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Dysregulation of visual motion inhibition in major depression

Daniel J. Norton [a,b,c,*], Ryan K. McBain [d], Diego A. Pizzagalli [b], Alice Cronin-Golomb [a],
Yue Chen [b]

[a] Department of Psychological and Brain Sciences, Boston University, Boston, MA, USA
[b] McLean Hospital, and Department of Psychiatry, Harvard Medical School, Belmont, MA, USA
[c] Massachusetts General Hospital, Boston MA, USA
[d] Department of Global Health and Population, Harvard School of Public Health, Boston, MA, USA

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ABSTRACT

Individuals with depression show depleted concentrations of the inhibitory neurotransmitter GABA in occipital (visual) cortex, predicting weakened inhibition within their visual systems. Yet, visual inhibition in depression remains largely unexplored. To fill this gap, we examined the inhibitory process of center-surround suppression (CSS) of visual motion in depressed individuals. Perceptual performance in discriminating the direction of motion was measured as a function of stimulus presentation time and contrast in depressed individuals (n=27) and controls (n=22). CSS was operationalized as the accuracy difference between conditions using large (7.5°) and small (1.5°) grating stimuli. Both depressed and control participants displayed the expected advantage in accuracy for small stimuli at high contrast. A significant interaction emerged between subject group, contrast level and presentation time, indicating that alterations of CSS in depression were modulated by stimulus conditions. At high contrast, depressed individuals showed significantly greater CSS than controls at the 66 ms presentation time (where the effect peaked in both groups). The results' specificity and dependence on stimulus features such as contrast, size and presentation time suggest that they arise from changes in early visual processing, and are not the results of a generalized deficit or cognitive bias.

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1. Introduction

Perceptual changes in depression represent an understudied and promising area, one that lends itself to addressing a major shortcoming of research on this mood disorder. While progress has been made in understanding major depression at both biological and psychological levels (Sanacora et al., 1999; Kircanski et al., 2012; Belzung et al., 2014; Treadway and Pizzagalli, 2014) there is often a disconnect between biological and behavioral levels of analysis–in part due to the complexity of the phenomena being studied. From a neurobiological perspective, perceptual changes are simpler, and better understood. The visual system in particular may be used as a model to study altered brain function in depression at both levels. Basic perceptual processing deficits, including non-affective stimuli, have been shown in currently and formerly depressed individuals (Golomb et al., 2009; Bubl et al., 2010). In addition, perceptual changes may be important factors in the etiology and maintenance of major depression. For example, depressed individuals gaze disproportionately more at dysphoric stimuli and less at positive stimuli during free viewing or search tasks (Armstrong & Olatunji, 2012).

The present study represents an effort to understand functional consequences of brain changes in depression at a perceptual level. We studied a basic visual process in depression, specifically, an inhibitory process within the visual motion system called center surround suppression (CSS). CSS was chosen because depressed individuals, as well as those who have recovered from depression, show reduced concentrations of gamma-aminobutyric acid (GABA) – the main inhibitory neurotransmitter – in the occipital cortex (Sanacora et al., 1999; Bhagwagar et al., 2008). The established GABA deficit in depression suggests that inhibitory processing within the visual system might be altered, and perhaps more specifically, weakened. Indeed, a previous study on CSS in recovered depressed individuals showed reduced CSS of visual motion in these individuals despite a lack of depressive symptoms (Golomb et al., 2009), but data on currently depressed individuals are not available. CSS is well understood at both the neurobiological and perceptual levels (Born, 2000; Tadin et al., 2003), and holds promise to shed light on how depression-associated brain changes manifest at a perceptual level.

CSS refers to the organization of a neuron's receptive field, or the area of visual space which, when stimulated, causes the
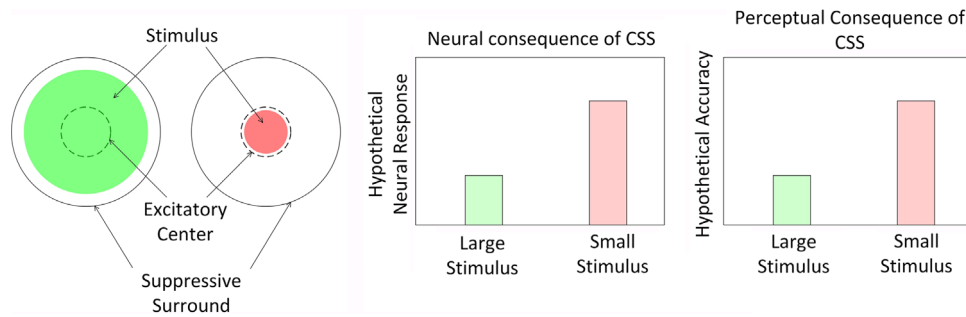
Fig. 1. Illustration of center-surround suppression. The inhibitory process occurs for a variety of stimuli processed in various parts of the visual system. Note that a larger stimulus generates a smaller neural response and lower performance accuracy (i.e., perceptual response).

neuron to respond. If the center portion of the receptive field is stimulated with light, the neuron's firing rate increases, and if the area immediately surrounding this center portion is stimulated, the neuron's firing rate decreases (Hubel and Wiesel, 1959; Born, 2000; Born and Bradley, 2005) (Fig. 1). This visual organization has been well-studied at the cellular level in animals, and at the population level in humans using transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) (Hubel and Wiesel, 1968; Williams et al., 2003; Born and Bradley, 2005; Sincich and Horton, 2005; Moutsiana et al., 2011; Tadin et al., 2011). CSS has also been demonstrated psychophysically: as predicted by the neurobiological mechanisms at work, individuals determine the direction of motion in a small object more easily than in a large one, when both have high contrast (Tadin et al., 2003).

