Published in final edited form as:
Neuroimage. 2013 February 15; 67: 153–162. doi:10.1016/j.neuroimage.2012.11.019.

Comparison of Psychophysical, Electrophysiological, and fMRI Assessment of Visual Contrast Responses in Patients with Schizophrenia

Daniel J. Calderone[a,b,c], **Antígona Martinez**[a,d], **Vance Zemon**[a,e], **Matthew J. Hoptman**[a,b,c], **George Hu**[f], **Jade E. Watkins**[a], **Daniel C. Javitt**[a,c,g], and **Pamela D. Butler**[a,b,c]

[a]Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, NY 10962, USA

[b]Department of Psychiatry, NYU School of Medicine, 550 First Avenue, New York, NY 10016, USA

[c]Department of Psychology, The Graduate Center, City University of New York, 365 Fifth Avenue, New York, NY 10016, USA

[d]Department of Neurosciences, University of California San Diego, 9500 Gilman Drive, La Jolla, California 92093, USA

[e]Ferkauf Graduate School of Psychology, Rousso Building, Albert Einstein College of Medicine, 1165 Morris Park Avenue, Bronx, NY 10461, USA

[f]Verisci Corporation, Raritan, NJ 08869, USA

[g]Department of Psychiatry, Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York, NY 10032, USA

Abstract

Perception has been identified by the NIMH-sponsored Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) group as a useful domain for assessing cognitive deficits in patients with schizophrenia. Specific measures of contrast gain derived from recordings of steady-state visual evoked potentials (ssVEP) have demonstrated neural deficits within the visual pathways of patients with schizophrenia. Psychophysical measures of contrast sensitivity have also shown functional loss in these patients. In the current study, functional magnetic resonance imaging (fMRI) was used in conjunction with ssVEP and contrast sensitivity testing to elucidate the neural underpinnings of these deficits. During fMRI scanning, participants viewed 1) the same low and higher spatial frequency stimuli used in the psychophysical contrast sensitivity task, at both individual detection threshold contrast and at a

Corresponding Author: Daniel Calderone, dcalderone@nki.rfmh.org, 412-491-0527, 140 Old Orangeburg Road, Orangeburg, NY 10962.

Conflicts of Interest: The authors report the following conflicts of interest: Dr. Daniel Javitt holds intellectual property rights for use of NMDA agonists, including glycine, D-serine, and glycine transport inhibitors in treatment of schizophrenia. Dr. Daniel Javitt is a major shareholder in Glytech, Inc. and Amino Acids Solutions, Inc. Within the past year, Dr. Javitt has served as a paid consultant to Sepracor, AstraZeneca, Pfizer, Cypress, Merck, Sunovion, Eli Lilly, and BMS. Drs. George Hu and Vance Zemon are major shareholders in VeriSci Corp. Daniel Calderone, Antigona Martinez, Matthew Hoptman, Jade Watkins, and Pamela Butler have no conflicts of interest in relation to the subject of this study.

high contrast; and 2) the same stimuli used in the ssVEP paradigm, which were designed to be biased toward either the magnocellular or parvocellular visual pathway. Patients showed significant impairment in contrast sensitivity at both spatial frequencies in the psychophysical task, but showed reduced occipital activation volume for low, but not higher, spatial frequency at the low and high contrasts tested in the magnet. As expected, patients exhibited selective deficits under the magnocellular-biased ssVEP condition. However, occipital lobe fMRI responses demonstrated the same general pattern for magnocellular- and parvocellular-biased stimuli across groups. These results indicate dissociation between the fMRI measures and the psychophysical/ssVEP measures. These latter measures appear to have greater value for the functional assessment of the contrast deficits explored here.

Keywords

contrast sensitivity; fMRI; gain control; magnocellular; schizophrenia; visual

1. Introduction

Over recent years it has become clear that patients with schizophrenia exhibit sensory processing deficits in a number of modalities (Javitt, 2009, Koychev et al., 2011, Leitman et al., 2011, Silverstein and Keane, 2011, Butler et al., 2012). Indeed, perception was chosen as one of the key domains for development of measures that could be used in clinical trials in schizophrenia by the NIH-sponsored Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative (Green et al., 2009, Butler et al., 2012). In the visual system, behavioral, electrophysiological, and functional magnetic resonance imaging (fMRI) studies have revealed early-stage sensory deficits, including deficient processing of contrast (Slaghuis, 1998, Kéri et al., 2002, Kéri et al., 2004, Butler et al., 2005, Butler et al., 2009, Green et al., 2009), motion (Chen et al., 2003b, Chen et al., 2004, Kim et al., 2006), and spatial frequency information (O'Donnell et al., 2002, Martinez et al., 2008, Martinez et al., 2012). These visual sensory processing deficits appear to contribute to higher level dysfunction in reading (Revheim et al., 2006), object processing and grouping (Doniger et al., 2002, Kurylo et al., 2007, Sehatpour et al., 2010, Calderone et al., 2012), and emotion processing (Turetsky et al., 2007, Butler et al., 2009).

Within the domain of perception, the CNTRICS initiative included the neurophysiological and psychophysical tasks that are the focus of the current study. The measures of interest here are ones that quantify the gain and sensitivity of contrast responses and their underlying mechanisms (Green et al., 2009, Butler et al., 2012). The neurophysiological measures are based on the use of visual stimuli designed to emphasize either the magnocellular or parvocellular contributions to visual processing (Zemon and Gordon, 2006). The subcortical magnocellular pathway contains rapidly conducting neurons that project preferentially through primary visual cortex (V1) to dorsal stream cortical areas while the parvocellular pathway contains smaller, more slowly conducting neurons that project preferentially through V1 to ventral stream areas, with extensive interaction between these pathways following activation of V1 (Kaplan, 2003). While response properties of the two pathways overlap, they can be preferentially activated by stimuli that differ in contrast, spatial, and temporal frequency. With regard to contrast, magnocellular neurons have a nonlinear response function with steep initial slope as contrast increases through the low contrast region followed by decreasing slope (response compression) as contrast increases above ~12%. The steep initial slope reflects initial gain and is referred to as 'contrast gain.' Response compression which occurs with increases in contrast reflects a nonlinear inhibitory mechanism and is a component of 'contrast gain control' (Shapley and Victor, 1979, Ohzawa et al., 1982, 1985, Zemon et al., 1995, Carandini et al., 1997). The subcortical

parvocellular pathway and its recipient cortical neurons, on the other hand, do not respond much at low contrast (<10%), and parvocellular response functions exhibit a shallow linear slope in magnitude vs. contrast, i.e., low contrast gain (Kaplan and Shapley, 1982, 1986, Tootell et al., 1988, Shapley, 1990, Benardete et al., 1992).

Patients with schizophrenia exhibit contrast response deficits in the visual system, which are seen in electrophysiological (Butler et al., 2005, Green et al., 2009, Butler et al., 2012) as well as behavioral studies (Slaghuis, 1998, Kéri et al., 2002, Kéri et al., 2004, Butler et al., 2005, Butler et al., 2009, Green et al., 2009, Barch et al., 2012). An electrophysiological technique that involves recording steady-state visual evoked potentials (ssVEP) to isolated-check stimuli (Zemon et al., 1988, Zemon and Gordon, 2006) has previously been used to demonstrate contrast gain deficits in schizophrenia (Butler et al., 2001, Butler et al., 2005, Butler et al., 2008a). This technique can bias responses toward the magnocellular contribution by keeping stimuli in the low contrast range, and can bias responses toward the parvocellular contribution by modulating stimulus contrast around a high contrast “pedestal” to keep stimuli within the contrast range at which magnocellular response saturation occurs (Zemon and Gordon, 2006). Signal-to-noise ratios are obtained separately for magnocellular- and parvocellular-biased responses over a range of increasing contrasts. Schizophrenia patients have shown preferential deficits in the magnocellular-biased vs. the parvocellular-biased contrast response function (Butler et al., 2001, Butler et al., 2005, Butler et al., 2009). These deficits are thought to reflect a dysfunction in a nonlinear gain mechanism. To better understand the neural underpinnings of these deficits, the current study used the same stimuli from previous ssVEP work (Butler et al., 2005, Zemon and Gordon, 2006) in an fMRI paradigm.

