Research Paper

Reduced visual contrast suppression during major depressive episodes

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Background: Previous studies have suggested that processing of visual contrast information could be altered in major depressive disorder. To clarify the changes at different levels of the visual hierarchy, we behaviourally measured contrast perception in 2 centre-surround conditions, assessing retinal and cortical processing. **Methods:** As part of a prospective cohort study, our sample consisted of controls (n = 29; 21 female) and patients with unipolar depression, bipolar disorder and borderline personality disorder who had baseline major depressive episodes (n = 111; 74 female). In a brightness induction test that assessed retinal processing, participants compared the perceived luminance of uniform patches (presented on a computer screen) as the luminance of the backgrounds was varied. In a contrast suppression test that assessed cortical processing, participants compared the perceived contrast of gratings, which were presented with collinearly or orthogonally oriented backgrounds. **Results:** Brightness induction was similar for patients with major depressive episodes and controls (p = 0.60, d = 0.115, Bayes factor = 3.9), but contrast suppression was significantly lower for patients than for controls (p < 0.006, d = 0.663, Bayes factor = 35.2). We observed no statistically significant associations between contrast suppression and age, sex, or medication or diagnostic subgroup. At follow-up (n = 74), we observed some normalization of contrast perception. **Limitations:** We assessed contrast perception using behavioural tests instead of electrophysiology. **Conclusion:** The reduced contrast suppression we observed may have been caused by decreased retinal feedforward or cortical feedback signals. Because we observed intact brightness induction, our results suggest normal retinal but altered cortical processing of visual contrast during a major depressive episode. This alteration is likely to be present in multiple types of depression and to partially normalize upon remission.

Introduction

During the last decade, several studies have investigated abnormal retinal and cortical visual processing in major depressive disorder (MDD). Retinal processing in MDD has been assessed using pattern electroretinogram (PERG; for reviews, see Schwitzer and colleagues[1,2]), and some studies revealed that the slope of the increase in PERG signal amplitude as a function of contrast is lower in people with MDD than controls, suggesting reduced retinal contrast gain in people with MDD.[3] Lower retinal gain indicates that a weaker contrast signal is being sent from the retina to the cortex and it may cause changes in perceptual experience. Physiologic changes in retinal processing have been associated with elevated contrast-detection thresholds measured with behavioural tests;[4] this abnormality returned to normal after successful therapy intervention.[5] However, some studies have not revealed a difference in PERG findings, although participant groups differed in contrast sensitivity.[6] Cortical electroencephalogram (EEG) responses to checkerboard stimuli at occipital electrodes was also reduced in patients with MDD compared to controls.[7] The lower PERG and EEG amplitudes and higher contrast-detection thresholds suggest that the subjective perceptual experience is also changed in MDD. However, the subjective perception of contrast in MDD has not been assessed before. In addition to contrast perception, other changes in visual processing have been reported in MDD. Two studies that used behavioural measurements to evaluate the cortical processing of visual motion and contour integration found increased suppression of visual motion[8] and decreased integration of nearby collinear elements[9] in people with MDD.

The physiology and neural processes of the visual system have been extensively studied and are well known; as a result, studying changes in patients' visual processing might provide insights into the neural mechanisms of MDD. Concentration of neurotransmitters, neural plasticity and connectivity to other areas differ in the retinal and cortical circuits; characterizing deficits at different levels of processing might have implications for our understanding of the causes and treatment

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of MDD. Although the literature suggests that visual processing may be altered in MDD, whether the deficit is in retinal or cortical processing (or both) is not yet fully understood. A purely retinal deficit would indicate more local changes in the processing of visual information; a cortical deficit could indicate more widespread abnormality.

Visual contrast perception can be understood as a hierarchical sequence of normalization processes that discount environmental variability and optimize neural processing.[10] In the retina, the centre-surround organization of the receptive fields of ganglion cells[11] discounts the effect of prevailing luminance and enables lightness constancy. This process enhances the role of contrast borders and is perceptually visible in several visual illusions, such as simultaneous contrast, in which identical central patches appear different in lightness or brightness because of different border contrasts between the centre and the surround.[12–16] This effect of surround luminance on brightness is often referred to as brightness induction; it occurs before binocular fusion and is found immediately after congenitally blind vision has been surgically restored.[16] Reduced retinal contrast gain in MDD could lead to reduced strength of the brightness induction illusion.

In the primary visual cortex, the neurons optimally respond to contrast patterns at a certain orientation and at a certain spatial scale.[17–19] In addition, neural activity is divided by the pooled activity of the surrounding neurons, causing surround suppression.[20–23] When a small luminance-modulated patch is embedded on a larger, similarly modulated patch with higher contrast, surround suppression is visible in reduced perceived contrast of the central patch.[24] Importantly, contrast suppression is specific to orientation; there is no suppression if the centre and surround have orthogonal orientations. This suggests a cortical component of the surround effect, because the primary visual cortex is the first level of the visual processing hierarchy to contain orientation-specific mechanisms. Therefore, surround suppression involves 2 components — retinal feedforward and cortical feedback signals — that have different thresholds and gains. In MDD, both reduced retinal contrast gain and changes in cortical processing could change the strength of the contrast suppression illusion.

