Title

fMRI evidence of aberrant neural adaptation for objects in schizophrenia and bipolar disorder

Journal

Human Brain Mapping, 40(5)

ISSN

1065-9471

Authors

Lee, Junghee
Reavis, Eric A
Engel, Stephen A
et al.

Publication Date

2019-04-01

DOI

10.1002/hbm.24472

Peer reviewed

Received: 26 July 2018 | Revised: 26 October 2018 | Accepted: 31 October 2018

DOI: 10.1002/hbm.24472

WILEY

RESEARCH ARTICLE

fMRI evidence of aberrant neural adaptation for objects in schizophrenia and bipolar disorder

Junghee Lee[1,2] | Eric A. Reavis[1,2] | Stephen A. Engel[3] | Lori L. Altshuler[1†] | Mark S. Cohen[1] | David C. Glahn[4,5] | Keith H. Nuechterlein[1,6] | Jonathan K. Wynn[1,2] | Michael F. Green[1,2]

[1]Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, California

[2]Desert Pacific Mental Illness Research, Education and Clinical Center, Greater Los Angeles Veterans Affairs Healthcare System, Los Angeles, California

[3]Department of Psychology, University of Minnesota, Minneapolis, Minnesota

[4]Department of Psychiatry, Yale University, New Haven, Connecticut

[5]Olin Neuropsychiatric Research Center, Institute of Living, Hartford Hospital Whitehall Research Building, Hartford, Connecticut

[6]Department of Psychology, University of California Los Angeles, Los Angeles, California

Correspondence
Junghee Lee, PhD, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, 760 Westwood Plaza, 72-460, Los Angeles, CA 90024.
Email: jungheelee@ucla.edu

Funding information
National Institute of Mental Health, Grant/Award Number: MH095878

Abstract

Functional magnetic resonance imaging (fMRI) adaptation (also known as fMRI repetition suppression) has been widely used to characterize stimulus selectivity in vivo, a fundamental feature of neuronal processing in the brain. We investigated whether SZ patients and BD patients show aberrant fMRI adaptation for object perception. About 52 SZ patients, 55 BD patients, and 53 community controls completed an object discrimination task with three conditions: the same object presented twice, two exemplars from the same category, and two exemplars from different categories. We also administered two functional localizer tasks. A region of interest analysis was employed to evaluate a priori hypotheses about the lateral occipital complex (LOC) and early visual cortex (EVC). An exploratory whole brain analysis was also conducted. In the LOC and EVC, controls showed the expected reduced fMRI responses to repeated presentation of the same objects compared with different objects (i.e., fMRI adaptation for objects, $p < .001$). SZ patients showed an adaptation effect that was significantly smaller compared with controls. BD patients showed a lack of fMRI adaptation. The whole brain analyses showed enhanced fMRI responses to repeated presentation of the same objects only in BD patients in several brain regions including anterior cingulate cortex. This study was the first to employ fMRI adaptation for objects in SZ and BD. The current findings provide empirical evidence of aberrant fMRI adaptation in the visual cortex in SZ and BD, but in distinctly different ways.

KEYWORDS

bipolar disorder, fMRI adaptation, neural tuning, object processing, schizophrenia

1 | INTRODUCTION

Functional magnetic resonance imaging (fMRI) adaptation (also known as fMRI repetition suppression) is a phenomenon in which the fMRI response to a repeated stimulus is smaller than the response to a novel stimulus (Malach, 2012). fMRI adaptation is closely related to repetition suppression effects measured with single unit recording, in which a neuron that responds strongly to a stimulus will respond less vigorously to a second presentation of the same stimulus (De Baene & Vogels, 2010; Solomon & Kohn, 2014). In other words, repetition suppression is observed when a second stimulus shares features to which a neuron responds selectively with a preceding stimulus. The fMRI response to a repeated stimulus is thought to arise from repeated activation of a set of neurons, resulting in a reduced fMRI response. By contrast, two alternating stimuli that share few features should engage relatively nonoverlapping sets of neurons, resulting in a stronger fMRI response overall. Accordingly, fMRI adaption has been widely used to characterize the stimulus selectivity of neuronal populations in humans. The stimulus selectivity of neurons corresponds to the property of neural tuning, which refers to the selective responsivity of neurons to certain stimulus features (Barron, Garvert, & Behrens, 2016; Larsson, Solomon, & Kohn, 2016). Aberrant neural tuning has recently been proposed as a potential mechanism underlying cognitive and perceptual abnormalities in severe psychiatric disorders,

[†]Deceased.

including schizophrenia (SZ) and bipolar disorder (BD) (Green, Lee, Wynn, & Mathis, 2011; Krystal et al., 2017), but empirical evaluation of this possibility has been sparse. With a focus on perceptual abnormalities, this study examined whether SZ patients and BD patients show aberrant tuning for objects using fMRI adaptation.

Fine neural tuning for specific visual features is a defining characteristic of specific areas of visual cortex, suggesting that visual cortex is well suited for evaluating the presence of aberrant neural tuning in psychiatric disorders. For example, neurons in early visual cortex (EVC) are tuned for orientation such that neurons preferentially respond to stimuli with a certain orientation (Hubel & Wiesel, 1962). Similarly, neurons in lateral occipital complex (LOC) are tuned for objects such that neurons respond preferentially to a certain visual object over others (Mruczek & Sheinberg, 2007; Wang, Fujita, & Murayama, 2000). fMRI adaptation has been widely used to examine stimulus selectivity in areas such as these, both in humans and nonhuman primates (Barron et al., 2016; Larsson et al., 2016). For example, fMRI responses to repeated presentations of an object are reduced compared with different objects in LOC (Kovacs, Kaiser, Kaliukhovich, Vidnyanszky, & Vogels, 2013; Pourtois, Schwartz, Spiridon, Martuzzi, & Vuilleumier, 2009; Sayres & Grill-Spector, 2006), supporting the view that neurons in LOC are tuned for individual objects. While fMRI adaptation is commonly observed for repeated stimuli, some studies have found the opposite pattern—enhanced fMRI responses to repeated stimuli (Henson, Shallice, & Dolan, 2000). While fMRI adaptation is associated with stimulus selectivity of neuronal populations, enhanced fMRI responses to repeated stimuli are thought to be related to other factors as well, including attention to novel stimuli and expectation (Segaert, Weber, de Lange, Petersson, & Hagoort, 2013).

