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The Clinical Translation of a Measure of Gain Control: The Contrast-Contrast Effect Task

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The goal of the current project was to further develop a measure of gain control—the Contrast-Contrast Effect (CCE)—for use in clinical studies of schizophrenia. The CCE is based on an illusion in which presenting a medium contrast patch surrounded by a high-contrast patch induces individuals to perceive that center patch as having lower contrast than when the patch is presented in isolation. Thus, in the CCE, impaired gain control should lead to more accurate perceptions of the center patch. We tested 132 individuals with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, schizophrenia or schizoaffective disorder and 130 demographically similar healthy controls. The results indicated that the CCE effect can be obtained with standard equipment, simplified scoring, and a short interstimulus interval (100 ms), revealing a robust suppression of perceived contrast of the center patch when surrounded by a high-contrast annulus. Furthermore, we found a significant reduction in the effect of the high-contrast surround among individuals with schizophrenia, though the effect size was smaller than original reported by Dakin. However, when we eliminated subjects who performed poorly on "catch" trials that controlled for off-task performance, the reduced surround effect among patients was no longer significant in the main analyses. Importantly, this suggests that at least part of the reduced surround effect (if not all) in schizophrenia could be attributable to impaired attentional mechanisms that contribute to off-task performance. Additional analyses suggested that the length of the task could be shortened without losing power to detect surround effects in healthy individuals.

Key words: perception/visual cortex/clinical trials

A critical component of perception highlighted at the first Cognitive Neuroscience Treatment Research to Improve Cognition (CNTRICs) meeting was gain control, which refers to processes that amplify or attenuate overall levels of neural activity to optimize operation of systems with limited dynamic signaling range.[1] The characterization of gain control mechanisms has a long history in cognitive neuroscience.[2–5] It has been used to link together various types of phenomena, including those involving pop-out phenomena where neurons coding similar features inhibit each other,[6] effects of surrounding contrast on contrast thresholds,[7] texture segregation,[8] and figure-ground segregation.[9] Moreover, there is convergence between theoretical work, eg,[10] psychophysical studies, eg,[11] electrophysiology,[12,13] and functional Magnetic Resonance Imaging (fMRI),[14] in supporting the existence of gain control mechanisms and their effects on neurons in visual cortex. Recent work has also provided some clarification on local circuit and synaptic processes involved in gain control, with contributions by both excitatory and inhibitory elements in these circuits that may be influenced by Gamma Amino Butyric Acid (GABA)-ergic and glutametergic function.[15,16]

Gain Control Impairment in Schizophrenia

Gain control impairments are found in vision, eg,[17] as well as in audition, eg,[18] in schizophrenia. For example, patients demonstrate less visual suppression (as assessed by contrast sensitivity functions) due to effects of surrounding contrast.[19] Mechanisms of gain control dysfunction have also been hypothesized to include GABA-ergic and/or NMDA receptor dysfunction. For example, NMDA receptor dysfunction appears linked to gain

control in the M-pathway and has been hypothesized to be linked to schizophrenia.[20] In recent work, Yoon and colleagues[21] found evidence that reduced gain control was associated with reduced GABA levels (as measured by Magnetic Resonance Spectroscopy) in visual cortex. There is also evidence that gain control deficits are important in outcome. For instance, impaired contrast detection in steady-state and transient Visual Evoked Potential studies is related to poorer functional outcome in schizophrenia as assessed with the problem-solving factor of the Independent Living Scales.[22] Finally, abnormal contrast sensitivity and backward-masking functions have been linked to negative symptoms and poor treatment outcome in schizophrenia.[23]

There are a number of different approaches to measuring gain control.[24,25] One approach—referred to as the Contrast-Contrast Effect (CCE)—examines the perception of contrast utilizing an illusion in which the contrast of the elements in a small target circle appears reduced when presented within a high-contrast surround compared with when the same target is presented in isolation.[7] When asked to match a variable contrast patch to the central patch, controls indicate that the central patch had a substantially lower contrast than it actually does (see figure 1 for an illustration). Converging evidence from psychophysics and fMRI indicates that the CCE is linked to gain control within primary visual cortex (V1),[14] reflecting both intrinsic V1 circuitry and top-down feedback from higher object-processing areas to V1.[26] Because 90% of cells in V1 are subject to suppression from neighboring cells, tasks such as this that act on V1 neurons are ideal methods for the study of gain control.