Schizophrenia patients also exhibit visual deficits in a psychophysical contrast sensitivity task, in which contrast detection thresholds are found for grating stimuli of different spatial frequencies. The magnocellular pathway responds preferentially to low contrasts (<10%) as well as low spatial and high temporal frequencies, while the parvocellular pathway preferentially responds to high spatial and low temporal frequencies (Tootell et al., 1988, Shapley, 1990, Merigan and Maunsell, 1993, Wurtz and Kandel, 2000, Norman, 2002). For contrast sensitivity tasks, shorter duration stimuli (i.e. higher temporal frequency), produce the highest contrast sensitivities at low spatial frequencies, whereas longer duration stimuli produce the highest contrast sensitivities at mid-range spatial frequencies (Tolhurst, 1975, Legge, 1978). A number of studies show that patients with schizophrenia have higher contrast thresholds (i.e., impaired contrast sensitivity) compared to healthy controls (Slaghuis, 1998, Kéri et al., 2002, Chen et al., 2003a, Slaghuis, 2004, Butler et al., 2005, Butler et al., 2008b, Norton et al., 2009, Dias et al., 2011). Selective deficits have been found at low spatial frequencies in some studies (Butler et al., 2005, Butler et al., 2009), though others found deficits across spatial frequencies (Slaghuis, 1998, Kéri et al., 2002) or showed contradictory results of increased contrast sensitivity for first-episode schizophrenia patients (Kiss et al., 2010).

The goal of the current study was to explore the cortical areas that underlie the deficits in contrast responses in schizophrenia using stimuli from electrophysiological (Butler et al., 2005, Zemon and Gordon, 2006) and psychophysical paradigms (Butler et al., 2001, Butler et al., 2005, Butler et al., 2009). It is hoped that this work will assist in task development for measures to be used in clinical trials aimed at assessing cognition in schizophrenia.

2. Methods

2.1. Participants

Fifteen patients who met DSM-IV criteria for schizophrenia and 15 healthy volunteers participated. Patients were recruited through inpatient and outpatient facilities associated with the Nathan Kline Institute for Psychiatric Research. Diagnoses were obtained using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997) and available clinical information. Controls were recruited through the Volunteer Recruitment Program at the Nathan Kline Institute. All participants provided informed consent and received cash compensation for their time. The study was approved by the Nathan Kline Institutional Review Board. Healthy volunteers with a history of SCID-defined Axis I psychiatric disorders were excluded. Patients and controls were excluded if they had any neurological or ophthalmological disorders, including glaucoma or cataracts, that might affect performance or if they met criteria for alcohol or substance dependence within the last six months or abuse within the last month. All participants had normal or corrected-to-normal visual acuity of 20/32 or better on the Logarithmic Visual Acuity Chart (Precision Vision). All patients were receiving antipsychotic medication at the time of testing. Chlorpromazine equivalents were calculated as previously described (Woods, 2003, 2005, 2011). All data reported below are means ± standard deviation.

Controls and patients did not differ in gender (patients: 13 males, 2 females; controls: 12 males, 3 females; $\chi^2(1) = .240$, $p = .63$) or age (patients: 40.40 ± 9.90; controls: 36.87 ± 10.01; $t(28) = .972$, $p = .27$). Patients had significantly lower socioeconomic status (SES) as measured by the 4-factor Hollingshead Scale (patients: 23.31 ± 6.80; controls: 44.57 ± 9.88; $t(25) = -6.463$, $p < .001$), but parental SES did not differ between groups (patients: 39.92 ± 9.39; controls: 46.68 ± 14.05; $t(14.17) = 1.260$, $p = .23$). Patients had significantly reduced IQ (patients: 97.46 ± 7.00; controls: 104.71 ± 8.65; $t(25) = -2.38$, $p = .03$) and education as measured by highest grade achieved (patients: 11.54 ± 1.20; controls: 14.50 ± 1.99; $t(25) = -4.64$, $p < .001$). Patients were ill for 14.58 ± 7.42 years, had an average Global Assessment of Functioning (GAF) score of 48.67 ± 13.84, and were receiving antipsychotic doses equivalent to an average of 783.33 ± 611.54 mg of chlorpromazine per day. Although demographic data for some variables were unavailable for some participants, the overall sample characteristics were similar to those in recent publications from our group (Dias et al., 2011, Calderone et al., 2012, Martinez et al., 2012).

2.2. Psychophysical Contrast Sensitivity

Horizontal sine-wave gratings were presented on the left or right half of a computer screen (VENUS system, Neuroscientific Corp., Farmingdale, NY), with the other side of the screen blank. The mean luminance of each side of the display was 84 cd/m^2. Participants indicated on which side the grating pattern appeared in a two-alternative forced-choice paradigm (Figure 1). Two sine-wave gratings of different spatial frequencies expressed in cycles per degree of visual angle (c/deg) were used. The low spatial frequency (0.5 c/deg) stimuli were shown for a short (32 ms) duration and the higher spatial frequency (4 c/deg) stimuli were shown for a longer (500 ms) duration to bias stimuli toward eliciting responses from the transient (magnocellular-like) and sustained (parvocellular-like) mechanism, respectively. The entire display subtended 6 x 6 degrees of visual angle, viewed from a distance of 190 cm. For each spatial frequency, an up-down transformed rule (UDTR) procedure (Wetherill and Levitt, 1965) estimated the threshold contrast at which participants correctly identified the location of the stimulus on 70.7% of the trials. Initially, contrast was changed in 6 decibel (dB) steps for each correct (−6 dB) or incorrect (+ 6 dB) responses. After two incorrect responses, the UDTR was implemented with 3 dB steps. Following two correct responses, contrast was decreased by 3 dB, whereas following one incorrect response,

contrast was increased by 3 dB. The threshold contrast was taken as the mean of ten contrast reversals, and contrast sensitivity was calculated as the reciprocal of this threshold.

2.3. Steady-State Visual Evoked Potentials (ssVEP)

2.3.1. Apparatus—Stimulus presentation, ssVEP recording, and data analysis were performed with a Neucodia system (VeriSci Corp., Raritan, NJ). For improved measurement of responses, this system uses synchronized data collection: electroencephalographic (EEG) signal sampling at integer multiples (4x) of the stimulus display's frame rate (150 Hz). A single channel of EEG recording was used (gain = 20,000, bandpass: 0.5–100 Hz) with one (active) electrode at O_z, referenced to a second one at C_z with a floating ground at P_z, in accordance with the 10–20 system (Jasper, 1958).

2.3.2. Stimuli and Procedure—Isolated dark checks, subtending 18.75 minutes of arc of visual angle each, were shown in 16 × 16 check arrays subtending a total of 10 × 10° of visual angle viewed from a distance of 114 cm. The background luminance was ~50 cd/m^2. Check luminance was modulated sinusoidally at 12.5 Hz. Seven depths of modulation (DOM) (0, 1, 2, 4, 8, 16, and 32%) were presented for one second each in a seven-second swept-parameter run. Ten such runs were obtained for M-biased and P-biased stimuli separately, for each participant. For all runs, a standing check luminance (pedestal) was used, with check luminance modulated above and below the pedestal according to the DOM. In M-biased runs, the pedestal equaled the DOM, creating appearing and disappearing stimuli (Figure 2). In P-biased runs, the pedestal was fixed at 48% Weber contrast, so that stimuli never dropped below 16% contrast (Zemon and Gordon, 2006).

2.3.4. Analysis—A discrete Fourier transform was used to analyze the fundamental frequency component of the ssVEP (response at the stimulus frequency) averaged for M- and P-biased conditions separately. Signal-to-noise ratios (SNR) of the fundamental frequency component computed for each set of 10 runs were used as the dependent measure (Victor and Mast, 1991, Zemon et al., 1997) in a three-way ANOVA with group, DOM, and bias condition as factors. A modified measure of initial gain was calculated as the slope of the response function between 4 and 16% DOM, i.e. the change in SNR from 4 to 16% DOM divided by the change in DOM (12%). A measure of maximal SNR was calculated as the mean of the SNRs at 16 and 32% DOM.