The findings of electrophysiological and behavioural assessments of contrast perception in MDD have been inconsistent, and most previous behavioural studies have measured contrast detection at threshold. In the present study, we assessed the subjective perceptual appearance of contrast patterns. Furthermore, the retinal and cortical processing of contrast has not been compared in the same sample of patients. To clarify the role of different levels of contrast processing during major depressive episodes (MDEs), we undertook psychophysical measurement of the amount of brightness induction and contrast suppression in patients experiencing an MDE and compared those to the contrast perception of control participants. Because brightness induction appears to be linked to low-level visual processing (e.g., retinal ganglion cells) and contrast suppression includes an orientation-specific cortical component, we can assess contrast processing behaviourally at different levels of the visual hierarchy. Understanding changes in visual processing may provide insight into putatively abnormal cortical information processing during MDEs and open up opportunities to develop easily accessible biomarkers for changes in visual processing in depression. We also replicated the contrast tests in a follow-up measurement at 7 months and tested whether contrast test scores normalized upon remission of the depression.

Methods

Participants

Patients were recruited from Helsinki City psychiatric outpatient facilities. Briefly, we first screened 1655 referrals of patients (2013 to 2016) with a probable MDE. Based on stratification by probable principal diagnosis, we then interviewed 155 patients and recruited 124 patients who fulfilled all of the inclusion criteria (score ≥ 15 on the Montgomery–Åsberg Depression Rating Scale [MADRS]; age 18–50 years) and none of the exclusion criteria. For more details of the recruitment process, the inclusion and exclusion criteria, and detailed statistics, please see Söderholm and colleagues[25] and Socada and colleagues.[26] We further excluded 13 patients because they did not successfully complete the visual contrast tests. Altogether, we assessed 111 patients and 29 controls. We tested 74 patients again in follow-up measurements after 7 months.

The MDE patient group was divided into 3 subcohorts according to their principal diagnosis: unipolar MDD (n = 46); bipolar disorder with a current MDE (n = 38); and borderline personality disorder with a current MDE (n = 27). Diagnoses of unipolar MDD and bipolar disorder were based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I); diagnosis of borderline personality disorder was based on the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II). We found excellent inter-rater reliability (κ 0.898–1.0) in videotaped interviews.

In addition to the MADRS, other measures used included the Social and Occupational Functioning Assessment Scale, the Young Mania Rating Scale and modification of the bipolar specifier.[27] We assessed symptoms of borderline personality disorder using the Borderline Personality Disorder Severity Index-IV.[28] Patients completed several self-rating scales, including the Alcohol Use Disorders Identification Test, the Beck Depression Inventory II, the Beck Hopelessness Scale, the Overall Anxiety Severity and Impairment Scale, the McLean Screening Instrument for Borderline Personality Disorder and the SCID-II screen. Inclusion criteria included no uncorrected hearing or vision impairment.

Control participants were health care services personnel from the City of Helsinki; most were nurses. Controls were demographically matched to the patients. They were interviewed using SCID-I and the SCID-II borderline personality disorder section. The inclusion criteria for controls were as follows: age 18–50 years, sufficient proficiency in the Finnish language and no uncorrected hearing or vision impairment. The exclusion criteria for controls were as follows: a lifetime MDE, bipolar disorder, any current psychiatric disorder,

a substance use disorder, any current excessive substance use (alcohol or recreational drugs), or current use of any psychopharmaceuticals.

Written informed consent was collected from each patient and control participant. The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District and the research board of the Health and Social Department of the City of Helsinki.

Stimuli

The stimuli were simple visual patterns presented in centre-surround organization. In the brightness induction test, an unmodulated luminance patch was surrounded by a larger unmodulated background with lower or higher luminance than the centre patch (Figure 1, top). The centre and surround had a small (low Weber contrast, 5%) or large (high Weber contrast, 30%) differences in luminance. In the contrast suppression test, the sine-wave modulated luminance patch was surrounded by a larger, similarly modulated surround, or it was presented without a surround. The surround had high contrast (60% Michelson contrast) and was either collinear or orthogonal relative to the centre patch (Figure 1, bottom), which always had low contrast (20% Michelson contrast). The stimuli were displayed on a laptop computer (HP Probook 4540, 15.6-inch LED, resolution 1366 × 768) with equal screen resolution and brightness settings in standard office lighting.

Procedure

The perceived luminance and perceived contrast of the stimuli were measured using a standard 1-interval 1–1 adaptive staircase method with a 2-alternative forced-choice task (for a similar method, see Schallmo and colleagues[29]).

During each trial of the brightness induction test, participants saw a pair of unmodulated centre-surround stimuli and were required to choose which centre patch (left or right) appeared brighter. Two series were randomly interleaved: a test patch on a darker surround was kept constant and the comparison patch on the lighter surround was varied; or a test patch on a lighter surround was kept constant and the comparison patch of the darker surround was varied. The light or dark surround was randomly positioned on the left or right