SZ is associated with visual perceptual abnormalities, and SZ patients show aberrant fMRI activity in visual cortex—especially LOC—during perceptual tasks. For instance, compared with controls, SZ patients show sometimes lower, and sometimes higher, fMRI activation in LOC during visual tasks that involve object recognition (Green et al., 2009; Sehatpour et al., 2010; Silverstein et al., 2015). Also, the size of LOC may be larger in SZ than in controls (Wynn et al., 2008). These findings suggest that object-related processing in LOC is inefficient and less specialized in SZ, potentially due to aberrant neural tuning for objects.

Bipolar disorder (BD) shares several characteristics with SZ, including genetic risk and cognitive dysfunction (Cardno & Owen, 2014). While cognitive dysfunction in BD has been reported consistently (Bora & Pantelis, 2015; Glahn et al., 2010), findings on visual perception have been mixed. On object perception tasks, early studies found impairment in BD that was intermediate between SZ patients and controls (Green, Nuechterlein, & Mintz, 1994a, 1994b; MacQueen, Young, Galway, & Joffe, 2001). However, some recent studies have failed to find impairment in BD compared with controls (Jahshan et al., 2014; Sponheim, Sass, Noukki, & Hegeman, 2013). Further, few studies have examined the neural mechanisms of visual processing in BD. We recently showed that the cortical thickness of BD patients in LOC was intermediate between that of controls and SZ patients (Reavis, Lee, Wynn, Engel, Jimenez, et al., 2017).

In this study, we assessed whether SZ and BD patients showed reduced fMRI adaptation to objects compared with controls using an object discrimination task. We focused on two a priori regions of interest (ROIs), LOC, and EVC. LOC was chosen as an object processing region and EVC was chosen as a control region of visual cortex. The object discrimination task had three conditions: the same object presented twice, two exemplars from the same category, and two exemplars from different categories. We included two exemplars from the same category because this condition allowed us to examine whether fMRI adaptation for objects was modulated by only physical features or by both physical and semantic features to better characterize how objects are represented (Harvey & Burgund, 2012; Simons, Koutstaal, Prince, Wagner, & Schacter, 2003). We first examined responses in healthy controls to determine whether fMRI activation was reduced for pairs of repeated versus novel objects (i.e., fMRI adaptation) and whether fMRI adaptation for objects was modulated by only physical features or by both physical and semantic features of objects. Then, we examined fMRI adaptation in SZ patients and BD patients. Based on previous studies of visual perception in SZ and BD, we hypothesized that SZ patients would show reduced fMRI adaptation compared with controls and BD patients would show levels of fMRI adaption that are intermediate to controls and SZ patients.

2 | METHOD

2.1 | Participants

Fifty-three SZ outpatients, 55 BD outpatients, and 53 community controls enrolled in the study. Patients were recruited from local board and care facilities in Los Angeles, outpatient clinics at University of California Los Angeles (UCLA) and the Veterans Affairs Greater Los Angeles Healthcare System (VAGLAHS). Controls were recruited through website postings. All participants were evaluated for the capacity to give informed consent and provided written informed consents after procedures were fully explained, as approved by the Institutional Review Boards at UCLA and VAGLAHS. Diagnostic eligibility for all participants was determined with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, Spitzer, Gibbon, & Williams, 1997) for all participants and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (First, Gibbon, Spitzer, Williams, & Benjamin, 1996) for controls.

Inclusion criteria for patients were: (1) a diagnosis of SZ or BD based on SCID-I; and (2) clinical stability (i.e., no inpatient hospitalization for 3 months prior to enrollment, no change in psychoactive medication in the 4 weeks prior to enrollment). Inclusion criteria for controls were: (1) no history of psychotic disorder, bipolar spectrum disorder or other major mood disorder based on SCID-I; (2) no diagnosis of avoidant, paranoid, schizotypal, schizoid, or borderline personality disorders based on SCID-II; and (3) no first-degree relative with a psychotic disorder or BD based on self-report. We did not exclude controls for other Axis-I disorders, including obsessive–compulsive disorder or post-traumatic stress disorder. Additional inclusion criteria for all participants were: (1) age 18–65 years; (2) sufficient fluency in English to understand study procedures; (3) no evidence of IQ < 70 or development disability based on medical record and/or the Wide Range Achievement Test, Reading-Recognition subtest (Wilkinson, 1993); (4) no substance or alcohol dependence in the past 3 months

and no evidence of substance or alcohol abuse in the past month; (5) no clinically significant neurological disorder that could affect cognitive function (e.g., epilepsy); (6) no loss of consciousness greater than 1 hr, neuropsychological sequelae or cognitive rehabilitation post head injury; (7) normal or corrected to normal vision; (8) no history of mood episode in the past 2 months; (9) no known contraindications for MRI scanning; and (10) no sedatives or benzodiazepines within 12 hr of testing and no positive urine toxicology screening on the day of assessment.

Clinical characteristics for patients were assessed with the Expanded 24-item version of the Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993), the Clinical Assessment Interview for Negative Symptoms (Blanchard, Kring, Horan, & Gur, 2011), Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978), and Hamilton Depression Rating Scale (HAMD; Hamilton, 1960). Cognitive function was assessed using MATRICS Consensus Cognitive Battery (Kern et al., 2008). All interviewers were trained through the Treatment Unit of the Department of VA VISN 22 Mental Illness Research, Education, and Clinical Center. SCID interviewers were trained to a minimum kappa of 0.75 for key psychotic and mood items, and symptom raters were trained to a minimum intraclass correlation of 0.80.

2.2 | Procedures

All participants completed the object discrimination task, along with two localizer tasks (EVC and LOC), in the MRI scanner.

The object discrimination task consisted of three conditions, each trial of which presented a pair of objects in sequence: (1) two of the same object (SS), (2) different exemplars from the same category (SD); and (3) different exemplars from different categories (DD). Stimuli subtended approximately 6° of visual angle and comprised two exemplars from five categories of common household objects (i.e., chair, couch, desk, glass, table). In a rapid event-related design, each trial started with two 100 ms flashes of a fixation cross. Then, a pair of objects was shown for 400 ms each, separated by a 200-ms interstimulus interval (Figure 1). The two objects were presented in slightly different locations (jittered by ~1° of visual angle). Participants were asked to decide whether the second object was the same as the first. They had 2,100 ms to make a response, and a complete trial lasted 3.5 s. The task had 3 runs, each with 24 trials per condition and 24 null trials that included fixation but no stimuli. Within each run, the order of trials was randomized using maximum-length shift register sequences or m-sequence (Buracas & Boynton, 2002).