2.4. Functional Magnetic Resonance Imaging (fMRI)

2.4.1. Apparatus—A 3T Siemens TIM Trio magnetic resonance scanner at the Nathan Kline Institute was used for all functional and structural scans. Functional scans contained 34 axial slices, with TR=2000ms, TE=30ms, and voxel size=2.5×2.5×2.8 mm, with a 0.7 mm gap. High-resolution structural scans were performed with a 3-D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence, having 192 sagital slices with TR=2500ms, TE=3.5ms, FA=8°, and voxel size =1 mm^3. Slice time correction, motion correction, normalization to a value of 100, smoothing (8mm FWHM Gaussian kernel), skull stripping, deconvolution of relevant time series, and first-order regression analyses were performed using the AFNI (http://afni.nimh.nih.gov/; (Cox, 1996)). Functional and structural scans were coregistered and transformed into a common Talairach space using the Automatic Registration Toolbox (Ardekani et al., 2004, Klein et al., 2009).

2.4.2. Stimuli and Procedure—Similar isolated-check stimuli as those used in the ssVEP paradigm were presented to create M-biased and P-biased fMRI scanning runs. Check size was slightly larger, with each isolated check subtending 24 minutes of arc of visual angle. The background luminance was ~100 cd/m^2. Check luminance was modulated sinusoidally at 12 Hz. Five DOMs (2, 4, 8, 16, and 32%) were presented in a block design

for both M-biased and P-biased conditions. For each DOM, 12 seconds of pattern presentation was followed by 12 seconds of blank background luminance, and this cycle was repeated four times. To maintain attention to the stimuli, participants pressed a response button when a fixation cross in the center of the screen changed into a dot for 300ms. The dot appeared randomly during half of the stimulus presentations.

Contrast sensitivity tasks were performed during fMRI scanning for the same two sinusoidal grating stimulus conditions used in the psychophysical task: 0.5 c/deg displayed for 32 ms, and 4 c/deg displayed for 500 ms. The mean luminance of each half of the display was 68.6 cd/m^2. During structural scans, participants performed the task starting at 50% contrast. A UDTR procedure similar to the one described above in section 2.2 that estimated an accuracy of 84.09% changed stimulus contrast by 6 dB until the first incorrect response, and then changed stimulus contrast by 3 dB afterwards. Following four correct responses, contrast was decreased by 3 dB, whereas following 1 incorrect response, contrast was increased by 3 dB. When five contrast reversals were obtained, the task paused until structural scanning was complete. The threshold contrast was taken as the mean of the two contrasts comprising the fifth contrast reversal. During a subsequent functional scan, the task resumed at the contrast level reached at the end of the fifth reversal. Participants continued performing the task at threshold contrast for 45 TRs, and then performed the task at an unchanging high contrast of 71% for an additional 45 TRs. This entire procedure was completed for each spatial frequency separately.

Display equipment used for the fMRI paradigm was limited to 256 gray levels, in contrast to the 4096 gray levels utilized by the VENUS system for the psychophysical contrast sensitivity task. Thus, the lowest contrast that could be displayed in the fMRI paradigm was ~1%. To partially compensate for this, a neutral density filter was used to reduce the luminance of the display by 1 log unit during the contrast sensitivity paradigm only, resulting in a mean luminance of 6.8 cd/m^2. Contrast sensitivities, particularly to higher spatial frequencies, are known to be reduced under conditions of lower luminance (Patel, 1966, Sperling, 1970, Peli, 1990). The fMRI paradigm utilized lower luminance in order to bias threshold contrasts to be higher, though the display's inability to show contrasts below 1% remained a limitation.

All stimuli were viewed through a mirror system mounted on the head coil that reflected a projection screen behind the scanner. The luminance of the projection display was obtained for the complete range of grayscale values by using a photometer (Photoresearch, Inc. Spectrascan Model 650). This information was used to accurately calculate contrast when designing stimuli.

2.4.3. Analysis—For each participant, first-order regression analyses isolated fMRI activity related to specific task conditions, generating brain maps (termed "beta maps") in which each voxel contained a beta coefficient. The square of these beta coefficients represent the amount of variance explained by the activity in that voxel during a specific task condition. These analyses were restricted to the occipital lobe, based on the a priori assumption that deficits in schizophrenia to these particular tasks occur in early visual processing areas. These beta maps were used as input for higher-order group analyses and averages. All p values were corrected for multiple comparisons using AlphaSim, such that only clusters of 48 voxels or more were considered significant. For each task, two measures were assessed. Volume of activation in milliliters was obtained for each individual based on beta maps for each condition thresholded at $p = .001$. Strength of activation was measured as the proportion of total variance explained by each condition obtained by squaring the beta values and calculating the mean squared beta value over occipital cortex for values surviving $p = .001$.

Data from the isolated-check scans included activity related to each DOM (2, 4, 8, 16, and 32%) separately for M-biased and P-biased conditions. Measures of activation volume and strength were used as dependent variables in two separate three-way ANOVAs with group as a between-subjects factor and DOM and bias condition as within-subjects factors. In addition, location and direction of activation were determined by group averages of beta coefficient maps thresholded at $p = .001$. These were displayed on a flattened anatomical map of the occipital cortex.

Contrast sensitivity scans included four task conditions: 0.5 and 4 c/deg for near threshold contrast and for high contrast conditions separately. Because this task showed stimuli on the left or right visual field, first-order regression analysis yielded separate beta maps for left vs. right hemispheric activation for each of the four task conditions. Volume of activation and strength of activation were obtained for each task condition as described above, for combined left-stimuli and right-stimuli beta maps.

3. Results

3.1. Psychophysical Contrast Sensitivity

A main effect of group ($F(1,56) = 11.769$, $p < .005$) showed that patients had lower contrast sensitivities than did healthy controls to both the 0.5 and 4 c/deg spatial frequency conditions (Figure 3). Further, a two-way Group × Condition interaction ($F(1,56) = 4.632$, $p < .05$) indicated that this deficit in contrast sensitivity was greater for the higher spatial frequency as compared to the low spatial frequency condition.

3.2. Steady-State Visual Evoked Potentials

Signal-to-noise ratios (SNR) of the evoked potential response were used as the dependent measure (Victor and Mast, 1991, Zemon et al., 1997). A significant three-way interaction for Group × Condition × DOM ($F(6,392) = 7.001$, $p < .001$) suggested greater deficits for patients in the M-biased than the P-biased condition, which was confirmed by a significant two-way interaction for Group × Condition ($F(1,56) = 14.517$, $p = .001$). Post-hoc t-tests showed that these deficits occurred at 4, 8, 16, and 32% DOM, where controls had signals greater than the noise (Figure 4).

For controls, the M-biased condition generated an initial steep rise in response indicative of strong contrast gain. There was response compression and the response function exhibited the greatest SNR at 16% DOM. Patients had decreased initial gain (i.e., decreased slope from 4 to 16% DOM) ($t(28) = 2.587$, $p < .05$) and lower maximal SNR (i.e., mean SNR for 16 and 32% DOM) ($t(28) = 3.335$, $p < .005$) compared to controls. For both controls and patients, the P-biased condition generated a steadily rising response function. No group differences in SNR were found for any DOM where the signal was greater than the noise. Initial gain ($t(28) = 1.091$, $p > .28$) and maximal SNR ($t(28) = 1.815$, $p > .08$) measures did not significantly differ between groups.

3.3. Functional Magnetic Resonance Imaging (fMRI): Contrast Sensitivity Task

Contrast sensitivity tasks were performed during fMRI scanning at 0.5 and 4 c/deg, at near threshold levels for each observer and at a fixed 71% contrast. Five controls were outliers with near threshold contrast levels above 50% and one patient was an outlier with an error in blood oxygenation level dependent (BOLD) signal acquisition, and they were removed from all analyses. Controls and patients had similar contrast sensitivities for 0.5 c/deg at 32 ms (M ± SD contrast sensitivity: controls: 54.69 ± 17.03; patients: 50.70 ± 19.15) as well as for 4 c/deg at 500 ms (M ± SD contrast sensitivity: controls: 41.43 ± 24.17; patients: 23.52 ± 21.68) (data not graphed).

For volume of activation, no interactions were found, but a main effect of group indicated greater occipital recruitment for controls than for patients ($F(1,88) = 17.583$, $p < .001$). This difference was significant for the 0.5 c/deg condition at both near threshold contrast and at high contrast, but not for 4 c/deg condition at either contrast level (Figure 5A). For strength of activation, no interactions or main effects were found, indicating equivalent activation strength for all task conditions and both groups (Figure 5B).