In a previous study with the CCE task, patients with schizophrenia were not susceptible to the illusion and 12 of 15 patients were more accurate than the most-accurate control subject.[19] These results are consistent with decreased center-surround antagonism and hence decreased gain control in schizophrenia patients.[27,28] However, the Dakin et al[19] study used forensic inpatients with schizophrenia, who were presumably chronically and actively ill. Thus, it would be important to determine if such results can be replicated in an outpatient sample of individuals with schizophrenia to assess the generalizability of the results. The use of tasks such as the CCE is also beneficial because they afford the ability to rule out a generalized deficit interpretation.[29] Specifically, reduced gain control, or contextual modulation, is indicated by "more" accurate contrast judgments regarding the inner circle compared with controls.

The purpose of this study was to evaluate the sensitivity of the CCE task to schizophrenia after it was modified to make it more amenable for use in clinical trials of cognitive enhancers or rehabilitation efforts. First, the task was originally presented using specialized equipment and software that would not be easy to use or readily available for clinical trials. Thus, we wished to determine if the task could be validly implemented using standard computer platforms, standardized easily available presentation software (E-prime), and less rigidly controlled presentation parameters (eg, ambient lighting, subject eye fixation) than in a typical psychophysical study. Second, the version of the task used in the Dakin et al[19] study included a modest delay (1000 ms) between the presentation of the first patch (center patch either presented alone or with a high-contrast surround) and the comparison patch. The 1000 ms delay generates the possibility that sensory memory or working memory functions could influence performance on the task and could be part of the explanation of impairments in schizophrenia (see, for example,[30]). Thus, we compared performance on the original version of the task with a version with only a 100 ms delay (some delay was necessary to facilitate participants' understanding that there were 2 separate patches in the no-surround condition). Third, studies examining illusions such as the CCE frequently involve testing performance at many different levels of contrast, requiring a large number of trials. The advantage of such approaches is that they can be used to generate full psychometric functions for each subject. However, they are also very time-consuming. We used an adaptive staircase procedure instead, which can be much faster. We included several different staircase procedures to determine the conditions that would provide the most robust and reliable estimate of the CCE illusion. One potential downside of the adaptive staircase approach is that attention lapses can distort the results.[31] Accordingly, we included catch trials to explicitly assess lapse rates for each participant.

Methods

Participants

The participants for this study, their recruitment, inclusion/exclusion criteria, and their clinical assessment are described in detail in the first article in this set of articles.[32]

CCE Task

Two versions of the CCE task were administered to all subjects: (1) the original version of the CCE, as described by Dakin et al[19] and (2) a version that reduced the delay between the first patch and the comparison patch to shorten the task and reduce memory demands. On each trial, subjects viewed (from a distance of approximately 24 inches) a circular region (1.3° diameter) of blob-like shapes (8 c/degree bandpass-filtered noise with a bandwidth of 3.2 c/degree) presented for 500 ms at an intermediate contrast level (40% Michelson contrast). After either a 1000-ms blank period (interstimulus interval [ISI], original version) or a 100-ms blank period, an isolated central comparison patch was presented, and subjects indicated whether the first or the second patch had higher contrast (figure 1). The first patch was presented either in isolation or surrounded by a