Full descriptions of the two localizer tasks are provided elsewhere (Green et al., 2009; Wynn et al., 2008). For the EVC, participants viewed slowly rotating wedges of a contrast-reversing checkerboard. For the LOC localizer, participants viewed alternating blocked presentations of pictures of abstract sculptures and scrambled sculptures.

2.3 | fMRI data acquisition

All MR data were collected at the UCLA Staglin Center for Cognitive Neuroscience on a 3 T Siemens Tim Trio scanner with a 12-channel head coil (Siemens Medical Solutions, Erlangen, Germany) using MR-compatible LCD goggles (Resonance Technology, Northridge, CA) (see Supporting Information for details). All tasks were presented using E-prime software and behavioral performance was recorded using an MR-compatible 4-button response box (Resonance Technology, Northridge, CA).

2.4 | fMRI data analysis

fMRI data were analyzed using the FMRIB Software Library (FSL version 5.0.9, Smith et al., 2004). To examine neural adaptation for object, we conducted fMRI analyses in two complementary ways: an ROI-based analysis and an exploratory whole brain analysis. Additional details are provided in the Supporting Information.

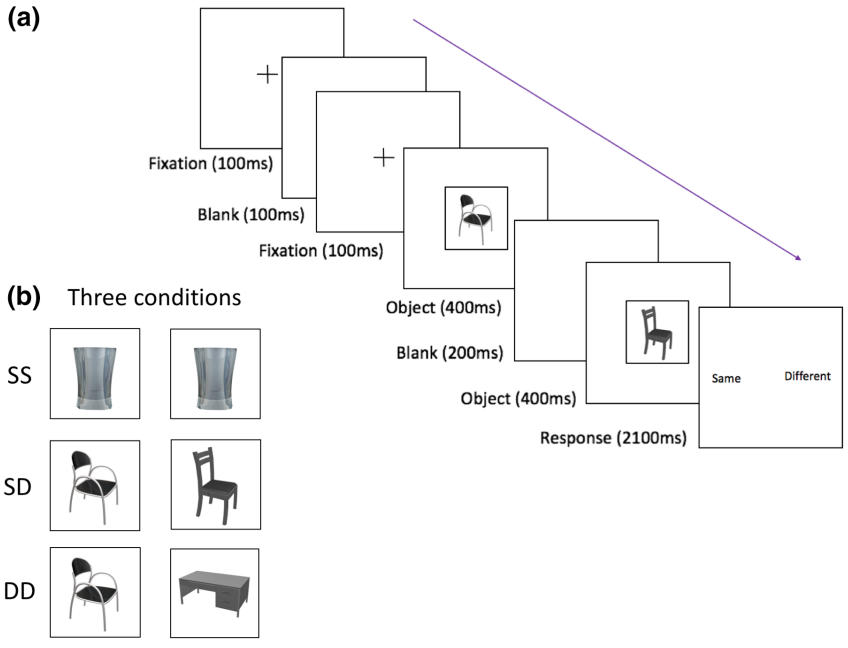

FIGURE 1 A schematic diagram of the object discrimination task [Color figure can be viewed at wileyonlinelibrary.com]

In the ROI analysis, we first identified EVC and LOC in each participant using the functional localizer tasks. The EVC was defined as a set of contiguously activated voxels ($p < .001$, uncorrected; ≥ 10 voxels) on the medial surface of the occipital lobe that was temporally correlated with a sinusoid at the stimulus frequency (Engel, Glover, & Wandell, 1997). The EVC primarily includes, but is not limited to, V1. LOC was identified as a cluster of contiguously activated voxels (object > scrambled) within the lateral occipital cortex bilaterally ($p < .001$, uncorrected; ≥ 10 voxels). Three groups did not differ in terms of the size of LOC (voxels, SZ = 500 ± 764, BD = 442 ± 568, CO = 560 ± 664; $F_{2,156} = .42$, NS) or EVC (voxels, SZ = 3,223 ± 1,691, BD = 3,790 ± 1,608, CO = 3,554 ± 1,432; $F_{2,156} = 1.79$, NS). See the Supplement for representative images of LOC and EVC.

After identifying each ROI for each participant, we extracted response-amplitudes for each ROI during the object discrimination task. Specifically, we modeled hemodynamic response functions (HRFs) for each condition using 7 finite impulse responses (FIR), one for each peristimulus time-point (total window = 17.5 s). The FIR model is well suited to average each trial type in this study because it provides unbiased and statistically efficient estimates of hemodynamic responses associated with task conditions in a rapid event-related design with few assumptions about the exact shape of the HRF (Boynton, Engel, Glover, & Heeger, 1996; Ollinger, Corbetta, & Shulman, 2001; Ollinger, Shulman, & Corbetta, 2001). Next, response amplitudes were calculated by averaging event-related responses across trials, separately for each condition, within each ROI. To identify the peak activation, mean amplitudes of three peristimulus time-points (2.5, 5, and 7.5 s post-stimulus) were averaged for each condition in each ROI and utilized for further analyses.

3 | RESULTS

One SZ patient was excluded from all analyses due to excessive motion (i.e., relative motion = 0.67; see Supporting Information Table S1 for details). Thus, 52 SZ patients, 55 BD patients, and 53 controls were included in the following analyses.

3.1 | Demographic characteristics and performance

Table 1 presents demographic and clinical characteristics of the participants, including medication level (i.e., chlorpromazine [CPZ] equivalents; Leucht et al., 2014). The groups were comparable for age, gender, and parental education, but not for personal education. SZ and BD groups did not differ for age of onset, HAMD total, or YMRS total. SZ patients had higher psychiatric symptom scores (i.e., BPRS and CAINS). In the BD group, 48 patients were euthymic at the time of assessment (defined by a HAMD score < 15 and a YMRS score < 12) (Pizzagalli, Goetz, Ostacher, Iosifescu, & Perlis, 2008). See the Supporting Information for BD subgroup analyses based on medication and clinical features.

Performance during the object discrimination task was analyzed for accuracy and reaction time, separately, using a 3 × 3 repeated measures ANOVA with condition as a within-subject factor and group as a between-subject factor (see Table 2). For accuracy, the condition effect was significant ($F_{2,310} = 5.53$, $p < .01$, $\eta_p^2 = 0.03$), but no others were. Across groups, accuracy was lower for the DD condition compared with the SS and SD conditions (p's < .01), which did not differ from each other. For reaction time, a significant condition effect was observed ($F_{2,310} = 36.18$, $p < .001$, $\eta_p^2 = 0.02$), but no other effect was significant. Across groups, reaction time was longest for the SD condition, followed by the DD condition and SS condition (SD vs. DD, $p < .01$; DD vs. SS, $p < .05$). Importantly, the groups did not differ on accuracy or reaction time, and there were no group by condition interactions.