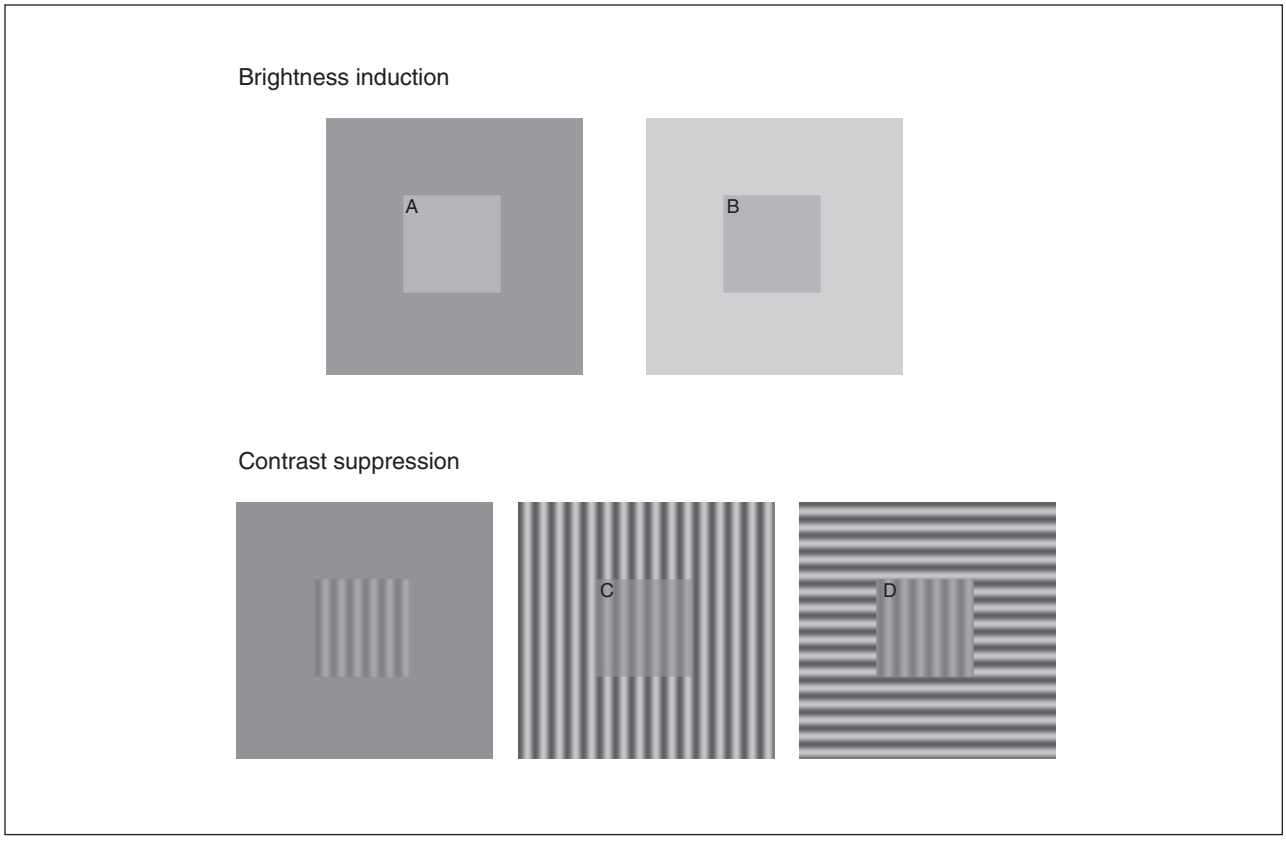

Fig. 1: Brightness induction and contrast suppression tests. Top: Brightness induction refers to the effect of surround luminance on centre brightness (i.e., perceived luminance). The centre patches A and B are equal in luminance, but they appear different in brightness because of the difference in background luminance. A dark background enhances brightness; a bright background decreases brightness. Bottom: Contrast suppression refers to the effect of background on the apparent contrast of the centre. The centre patches C and D have identical contrast, but the contrast of C appears to be reduced or suppressed because of the collinear background. The contrasts of the backgrounds are identical, and only the orientation relative to the centre grating is different.

side of the display. After each "brighter" response, the luminance of the comparison patch was decreased (3%), and after each "darker" response, the luminance was increased (3%).

In the contrast suppression test, participants were asked to choose the patch that appeared to be higher in contrast. A test patch was embedded in a collinear or orthogonal surround, and a comparison patch was presented without a surround. The test and comparison patches were always in vertical orientation. The test and comparison stimuli appeared randomly on the left or right side of the display. Each "higher" response decreased (3%) the contrast of the comparison patch, and each "lower" response increased (3%) the contrast of the comparison patch.

Because of the adaptive method in both tests, the perceived luminance or contrast of the centre patches became perceptually indistinguishable and reached the point of subjective simultaneity, in which the participant could not tell the difference between the patches. We used these points of subjective simultaneity as a measure of perceived contrast. Both tests contained 4 blocks (2 repetitions of low or high and collinear or orthogonal conditions) measured in random order. Each block contained 30 trials. The procedure included 8 measurement series in total, each containing 15 trials. Brightness induction and contrast suppression were measured at baseline for both patients and controls. Most patients repeated the measurements at follow-up (31 weeks after the baseline assessment, on average). This was an observational study, and participants in the patient group received their usual psychiatric outpatient treatment between measurements.

Data analysis

We calculated the mean of the last 4 trials for each series and used it as the measure of perceived contrast or luminance. We calculated the strength of brightness induction as the difference of the perceived luminance of the test patches embedded in the light and dark surround divided by the sum of the perceived luminance of the patches (Figure 1; [A−B]/[A+B]). The strength of contrast suppression was similarly calculated as the difference of the perceived contrast of the test patches embedded in the collinear and orthogonal surround divided by the sum of the perceived contrasts of the test patches (Figure 1; [D−C]/[D+C]). Patient outliers (those with contrast suppression or brightness induction more than 3 standard deviations above or below the mean of all patients) were excluded from the analyses. We found 7 outlier data points at baseline (6 in brightness induction and 1 in contrast suppression tests) and 4 outliers at follow-up (all in brightness induction tests). No control data were excluded as outliers.