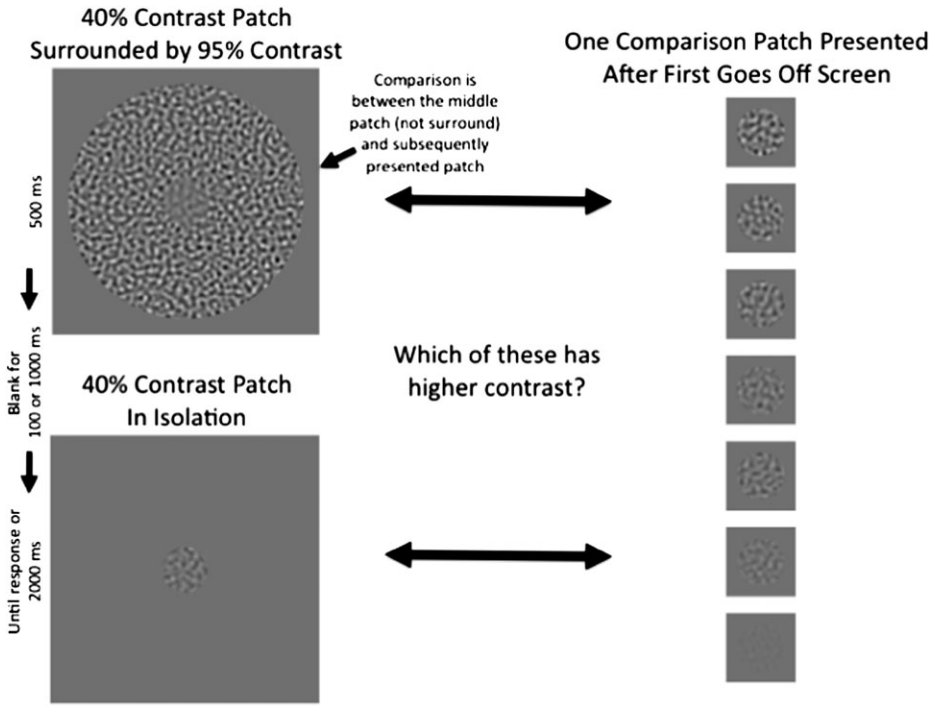

Fig. 1. Illustration of the Contrast-Contrast Effect (CCE) paradigm. On each trial, participants are presented with a patch, either in isolation (left bottom patch) or surrounded by a high-contrast annulus (95% contrast, left top patch) for 500 ms. After either 1000 or 100 ms, participants were then presented with a single patch in isolation (example patches on right) and asked to decide whether the first or second patch had higher contrast. When the first patch was presented with the high-contrast surround, it was made clear to participants that the comparison was between the center patch and the subsequent patch.

high-contrast (95%) annulus of the blob-like shapes (8° diameter). Participants had up to 2000 ms to respond, and there was a 1000-ms intertrial interval.

Participants completed 4 blocks: 2 of the 1000-ms blank period version and 2 of the 100-ms blank period version. One block of each version had the first patch presented in isolation (''no-surround'' condition), and one had the first patch surrounded by a high-contrast stimulus. Participants always completed the no-surround block before the surround block in a particular ISI version, but the order in which they completed the ISI versions was counterbalanced across participants. Within each of the 4 blocks, 180 trials were presented, drawn psuedorandomly from 1 of 5 ''streams,'' where the information used to compute trial types in each stream was kept separate. An adaptive staircase procedure was used to move participants to either 50% (2 streams of 40 trials each) or 79% (2 streams of 40 trials each) accuracy.

One 50% and one 79% stream started with a higher contrast comparison patch (70% contrast), and the other streams started with a lower contrast comparison patch (10%). In the 50% accuracy streams, if participants responded correctly, then the next comparison patch was more similar to the target patch. In the 79% accuracy streams, if participants responded correctly 3 times in a row, then the next comparison patch was more similar to the target patch. In either the 50% or 79% accuracy streams, if the participant responded incorrectly, the next comparison patch was less similar to the target patch. For the first 15 trials, the contrast was changed in increments of 5%; for the next 15 trials, 2.5%; and for the last 10 trials, the increment was 1%. There was also one stream of ''catch'' trials ($N = 20$) in which the comparison patch was always either 70% contrast or 10% contrast. These trials were included to assess the ongoing attention level of participants: If participants are paying attention, they should be nearly 100% correct on these trials.

The task was implemented in E-Prime (version 2.0) and presented using a Dell OptiPlex 960 Minitower with an Intel(R) Core 2 Duo Processor E8400 (3.0 GHz, 6M, 1333 MHz FSB) running Windows XP and a Samsung 2243BWX 22'' DVI Widescreen LCD monitor. In addition, we used Spyder 3 Elite software to calibrate monitors across sites at the start of the study and weekly throughout the course of the study (gamma = 2.2, white point = 6500 K).