CSS is hypothesized to be sensitive to GABA dysfunction, for several reasons. First, GABA is the primary inhibitory neurotransmitter in the brain, and is thought to play a role in surround suppression (Betts et al., 2005), which is an intrinsically inhibitory process as described above. Second, administration of GABA antagonists has been shown to modulate the size of the surround portion of the receptive field (Pernberg et al., 1998; Murthy and Humphrey, 1999). Third, individuals who have recovered from depression, as well as individuals with schizophrenia, show both depleted GABA levels in occipital cortex, and abnormalities in CSS (Bhagwagar et al., 2008; Golomb et al., 2009; Yoon et al., 2010).

We investigated CSS within the motion processing system, where GABA has been shown to play a key role in making cells selective to direction of motion (Barlow et al., 1964; Grzywacz, 1997), in depression. We aimed to determine whether and how depression is associated with altered inhibitory processing (operationalized using CSS) within the visual system. Based on a previous study in recovered-depressed individuals (Golomb et al., 2009) and findings of diminished GABA levels in occipital cortex in depression (Sanacora et al., 1999), we hypothesized that CSS would be weakened in depressed individuals. Based on prior reports (Churan et al., 2009), we further anticipated that CSS itself would be present in both subject groups only at brief presentation times.

2. Methods

2.1. Participants

Twenty-seven individuals with depression and 22 normal controls participated in the study. Demographic and clinical characteristics of the sample are provided in Table, 1. Depressed participants were diagnosed using the Structured Clinical Interview for DSM Disorders, 4th edition, (SCID-IV; First et al., (2002)), and control participants were screened for Axis I disorders using the non-patient version of the SCID (First et al., 2002). Twenty-two

Table 1
Demographic and clinical information of the sample.

	Control (n=22)	Depressed (n=27)	Test statistic (DF)	p
Age	34.5 (14.8)	40.3 (12.4)	T (47)=1.49	0.14
Education	15.9 (2.1)	16.07 (2.2)	T (47)=0.23	0.82
Gender (M/F)	10/12	11/16	χ^2 (1)=0.11	0.74
WRAT[*]	49.3 (4.9)	50.4 (2.9)	T (40)=0.95	0.35
BDI-II[**]	0.59 (0.85)	29.6 (10.3)	T (47)=13.12	< 0.001

[*] Wide Range Achievement Test Word Reading Score.
[**] Beck Depression Inventory – 2.

of the depressed individuals met full criteria for a major depressive episode at the time of the study, and five met criteria for a major depressive episode in the last year and were in a state of partial remission with significant residual clinical symptoms. Depression levels at the time of testing were assessed using the Quick Inventory of Depressive Symptomatology (QIDS) and Beck Depression Inventory (BDI-II) (Beck et al., 1996; Rush et al., 2003). QIDS data were missing for one depressed individual, and four controls, to whom it was not administered.

None of the depressed participants had a co-morbid diagnosis of any psychotic disorder. There was also no immediate family history of psychotic disorders such as schizophrenia or bipolar disorder with psychosis. Twelve of the depressed participants had co-morbid Axis I disorders (eight anxiety disorders, three eating disorders not including anorexia, and one PTSD), but depression was their primary diagnosis. Eleven of the depressed participants had a past but not current history of alcohol or substance abuse or dependence. Thirteen of them were unmedicated, while 14 were taking antidepressant medications. Of these, 6 were also taking an anxiolytic, and 3 were taking an antipsychotic (aripiprazole) along with a typical antidepressant to achieve autoreceptor activation. The Wide Range Achievement Test (WRAT; Wilkinson (1993)) was administered as a proxy of premorbid intellectual ability, though this score was missing for 7 control subjects who were tested prior to its adoption in the study protocol.

Twenty-two depressed individuals were recruited from McLean Hospital outpatient and partial hospital clinics, while five depressed individuals – as well as all control participants – were recruited via advertisements in the greater Boston community. All participants were fluent English speakers, with no history of neurological diseases or head injuries with loss of consciousness for more than one minute.