3.2 | ROI analysis

Figure 2 presents the time series of percent signal change for each ROI during the object discrimination task. To confirm that this paradigm yielded the expected condition effect (i.e., fMRI adaptation), we first examined the results in controls, using a 2 × 3 repeated-measures

TABLE 1 Demographic and clinical characteristics

	SZ (n = 52)	BD (n = 53)	Controls (n = 53)	Statistics	Post-hoc comparisons
Age	46.2 (11.3)	45.3 (12.1)	47.1 (8.0)	$F_{(2,155)} = .36$, $p = .69$	
Gender (female %)	27%	33.8%	39.2%	$\chi^2 = 2.78$, $p = .24$	
Personal Edu (yrs)	12.9 (2.2)	14.1 (2.4)	14.4 (1.7)	$F_{(2,155)} = 6.71$, $p < .01$	SZ < BD = controls
Parental Edu (yrs)	13.7 (2.8)	14.4 (3.2)	14.4 (3.1)	$F_{(2,155)} = .82$, $p = .44$	
Age of onset	22.4 (8.3)	20.9 (9.1)		$F_{(1,96)} = .57$, $p = .56$	
BPRS total	39.6 (10.7)	34.0 (6.5)		$F_{(2196)} = 10.83$, $p < .01$	SZ > BD
CAINS					
Motivation	1.5 (0.6)	1.1 (0.6)		$F_{(1,96)} = 17.12$, $p < .01$	SZ > BD
Expressive	1.3 (0.7)	0.4 (0.5)		$F_{(1,96)} = 19.88$, $p < .01$	SZ > BD
HAMD total	6.2 (5.1)	6. (4.7)		$F_{(1,96)} = .01$, $p = 95$	
YMRS total	4.6 (4.1)	3.8 (4.8)		$F_{(1,96)} = .88$, $p = .35$	
CPZ equivalent	138 (209)	100 (179)		$F_{(1,96)} = .64$, $p = .42$	
MCCB	36.8 (11.9)	43.4 (12.3)	47.8 (10.7)	$F_{(2,155)} = 11.8$, $p < .001$	SZ < BD = controls

Note. Abbreviations: BPRS = the brief psychiatric rating scale; CAINS = the clinical assessment interview for negative symptoms; HAMD = the hamilton depression rating scale; YMRS = the young mania rating scale; CPZ equivalent = chlorpromazine equivalent; MCCB = composite score of MATRICS consensus cognitive battery. Values are given as mean (standard deviation).

TABLE 2 Performance on the object discrimination task

	SZ (*n* = 52)	BD (*n* = 53)	Controls (*n* = 53)
Accuracy			
SS	.91 (.10)	.91 (.11)	.93 (.08)
SD	.91 (.15)	.91 (.10)	.94 (.07)
DD	.95 (.07)	.91 (.11)	.95 (.06)
Reaction time (ms)			
SS	726.7 (162.1)	679.5 (121.8)	698.6 (144.8)
SD	782.3 (141.1)	707.7 (131.5)	736.4 (141.5)
DD	750.7 (145.1)	677.8 (130.6)	708.2 (145.9)

Note. Values are given as mean (standard deviation).

ANOVA with ROI and condition as within-subject factors (Figure 3a). We found a significant ROI effect ($F_{1,50}$ = 145.28, p < .001, η_p^2 = 0.74), a significant effect of condition ($F_{2,100}$ = 7.01, p < .01, η_p^2 = 0.12), and a significant ROI by condition interaction effect ($F_{2,100}$ = 9.37, p < .001, η_p^2 = 0.15). Controls showed higher peak amplitude for LOC compared with EVC. As expected, controls showed reduced peak amplitude for the SS condition compared with the SD and DD conditions (p's < .01), which did not differ from each other. The condition effect was slightly larger in LOC (p < .001) than EVC (p < .05). Thus, for the following analyses, we combined the SD and DD conditions (i.e., SD + DD).

We next examined whether the two patient groups showed reduced fMRI adaptation compared with controls (i.e., a significant condition by group interaction), using a 2 × 2 × 3 repeated-measures ANOVA with ROI and condition as within-subject factors and group as a between-subject factor (Figure 3b). We observed a significant ROI effect ($F_{1,142}$ = 459.57, p < .001, η_p^2 = 0.76), a significant condition effect ($F_{1,142}$ = 11.79, p < .001, η_p^2 = 0.07), a significant ROI by condition interaction ($F_{1,142}$ = 31.65, p < .001, η_p^2 = 0.18), and a significant condition by group interaction ($F_{2,142}$ = 5.98, p < .01, η_p^2 = 0.07). No other effect was significant. All groups showed higher peak amplitudes for LOC than EVC. A post-hoc analysis of the ROI by condition interaction showed a larger condition effect in LOC (p < .001) than in EVC (p < .05), pooling across groups.

A post-hoc analysis of the significant condition by group interaction indicated that the SZ group showed a relatively smaller condition effect than controls, consistent with reduced fMRI adaptation (i.e., lower peak amplitude for the SS compared with the SD + DD condition; SZ, p < .05; and controls, p < .001), whereas the BD group showed comparable peak amplitudes across conditions. We did not observe any effect of clinical heterogeneity (i.e., clinical diagnosis or medication) in the BD group on fMRI adaptation (Supporting Information Figures S1 and S2). Finally, in both patient groups, we found no association between fMRI adaptation in either ROI and cognition (i.e., overall composite score of MCCB, working memory domain score, or the visual learning and memory domain score), antipsychotic medication dose (i.e., CPZ equivalents), or clinical symptoms (i.e., BPRS total, HAMD total, YMRS total, MAP, and Expressivity subscales of CAINS).