Data Analysis

We analyzed the data from the CCE in 3 ways. First, we computed the mean contrast on the last 10 trials of each of the 4 main streams (excluding the catch trials) separately for the 1000- and 100-ms ISI conditions, a very

Table 1. Demographic and Clinical Characteristics of Participants

Variable	Healthy Control (N = 130)		Schizophrenia (N = 132)		Group Comparison
	Mean	*SD*	Mean	*SD*	
Age (in y)	36.89	11.5	39.9	11.6	t = 2.14, P = .034
Gender (% males)	63		55		χ^2 = 1.85, P = .11
Ethnicity (% Caucasian)	55		57		χ^2 = 7.5, P = .37
Personal education (in y)	14.8	2.05	13.3	2.20	t = 5.832, P < .001
Father education	13.0	2.82	13.6	3.59	t = 1.38, P = .17.
Mother education	13.3	2.56	13.3	2.79	t = 0.07, P = .94
Personal SES	38.6	10.3	26.0	9.96	t = 9.97, P < .001
Parental SES	44.4	12.6	42.8	15.2	t = 0.94, P = .35.
BPRS positive symptoms	NA		8.7	4.82	
BPRS negative Symptoms	NA		7.4	2.95	
BPRS disorganized symptoms	NA		5.2	1.83	

Note: SES, Socio Economic Status; BPRS, Brief Psychiatric Rating Scale.

straightforward and simple approach to analysis. The goal of the adaptive staircase streams was to determine the point of subjective equality of the initial patch and the comparison patch. Thus, if the high-contrast surround induces individuals to perceive the center patch as having lower contrast, the final contrast values for the comparison patches in the surround condition should be lower than the final contrast values for the comparison patches in the no-surround condition. Second, we computed the mean contrast for the last 6 reversal trials (with a reversal defined as a change in the contrast level from that presented on the previous trial in that stream) of each of the 4 main streams, as focusing only on reversal trials is more typical in the visual psychophysics literature. We also fit cumulative Gaussian psychometric functions to raw response data and took the estimate of the mean of this function as an estimate of observer ''bias''and the slope of this function (the standard deviation of the fit) as an estimate of observer ''precision.'' Bias (aka ''accuracy'') refers to the stimulus level that leads observers to report that the comparison is higher contrast than the target, 50% of the time, and quantifies how prone observers are to experiencing the illusion (in surround conditions). Precision (aka ''threshold'') refers to the stimulus level that induces observers to report that the comparison was higher contrast than the target 83% of the time and is a measure of observer's reliability at reporting differences between the target and comparison. However, because the results were essentially the same as with the 2 methods above, we present the details of these analyses in the online supplementary figures 1, 2, and 3 along with graphs.

Results

Two hundred and eighty people performed at least one block of the CCE task; 273 performed both bocks of the 100-ms ISI condition (N = 134 controls [CON]; N = 139 schizophrenia patients [SCZ]). Two hundred and sixty-nine people performed both bocks of the 1000-ms ISI condition (N = 134 CON; N = 135 SCZ); 262 performed all 4 blocks (N = 130 CON, N = 132 SCZ). The analyses focus on

Table 2. Results of ANOVAs for Contrast-Contrast Effect Task

ANOVA effect	Mean Contrast on Last 10 trials			Mean Contrast on Last 6 Reversals		
	F Value (*df*)	P	Partial η^2	F Value (*df*)	P	Partial η^2
Group	2.74 (1,260)	.10	.009	2.33 (1,260)	.13	.009
ISI (100 vs 1000 ms)	0.54 (1,260)	.46	.002	0.71 (1,260)	.40	.003
Surround	**88.5 (1,260)**	**.001**	**.254**	**89.8 (1,260)**	**.001**	**.257**
Group × ISI	.22 (1,260)	.64	.001	0.64 (1,260)	.43	.002
Group × surround	**7.27 (1,260)**	**.007**	**.027**	**6.69 (1,260)**	**.01**	**.025**
ISI × surround	**4.38 (1,260)**	**.04**	**.017**	**8.83 (1,260)**	**.003**	**.033**
Group × ISI × surround	0.00 (1,260)	.99	.000	.067 (1,260)	.80	.000

Note: ISI, interstimulus interval. Bold values indicate significant effects in the ANOVAs.