We tested the differences between subgroups (controls and patients, comorbid diagnoses, medication and remission [no MDE criterion symptoms] at follow-up) using the χ^2 test, the 2-sample Welch t test, the Bayesian t test and analysis of variance. We used the Welch t test because it takes into account unequal sample sizes. Although the diagnostic subgroups did not differ significantly from controls in terms of sex distribution, we adjusted the test scores for age and sex because we found some trends for differences. We adjusted the brightness induction and contrast suppression scores by conducting 2 linear regression analyses, using age and sex as explanatory variables and the residuals of the analyses as adjusted scores. We conducted a linear regression analysis to test whether the contrast suppression score was associated with age, sex, comorbid disorders or personality traits. We also performed 2 linear regression analyses to test the effect of different medications on brightness induction and contrast suppression. In these analyses the explanatory variables were age, sex and medications.

Results

Participant characteristics are shown in Table 1. As noted above, we assessed 111 patients and 29 controls at baseline, and we tested 74 patients again in follow-up measurements after 7 months. We found no differences between groups in terms of race or sex, but the education level of controls was slightly higher, and their employment status was better (100%, v. 27%). We measured perceived contrast with 2 centre-surround tests. We observed no differences between patients and controls in the brightness induction test ($t_{39.8} = 0.534$, $p = 0.60$, $d = 0.115$; Figure 2A), but we did observe a highly significant difference between groups in the contrast suppression test ($t_{35.2} = 2.902$, $p = 0.006$, $d = 0.663$; Figure 2B). Contrast suppression was reduced in patients compared to controls; the strength of the illusion was lower for patients than for controls, and patients saw the stimuli as more veridical than controls did. To further confirm that this finding was due to suppression in the collinear condition and not to enhancement in the orthogonal condition, we compared the perceived contrast in these conditions separately. The groups differed significantly in the collinear condition ($t_{131} = 2.80$, $p = 0.006$), but not in the orthogonal condition ($t_{131} = 1.55$, $p = 0.12$), confirming the main results. Because the probability of the null hypothesis (a similar result between groups in brightness induction) could not be assessed with frequentist statistics (such as t tests), we conducted Bayesian t tests for group differences. Bayesian statistics further supported the results, and the Bayes factor (BF) provided positive evidence for similar results in the brightness induction test ($BF_{01} = 3.9$) and strong evidence for difference in the contrast suppression test ($BF_{10} = 35.2$). These findings further confirmed that patients saw the brightness induction illusion (Figure 2A) similarly to controls but saw the contrast suppression illusion (Figure 2B) more veridically than controls. Because contrast suppression illusion depends on orientation (and this involves cortical computation) but the brightness induction illusion does not, our results suggest that patients and controls did not differ in the processing of contrast signals, but they did differ in how the contrast signal was processed or normalized in the visual cortex.

The differences between the 2 tests were the stimulus (uniform patch v. modulated patch) and the perceptual task. Specifically, in the brightness induction test participants compared brightness, and in the contrast suppression test they compared contrast. All other aspects of the tests, as well as the overall structure, were identical. Both tests included a

Table 1: Participant characteristics

Characteristic	Patients				Controls
	Total	Major depressive disorder	Bipolar disorder	Borderline personality disorder	
Patients, *n*					
Baseline	111	46	38	27	29
F/M	74/37	27/19	27/11	20/7	21/8
Follow-up	74	33	24	17	—
Sex					
χ^{2*}	—	3.75	0.60	0.37	—
p value	—	0.053	0.44	0.54	—
Age, yr, mean ± SD	—	31.8 ± 10.1	32.0 ± 9.3	28.0 ± 7.3	32.1 ± 9.0
t†	—	$t_{62.0} = 0.30$	$t_{58.1} = 0.22$	$t_{53.0} = 1.63$	—
p value	—	0.76	0.83	0.11	—
MADRS score, mean ± SD	—	24.0 ± 6.2	21.7 ± 7.0	22.2 ± 6.5	2.3 ± 3.5
t†	—	$t_{76.0} = 19.6$	$t_{65.5} = 15.6$	$t_{46.7} = 15.1$	—
p value	—	< 0.001	< 0.001	< 0.001	—
YMRS score, mean ± SD	—	1.70 ± 2.66	3.44 ± 3.70	3.55 ± 2.62	0.74 ± 1.61
t†	—	$t_{73.94} = 1.97$	$t_{62.0} = 4.20$	$t_{50.64} = 4.99$	—
p value	—	0.053	< 0.001	< 0.001	—

F = female; M = male; MADRS = Montgomery–Åsberg Depression Rating Scale; SD = standard deviation; YMRS = Young Mania Rating Scale.
*χ^2 test difference versus controls.
†*t* test difference versus controls.