2.2. Stimulus and procedures

The stimulus was a drifting Gabor patch shown along with its parameters in Fig. 2. Size and contrast of the stimulus remained constant within a testing block; there were four blocks
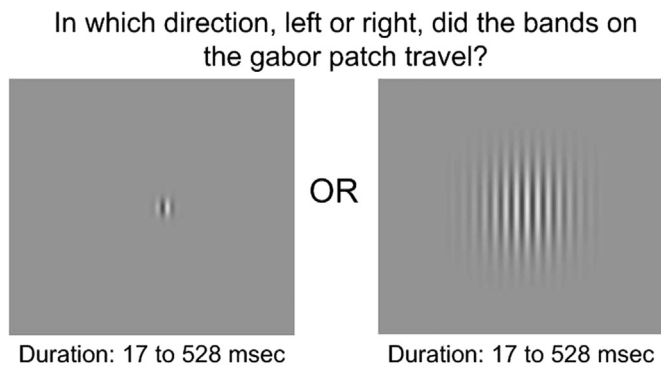
In which direction, left or right, did the bands on the gabor patch travel?

OR

Duration: 17 to 528 msec   Duration: 17 to 528 msec

Fig. 2. Gabor patches were either 1.5° (left panel) or 7.5° (right panel) in radius, presented at one of two contrast levels, low or high, as described in the text. The Gabor patches had a spatial frequency of 1 cycle per degree and drifted leftward or rightward at 2°/sec.

corresponding to the four combinations of size and contrast level. For each block, there were 6 presentation times (17, 33, 66, 132, 264 and 528 ms), 2 directions (left and right) and 4 repetitions, for a total of 48 trials. The stimulus characteristics are illustrated in Fig. 2. The participants' task was to report the direction of motion of the Gabor patch, left or right, by pressing the appropriate arrow button on a standard computer keyboard. Stimuli were programmed using psychophysics toolbox and MatLab (Brainard, 1997) and were presented on one of two 21″ CRT monitors. Twenty-two patients and 10 controls were tested on a Mitsubishi Diamond Pro 2070 sb, mean luminance 47.3 cd/m², which presented the low-contrast stimulus at 3.4% contrast, and the high contrast stimulus at 75.1% contrast. The remaining 7 patients and 12 controls were tested on one of two Hewlitt Packard FP2141sb, mean luminances of 58.4 and 56.2 cd/m²).The maximum contrast values for these two monitors were 4% and 3.8% respectively for the low contrast stimuli, and 81.8% and 79.2% respectively for the high contrast stimuli. All three monitors operated at 120 Hz.

2.3. Data analysis

For each presentation time, performance accuracies were averaged across 4 repetitions and the right and left directions (for a total of 8 trials). Group differences in accuracy for each patch size and contrast were analyzed using mixed model, 2-way analyses of variance (ANOVA). Stimulus presentation time (17, 33, 66, 132, 264, or 520 ms) was the within subjects variable, and group (Control or Depressed) the between subjects variable. For all ANOVAs, if the sphericity assumption was violated, the Huynh-Feldt correction was applied.

The primary measure of CSS was the CSS index. This index was derived by calculating the difference between the accuracies in the small and large conditions, at each presentation time and contrast. The main analysis on these data was a 3-way ANOVA with group (between subjects), contrast and presentation time (within subjects) as factors. In addition, secondary 2-way, mixed model ANOVAs were used to compare depressed and control participants on CSS index at each contrast in their CSS index (across 6 presentation times). The purpose of these secondary analyses was to follow up on the general 3-way ANOVA and examine the nature of the effects at each contrast level.

Finally, for each participant, the thresholds for detection of the direction of motion were calculated to determine the minimum stimulus duration required to adequately perform the task at each condition. These scores were calculated by fitting the data to a Weibull function, which is expressed in the equation: $y = 1 - .5 * e^{(\frac{-x}{a})^b}$ where y is the proportion of trials judged

correctly, x equals the presentation time of the grating, and a and b are two curve-fitting parameters (Norton et al., 2009). The threshold was defined as the minimum presentation time where the accuracy value of the function reached 80%. The purpose of using this metric was for comparison with the previous study on CSS in recovered-depressed individuals, where thresholds were the primary dependent variable (Golomb et al., 2009).

3. Results

3.1. Accuracy

Accuracy results are summarized in Fig. 3a. The results of ANOVA on these data are shown in Table 2.

At high contrast, control and depressed participants did not differ when the Gabor patch was small. When the patch was large, however, a significant interaction between presentation time and group was found (Table 2), owing to lower accuracy at 66 ms in depressed relative to healthy controls ($t_{47}=4.02$, $p < 0.001$). The depressed group performed below chance accuracy in this condition ($t_{26}=4.1$, $p < 0.001$), with the modal response in the depressed group being 25% accuracy.

At low contrast, groups did not differ for the large patch. For the small patch, there was an interaction between group and presentation time driven by depressed individuals' lower accuracy at 66 ms ($t_{47}=2.76$, $p=0.008$).