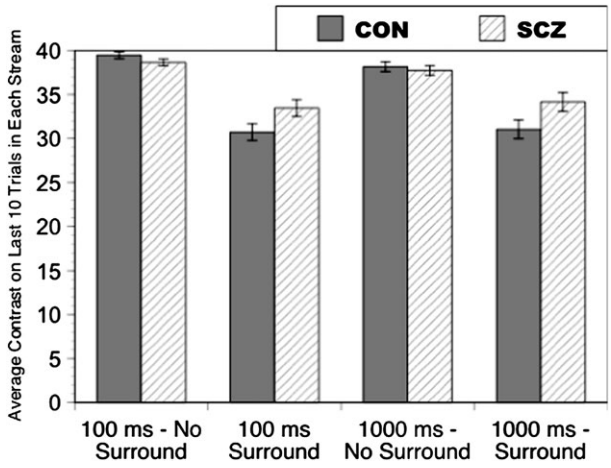

Fig. 2. Graph illustrating the mean contrast of the comparison patch on the last 10 trials of each stream, averaged across the 4 streams, separately for each task condition. Error bars are SEs.

the 262 individuals who completed all 4 blocks (some blocks were missing because of experimenter or equipment error). Demographics for this sample are shown in table 1. Accuracy data for all trials, and just the second half of the trials (when performance should be converging to the targeted levels) are shown in online supplementary table 1. These accuracy data validate the effectiveness of the staircase methods designed to move participants to 50% and 79% accuracy streams respectively. See online supplemental materials for examples of the evolution of contrast levels across the course of trials within each stream.

We began our analyses with the data based on the contrast levels for the last 10 trials in each stream. We used a repeated measures ANOVA with group as a between subject factor, and ISI (100 vs 1000 ms) and surround (no surround and surround) as within subject factors. ANOVA results are shown in table 2. As expected, there was a significant main effect of surround. As shown in figure 2, the point of subjective equality for patient and control subjects was very close to the actual 40% contrast value of the target when no surround was present. However, when the target was surrounded by a high-contrast annulus, the point of subjective equality was a lower contrast value. This finding is consistent with the operation of gain control mechanisms that reduced the perceived contrast of the center patch contrast when it was surrounded by the high-contrast annulus. There was no significant main effect of group, but the expected interaction of group × surround was significant. As shown in figure 2, this group by surround interaction reflected the fact that CON and SCZ did not differ in comparison patch contrast levels in the no-surround condition, but CON had lower contrast levels in the surround condition (ie, a greater illusory reduction in perceived contrast). This finding is consistent with less of an influence of the high-contrast surround in SCZ, leading to more veridical perception of the center patch.

There was also a significant interaction between ISI and surround, reflecting a larger effect of the surround in the 100-ms ISI condition than in the 1000-ms ISI condition. Follow-up analyses indicated lower comparison patch contrast levels in the no-surround condition with a 1000 ms ISI than with a 100 ms ISI ($F_{1,260} = 6.65$, $P < .01$) but no difference between ISIs in the surround condition ($F_{1,260} = 0.57$, $P = .45$). However, there was no significant interaction of group with ISI, and no significant 3-way interaction between group, ISI, and surround. To confirm that the group × surround interaction was present as both ISIs, we computed follow-up analyses separately for the 100 and 1000 ms ISI. The group × surround interaction was significant for both the 100 ms ($F_{1,260} = 6.33$, $P = .01$, $\eta^2 = .024$) and 1000 ms ISIs ($F_{1,260} = 4.69$, $P = .03$, $\eta^2 = .018$), with a slightly larger, though not significantly so, effect size for the 100 ms ISI.

As shown in table 2, results using the mean contrast on the last 6 reversal trials were essentially identical to results with the last 10 trials (see "Methods"). There was a significant main effect of surround, and significant interactions between group and surround, and surround and ISI, but no significant interaction between group and ISI or between group, ISI, and surround. Further, the group × surround interaction was significant for the 100 ms ($F_{1,260} = 6.60$, $P = .01$, $\eta^2 = .025$) ISI, with a trend for the 1000 ms ISI ($F_{1,260} = 3.66$, $P = .057$, $\eta^2 = .014$).