3.3 | Exploratory whole brain analyses

Details of an exploratory analyses are provided in the Supporting Information. To explore whether fMRI adaptation for objects occurred in brain regions other than the a priori ROIs, we focused on the contrast of [SS < SD + DD]. We observed significant effects in the

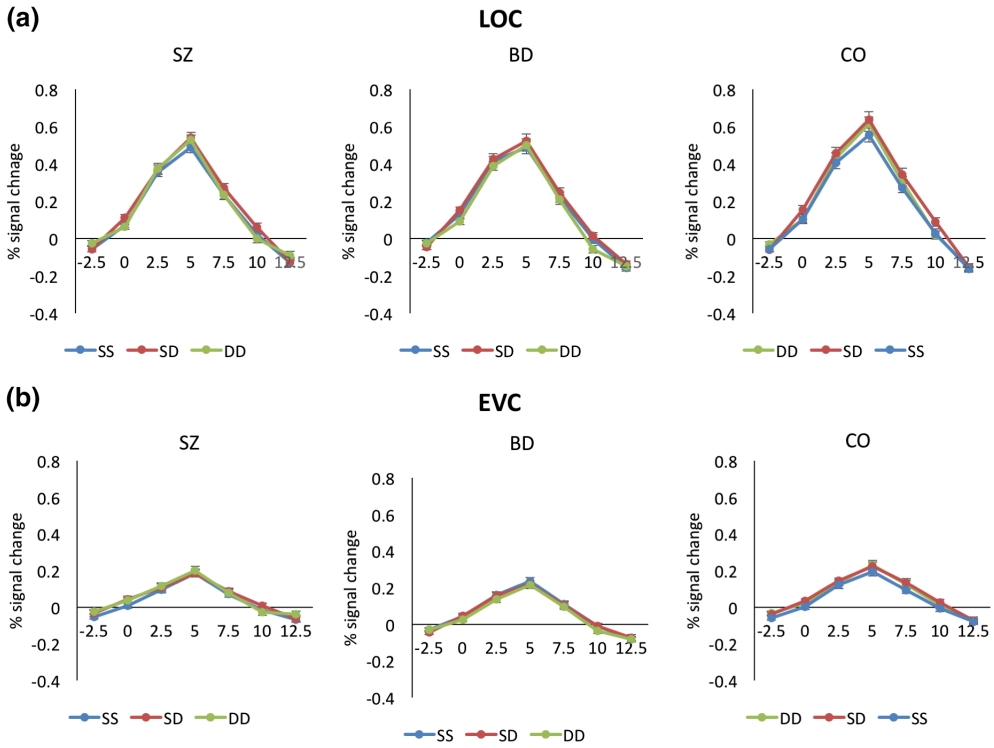

FIGURE 2 Time series of the two functional localizers during the object discrimination task. These figures show the time series of percent signal change of each group in the lateral occipital complex (LOC) (a) and early visual cortex (EVC) (b). The abscissa reflects the time since object-onset and the ordinate indicates percent signal change [Color figure can be viewed at wileyonlinelibrary.com]

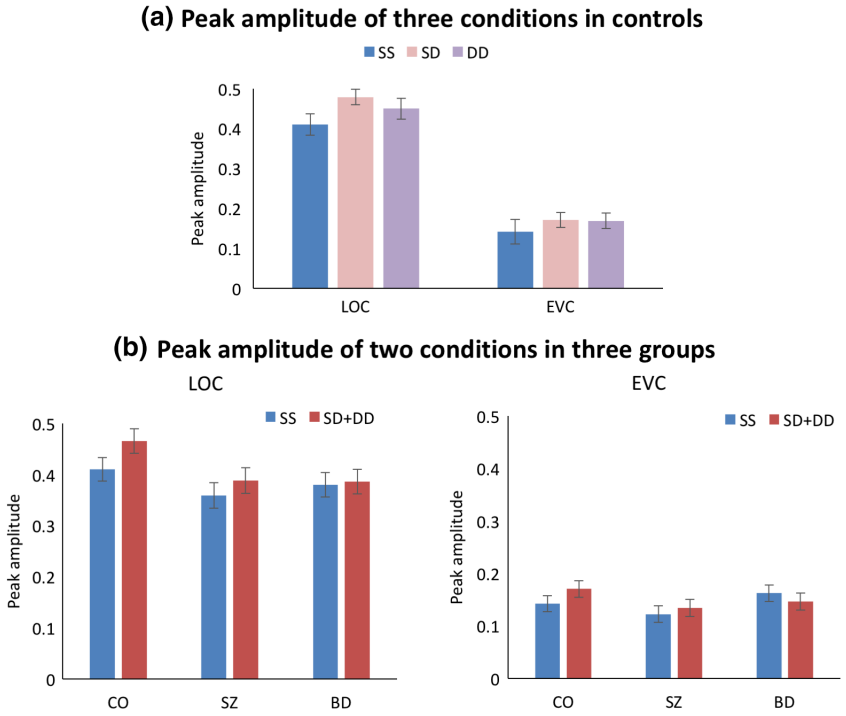

FIGURE 3 Peak amplitude of percent signal change during the object discrimination task. Figure 3a shows peak amplitude for the three conditions in the lateral occipital complex (LOC) and early visual cortex (EVC) in controls. Figure 3b shows peak amplitude for two conditions in LOC and EVC in three groups [Color figure can be viewed at wileyonlinelibrary.com]

occipital lobe (including LOC and EVC) in the SZ and control groups, but less so in the BD group (Supporting Information Table S2 and Supporting Information Figure S3). When each group was directly compared with each other on the contrast of SS < SD + DD, the control group showed greater activation in the occipital lobe (including LOC and EVC) than BD group.

Finally, we examined whether any brain regions showed enhanced (as opposed to reduced) activity for repeated stimuli compared with novel stimuli (i.e., the contrast of [SS > SD + DD]). In the SZ and control groups, we did not find any brain regions with significant effects for that contrast. However, within the BD group, we observed significant effects in several brain regions, including in the anterior cingulate cortex, supplementary motor cortex, thalamus, and Wernicke's area (i.e., planum polare) (Supporting Information Table S3 and Supporting Information Figure S4). When the groups were directly compared, BD group showed greater condition effects for this contrast in the supplementary motor cortex and postcentral gyrus compared SZ group. The BD group also showed greater condition effect for this contrast in the several brain regions, including supplementary motor cortex, LOC, and superior temporal gyrus, compared with the control group. There was no area of significant difference for this contrast between the SZ and BD groups.

4 | DISCUSSION

This study examined whether SZ patients and BD patients showed aberrant fMRI adaptation for objects during a visual object discrimination task. Controls showed reduced fMRI responses to repeated objects in both LOC and EVC, thereby demonstrating that the task validly induced fMRI adaptation. Previous studies in healthy controls have shown that fMRI adaptation for objects was present for the same exemplar with different viewpoints (Pourtois et al., 2009), but not for semantically similar objects (Chouinard, Morrissey, Kohler, & Goodale, 2008). Hence it appears that neural representations of objects in LOC are primarily based on physical features of objects, rather than the object category. Our finding in controls provides additional support to this view.