3.4. Functional Magnetic Resonance Imaging (fMRI): Isolated Check Task

Volume and strength of activation were assessed for each bias condition and DOM (Figure 6). In addition, location of activation is represented in group-averages displayed on flattened anatomical images of the occipital cortex, for each bias condition and DOM (Figure 7). For both volume and strength of activation measures, there was no significant main effect of group and no significant interactions containing group in a three-way ANOVA with group as a between subjects factor and condition (M- vs. P-biased) and DOM as within subjects factors. Collapsed across groups, there was a significant Condition × DOM interaction ($F(4,290) = 3.192$, $p < .05$) for activation volume. While both the M- and P-biased conditions showed a steep increase in volume of occipital activation from 2 to 8% DOM, and a decrease in activation volume from 8 to 16% DOM across groups, the P-biased condition yielded an increase in activation volume from 16 to 32% DOM whereas the M-biased condition did not (Table 1). For strength of activation, a main effect of DOM ($F(4,295) = 17.280$, $p < .001$) was found. The pattern of activation strength as DOM increased was strikingly different from the pattern of activation volume. Activation strength remained low over the 2 to 8% DOM range, and only increased at 16 and 32% DOM (Table 1).

Group-averages displayed on flattened maps of occipital cortex (corrected $p = .001$) showed differences in the location and direction of activation for different DOMs (Figure 7). For both bias conditions, the activation maps showed that the foveal representation was activated at all DOMs except 2%, where there was little activation. In addition, parafoveal areas showed positive activation (i.e. increased activation relative to rest) at 4 and 8% DOM, but negative activation (i.e. decreased activation relative to rest) at 16 and 32% DOM.

4. Discussion

This study investigated the cortical regions associated with contrast response deficits in the visual system in schizophrenia. An ssVEP paradigm utilizing contrast stimuli (Zemon et al., 1988, Zemon and Gordon, 2006) has previously revealed such deficits (Butler et al., 2001, Butler et al., 2005, Butler et al., 2008a, Butler et al., 2009), as have psychophysical contrast sensitivity tasks (Slaghuis, 1998, Kéri et al., 2002, Butler et al., 2005, Butler et al., 2009, Dias et al., 2011), but no study has localized these processes in the visual cortex of controls or patients. The current study utilized similar stimuli as those used in these electrophysiological and behavioral tasks in an fMRI paradigm in order to elucidate the neural substrates involved in visual contrast processing in healthy controls and patients with schizophrenia.

4.1. Psychophysical Contrast Sensitivity

Psychophysical contrast sensitivity results obtained with the VENUS system indicated that schizophrenia patients had contrast sensitivity deficits to both the shorter duration low spatial frequency and longer duration higher spatial frequency conditions, indicating that they were unable to detect low contrast stimuli as well as controls for both conditions. Contrast sensitivity for controls was greater for the higher spatial frequency condition, and the deficit for patients compared to controls was also larger for this condition. These results

are consistent with studies showing contrast sensitivity deficits across spatial frequencies (Slaghuis, 1998, Kéri et al., 2002), and suggest a robust and basic deficit in schizophrenia for the perception of low contrasts.

4.2. Functional Magnetic Resonance Imaging (fMRI): Contrast Sensitivity Task

In the fMRI paradigm, contrast sensitivity tasks were performed at low spatial frequency (0.5 c/deg) with short stimulus duration (32 ms) and at a higher spatial frequency (4 c/deg) with long stimulus duration (500 ms). For the 0.5 c/deg condition, mean threshold contrasts from the VENUS psychophysical paradigm (controls: 0.88%, patients: 1.22%) were close to the lowest contrast possible in the scanner (1%), and to mean thresholds obtained during fMRI scanning (controls: 1.83%, patients: 1.97%). On the other hand, for the 4 c/deg condition, mean threshold contrasts from the VENUS psychophysical paradigm (controls: 0.34%, patients: 0.57%) were well below 1%. However, a lower luminance was used for the scanner display (6.8 cd/m^2) compared to the VENUS display (84 cd/m^2) which increases threshold contrasts, particularly for higher spatial frequencies (Patel, 1966, Sperling, 1970, Peli, 1990). Indeed, the fMRI paradigm produced higher mean threshold contrasts for the 4 c/deg condition (controls: 2.41%, patients: 4.25%) than the 0.5 c/deg condition, though the inability to obtain thresholds below 1% contrast remained a limitation.

Schizophrenia patients had lower volume of activation measures for the low spatial frequency stimuli, at both threshold and high contrast (71%), but no significant differences were seen between groups for the higher spatial frequency stimuli at either threshold or high contrast. However, strength of activation measures were equivalent between groups and across all stimulus conditions. This indicates a selective deficit in processing low spatial frequency information for schizophrenia patients reflective of reduced volume of occipital activation, rather than reduced activation strength. The psychophysical and fMRI measures thus showed different deficits for schizophrenia patients. While psychophysical measures showed a deficit in perception of low contrast across spatial frequencies, fMRI measures showed a lack of cortical recruitment to low spatial frequencies across contrast. The loss of cortical recruitment for the 0.5 c/deg condition at threshold in schizophrenia patients may not be related to a deficit in psychophysical contrast sensitivity, as the same loss of recruitment was found at high contrast. However, the deficit in volume of activation for low spatial frequency is consistent with previous findings described below.

A recent study by Martinez and colleagues (Martinez et al., 2008) also found reduced volume of activation to low spatial frequency (0.2–1.4 c/deg) stimuli in schizophrenia at high (100%) and low (12%) contrast, in retinotopically defined V1 and V2. As in the current results, this study also did not find deficits to higher spatial frequencies (3.5–4.9 c/deg) at either contrast level. The current results extend this finding of a selective deficit in activation volume for low spatial frequencies to even lower contrasts (1–2%). Martinez and colleagues presented stimuli centrally and had participants press a button when a central fixation cross dimmed. The current results show that this deficit is also present during the frequently used psychophysical contrast sensitivity task. An even more recent study by Martinez and colleagues (Martinez et al., 2012) found reduced fMRI activation to an attended low spatial frequency (0.8 c/deg) compared to an attended high spatial frequency (5 c/deg) grating in schizophrenia patients. However, no group differences were found in areas known to be involved in feature-guided attention, suggesting that sensory processing of low spatial frequencies is impaired in schizophrenia independent of attentional deficits. Additionally, Calderone et al. (2012) recently found deficits in a network of cortical areas including occipital cortex to low spatial frequency object stimuli (~6 cycles per image) in schizophrenia. This finding indicates that low spatial frequency processing deficits are not limited to simple grating stimuli, but also occur with complex images. These previous

findings and the current results indicate a robust deficit in fMRI activation to low spatial frequency stimuli in schizophrenia, across stimulus contrast and complexity.

Neither controls nor patients showed differences in activation volume or strength between threshold and high contrast conditions for either spatial frequency. This is in contrast to the isolated-check paradigm, which showed dramatic changes in these ssVEP measures as contrast increased. Isolated check stimuli were passively viewed, while the contrast sensitivity task required responses based on stimulus location. Equivalent activation at threshold and high contrast may indicate that the active detection of a stimulus in this task recruits a specific volume and strength of occipital activation regardless of stimulus contrast.

4.3. Steady-State Visual Evoked Potentials

Consistent with our previous findings, schizophrenia patients showed a selective deficit in the magnocellular- vs. the parvocellular-biased condition (Butler et al., 2001, Butler et al., 2005, Butler et al., 2009). For the magnocellular-biased condition, healthy controls showed a steep initial increase in response as contrast increased over the low contrast range, followed by a peak SNR when contrast reached 16%. Patients showed a less steep initial increase in response, indicative of reduced signal amplification to low contrasts. In addition, maximal SNRs were lower for patients. For the parvocellular-biased condition, both groups demonstrated a linear increase in response with a shallow slope over the full range of contrasts, with no group differences for responses out of the noise (SNR > 1). The shape of the curves is consistent with nonlinear gain in the magnocellular-biased condition and supports previous studies (Butler et al., 2001, Butler et al., 2005, Zemon and Gordon, 2006, Butler et al., 2007, Butler et al., 2008a, Green et al., 2009) that show schizophrenia is associated with specific deficits in contrast gain.