As described in the "Methods," we included a stream of catch trials in the task to assess the attention level of participants because not attending to the trials (eg, "off-task" periods) could also lead to the appearance of reduced surround effects. Not surprisingly, the individuals with schizophrenia ($M = 86\%$, $SD = 13\%$) performed significantly worse than controls ($M = 94\%$, $SD = 6\%$) on these catch trials ($t_{260} = 6.89$, $P < .001$). To examine the influence of off-task performance on surround effects, we recomputed the analyses in 2 ways. First, we used only those participants who scored above chance on the catch trials, an objective threshold for eliminating participants for off-task performance (70% accuracy or above, 14/20 trials correct, $P < .05$ based on a binomial distribution). This eliminated 15 SCZ and 1 CON but did not eliminate the group difference in catch trial performance ($t_{242} = 5.7$, $P < .001$). The group × surround interaction for the mean contrast on the last 10 trials was at trend level ($F_{1,244} = 2.94$, $P = .088$, $\eta^2 = .012$) with these participants removed. However, the group × surround interaction remained significant for the last 6 reversals measure ($F_{1,244} = 2.6$, $P = .011$, $\eta^2 = .011$). Second, we used only those participants who performed at 90% or above on the catch trials, a more stringent criterion. This eliminated 66 patients and 21 controls and strongly reduced the difference between patients ($M = 95.5\%$, $SD = 3\%$) and controls ($M = 96.5\%$, $SD = 3\%$) on catch trial performance ($t_{173} = 2.2$, $P = .03$). The group × surround interaction for the

Table 3. Results of Bootstrapping Comparisons

	SCZ			CON			Group Comparison				
	Mean	Lower 90% CI	Upper 90% CI	Mean	Lower 90% CI	Upper 90% CI	Mean	Lower 90% CI	Upper 90% CI	Effect Size	*P*
100 ms ISI											
All streams	5.21	3.21	7.17	8.76	7.59	9.87	3.55	1.28	5.82	0.31	.014
50% accuracy streams	5.33	2.92	7.67	9.20	7.98	10.40	3.86	1.16	6.64	0.28	.023
79% accuracy streams	5.09	3.23	6.96	8.32	7.00	9.60	3.23	0.95	5.45	0.28	.022
1st comparison patch above 40% streams	4.23	0.27	5.82	8.22	5.36	9.35	3.98	0.93	7.05	0.26	.038
1st comparison patch below 40% streams	6.20	4.37	7.92	9.31	8.14	10.42	3.11	1.05	5.21	0.29	.019
1000 ms ISI											
All streams	3.59	1.52	5.58	7.13	5.52	8.71	3.53	0.86	6.18	0.27	.030
50% Accuracy Streams.	3.88	1.08	6.60	5.33	5.06	8.98	3.16	−0.31	6.74	0.18	.142
79% accuracy streams	3.32	1.60	5.02	7.22	5.61	8.77	3.91	1.70	6.16	0.34	.006
1st comparison patch above 40% streams	3.06	1.44	6.90	7.37	6.80	9.54	4.31	0.79	7.78	0.25	.046
1st comparison patch below 40% streams	4.13	1.97	6.15	6.89	5.4	9.35	2.76	0.19	5.37	0.21	.086

Note: SCZ, schizophrenia patients; CON, controls; ISI, interstimulus interval.

mean contrast on the last 10 trials was again at trend level ($F_{1,173} = 3.10$, $P = .08$, $\eta^2 = .018$) for this subset of participants, and the effect for the last 6 reversals measure was also now at trend level ($F_{1,173} = 3.40$, $P = .08$, $\eta^2 = .019$).

As an alternative way to assess the contribution of off-task performance, we also analyzed the data using regression analyses. We first conducted regressions using diagnostic group to predict surround effects (no surround—surround for mean contrast on last 10 trials). Consistent with the ANOVA results, diagnostic group was a significant predictor of surround effects for both the 100-ms ($\beta = -.15$, $P < .05$) and 1000-ms ($\beta = -.13$, $P < .05$) ISI conditions. We then conducted hierarchical regressions, in which we entered catch trial performance to predict surround effects in step 1, and then diagnostic group as a predictor in step 2, to determine whether diagnostic group continued to account for significant variance in surround effects after accounting for catch trial performance. Catch trial performance was a significant predictor of surround effects for both the 100-ms ($\beta = -.30$, $P < .001$) and 1000-ms ($\beta = -.25$, $P < .001$) ISI conditions. However, diagnostic group no longer accounted for any significant variance in surround effects after accounting for the variance associated with catch trial performance in both the 100 ms (group $\beta = -.05$, $P = .48$) and 1000-ms ISI conditions (group $\beta = -.03$, $P = .61$). The same results were found when analyzing the mean contrast on the last 6 reversals. Together, the analyses provide clear evidence that off-task performance may be an important contributor to reduced CCEs among individuals with schizophrenia.