Consistent with our hypothesis, SZ patients showed reduced fMRI adaptation for objects in LOC compared with controls, suggesting aberrant stimulus selectivity for objects in SZ. This finding is in line with previous studies on visual perception that suggested inefficient and less-specialized object-related processing in SZ (Green et al., 2009; Sehatpour et al., 2010; Silverstein et al., 2015; Wynn et al., 2008). However, reduced fMRI adaptation in SZ was also observed in EVC. The EVC is not specialized for object processing, but it is sensitive to more basic features of visual stimuli (e.g., orientation). Because the stimuli used in this study also varied along these basic features, reduced fMRI adaptation of the SZ group in EVC could be due to aberrant stimulus selectivity for low-level visual features. This possibility is consistent with recent studies suggesting broader tuning for orientation in SZ (Rokem et al., 2011; Schallmo, Sponheim, & Olman, 2013; Silverstein, Demmin, & Bednar, 2017). It is possible that such abnormalities in EVC could contribute to aberrant fMRI adaptation in LOC in SZ. Another possibility is that abnormal fMRI adaptation in EVC could be due to abnormal top-down feedback from higher processing areas such as LOC. Alternatively, abnormal fMRI adaptation could be an inherent characteristic of multiple visual processing regions in SZ. Future studies with object stimuli that are matched in

terms of basic visual features will be helpful to understand the properties of aberrant fMRI adaptation in SZ throughout visual cortex.

During the object discrimination task, two stimuli were presented briefly with an interstimulus interval of 200 ms. Because schizophrenia patients as a group have impairment in iconic memory impairment, one may wonder whether reduced fMRI adaptation in SZ could be due to that impairment. However, impaired iconic memory would weaken the representation of the first stimuli regardless of the second stimulus (i.e., identical stimulus or different stimulus), as well as the representation of the second stimulus. Thus, impaired iconic memory would lead to generally blunted neural activation regardless of conditions, rather than reduced fMRI adaptation (i.e., a condition effect).

This study did not find evidence of fMRI adaptation for objects in BD. This finding is unlikely to be explained by the clinical heterogeneity of BD patients. Further, fMRI responses of the BD patients during the localizer tasks were comparable to those of SZ patients and controls, suggesting that the lack of fMRI adaptation is not due to a lack of neural responses to visual stimuli per se. Unexpectedly, BD patients showed enhanced fMRI responses to repeated objects (i.e., fMRI enhancement) in the brain regions outside the visual cortex, including thalamus, anterior cingulate cortex, supplementary motor cortex, and Wernicke's area. Such enhanced responses were not observed in the SZ or control groups. It is possible that enhanced responses in the thalamus could come from thalamic nuclei involved in visual processing, such as the lateral geniculate nucleus or pulvinar, but imaging parameters of the current study did not provide sufficient spatial resolution to differentiate individual thalamic nuclei. While reduced fMRI responses to repeated stimuli are more common, several studies have reported enhanced fMRI responses to repeated presentations of unfamiliar stimuli (Henson et al., 2000; Soldan, Zarahn, Hilton, & Stern, 2008). Such effects have been reported in Wernicke's area (Harpaz, Lavidor, & Goldstein, 2013; Passeri, Capotosto, & Di Matteo, 2015) and the anterior cingulate cortex (Bressler & Menon, 2010). In other words, repeated presentation of the same objects may have been perceived as unexpected or otherwise salient among BD patients, resulting in fMRI enhancement, which is in line with previous findings of the role of attention or expectation-related effects of enhanced fMRI responses to repeated stimuli (Segaert et al., 2013).

While the present study found evidence of reduced fMRI adaptation in patients, we recently found no difference between patients and controls for how well object category could be decoded from LOC using multivariate pattern analysis (MVPA) (Reavis, Lee, Wynn, Engel, Cohen, et al., 2017). While both fMRI adaptation and MVPA have been used previously to estimate neural tuning, each method probes neuronal populations differently, which could produce conflicting results (Hatfield, McCloskey, & Park, 2016; Sapountzis, Schluppeck, Bowtell, & Peirce, 2010). Theories have been proposed to explain discrepancies between the two methods (Sapountzis et al., 2010; Van den Stock, de Jong, Hodiamont, & de Gelder, 2011) and MVPA may sometimes have reduced sensitivity to tuning relative to fMRI adaptation. For example, MVPA largely depends on clustering of neurons with similar tuning properties, which produces the voxel biases (i.e., activation changes for preferred stimuli) that are critical for decoding. The reduced fMRI adaptation that we observed in patients could be due to a subset of neurons in patients with broad tuning for objects which are not present in controls. Our previous MVPA findings could arise from more broadly tuned neurons in patients that are uniformly distributed across LOC and EVC, such that they do not influence voxel biases. At the other extreme, if the broadly-tuned neurons could be clustered in certain voxels that are not weighted heavily in MVPA analysis, minimizing their influence.

This study provides empirical evidence of abnormal stimulus selectivity of neuronal population (i.e., tuning) in SZ and BD. The stimulus selectivity of neuronal populations (i.e., neural tuning) is closely associated with NMDA and GABA systems (Katzner, Busse, & Carandini, 2011; Wang et al., 2000), both of which are key features of prominent pathophysiological theories of SZ (Coyle, 2012; Gonzalez-Burgos & Lewis, 2012; Lewis, Hashimoto, & Volk, 2005). Abnormal NMDA and GABA neurotransmission has also been implicated in the pathophysiology of BD (Ghasemi et al., 2014; Sim, Mohamed, Hatim, Rajagopal, & Habil, 2010). Thus, our finding of abnormal stimulus selectivity for objects raises an intriguing possibility that reduced stimulus selectivity may link to specific neuropharmacological systems implicated in the pathophysiology of both disorders. This could have important consequences for the development of interventions targeting those systems.

Given that this stimulus selectivity is considered a fundamental feature of neuronal processes responsible for information processing in the brain, one may wonder why this study failed to find an association between aberrant fMRI adaptation and cognitive function. It is possible that this relationship may not have been apparent in our data because we used MCCB to assess working memory and verbal memory. It is possible that abnormal object tuning might influence certain cognitive abilities that are related to specific stimuli. For example, several studies have shown that the magnitude of fMRI adaptation was related to subsequent memory of stimuli that were used to probe fMRI adaptation (Chee & Tan, 2007; Manelis, Wheeler, Paynter, Storey, & Reder, 2011; Turk-Browne, Yi, & Chun, 2006; Ward, Chun, & Kuhl, 2013), though it remains to be determined whether this relationship is specific to implicit memory or explicit memory or exist for both types of memory. Future studies with a wide range of stimuli could assess whether aberrant fMRI adaptation of SZ and BD patients is associated with memory performance.