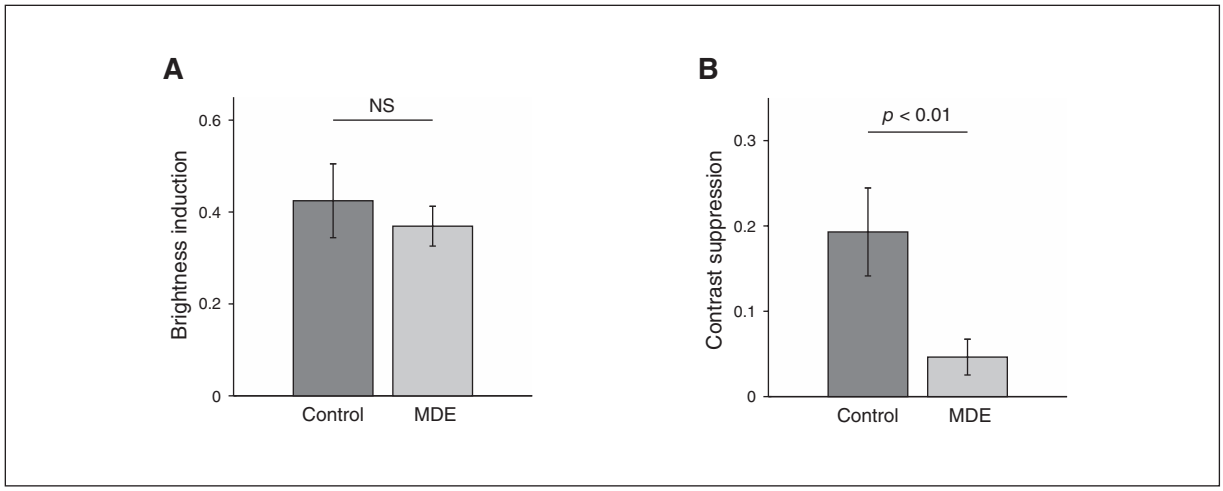

Fig. 2: (A) We observed no difference in brightness induction between patients experiencing an MDE and controls (i.e., the perceptual difference between patches A and B in Figure 1 was similar for both groups). (B) We observed a highly significant difference in contrast suppression between patients experiencing an MDE and controls (i.e., the perceptual difference between patches C and D in Figure 1 was larger for controls than for patients). Error bars depict standard errors of the mean. MDE = major depressive episode.

comparison of 2 patches of the same size on the same display; the same number of trials and blocks; and an identical adaptive staircase method. Therefore, because patients and controls performed similarly in the brightness induction test, we could exclude all general and cognitive differences between groups (such as age, intelligence and vigilance) as causes for the specific difference in contrast suppression. We further confirmed this finding with a linear regression analysis, which failed to explain the variance in contrast suppression using age, sex, patient subgroups, medication, alcohol consumption and the big 5 personality traits (extroversion, conscientiousness, openness, agreeableness and neuroticism; $F_{11,80} = 1.105$, $p = 0.37$, $R^2 = 0.132$). In the nonsignificant model, only the use of mood stabilizers ($p = 0.02$) was associated with contrast suppression scores.

To further test the effect of medication and diagnosis on the amount of brightness induction and contrast suppression, we divided the patient group into 3 diagnostic subgroups

and compared those with the control group. We found no significant differences between the diagnostic subgroups (brightness induction: $F_{2,104} = 1.014$, $p = 0.37$; contrast suppression: $F_{2,107} = 1.043$, $p = 0.36$), showing that in all subgroups brightness induction was intact (Figure 3A, top) but contrast suppression was reduced (Figure 3A, bottom). We further confirmed this finding in pair-wise t tests comparing the patient subgroups and controls (brightness induction: borderline personality disorder $t_{50} = –0.19$, $p = 0.85$, bipolar disorder $t_{62} = 1.14$, $p = 0.26$, MDD $t_{67} = 0.28$, $p = 0.78$; contrast suppression: borderline personality disorder $t_{52} = 2.66$, $p = 0.01$, bipolar disorder $t_{62} = 2.71$, $p = 0.009$, MDD $t_{71} = 2.06$, $p = 0.04$).

We also divided the patient group into 3 subgroups based on their medication use (Table 2) and compared those subgroups with patients taking no medication. The 3 medication subgroups partially overlapped because many patients were taking multiple medications. The correlations between groups were as follows: mood stabilizer and antipsychotic $r = 0.188$, $p = 0.037$; mood stabilizer and antidepressant $r = –0.019$, $p = 0.84$; antipsychotic and antidepressant $r = –0.152$, $p = 0.09$. Only the use of mood stabilizers had a small but significant effect ($F_{1,104} = 6.024$, $p = 0.016$, $\eta^2 = 0.053$) of increasing brightness induction (Figure 3B, top) and further decreasing contrast suppression (Figure 3B; bottom). However, in pairwise comparisons the effect of mood stabilizers was not significant (contrast suppression: $t_{17.26} = –2.095$, $p = 0.051$; brightness induction: $t_{16.46} = 1.269$, $p = 0.22$), although we did observe a trend for contrast suppression. In a linear regression analysis, the use of lamotrigine, valproate or pregabalin was associated with increased brightness induction; the use of valproate, lamotrigine or pregabalin was associated with decreased contrast suppression (Table 2, β coefficients).