3.2. CSS index

Center-surround indices are summarized in Fig. 3b. The group x presentation time x contrast level ANOVA on the CSS index revealed a significant triple interaction ($F_{3.6, 171.7}=4.88$, $p=0.001$, $\eta^2=0.09$), indicating that the inhibitory process was modulated in a different way across time and contrast levels in depressed individuals as compared to healthy individuals. Main effects were significant for contrast ($F_{1,47}=6.98$, $p=0.011$, $\eta^2=0.13$) and presentation time ($F_{4.1, 193.3}=11.14$, $p < 0.001$, $\eta^2=0.19$), but not for group ($F_{1,47}=0.39$, $p=.54$, $\eta^2=0.01$). No other interactions were significant (between contrast and group ($F_{1,47}=2.68$, $p=0.11$, $\eta^2=0.05$); between contrast and presentation time ($F_{3.7, 171.7}=1.35$, $p=0.26$, $\eta^2=0.03$); and between presentation time and group: $F_{4.1, 193.3}=0.35$, $p=0.85$, $\eta^2=0.01$). Depressed individuals with and without comorbid Axis I diagnoses did not differ from each other on any of the effects ($p > 0.05$).

To unpack the three-way interaction, a separate ANOVA was performed on the CSS index at low and high contrasts. The results from these analyses are shown in Table 2. At high contrast, depressed individuals showed greater CSS index scores than the control group at intermediate presentation times, especially at 66 ms ($t_{47}=3.39$, $p=0.001$). At low contrast, depressed individuals CS index scores were non-significantly lower than controls at 66 msec (Fig. 3b, $t_{47}=1.53$, $p=0.13$).

3.3. Medication effects

In order to determine whether the results above derive in part from medication effects, we analyzed the depressed participants who were not taking any medications separately and compared them to the control group on three key analyses. Repeating the main analysis on the CSS index with only the unmedicated depressed individuals (n=13), the three-way interaction remained significant ($F_{3.4,114.3}=5.19$, $p=0.001$, $\eta^2=0.14$). Repeating follow-up ANOVAs with just the unmedicated depressed individuals yielded the following results: for the high contrast condition, there was a trend toward an interaction between group and
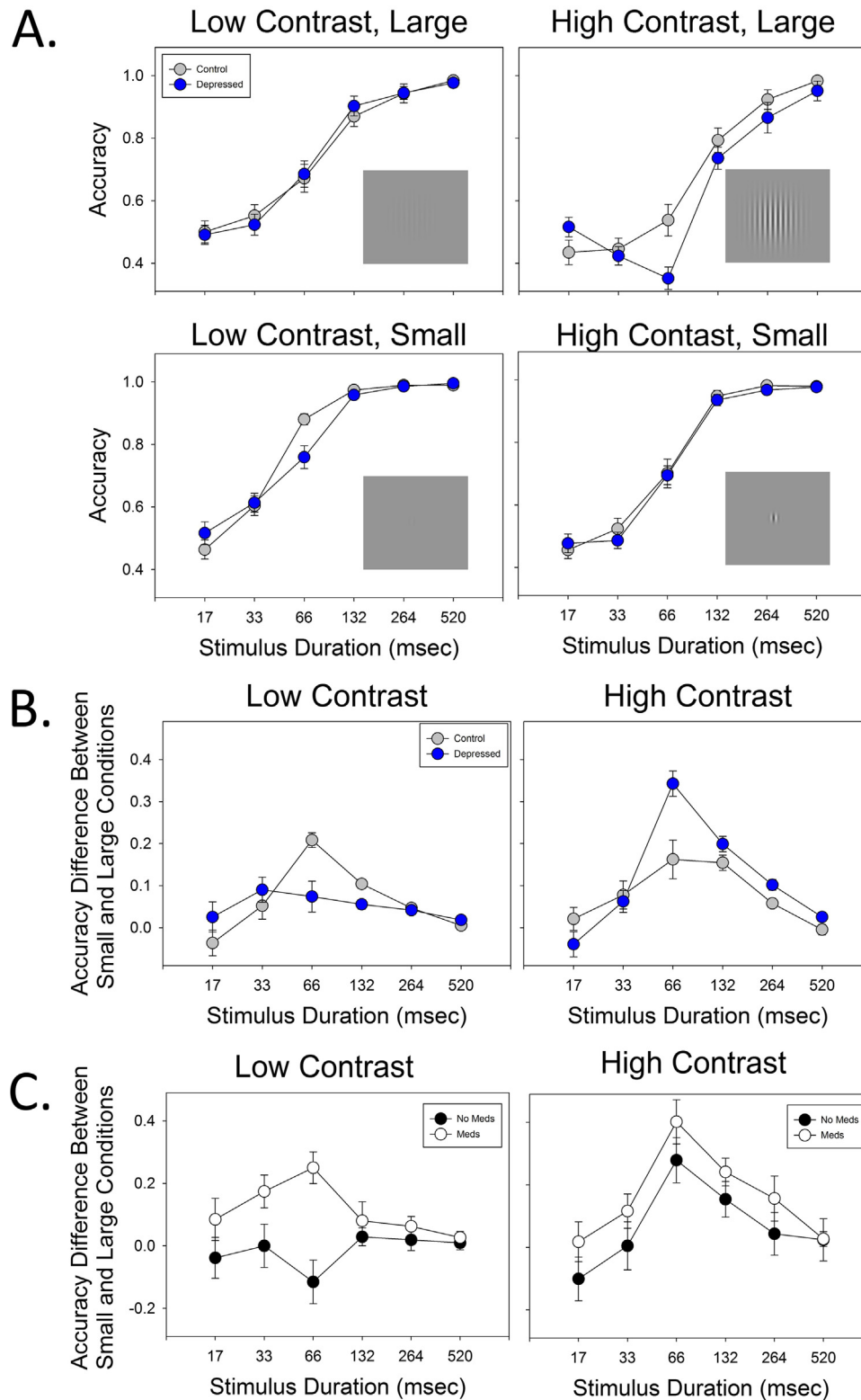
Fig. 3. A. Accuracy data on motion direction discrimination task under small, large, low and high contrast conditions (as labeled). Depressed participants differed significantly from controls on the large, high contrast condition, and the small, low contrast condition. B. Center Surround Suppression (CSS) Index for low and high contrast conditions. Stimulus duration modulated the CSS effect in both conditions, and there was a significant interaction between group and stimulus duration in the high contrast condition. C. CSS Index for depressed individuals taking antidepressant and/or anxiolytic medications and not. Main effect of medication status, and its interaction with presentation time were both significant.

