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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], 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, CA 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

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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 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.

Introduction

Over recent years it has become clear that patients with schizophrenia exhibit sensory processing deficits in a number of modalities (Butler et al., 2012; Javitt, 2009; Koychev et al., 2011; Leitman et al., 2011; Silverstein and Keane, 2011). 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 (Butler et al., 2012; Green et al., 2009). In the visual system, behavioral, electrophysiological, and functional magnetic resonance imaging (fMRI) studies have revealed early-stage sensory deficits, including deficient processing of contrast (Butler et al., 2005, 2009; Green et al., 2009; Kéri et al., 2002, 2004; Slaghuis, 1998), motion (Chen et al., 2003b, 2004; Kim et al., 2006), and spatial frequency information (Martinez et al., 2008, 2012; O'Donnell et al., 2002). These visual sensory processing deficits appear to contribute to higher level dysfunction in reading (Revheim et al., 2006), object processing and grouping (Calderone et al., in press; Doniger et al., 2002; Kurylo et al., 2007; Sehatpour et al., 2010), and emotion processing (Butler et al., 2009; Turetsky et al., 2007).

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 (Butler et al., 2012; Green et al., 2009). The neurophysiological measures are based on the use of visual stimuli designed to emphasize either the magnocellular or parvocellular contributions to visual

* Corresponding author at: Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, NY 10962, USA.
E-mail address: dcalderone@nki.rfmh.org (D.J. Calderone).

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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' (Carandini et al., 1997; Ohzawa et al., 1982, 1985; Shapley and Victor, 1979; Zemon et al., 1995). 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 (Benardete et al., 1992; Kaplan and Shapley, 1982, 1986; Shapley, 1990; Tootell et al., 1988).

Patients with schizophrenia exhibit contrast response deficits in the visual system, which are seen in electrophysiological (Butler et al., 2005, 2012; Green et al., 2009) as well as behavioral studies (Barch et al., 2012; Butler et al., 2005, 2009; Green et al., 2009; Kéri et al., 2002, 2004; Slaghuis, 1998). An electrophysiological technique that involves recording steady-state visual evoked potentials (ssVEP) to isolated-check stimuli (Zemon and Gordon, 2006; Zemon et al., 1988) has previously been used to demonstrate contrast gain deficits in schizophrenia (Butler et al., 2001, 2005, 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, 2005, 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 (Merigan and Maunsell, 1993; Norman, 2002; Shapley, 1990; Tootell et al., 1988; Wurtz and Kandel, 2000). 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 (Legge, 1978; Tolhurst, 1975). A number of studies show that patients with schizophrenia have higher contrast thresholds (i.e., impaired contrast sensitivity) compared to healthy controls (Butler et al., 2005, 2008b; Chen et al., 2003a; Dias et al., 2011; Kéri et al., 2002; Norton et al., 2009; Slaghuis, 1998, 2004). Selective deficits have been found at low spatial frequencies in some studies (Butler et al., 2005, 2009), though others found deficits across spatial frequencies (Kéri et al., 2002; Slaghuis, 1998) 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, 2005, 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.

Methods

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 (Calderone et al., in press; Dias et al., 2011; Martinez et al., 2012).

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 (Fig. 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,