Most of the patient group ($n = 74$) replicated the contrast tests in a follow-up measurement. Approximately half of the patients were in remission (no MDE criterion symptoms) at the end of follow-up (borderline personality disorder 52.2%, bipolar disorder 60.6%, MDD 56.4%). To assess the recovery of contrast perception, we calculated the change in test scores for brightness induction and contrast suppression by subtracting the baseline scores from the follow-up scores, and we compared these to the change in MADRS scores. The correlation between MADRS score and change in brightness induction was as follows: $r_{67} = 0.073$, $p = 0.556$ (Figure 4, top). The correlation between MADRS score and change in contrast suppression was as follows: $r_{73} = –0.156$, $p = 0.189$ (Figrue 4, bottom). The negative correlation between the change in contrast suppression and MADRS score indicates that a decrease in depression symptoms was associated with an increase in contrast suppression. The correlations were modest, but we found stronger correlations for contrast suppression than for brightness induction.

Finally, we performed sensitivity and specificity analyses with our sample to evaluate the classification accuracy and systematicity of changes in brightness induction and contrast suppression at the individual participant level. Using the mean of the controls as a cut-off point, the sensitivity of the contrast suppression test was 79% and the specificity was 45%. Using an optimal cut-off point based on receiver operating

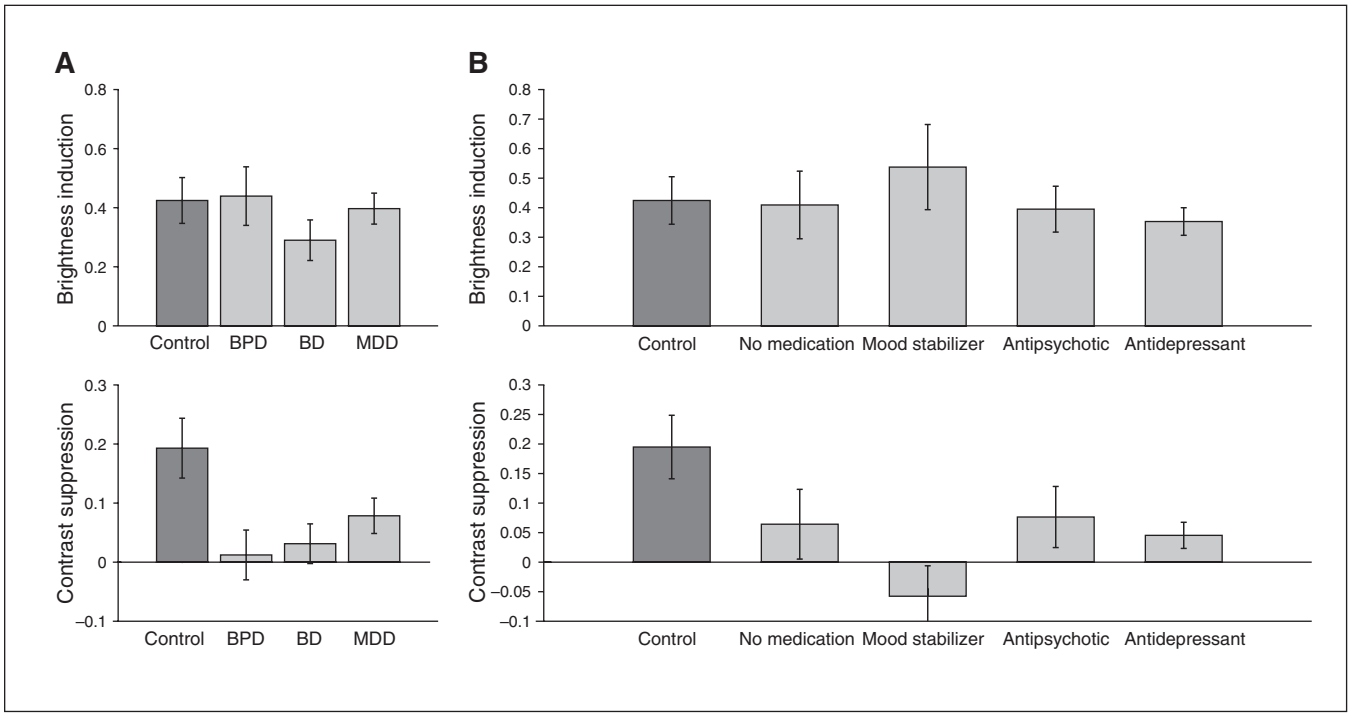

Fig. 3: Effect of (A) diagnostic subgroup and (B) medication on the strength of brightness induction (top) and contrast suppression (bottom). The error bars depict standard errors of the mean. BD = bipolar disorder; BPD = borderline personality disorder; MDD = major depressive disorder.

Table 2: Medication use* in the patient group

Medication	Subgroup (no. of patients)†			Brightness induction‡		Contrast suppression‡	
	Mood stabilizer (14)	Antipsychotic (21)	Antidepressant (78)	β	*p* value	β	*p* value
Valproate	0.29	0.10	0.03	0.060	0.58	–0.369	0.001§
Lamotrigine	0.43	0.14	0.05	0.136	0.18	–0.072	0.45
Pregabalin	0.29	—	0.05	0.054	0.63	–0.076	0.47
Benzodiazepine	0.07	0.05	0.05	0.040	0.71	0.060	0.55
SSRI, SARI or SMS	0.36	0.43	0.68	–0.103	0.35	–0.092	0.37
SNRI or tricyclic antidepressant	0.36	0.14	0.32	–0.001	0.99	–0.036	0.75
Tetracyclic antidepressant	0.07	—	0.10	–0.039	0.70	–0.036	0.71
NDRI	—	0.05	0.06	–0.032	0.75	–0.027	0.78
Agomelatine	—	—	0.01	–0.042	0.68	–0.029	0.77
Other	0.07	0.05	0.03	0.023	0.82	0.116	0.24

NDRI = norepinephrine–dopamine reuptake inhibitor; SARI = serotonin antagonist and reuptake inhibitor; SMS = serotonin modulator and stimulator (vortioxetine); SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
*Nineteen patients used no medication. Some patients used multiple medications.
†Proportion of patients using the medication in each subgroup.
‡Brightness induction and contrast suppression β coefficients and *p* values are from linear regression analysis.
§$p < 0.01$.

characteristic analysis,[30] the sensitivity was 50% and the specificity was 62%. The area under the curve was 0.66.

