press.