Our finding of aberrant fMRI adaptation in SZ and BD contributes to the extensive literature on experience-based plasticity in SZ and BD. fMRI adaptation arises from stimulus selectivity of neuronal populations, leading to diminished fMRI responses upon repetition of stimuli with similar features. In this way, it resembles auditory sensory gating (e.g., P50) or mismatch negativity paradigms that have been well-studied in SZ and BD. Previous studies have shown reduced sensory gating or mismatch negativity in both SZ and BD (Erickson, Ruffle, & Gold, 2016; Johannesen, O'Donnell, Shekhar, McGrew, & Hetrick, 2013). fMRI adaptation, similar to auditory sensory gating and mismatch negativity, is associated with the way that neural systems handle repeated information in the environment. It remains to be determined whether they are governed by similar or different neural mechanisms (Amado, Stoyanova, & Kovacs, 2018).

The findings of the current study should be interpreted in the context of several limitations. Because this study included chronic patients, we do not know if similar findings would be present in early

stage patients. All patients were medicated at the time of testing. While we did not find any association between medication dose and fMRI adaptation, the potential effects of medication on fMRI adaptation remain unclear. Our analyses that considered clinical heterogeneity involved a relatively small number of BD patients per subgroup. Finally, we employed a limited range of object stimuli in the current study, and do not know whether a similar pattern of fMRI adaptation in group would be observed with other stimulus sets.

In summary, this study examined whether SZ and BD patients showed abnormal fMRI adaptation during an object discrimination task. SZ patients showed reduced fMRI adaptation for objects, compared with controls, which is consistent with a recent hypothesis of nonspecific neural tuning in SZ (Green et al., 2011; Krystal et al., 2017). BD patients showed no evidence of fMRI adaptation for objects in the ROIs, but instead showed enhanced fMRI responses to repeated presentation of objects, suggesting a potential effect of other processes (e.g., attentional) in BD. Thus, this study suggests that aberrant fMRI adaptation occurs both in SZ and BD, but in different ways.

Funding and Disclosure

This study was supported by the National Institute of Mental Health R01MH095878 to MFG. The funder did not play any role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

Junghee Lee has been serving as a consultant for Takeda. Michael F. Green has been a paid consultant for a consultant for AiCure, Takeda, and Lundbeck, a member of the Scientific Board of Cadent, and has received unrelated research support from Forum. Michael F. Green and Keith Nuechterlein are officers within MATRICS Assessment, Inc., the publisher of the MCCB, but do not receive any financial remuneration for their respective roles. Keith Nuechterlein has been a consultant to Genentech, Janssen, Otsuka, and Takeda, and has received unrelated research grants from Genentech, Janssen Scientific Affairs and Posit Science. All the other authors do not have any conflict of interest.

ACKNOWLEDGMENT

We would like to thank Ana Ceci Myers and Julio Iglesias for their assistance in data collection and Michelle J. Dolinsky for the participant recruitment. We also would like to thank One Mind – Center for Cognitive Neuroscience at UCLA for their generous support to the CCN scanner. fMRI data analysis for this study used computational and storage services associated with the Hoffman2 Shared Cluster provided by UCLA Institute for Digital Research and Education's Research Technology Group.

ORCID

Junghee Lee https://orcid.org/0000-0001-9567-8700
Eric A. Reavis https://orcid.org/0000-0002-9843-9139
David C. Glahn https://orcid.org/0000-0002-4749-6977

REFERENCES

Amado, C., Stoyanova, P., & Kovacs, G. (2018). Visual mismatch response and fMRI signal adaptation correlate in the occipital-temporal cortex. *Behavioural Brain Research*, *347*, 77–87. https://doi.org/10.1016/j.bbr.2018.03.001

Barron, H. C., Garvert, M. M., & Behrens, T. E. (2016). Repetition suppression: A means to index neural representations using BOLD? *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *371*(1705), 20150355. https://doi.org/10.1098/rstb.2015.0355

Blanchard, J. J., Kring, A. M., Horan, W. P., & Gur, R. (2011). Toward the next generation of negative symptom assessments: The collaboration to advance negative symptom assessment in schizophrenia. *Schizophrenia Bulletin*, *37*(2), 291–299. https://doi.org/10.1093/schbul/sbq104

Bora, E., & Pantelis, C. (2015). Meta-analysis of cognitive impairment in first-episode bipolar disorder: Comparison with first-episode schizophrenia and healthy controls. *Schizophrenia Bulletin*, *41*, 1095–1104. https://doi.org/10.1093/schbul/sbu198

Boynton, G. M., Engel, S. A., Glover, G. H., & Heeger, D. J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *16*(13), 4207–4221.

Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: Emerging methods and principles. *Trends in Cognitive Sciences*, *14*(6), 277–290. https://doi.org/10.1016/j.tics.2010.04.004

Buracas, G. T., & Boynton, G. M. (2002). Efficient design of event-related fMRI experiments using M-sequences. *NeuroImage*, *16*(3 Pt 1), 801–813.

Cardno, A. G., & Owen, M. J. (2014). Genetic relationships between schizophrenia, bipolar disorder, and schizoaffective disorder. *Schizophrenia Bulletin*, *40*(3), 504–515. https://doi.org/10.1093/schbul/sbu016

Chee, M. W., & Tan, J. C. (2007). Inter-relationships between attention, activation, fMR adaptation and long-term memory. *NeuroImage*, *37*(4), 1487–1495. https://doi.org/10.1016/j.neuroimage.2007.07.006

Chouinard, P. A., Morrissey, B. F., Kohler, S., & Goodale, M. A. (2008). Repetition suppression in occipital-temporal visual areas is modulated by physical rather than semantic features of objects. *NeuroImage*, *41*(1), 130–144. https://doi.org/10.1016/j.neuroimage.2008.02.011

Coyle, J. T. (2012). NMDA receptor and schizophrenia: A brief history. *Schizophrenia Bulletin*, *38*(5), 920–926. https://doi.org/10.1093/schbul/sbs076

De Baene, W., & Vogels, R. (2010). Effects of adaptation on the stimulus selectivity of macaque inferior temporal spiking activity and local field potentials. *Cerebral Cortex*, *20*(9), 2145–2165. https://doi.org/10.1093/cercor/bhp277

Engel, S. A., Glover, G. H., & Wandell, B. A. (1997). Retinotopic organization in human visual cortex and the spatial precision of functional MRI. *Cerebral Cortex*, *7*(2), 181–192.