Discussion

We assessed visual perception in patients experiencing a major depressive episode and healthy controls using 2 contrast tests that reflected the retinal and cortical processing of contrast information. In the brightness induction test, we measured the effect of surround luminance on perceived luminance; in the contrast suppression test, we measured the effect of collinear surround on perceived contrast. When comparing the patient group with controls, we observed a strong and highly significant reduction in contrast suppression but not in brightness induction. Both patients and controls perceived the brightness induction illusion similarly, but patients perceived the contrast suppression illusion more veridically. Because contrast suppression is orientation-specific and relies on cortical processing, our results suggest that people experiencing a major depressive episode have normal retinal processing but altered cortical contrast normalization. Furthermore, contrast suppression was similarly reduced in patients with unipolar MDD, bipolar disorder and borderline personality disorder.

Contrast suppression in the primary visual cortex is achieved via the interaction of 2 mechanisms: an excitatory feedforward signal (originating from the retina) and an inhibitory feedback signal (from higher cortical areas), both of which have different thresholds and gains.[31–33] Therefore, reduced contrast suppression might be caused by lower retinal contrast gain or by a decreased amount of feedback. The former possibility is supported by previous reports of decreased retinal gain in depression.[1,3–5,7] The latter possibility is supported by reports suggesting changes in processing in the visual cortex in MDD.[8,9] We assessed both retinal and cortical contrast processing in the same sample of patients using 2 behavioural tests that depended differently on cortical (i.e., orientation-specific) processing. We observed no difference in the brightness induction test; thus, our results support altered feedback as the explanation for the reduced contrast suppression.

We had a relatively large sample of patients that we divided into 3 subgroups. Interestingly, we found a highly similar reduction in contrast suppression during an MDE for patients with unipolar depression, patients with bipolar disorder and patients with borderline personality disorder. The reduction in contrast suppression was strongest for patients with borderline personality disorder, followed by patients with bipolar disorder and then patients with unipolar MDD. However, this trend was not statistically significant, so our results suggest similar changes in visual contrast processing for the 3 subgroups. Contrast suppression in the patient group had not normalized completely by the follow-up measurement, although we did observe some recovery and found a trend for an association between recovery of contrast suppression and change in MADRS score.

The inhibitory signals in centre-surround effects could be mediated via γ-aminobutyric acid (GABA)-ergic interneurons.[34] Previous studies have shown reduced GABA and glutamate function in patients with MDD.[35–38] Thus, if GABA or glutamate neurons (or both) mediate a centre-surround interaction, their dysfunction might explain the reduced contrast suppression we observed. The use of mood stabilizers may affect contrast perception. The use of lamotrigine, valproate or pregabalin was associated with increased brightness induction, and the use of valproate, lamotrigine or pregabalin was associated with decreased contrast suppression. Lamotrigine acts on voltage-sensitive sodium channels to stabilize neuronal membranes and inhibit glutamate release. It has no direct effect on GABA neurons. Valproate, on the other hand, is an inhibitor of GABA transaminase, the major catabolic enzyme of GABA, leading to increased concentrations of