presentation time ($F_{3.5,\ 5.5}=2.23$, $p=0.067$). The main effect was significant for presentation time ($F_5=6.29$, $p<0.001$), but not for group ($F_1=0.04$, $p=0.85$). For low contrast, the interaction was significant ($F_{3.5,\ 115.1}=3.31$, $p=0.018$). The effect of group was

significant ($F_{1,33}=5.02$, $p=0.032$), with depressed individuals showing lower CSS scores than controls, but the effect of presentation time was not ($F_{3.15,\ 114.1}=1.22$, $p=0.31$).

Results of a comparison between depressed individuals taking

Table 2
Summary of analysis by stimulus condition (accuracy and CSS).

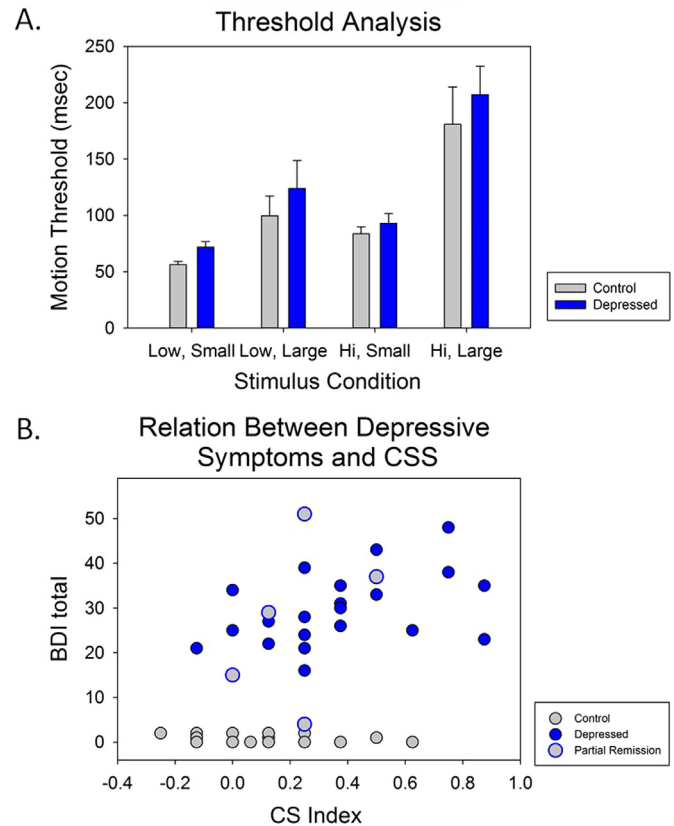| Condition (size, contrast)	Presentation time	Group difference	Interaction
Accuracy: Large, low contrast	$F_{3.88, 182.3}=100.38$ $p<0.001$, $\eta^2=0.68$	$F_{1,47}=0.012$ $p=0.91$ $\eta^2=0.00$	$F_{3.88, 182.3}=0.44$ $p=0.77$ $\eta^2=0.01$
Large, high contrast	$F_{4.1, 194.8}=98.94$ $p<0.001$ $\eta^2=0.68$	$F_{1, 47}=3.36$ $p=0.07$, $\eta^2=0.07$	$F_{4.1, 194.8}=\mathbf{4.42}$ $p=\mathbf{0.002}$ $\eta^2=\mathbf{0.09}$
Small, low contrast	$F_{3.4, 158.2}=165.27$ $p<0.001$ $\eta^2=0.78$	$F_{1, 47}=.67$ $p=0.41$ $\eta^2=0.01$	$F_{3.4, 158.2}=\mathbf{2.95}$ $p=\mathbf{0.029}$ $\eta^2=\mathbf{0.06}$
Small, high contrast	$F_{3.4, 159.1}=185.09$ $p<0.001$ $\eta^2=0.80$	$F_{1, 47}=0.13$ $p=0.72$ $\eta^2=0.00$	$F_{3.4, 159.1}=0.29$ $p=0.86$ $\eta^2=0.01$
CSS index low contrast	$F_{3.7,172.63}=3.27$ $p=0.016$ $\eta^2=0.07$	$F_{1, 47}=0.09$ $p=0.77$ $\eta^2=0.00$	$F_{3.7,172.6}=1.51$ $p=0.21$ $\eta^2=0.03$
CSS Index	$F_{4.2, 200.0}=9.71$	$F_{1, 47}=1.80$	$F_{4.2, 200.0}=\mathbf{3.17}$
high contrast	$p<0.001$ $\eta^2=0.17$	$p=0.18$ $\eta^2=0.04$	$p=\mathbf{0.013}$ $\eta^2=\mathbf{0.06}$