Our previous ssVEP results (Butler et al., 2001, Butler et al., 2005, Butler et al., 2009) were obtained utilizing a VENUS system (Neuroscientific Corp., Farmingdale, NY) for stimulus presentation, VEP recording, and analysis, which is no longer manufactured. The current results were obtained utilizing a recently developed Neucodia system (VeriSci Corp., Raritan, NJ) which includes the feature of synchronized data collection, utilizes modern equipment, and provides ease of use. Thus, this deficit in contrast gain seen in the ssVEP paradigm is robust across assessment systems and cohorts of patients.

4.4. Functional Magnetic Resonance Imaging: Isolated-Check Task

Similar stimuli to those used in the ssVEP paradigm were shown in the fMRI task in order to localize the ssVEP response to specific visual cortical areas. Across groups and for both magnocellular- and parvocellular-biased stimuli, a general pattern emerged in which increasingly greater volumes of occipital cortex were recruited as contrast increased through the low contrast range, while higher contrasts showed reduced volume of activation (Figure 6A). Conversely, strength of activation remained low over the low contrast range, and increased dramatically at higher contrasts (Figure 6B). These fMRI results conflict with the ssVEP results, since they show similar patterns for magnocellular- and parvocellular-biased conditions, as well as for controls and patients. Likewise, the lack of increase in fMRI activation strength over the low contrast region conflicts with previous single-cell work, which has shown increases in the firing rates of individual cells as contrast increases (Kaplan and Shapley, 1986, Shapley, 1990). This indicates a dissociation between ssVEP and fMRI for this task, and suggests that patients may recruit the same occipital areas with the same amount of metabolic energy as controls, but are not able to utilize these areas for enhanced contrast gain.

Several studies have shown correspondence between negative VEP deflections and positive BOLD activity under certain stimulus conditions (Whittingstall et al., 2007, Whittingstall et al., 2008, Yesilyurt et al., 2010). Other studies, however, have shown VEP and BOLD responses to be unrelated for particular stimuli (Janz et al., 2001), and that pharmacological treatment can reduce BOLD activity without affecting VEP responses (Seaquist et al., 2007). Di Russo and colleagues (Di Russo et al., 2007) recently demonstrated both correspondence and dissociation between ssVEP and BOLD responses, such that some areas of occipital BOLD activation were shown to contribute to ssVEP response, while other occipital BOLD activation did not. The current results showing an overall pattern of similar BOLD responses for magnocellular- and parvocellular-biased conditions across groups suggests that the neural processes measured by ssVEPs are divergent from the broader class of processes measured by fMRI, and that patient deficits to these particular stimuli occur at the neural level measured by ssVEP.

4.5. Conclusions

Utilizing the CNTRICS domain of perception, this study examined the cortical underpinnings of two tasks that utilized contrast responses and that have previously been used to demonstrate deficits in early-stage visual perception in schizophrenia. Both psychophysical contrast sensitivity and ssVEP measures demonstrated dysfunctional processing of low contrasts for schizophrenia patients, while fMRI revealed only a deficit in cortical recruitment for low spatial frequencies. The similarity between magnocellular- and parvocellular-biased fMRI responses to the isolated-check paradigm, as well as equivalent fMRI activation to high and low contrast in the contrast sensitivity paradigm, indicate that these ssVEP and psychophysical techniques are of greater assessment value for the contrast deficits explored. Further work is required to investigate the neural correlates of contrast response deficits in schizophrenia.

References

Ardekani BA, Bachman AH, Strother SC, Fujibayashi Y, Yonekura Y. Impact of inter-subject image registration on group analysis of fMRI data. International Congress Series. 2004; 1265:49–59.

Barch DM, Carter CS, Dakin SC, Gold J, Luck SJ, Macdonald A 3rd, Ragland JD, Silverstein S, Strauss ME. The clinical translation of a measure of gain control: the contrast-contrast effect task. Schizophrenia Bulletin. 2012; 38:135–143. [PubMed: 22101963]

Benardete EA, Kaplan E, Knight BW. Contrast gain control in the primate retina: P cells are not X-like, some M cells are. Visual Neuroscience. 1992; 8:483–486. [PubMed: 1586649]

Butler PD, Abeles IY, Weiskopf NG, Tambini A, Jalbrzikowski M, Legatt ME, Zemon V, Loughead J, Gur RC, Javitt DC. Sensory contributions to impaired emotion processing in schizophrenia. Schizophrenia Bulletin. 2009; 35:1095–1107. [PubMed: 19793797]

Butler PD, Chen Y, Ford JM, Geyer MA, Silverstein SM, Green MF. Perceptual measurement in schizophrenia: promising electrophysiology and neuroimaging paradigms from CNTRICS. Schizophrenia Bulletin. 2012; 38:81–91. [PubMed: 21890745]

Butler PD, Martinez A, Foxe JJ, Kim D, Zemon V, Silipo G, Mahoney J, Shpaner M, Jalbrzikowski M, Javitt DC. Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. Brain. 2007; 130:417–430. [PubMed: 16984902]

Butler PD, Schechter I, Zemon V, Schwartz SG, Greenstein VC, Gordon J, Schroeder CE, Javitt DC. Dysfunction of early-stage visual processing in schizophrenia. American Journal of Psychiatry. 2001; 158:1126–1133. [PubMed: 11431235]

Butler PD, Silverstein SM, Dakin SC. Visual perception and its impairment in schizophrenia. Biological Psychiatry. 2008a; 64:40–47. [PubMed: 18549875]

Butler PD, Tambini A, Yovel G, Jalbrzikowski M, Ziwich R, Silipo G, Kanwisher N, Javitt DC. What's in a face? Effects of stimulus duration and inversion on face processing in schizophrenia. Schizophrenia Research. 2008b; 103:283–292. [PubMed: 18450426]

Butler PD, Zemon V, Schechter I, Saperstein AM, Hoptman MJ, Lim KO, Revheim N, Silipo G, Javitt DC. Early-stage visual processing and cortical amplification deficits in schizophrenia. Archives of General Psychiatry. 2005; 62:495–504. [PubMed: 15867102]

Calderone DJ, Hoptman MJ, Martinez A, Nair-Collins S, Mauro CJ, Bar M, Javitt DC, Butler PD. Contributions of Low and High Spatial Frequency Processing to Impaired Object Recognition Circuitry in Schizophrenia. Cerebral Cortex. 2012 In Press.

Carandini M, Heeger DJ, Movshon JA. Linearity and normalization in simple cells of the macaque primary visual cortex. J Neurosci. 1997; 17:8621–8644. [PubMed: 9334433]

Chen Y, Levy DL, Sheremata S, Holzman PS. Compromised late-stage motion processing in schizophrenia. Biological Psychiatry. 2004:55.

Chen Y, Levy DL, Sheremata S, Nakayama K, Matthysse S, Holzman PS. Effects of typical, atypical, and no antipsychotic drugs on visual contrast detection in schizophrenia. The American Journal of Psychiatry. 2003a; 160:1795–1801. [PubMed: 14514493]

Chen Y, Nakayama K, Levy D, Matthysse S, Holzman P. Processing of global, but not local, motion direction is deficient in schizophrenia. Schizophrenia Research. 2003b; 61:215–227. [PubMed: 12729873]

Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res. 1996; 29:162–173. [PubMed: 8812068]

Di Russo F, Pitzalis S, Aprile T, Spitoni G, Patria F, Stella A, Spinelli D, Hillyard SA. Spatiotemporal analysis of the cortical sources of the steady-state visual evoked potential. Hum Brain Mapp. 2007; 28:323–334. [PubMed: 16779799]

Dias EC, Butler PD, Hoptman MJ, Javitt DC. Early sensory contributions to contextual encoding deficits in schizophrenia. Archives of General Psychiatry. 2011; 68:654–664. [PubMed: 21383251]

Doniger GM, Foxe JJ, Murray MM, Higgins BA, Javitt DC. Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. Archives of General Psychiatry. 2002; 59:1011–1020. [PubMed: 12418934]

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders. New York: New York State Psychiatric Institute; 1997.