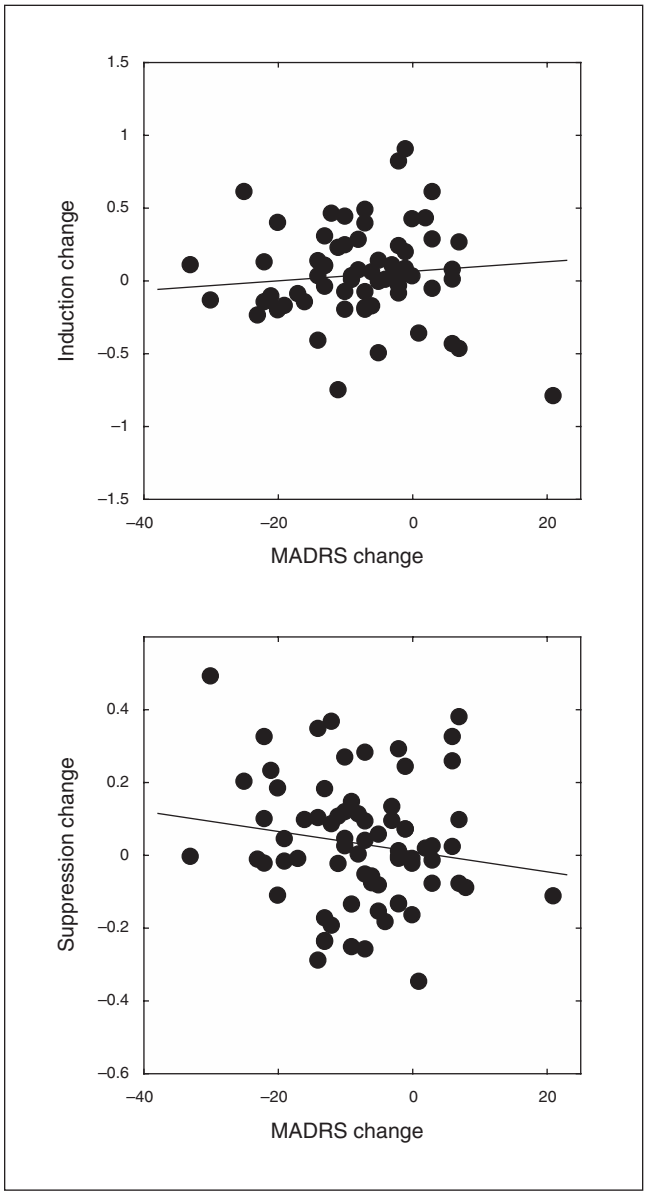

Fig. 4: Follow-up results. The change in brightness induction (top) and contrast suppression (bottom) test scores at the end of follow-up plotted against the change in MADRS scores at the end of follow-up. MADRS = Montgomery–Åsberg Depression Rating Scale.

GABA. Pregabalin has no direct effects on GABA transmission, but it reduces the release of glutamate. Thus, the association of these medications with brightness induction and contrast suppression scores might support a role for GABA or glutamate in mediating reduced contrast suppression, although these relationships are complex and should be interpreted with caution.

A reduction in contrast suppression similar to what we reported has been shown in people with schizophrenia and bipolar disorder.[29,39] These patient groups showed reduced contrast suppression and thus more veridical perception than controls. Furthermore, dissociation of luminance and contrast, akin to our observation in MDEs, has also been reported in schizophrenia.[40] This suggests that changes in visual processing may be a general feature of many psychopathologies. In schizophrenia, a reduction in contrast suppression is associated with GABA concentrations.[41]

Changes in surround suppression of visual motion has been found in MDD[8] and schizophrenia.[42] In MDD,[8] the amount of surround suppression depends on the contrast level: suppression is reduced at low contrast levels and increased at high contrast levels. We tested only 1 contrast level, so we could not directly compare our results for contrast-dependent motion suppression. However, because contrast normalization is dysfunctional in depression, an interaction of contrast level and suppression strength could be expected. Centre-surround effects of visual motion and contrast have common properties, and both seem to be reduced in MDD and schizophrenia. However, in a healthy population, contrast and motion suppression are not correlated and thus might be mediated via different neural mechanisms.[43] In future studies, systematic effects of contrast level and contrast- and motion-related surround suppression in depression should be further investigated to test whether contrast suppression could serve as a biomarker for changes in visual processing during MDEs.

Limitations

In previous studies, retinal contrast gain was assessed using pattern retinogram[3] and by behavioural measurement of contrast detection thresholds.[6] We assessed retinal contrast gain using a brightness induction test. Because of retinal normalization of overall luminance level, only the contrast signal at the luminance border is passed to the visual cortex; that contrast signal is used to compute the brightness of the whole surface, and the contrast spreads or fills the whole surface.[15] Thus, perceived brightness in the brightness induction test is determined both by (retinal) contrast at the luminance border and (cortical) filling of the surface. In theory, if retinal contrast gain is reduced, the cortical filling-in mechanism could compensate and retinal reduction would not be visible in the brightness induction test.

We measured visual perception using behavioural tests, which are subjective in nature. Although we controlled for the subjectivity of the tests with the psychophysical method (e.g., randomly interleaving stimuli), patients might still have had (for example) lower vigilance than controls, and this could have explained some differences. However, because we had 2 tests (brightness induction and contrast suppression) with a highly similar structure, it is unlikely that any general difference would explain the result specific to contrast suppression we observed. One limitation in our study was that we could infer retinal and cortical processing only indirectly using behavioural tests. More direct evidence on the neural loci of differences in visual perception could be assessed using PERG or EEG. In future studies, both PERG or EEG and different contrast tests should be conducted in the same sample of patients to resolve the exact neural cause of the reduced contrast suppression in MDEs.

There was a difference in our sample sizes (111 patients, 29 controls), but we controlled for this difference by using the Welch *t* test and comparing each patient subgroup to controls separately. Additional differences between controls and patients were employment status and level of education. However, because we assessed low-level visual processing, these differences were not likely to explain our results.

Our results were clear at the group level, but we found considerable variability in individual performances on the contrast tests. The preliminary sensitivity and specificity values we obtained were quite low, and follow-up effects were modest. To use behavioural contrast tests as biomarkers, the tests could be improved by reducing measurement noise, for example, by increasing the number of trials and measurement blocks.

Conclusion

Using 2 visual contrast tests in a large sample of patients, we showed that cortical contrast suppression was reduced during MDEs and retinal brightness induction was intact. We found this deficit patients with unipolar MDD, bipolar disorder and borderline personality disorder. Combined with the findings of previous studies, it appears that MDEs involve changes at different levels in the visual processing hierarchy, from retina to cortex. From a practical point of view, visual contrast tests are a rapid, simple and noninvasive method that could be further developed to serve as biomarkers for the abnormal processing of visual information in depression.

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