Fig. 4. A. Motion direction discrimination performance as a function of stimulus contrast and size, quantified by duration threshold (minimum durations for which performances reach the 80% correct level). B. Relation between CSS index at high contrast and depressive symptoms (total score on Beck Depression Inventory II).

medications and not taking medications are shown in Fig. 3c. The comparison yielded the following results: At high contrast, the effect of presentation time was significant ($F_{4.4}=10.51$, $p<0.001$) but the effect of medication status was not ($F_{1}=4.19$, $p=0.051$), nor was the interaction between the two ($F_{1}=0.29$, $p=0.90$). At low contrast the effect of presentation time was not significant ($F_{3.7}=0.56$, $p=0.68$), but the effect of medication status was ($F_{1}=15.4$, $p=0.001$), as was the interaction between the two ($F_{1,3.7}=3.37$, $p=0.007$).

3.4. Threshold analysis

Threshold data are shown in Fig. 4a. The threshold data were first analyzed using a three-way ANOVA between group, contrast and size, which revealed main effects for size ($F_{22.1,47}=22.2$, $p<0.001$, $\eta^2=0.32$), contrast ($F_{1,47}=42.1$, $p<0.001$, $\eta^2=0.47$), but not for group ($F_{1,47}=1.18$, $p=0.28$, $\eta^2=0.03$). The only significant interaction was that between contrast and size ($F_{1,47}=11.6$, $p=0.001$, $\eta^2=0.20$). We then conducted two follow-up ANOVAs, one at each contrast level, using stimulus size (within subjects) and group (between subjects) as the independent variables, and threshold as the dependent variable. For the high contrast, there was a significant effect of size ($F_{1,47}=26.47$, $p<0.001$), but not of group ($F_{1,47}=0.64$, $p=0.43$, $\eta^2=0.01$), and there was no size by group interaction ($F_{1,47}=0.13$, $p=0.72$, $\eta^2=0.00$). For the low contrast, there was a significant effect of size ($F_{1,47}=8.9$, $p=0.004$, $\eta^2=0.16$, but there was no effect for group ($F_{1,47}=1.49$, $p=0.22$, $\eta^2=0.03$), nor was there a size by group interaction ($F_{1,47}=0.07$, $p=0.79$, $\eta^2=0.00$).

3.5. Relation between CSS and depressive symptoms

For these correlational analyses, we used the CSS index score at 66msec, where depressed individuals and control participants differed the most. When including all participants, a positive correlation was found between BDI score and the CSS index for the high contrast condition ($\rho_{49}=0.44$ $p=0.001$) (however, the

correlation was not significant when including only the depressed participants ($\rho_{27}=0.30$, $p=0.13$) (Fig. 4b), but not for the low contrast condition ($\rho_{49}=-0.10$, $p=0.50$). The high and low contrast correlations with the BDI differed significantly using Steiger's Z test ($Z_{46}=2.76$, $p=0.006$). Using the QIDS total yielded similar results (high contrast: $\rho_{44}=0.43$, $p<0.01$; low contrast: $\rho_{44}=-0.03$, $p=0.86$). These two correlations also differed significantly ($Z_{41}=2.36$, $p=0.02$).

4. Discussion

This study found that an inhibitory perceptual process, CSS of visual motion, is altered in currently depressed individuals. The nature of this alteration is sensitive to stimulus factors such as contrast and presentation time (as shown by the triple interaction between group, contrast and presentation time for the CSS index). Contrary to our original hypothesis, depressed participants showed greater CSS than controls at high contrast, as evinced by decreased (significantly-below-chance) accuracy in the high contrast condition at the 66 msec presentation time. Presumably this reduced accuracy in the depressed group is due to CSS. What is happening in depressed individuals in this condition may be a visual effect where the suppressive signal from the surround portion of the stimulus actually overpowers the signal from the center, which normally provides the basis for perceptual decisions. For example, in a rightward stimulus, the rightward signal from the center is suppressed so strongly by the surround that the baseline activity of leftward direction neurons outweighs the rightward signal, and forms a basis for perceived direction.