Green MF, Butler PD, Chen Y, Geyer MA, Silverstein S, Wynn JK, Yoon JH, Zemon V. Perception measurement in clinical trials of schizophrenia: Promising paradigms from CNTRICS. Schizophrenia Bulletin. 2009; 35:163–181. [PubMed: 19023123]

Janz C, Heinrich SP, Kornmayer J, Bach M, Hennig J. Coupling of neural activity and BOLD fMRI response: new insights by combination of fMRI and VEP experiments in transition from single events to continuous stimulation. Magn Reson Med. 2001; 46:482–486. [PubMed: 11550239]

Jasper HH. The ten twenty electrode system of the International Federation. Electroencephalography Journal. 1958; 10:371–375.

Javitt DC. When doors of perception close: Bottom-up models of disrupted cognition in schizophrenia. The Annual Review of Clinical Psychology. 2009; 5:249–275.

Kaplan, E. The M,P, and K pathways of the primate visual system. In: Chalupa, L.; Werner, J., editors. The Visual Neurosciences. Cambridge, Mass: MIT Press; 2003.

Kaplan E, Shapley RM. X and Y cells in the lateral geniculate nucleus of macaque monkeys. The Journal of Physiology. 1982; 330:125–143. [PubMed: 7175738]

Kaplan E, Shapley RM. The primate retina contains two types of ganglion cells, with high and low contrast sensitivity. Proceedings of the National Academy of Sciences USA. 1986; 83:2755–2757.

Kéri S, Antal A, Szekeres G, Benedek G, Janka Z. Spatiotemporal visual processing in schizophrenia. Journal of Clinical Neuroscience. 2002; 14:190–196.

Kéri S, Kelemen O, Benedek G, Janka Z. Vernier threshold in patients with schizophrenia and in their unaffected siblings. Neuropsychology. 2004; 18:537–542. [PubMed: 15291731]

Kim D, Wylie G, Pasternak R, Butler PD, Javitt DC. Magnocellular contributions to impaired motion processing in schizophrenia. Schizophrenia Research. 2006; 82:1–8. [PubMed: 16325377]

Kiss I, Fabian A, Benedek G, Keri S. When doors of perception open: visual contrast sensitivity in never-medicated, first-episode schizophrenia. Journal of Abnormal Psychology. 2010; 119:586–593. [PubMed: 20677847]

Klein A, Andersson J, Ardekani BA, Ashburner J, Avants B, Chiang MC, Christensen GE, Collins DL, Gee J, Hellier P, Song JH, Jenkinson M, Lepage C, Rueckert D, Thompson P, Vercauteren T, Woods RP, Mann JJ, Parsey RV. Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. Neuroimage. 2009; 46:786–802. [PubMed: 19195496]

Koychev I, El-Deredy W, Deakin JF. New visual information processing abnormality biomarker for the diagnosis of Schizophrenia. Expert Opin Med Diagn. 2011; 5:357–368. [PubMed: 22003364]

Kurylo DD, Pasternak R, Silipo G, Javitt DC, Butler PD. Perceptual organization by proximity and similarity in schizophrenia. Schizophrenia Research. 2007; 95:205–214. [PubMed: 17681736]

Legge GE. Sustained and transient mechanisms in human vision: temporal and spatial properties. Vision Research. 1978; 18:69–81. [PubMed: 664278]

Leitman DI, Wolf DH, Laukka P, Ragland JD, Valdez JN, Turetsky BI, Gur RE, Gur RC. Not pitch perfect: sensory contributions to affective communication impairment in schizophrenia. Biological Psychiatry. 2011; 70:611–618. [PubMed: 21762876]

Martinez A, Hillyard SA, Bickel S, Dias EC, Butler PD, Javitt DC. Consequences of magnocellular dysfunction on processing attended information in schizophrenia. Cerebral Cortex. 2012; 22:1282–1293. [PubMed: 21840846]

Martinez A, Hillyard SA, Dias EC, Hagler DJ, Butler PD, Guilfoyle DN, Jalbrzikowski M, Silipo G, Javitt DC. Magnocellular pathway impairment in schizophrenia: Evidence from functional magnetic resonance imaging. The Journal of Neuroscience. 2008; 28:7492–7500. [PubMed: 18650327]

Merigan WH, Maunsell JHR. How parallel are the primate visual pathways? Annu Rev Neurosci. 1993; 16:369–402. [PubMed: 8460898]

Norman J. Two visual systems and two theories of perception: An attempt to reconcile the constructivist and ecological approaches. Behavioral and Brain Sciences. 2002; 25:73–144. [PubMed: 12625088]

Norton D, McBain R, Holt DJ, Ongur D, Chen Y. Association of impaired facial affect recognition with basic facial and visual processing deficits in schizophrenia. Biological Psychiatry. 2009; 65:1094–1098. [PubMed: 19268917]

O'Donnell BF, Potts GF, Nestor PG, Stylianopoulos KC, Shenton ME, McCarley RW. Spatial frequency discrimination in schizophrenia. Jounral of Abnormal Psychology. 2002; 111:620–625.

Ohzawa I, Sclar G, Freeman RD. Contrast gain control in the cat visual cortex. Nature. 1982; 298:266–268. [PubMed: 7088176]

Ohzawa I, Sclar G, Freeman RD. Contrast gain control in the cat's visual system. Journal of Neurophysiology. 1985; 54:651–667. [PubMed: 4045542]

Patel AS. Spatial resolution by the human visual system. The effect of mean retinal illuminance. J Opt Soc Am. 1966; 56:689–694. [PubMed: 5963523]

Peli E. Contrast in complex images. J Opt Soc Am A. 1990; 7:2032–2040. [PubMed: 2231113]

Revheim N, Butler PD, Schechter I, Jalbrzikowski M, Silipo G, Javitt DC. Reading impairment and visual processing deficits in schizophrenia. Schizophrenia Research. 2006; 87:238–245. [PubMed: 16890409]

Seaquist ER, Chen W, Benedict LE, Ugurbil K, Kwag JH, Zhu XH, Nelson CA. Insulin reduces the BOLD response but is without effect on the VEP during presentation of a visual task in humans. J Cereb Blood Flow Metab. 2007; 27:154–160. [PubMed: 16639425]

Sehatpour P, Dias EC, Butler PD, Revheim N, Guilfoyle DN, Foxe JJ, Javitt DC. Impaired visual object processing across an occipital- frontal-hippocampal brain network in schizophrenia: An integrated neuroimaging study. Archives of General Psychiatry. 2010; 67:772–782. [PubMed: 20679585]

Shapley R. Visual sensitivity and parallel retinocortical channels. The Annual Review of Psychology. 1990; 41:635–658.

Shapley R, Victor JD. The contrast gain control of the cat retina. Vision Research. 1979; 19:431–434. [PubMed: 473613]

Silverstein SM, Keane BP. Perceptual organization impairment in schizophrenia and associated brain mechanisms: review of research from 2005 to 2010. Schizophrenia Bulletin. 2011; 37:690–699. [PubMed: 21700589]

Slaghuis WL. Contrast sensitivity for stationary and drifting spatial frequency gratings in positive- and negative-symptom schizophrenia. Journal of Abnormal Psychology. 1998; 107:49–62. [PubMed: 9505038]

Slaghuis WL. Spatio-temporal luminance contrast sensitivity and visual backward masking in schizophrenia. Experimental Brain Research. 2004; 156:196–211.

Sperling G. Model of visual adaptation and contrast detection. Perception & Psychophysics. 1970; 8:143–157.