Each version of the CCE (100 vs 1000 ms ISI) contained 4 independent streams of trials. One critical question is whether the task can be shortened by eliminating some of these streams without a consequent loss of power to detect group differences. To address this question, we used bootstrapping analyses (implemented in SPSS V. 18) with 10 000 replications. To simplify the presentation of these analyses, we computed difference scores of the contrast in the last 10 trials for the no-surround vs the surround condition (see online supplementary tables 2 and 3 for values for each condition individually). A positive value indicated that the comparison patch contrast values were higher in the no-surround vs surround condition, with a larger value indicating more of an influence of the surround. We did this for the mean off all 4 streams, the mean of just the 50% and 79% streams, and the mean of the streams where the first comparison patch was greater than 40% vs less than 40%. As shown in table 3, upper and lower bias-corrected accelerated CIs overlapped for all of these estimates for both the 100- and 1000-ms ISI conditions. Further, in the 100-ms ISI condition, effect sizes for the computations with fewer trials were not appreciably lower than effect sizes for the measure including all streams. This was less true for the 1000 ms condition, where there was more variability in effect sizes across the different measures, with 2 measures (50% accuracy streams only and 1st comparison patch below 40% contrast) producing non-significant group differences. Such results suggest that the data in the 100 ms condition are more stable and that a shorter task with only 2 of the 4 streams may be feasible, a possibility considered further below (One

reaches essentially the same conclusions about shortening the task if analyses are computed with the restricted data set of individuals performing at greater than 70% accuracy in the catch trials: (1) the upper and lower bias-corrected accelerated CIs overlapped for all (30/30 estimates in full data, 28/30 in the reduced data set) of these estimates for both the 100 and 1000 ms ISI conditions; (2) in the 100-ms ISI condition, the effect sizes for the computations with fewer trials were not appreciably lower than effect sizes for the measure including all streams; (3) there was more variability in effect sizes across the different measures within the 1000 ms ISI condition; and (4) we would conclude that the data in the 100 ms condition are more stable and that a shorter task with only 2 of the 4 streams may be feasible.).[1] See online supplementary materials, including Supplementary Table 4, for additional analyses on the correlations between the 2 different streams (1st comparison patch above and below 40%) within each of the 50% and 79% accuracy conditions as a way of assessing reliability.

Discussion

The goal of the current study was to determine if we could develop and implement a version of the CCE that: (1) used a standardized and easily accessible software platform (E-prime); (2) reduced confounds associated with short-term memory (100 vs 1000 ms ISI); (3) included a method to assess attentional or ''off-task'' confounds; and (4) could potentially be presented in a shorter format than typical psychophysical tasks. We will discuss the results in regards to each of these goals in more detail below.

We were able to replicate previous findings in both CON and SCZ using our E-prime version of the CCE task, presented on standard computer and monitor equipment at standard brightness and contrast settings. Control participants showed clear evidence that they perceived the middle patch to be of lower contrast when embedded in the high-contrast surround compared with when the patch was presented in isolation. More importantly, we found a reduction in this effect among individuals with schizophrenia, consistent with reduced operation of gain control mechanisms. However, the magnitude of the effect in the control group alone was smaller than in the previous study by Dakin,[19] and the magnitude of the group difference effect size was rather small (eg, Cohen's $D = 0.31$ in the 100 ms condition) compared with the Dakin study. There are at least 3 factors that could be leading to smaller effect sizes in the current study compared with the Dakin study. First, Dakin used more sophisticated software and equipment and more tightly controlled testing conditions (eg, lighting, etc.), which could have enhanced the magnitude of the CCE effect in controls and allowed greater power to detect reduced CCE effects in patients. Second, we studied stable outpatients to maximize generalizability to the type of participants likely to be included in a procognitive treatment trial. The Dakin et al[19] study used forensic inpatients with schizophrenia, who were presumably more chronically and actively ill than outpatients. Lastly, the present sample was approximately 10 times the size of the Dakin study, and effect sizes tend to be enhanced in small N studies compared with large N studies.[33]

In regard to the second goal, we were able to replicate the findings of the Dakin study (which used a 1000 ms ISI) with a shorter ISI (100 ms) that reduced the potential influence of short-term memory impairments on contrast comparisons. Since there was no apparent decrement in the sensitivity of the task in the 100 ms version, only this version is being used in ongoing test-retest reliability studies in the CNTRACs consortium. We should also note that we were able to obtain significant effects using a simple analysis approach, which was to mean the contrast on the last 10 trials of each stream. This can be easily implemented within the E-prime scripts themselves to provide summary measures.