This decrease in accuracy translated to an increase in the CSS

index because depressed individuals showed normal performance on the small high contrast stimulus (consistent with previous studies that found normal performance in depressed individuals on visual tasks; Wesner and Tan, 2006; Zomet et al., 2008). At lower contrast, depressed individuals showed a trend toward *reduced* CSS, which became significant when including only the unmedicated group. The magnitude of the CSS effect in both groups and its alteration in the depressed group were dependent upon the stimulus presentation time, both peaking at 66 ms (Fig. 3). The specific alteration of this inhibitory process appears to reflect a specific pathophysiological effect in the visual system of depressed individuals, which has not been described before. In light of these findings, and of the correlation between CSS and symptoms (Fig. 4b), future studies should evaluate whether the current paradigm could be used as a biomarker of depression or to predict treatment response.

4.1. Altered CSS and the implications of inhibitory neurotransmission

The present results of increased CSS in depression are surprising in light of the previous finding that depressed individuals have decreased levels of GABA in occipital cortex overall (Sanacora et al., 1999; Bhagwagar et al., 2007). If GABA is reduced in the occipital cortex in depression, why would inhibition of a visual process be increased, as we found in the high-contrast condition? There are two potential explanations for this. The first is that the concentration of GABA may not dictate the strength of inhibition at a functional level. As no study has investigated GABA levels and CSS in the same individuals, this interpretation awaits further testing. In line with this suggestion though, a recent study showed normal GABA concentration levels yet reduced visual evoked potential in the occipital cortex of remitted depressive individuals (Shaw et al., 2013). A second explanation is that GABA levels are not actually depleted in the areas critical for this task and perceptual effect. In addition to primary visual cortex, area MT in extra-striate cortex is also critical for the performance of this task (Huk and Heeger, 2000; Tadin et al., 2011). While GABA has been shown to be depleted in the portion of occipital cortex that has been sampled in depression, it may not be uniformly depleted, and perhaps could even be increased in some areas. It is unknown whether GABA in depression is depleted, heightened or normal in area MT.

The results comparing medicated and non-medicated depressed individuals in the present study are also interesting to consider. At high contrast, the medicated and non-medicated depressed individuals differed marginally, and at low contrast they differed starkly. At low contrast, the unmedicated group displayed essentially no CS effect whereas the medicated group showed a strong one (Fig. 3c), on the order of what is seen in the control group (Fig. 3b). This presence of a normal CSS index at low contrast in the medicated group derives from their lower accuracy in the large 3% contrast condition. Despite the medicated subgroup's lower accuracy on the large 3% contrast stimulus, one interpretation of the result-pattern would be that the medications normalize the inhibition effect that should be present in the depressed individuals, but which is absent at low contrast. This result is consistent with the closer-to-normal PERG contrast gain slopes in the medicated group in another study on visual functioning in depression (Bubl et al., 2010).

The co-occurrence of weakened and heightened CSS during visual motion perception has been reported in patients with schizophrenia, who showed increased surround suppression for global motion stimuli (Chen et al., 2008), and decreased surround suppression for local motion stimuli like the ones used in the present study (Tadin et al., 2006). Contextual effects of surrounding contrast upon a central stimulus have also been shown

to be weakened in this patient group (Yang et al., 2013). Like depression, schizophrenia also implicates GABAergic processes (Benes 2000). However, the effects of contrast and presentation time upon CSS of motion have not been studied in schizophrenia in a systematic way. It will be useful to determine whether stimulus-condition-dependent dysregulation of inhibitory process may be a plausible mechanism for abnormal visual processing across multiple psychiatric disorders.

4.2. Comparison of CSS between depressed individuals and those in remitted depression

The present results stand in contrast to those from a previous study by Golomb et al. (2009). At high contrast, Golomb et al. found weakened CSS in non-depressed individuals who had recovered from previous depressive episodes. The present study found heightened CSS in currently depressed individuals. There are two potential, not mutually exclusive, explanations for the discrepancy.

One explanation is that the visual inhibition for high contrast stimuli substantially changes depending on depressed state (from down-regulated to up-regulated, as depression goes from remitted to acute state). The significant correlation between the QIDS/BDI depression index and CSS in this study, and opposite directions of CSS alteration in Golomb et al. and the present study, are both consistent with this possibility.

Another explanation is that the spatial and temporal characteristics of the stimuli differed between the two studies. The present study systematically varied presentation time, allowing the dynamic temporal profile of the CSS effect to be revealed in depressed individuals (and in control participants). Heightened CSS was found only around the 66 ms stimulus presentation time and diminished at presentation times at and beyond 132 ms. The study by Golomb et al. used a QUEST staircase procedure (Watson and Pelli, 1983), which does not allow comparison of performance at particular presentation times across subjects. Overall though, the average threshold in that study was longer than 66 ms, meaning that the CSS effects were generally acquired at longer presentation times (around 150 ms for the large, high contrast stimulus). It is unknown what Golomb and colleagues would have found had they systematically collected data on large, high contrast stimuli in the vicinity of 66 msec. The dependence of the effect on temporal factors of the stimulus underscores the likelihood that it arises from early visual processing areas in the brain, rather than higher order cognitive areas.