Tolhurst DJ. Reaction times in the detection of gratings by human observers: a probabilistic mechanism. Vision Research. 1975; 15:1143–1149. [PubMed: 1166615]

Tootell RBH, Hamilton SL, Switkes E. Functional anatomy of macaque striate cortex. IV. Contrast and magno-parvo streams. The Journal of Neuroscience. 1988; 8:1594–1609. [PubMed: 3367212]

Turetsky BI, Kohler CG, Indersmitten T, Bhati MT, Charbonnier D, Gur RC. Facial emotion recognition in schizophrenia: when and why does it go awry? Schizophrenia Research. 2007; 94:253–263. [PubMed: 17583481]

Victor JD, Mast J. A new statistic for steady-state evoked potentials. Electroencephalogr Clin Neurophysiol. 1991; 78:378–388. [PubMed: 1711456]

Wetherill GB, Levitt H. Sequential Estimation of Points on a Psychometric Function. Br J Math Stat Psychol. 1965; 18:1–10. [PubMed: 14324842]

Whittingstall K, Stroink G, Schmidt M. Evaluating the spatial relationship of event-related potential and functional MRI sources in the primary visual cortex. Hum Brain Mapp. 2007; 28:134–142. [PubMed: 16761265]

Whittingstall K, Wilson D, Schmidt M, Stroink G. Correspondence of visual evoked potentials with FMRI signals in human visual cortex. Brain Topogr. 2008; 21:86–92. [PubMed: 18841455]

Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry. 2003; 64:663–667. [PubMed: 12823080]

Woods SW. Calculation of CPZ Equivalents. 2005; 2012

Woods SW. Chlorpromazine Equivalent Doses for the Newer Atypical Antipsychotics. 2011; 2012

Wurtz, RH.; Kandel, ER. Central Visual Pathways. In: Kandel, ER., et al., editors. Principles of Neural Science. New York, NY: McGraw-Hill; 2000. p. 523-545.

Yesilyurt B, Whittingstall K, Ugurbil K, Logothetis NK, Uludag K. Relationship of the BOLD signal with VEP for ultrashort duration visual stimuli (0.1 to 5 ms) in humans. J Cereb Blood Flow Metab. 2010; 30:449–458. [PubMed: 19844243]

Zemon V, Eisner W, Gordon J, Grose-Fifer J, Tenedios F, Shoup H. Contrast-dependent responses in the human visual system: childhood through adulthood. Int J Neurosci. 1995; 80:181–201. [PubMed: 7775048]

Zemon V, Gordon J. Luminance-contrast mechanisms in humans: Visual evoked potentials and a nonlinear model. Vision Research. 2006; 46:4163–4180. [PubMed: 16997347]

Zemon V, Gordon J, Welch J. Asymmetries in ON and OFF visual pathways of humans revealed using contrast-evoked cortical potentials. Visual Neuroscience. 1988; 1:145–150. [PubMed: 3154786]

Zemon V, Hartmann EE, Gordon J, Prunte-Glowazki A. An electrophysiological technique for assessment of the development of spatial vision. Optom Vis Sci. 1997; 74:708–716. [PubMed: 9380368]

Highlights

- Previous findings of psychophysical contrast sensitivity deficits were replicated.
- MRI deficits to only some of the contrast sensitivity stimuli were found.
- Deficits in electrophysiological measures of visual gain control were replicated.
- Normal recruitment of visual cortical areas was seen in a corresponding fMRI task.
- Psychophysical, electrophysiological, and fMRI measures were dissociated.

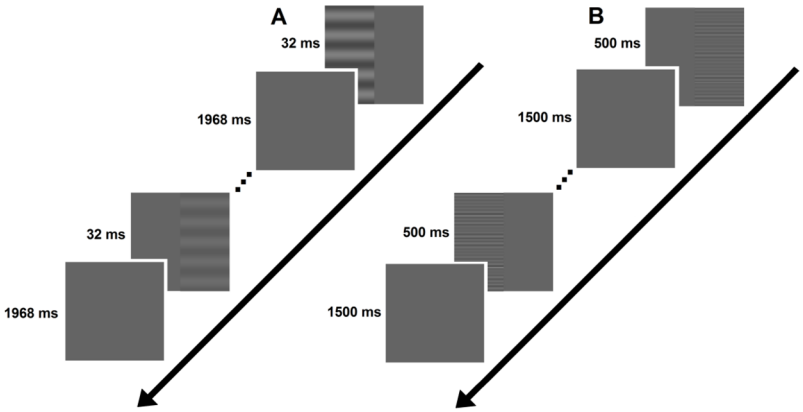

Figure 1.
Contrast sensitivity task used in the fMRI paradigm. Participants indicated whether stimuli appeared on the left or right side of the screen. A. Low spatial frequency condition: stimuli were presented at 0.5 c/deg for approximately 32 ms. B. High spatial frequency condition: stimuli were presented at 4 c/deg for approximately 500 ms.

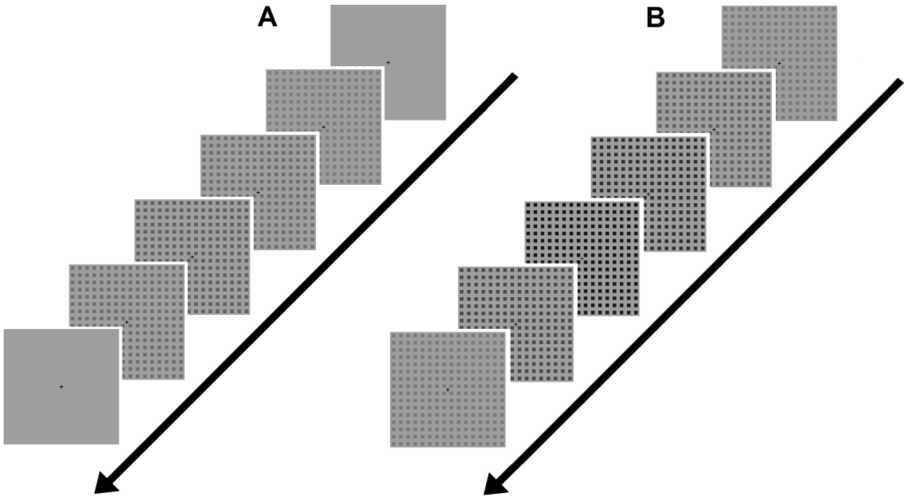

Figure 2.
Sinusoidal modulation of isolated check stimuli used in the ssVEP and fMRI paradigms. Stimuli were sinusoidally modulated at ~12 Hz, such that each cycle through contrast levels shown in A and B occurred ~12 times per second. A. Magnocellular-biased condition: pedestal around which contrast was modulated equaled the depth of modulation, resulting in appearance/disappearance stimuli. B. Parvocellular-biased condition: pedestal around which contrast was modulated equaled 48%, so that contrast remained high during modulation.

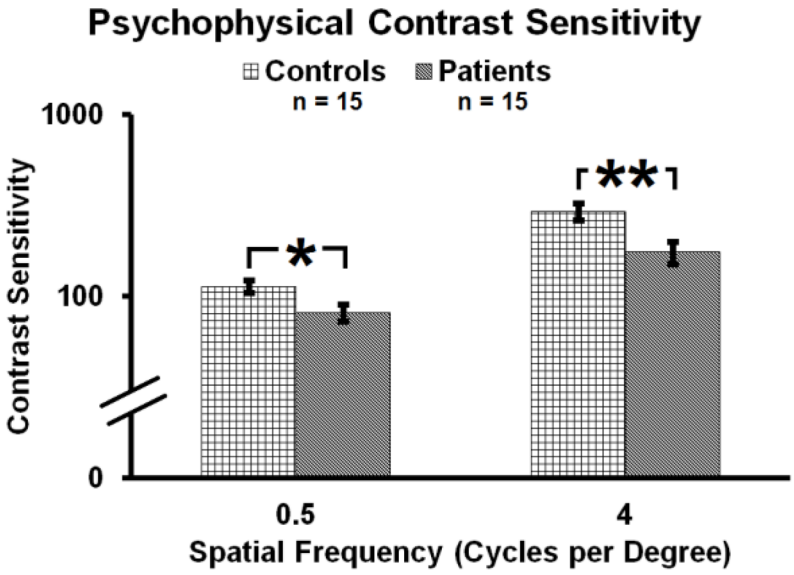

Figure 3.
Psychophysical contrast sensitivities obtained with the VENUS system, displayed on a log base 10 scale. Error bars show standard error. *$p < .05$, **$p < .01$.