Of considerable importance in interpreting our results was the inclusion of catch trials with a large contrast difference (70% or 10%) from the first patch (40%) in both surround and no-surround conditions to have a means to assess whether participants were attending to the task. This is critical because if participants are not attending to the stimuli—a possibility in studies of people with schizophrenia—the high-contrast surround will not suppress the perceived contrast of the embedded patch, and this could be mistakenly interpreted as reduced contrast-surround suppression rather than off-task performance. Analysis of the data excluding those participants whose performance was worse than chance and of participants who performed at less than 90% accuracy on these catch trials suggested the strong possibility that off-task performance can contribute substantially to the appearance of reduced contrast-surround effects because the effect size of the group difference was reduced to a trend level effect in the primary analysis with the mean of the last 10 trials. Further, regression analyses using catch trial performance to predict surround effects showed that group no longer significantly predicted surround performance after catch trial performance was entered into the prediction equation. These results are in contrast to the findings of Dakin, who did not find evidence for increased random responding in their sample.[19] Such results with catch trial performance confirm the need to have a method to assess on-task performance in order to validly interpret results as reflecting altered gain control mechanisms compared with more general attentional deficits that may contribute to a wide range of cognitive impairments in individuals with psychiatric disorders.

There are a number of reasons why the individuals with schizophrenia may have shown more evidence of lapses

of attention. One possibility is that some individuals did not understand the task instructions, and responded randomly, though all participants were provided with detailed instructions and practice trials before the start of the task. Another possibility is that some participants became tired during the course of the task and then started to respond randomly or were not attending to the computer screen on some trials. Of course, one of the conundrums raised by these data is the possibility that those individuals with greater attentional lapses also have poorer gain control. If so, "controlling" for attentional effects may eliminate exactly the variance in which one is interested. One example of a mechanism that might lead to such a correlation of attentional and gain control impairments is GABA-ergic deficits because these have been hypothesized to contribute to impairments in the maintenance of goal representations in schizophrenia[34,35] (which might include task representations necessary to guide on-task performance) as well as to impaired surround suppression effects in schizophrenia that contribute to the CCE illusion.[21] However, in the current data set, we did not find significant correlations between CCE task performance and goal-maintenance performance (see ref.[36]). As such, our findings suggest that the need for further research to establish the degree to which patients with schizophrenia show evidence of gain control abnormalities during visual perception independent of the effects of lapses in attention during the performance of this demanding task.

Although the versions of the tasks implemented in the current study were relatively short relative to typical psychophysical tasks (~20 min), they are still longer than ideal for a clinical trial context. Thus, we examined whether using only data from 2 of the 4 streams provided similar effect sizes as the data from all 4 streams. For the 100 ms condition, using only 2 streams resulted in significant group × surround effects that were similar in effect size to the results with all of the data. This suggests that we may be able to reduce the length of the task further, should the results of the test-retest reliability study currently ongoing indicate that dependent measures based on 2 rather than 4 streams provide similar levels of reliability.

In summary, current data provide evidence that one can implement a contrast-surround suppression task such as the CCE to measure gain control using standardized software (E-prime) and standard computer and monitor equipment. The task can be shortened by reducing the ISI to 100 ms without decreasing the effect size of group differences and may be able to be shortened further by eliminating some of the staircase streams if test-retest reliability results support this change. The magnitude of the effect sizes found in the current study were smaller than those in the previous Dakin study but may reflect differences in the testing conditions, the length of the task, and the nature of the patients studied. Furthermore, before taking into account catch trial performance analyses, we replicated prior results showing reduced surround effects among individuals with schizophrenia. However, the analyses of catch trial performance clearly raise the issue of whether reduced surround effects among individuals with schizophrenia are just an artifact of lapses of attention. At the same time, this is just one study (albeit a large one), and we are hesitant to draw absolute conclusions based on the results of a single study. We are currently following up these initial results with a test-retest reliability study. Should the subsequent test-retest reliability study show the same results (and/or poor reliability), then we would not necessarily recommend the task for use in subsequent clinical trials. However, should this subsequent study show good reliability and provide any data to counteract the concerns associated with lapses of attention, then we will have developed an easy to use measure of gain control that could be implemented in studies of both pathophysiology and treatment effects.

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Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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