Both the present study and Golomb et al. found deficient performance in the depressed group at low contrast in the small stimulus condition. This is the condition where motion signals are the weakest, and therefore it may be the most sensitive to uncover problems in detecting the direction of motion, regardless of CSS processes which should not have significant influence in this condition. Since computing the direction of motion also involves GABAergic processing (Thiele et al., 2004), it may be that GABA depletion is responsible for the poor ability to discriminate direction of motion in the small low contrast condition.

4.3. Limitations and future directions

The present study had a limited sample size. If the results are replicated, the paradigm used here will be a powerful one for measuring inhibitory processing at a functional level in depression and other disorders. Moreover, a systematic study of the effect of antidepressant and anxiolytic medication on visual motion inhibition would be informative, though the main result of this study (3-way interaction between group, contrast and presentation time) remained significant when only including unmedicated

depressed individuals. Therefore, the result seems to be intrinsic to depression itself, not medication status. In magnetic resonance spectroscopy studies, antidepressant medications have been shown to increase GABA levels in depressed individuals (Sanacora et al., 2002, 2006), whereas cognitive behavioral therapy appears to decrease GABA levels in depressed individuals (Sanacora et al., 2006). Both therapies are equally effective at mitigating depression, but apparently have very different effects upon neurotransmitter concentrations, raising the question of the effect that these treatments might have upon motion processing in general and CSS in particular. In order to strengthen the link between biological and psychological levels of understanding of inhibitory processing in depression, the present study should be repeated while measuring GABA levels in the depressed individuals being studied, perhaps while also administering GABAergic medications to some participants.

Depressed individuals showed reduced accuracy in the high contrast large condition, and the low contrast small condition. One interpretation of this would be that these are the two most challenging conditions perceptually (faint and small, and high-inhibition due to CSS), and the altered performance in depressed individuals arose from a lack of concentration or general deficit on these challenging conditions. However, this interpretation is problematic, since all four conditions involved difficult presentation times which required subjects to guess on roughly half of the trials. If extent of challenge were a factor in depressed individuals' deficient accuracy, we would expect to see a consistent deficiency in their performance on the difficult trials (short presentation times) on each of the graphs in Fig. 3a, but this is not the case. The specificity of the alterations in depression, and their dependence on stimulus parameters suggest an abnormality in visual inhibitory process rather than a generalized perceptual or attentional deficit.

The present study used stimuli which differed slightly from previous ones (Tadin et al., 2003; Golomb et al., 2009). The small stimuli were slightly larger, and the low-contrast stimuli had slightly higher contrast than in previous studies. A second difference between ours and previous studies is that the original paper by Tadin on CSS, as well as others that replicated it, used a pause of 1500 ms while viewing a flickering fixation cross, followed by a 500 ms blank screen before the stimulus was presented. After stimulus presentation we showed a blank screen during subjects' response, and kept the screen blank until the next stimulus was presented, 1000 ms after the button press indicating the subject's answer. We made these adjustments for the sake of time, and because we anticipated that larger, higher contrast stimuli would be less discouraging and easier to concentrate on for depressed participants. We did not anticipate that these spatial and temporal changes would affect the results, based on the known patterns of performance in healthy adults (Tadin et al. 2003). However, they might have been responsible for the presence of a CSS effect in healthy controls at low contrast in the present study. Interestingly, this unexpected result in the control group allowed an interesting effect to emerge in the depressed group namely that unmedicated depressed individuals did not show CSS at low contrast, but medicated depressed individuals did. Finally, the use of multiple monitors may have potentially added noise to the data, and therefore, the degree to which CS suppression occurred. The results for the high-contrast condition unlikely varied from monitor to monitor here, since the CS suppression effect is robust across a much wider range of contrasts than those we used for our high-contrast stimulus (Tadin et al., 2003). Note that the main results of the study, the three way interaction between contrast, presentation time and group for the CS effect, and the interaction between group and presentation time at high contrast, remained significant if the 12 controls and 5 patients tested on the HP monitors were removed from the analysis, suggesting that the main finding of this study stands with use of a single monitor.

4.4. Conclusion

In combination with the results from Golomb et al. (2009), the present results suggest that a basic visual inhibitory process, as indexed by CSS, changes in a very pronounced way as individuals fluctuate from the acutely depressed state (heightened CSS at high contrast) to the recovered state (weakened CSS at high contrast). If confirmed, CSS represents a promising state marker of depression, which is unaffected by baseline (general) performance deficits associated with this psychiatric disorder. The results suggest that studying the visual system, particularly across perceptual conditions with strong physiological correlates, in depression may be a valuable endeavor.

DJN and YC developed the study concept and design. Subject recruitment, testing and data analysis were performed by DJN under the supervision of YC, DAP and ACG. DJN drafted the paper, and RKM, ACG, DAP and YC provided critical revisions. All authors approved the final version of the paper for submission.

5. Disclosure

Over the past three years, Dr. Pizzagalli has received honoraria/consulting fees from Ono Pharma USA, Otsuka Pharmaceutical, Pfizer, and Servier for studies unrelated to this project.

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