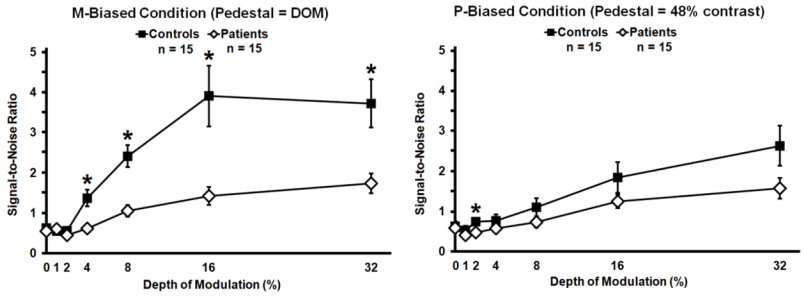

Figure 4.
Contrast response functions for the ssVEP paradigm. Error bars show standard error. *$p <$. 05.

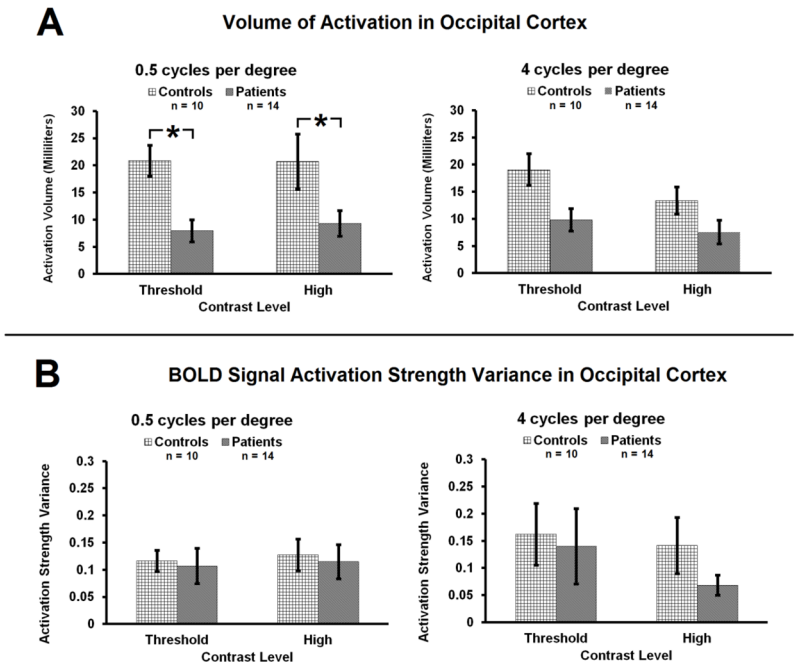

Figure 5.

fMRI measures obtained during the contrast sensitivity task for 0.5 and 4 c/deg at either near threshold contrast or at high contrast. A. Volume of activation measured in milliliters. B. Strength of activation measured as first-order regression betas squared (percent of total variance). Error bars show standard error. *$p < .05$.

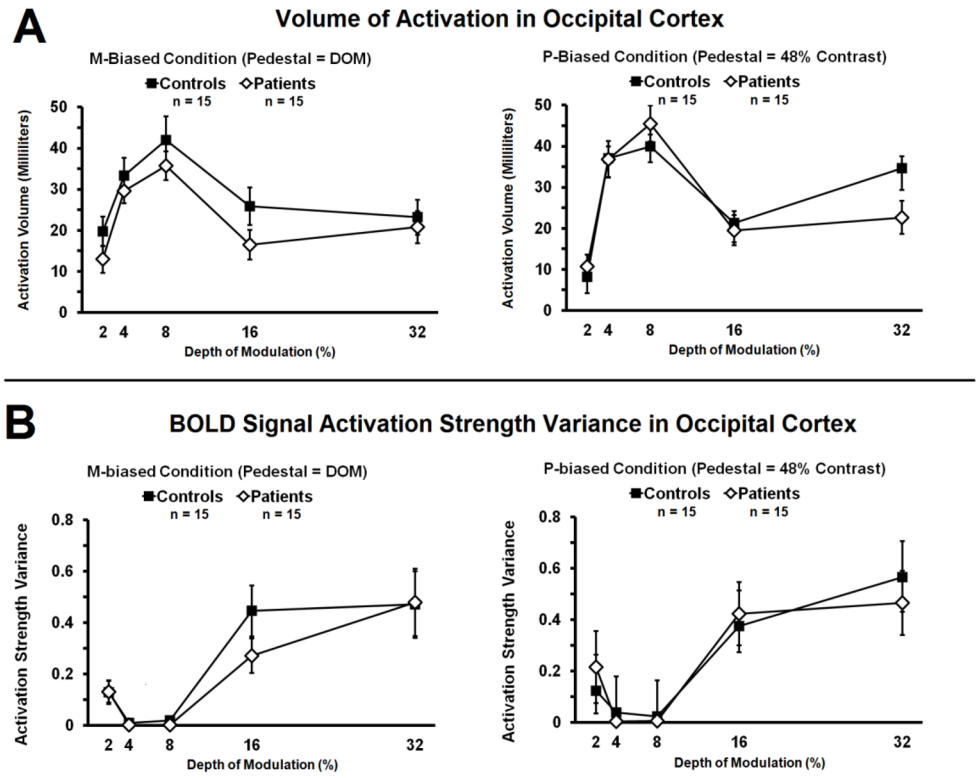

Figure 6.

fMRI measures for isolated check stimuli calculated for occipital cortex. A. Volume of activation measured in microliters. B. Strength of activation measured as first-order regression beta squared (variance). Error bars show standard error.

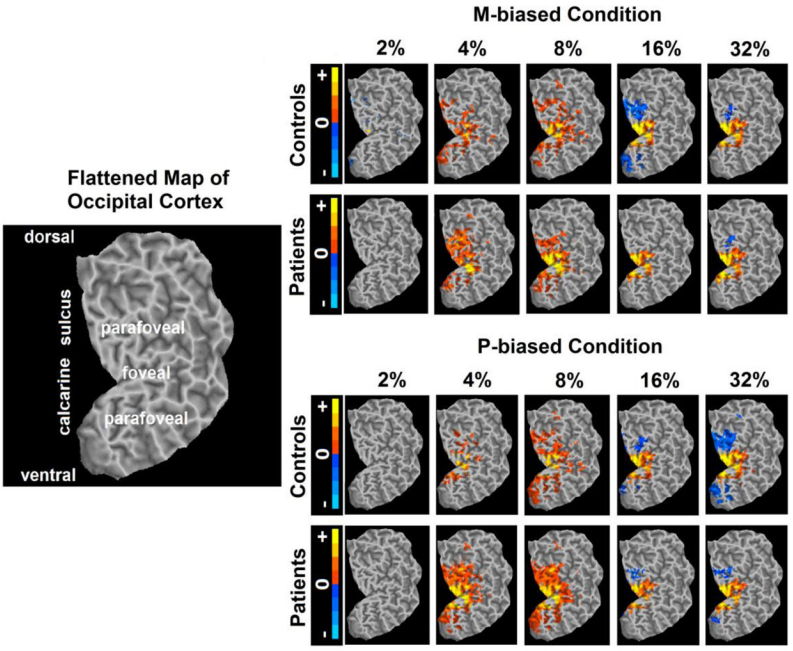

Figure 7.

Flattened anatomical maps of occipital cortex showing direction and location of fMRI activation to isolated check stimuli. Each map shows a group-average of first-order regression beta values thresholded at $p = .001$. No differences between hemispheres were found for any condition at $p = .001$, and thus right hemisphere maps are shown here as representative of all occipital activation.

Table 1

fMRI Isolated check task: Differences in occipital activation volume and activation strength across groups as depth of modulation increases in the M-biased and P-biased conditions.

		Volume of Activation		Activation Strength	
Condition	**Depth of Modulation**	***t*(29)**	***p***	***t*(29)**	***p***
M-biased	2% vs. 4%	−4.033	<0.001*	4.028	<0.001*
M-biased	4% vs. 8%	−3.135	<0.005*	−1.653	0.109
M-biased	8% vs. 16%	5.639	<0.001*	−5.862	<0.001*
M-biased	16% vs. 32%	−0.393	0.697	−1.751	0.091
P-biased	2% vs. 4%	−6.603	<0.001*	1.798	0.083
P-biased	4% vs. 8%	−2.217	<0.050*	0.854	0.400
P-biased	8% vs. 16%	8.050	<0.001*	−4.868	<0.001*
P-biased	16% vs. 32%	−3.611	<0.005*	−2.396	<0.050*