Erickson, M. A., Ruffle, A., & Gold, J. M. (2016). A meta-analysis of mismatch negativity in schizophrenia: From clinical risk to disease specificity and progression. *Biological Psychiatry*, *79*(12), 980–987. https://doi.org/10.1016/j.biopsych.2015.08.025

First, M. B., Gibbon, M., Spitzer, R. L., Williams, J. B. W., & Benjamin, L. (1996). *Structured clinical interview for DSM-IV Axis II personality disorders*. New York, NY: Biometrics Research Department.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). *Structured clinical interview for DSM-IV axis I disorders - patient edition*. New York, NY: Biometrics Research Department.

Ghasemi, M., Phillips, C., Trillo, L., De Miguel, Z., Das, D., & Salehi, A. (2014). The role of NMDA receptors in the pathophysiology and treatment of mood disorders. *Neuroscience and Biobehavioral Reviews*, *47*, 336–358. https://doi.org/10.1016/j.neubiorev.2014.08.017

Glahn, D. C., Almasy, L., Barguil, M., Hare, E., Peralta, J. M., Kent, J. W., Jr., … Escamilla, M. A. (2010). Neurocognitive endophenotypes for bipolar disorder identified in multiplex multigenerational families. *Archives of General Psychiatry*, *67*(2), 168–177. https://doi.org/10.1001/archgenpsychiatry.2009.184

Gonzalez-Burgos, G., & Lewis, D. A. (2012). NMDA receptor hypofunction, parvalbumin-positive neurons, and cortical gamma oscillations in

schizophrenia. *Schizophrenia Bulletin*, *38*(5), 950–957. https://doi.org/10.1093/schbul/sbs010

Green, M. F., Lee, J., Cohen, M. S., Engel, S. A., Korb, A. S., Nuechterlein, K. H., … Glahn, D. C. (2009). Functional neuroanatomy of visual masking deficits in schizophrenia. *Archives of General Psychiatry*, *66*(12), 1295–1303. doi:66/12/1295[pii]. https://doi.org/10.1001/archgenpsychiatry.2009.132

Green, M. F., Lee, J., Wynn, J. K., & Mathis, K. I. (2011). Visual masking in schizophrenia: Overview and implications for theories of aberrant visual processing. *Schizophrenia Bulletin*, *37*, 700–708.

Green, M. F., Nuechterlein, K. H., & Mintz, J. (1994a). Backward masking in schizophrenia and mania. I. Specifying a mechanism. *Archives of General Psychiatry*, *51*(12), 939–944.

Green, M. F., Nuechterlein, K. H., & Mintz, J. (1994b). Backward masking in schizophrenia and mania. II. Specifying the visual channels. *Archives of General Psychiatry*, *51*(12), 945–951.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, *23*, 56–62.

Harpaz, Y., Lavidor, M., & Goldstein, A. (2013). Right semantic modulation of early MEG components during ambiguity resolution. *NeuroImage*, *82*, 107–114. https://doi.org/10.1016/j.neuroimage.2013.05.060

Harvey, D. Y., & Burgund, E. D. (2012). Neural adaptation across viewpoint and exemplar in fusiform cortex. *Brain and Cognition*, *80*(1), 33–44. https://doi.org/10.1016/j.bandc.2012.04.009

Hatfield, M., McCloskey, M., & Park, S. (2016). Neural representation of object orientation: A dissociation between MVPA and repetition suppression. *NeuroImage*, *139*, 136–148. https://doi.org/10.1016/j.neuroimage.2016.05.052

Henson, R., Shallice, T., & Dolan, R. (2000). Neuroimaging evidence for dissociable forms of repetition priming. *Science*, *287*(5456), 1269–1272.

Hubel, D. H., & Wiesel, T. N. (1962). Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *Journal of Physiology*, *160*, 106–154.

Jahshan, C., Wynn, J. K., McCleery, A., Glahn, D. C., Altshuler, L. L., & Green, M. F. (2014). Cross-diagnostic comparison of visual processing in bipolar disorder and schizophrenia. *Journal of Psychiatric Research*, *51*, 42–48. https://doi.org/10.1016/j.jpsychires.2013.12.014

Johannesen, J. K., O'Donnell, B. F., Shekhar, A., McGrew, J. H., & Hetrick, W. P. (2013). Diagnostic specificity of neurophysiological endophenotypes in schizophrenia and bipolar disorder. *Schizophrenia Bulletin*, *39*(6), 1219–1229. https://doi.org/10.1093/schbul/sbs093

Katzner, S., Busse, L., & Carandini, M. (2011). GABAA inhibition controls response gain in visual cortex. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *31*(16), 5931–5941. https://doi.org/10.1523/JNEUROSCI.5753-10.2011

Kern, R. S., Nuechterlein, K. H., Green, M. F., Baade, L. E., Fenton, W. S., Gold, J. M., … Marder, S. R. (2008). The MATRICS consensus cognitive battery: Part 2. Co-norming and standardization. *American Journal of Psychiatry*, *165*, 214–220.

Kovacs, G., Kaiser, D., Kaliukhovich, D. A., Vidnyanszky, Z., & Vogels, R. (2013). Repetition probability does not affect fMRI repetition suppression for objects. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *33*(23), 9805–9812. https://doi.org/10.1523/JNEUROSCI.3423-12.2013

Krystal, J. H., Anticevic, A., Yang, G. J., Dragoi, G., Driesen, N. R., Wang, X. J., & Murray, J. D. (2017). Impaired tuning of neural ensembles and the pathophysiology of schizophrenia: A translational and computational neuroscience perspective. *Biological Psychiatry*, *81*(10), 874–885. https://doi.org/10.1016/j.biopsych.2017.01.004

Larsson, J., Solomon, S. G., & Kohn, A. (2016). fMRI adaptation revisited. *Cortex*, *80*, 154–160. https://doi.org/10.1016/j.cortex.2015.10.026

Leucht, S., Samara, M., Heres, S., Patel, M. X., Woods, S. W., & Davis, J. M. (2014). Dose equivalents for second-generation antipsychotics: The minimum effective dose method. *Schizophrenia Bulletin*, *40*(2), 314–326. https://doi.org/10.1093/schbul/sbu001

Lewis, D. A., Hashimoto, T., & Volk, D. W. (2005). Cortical inhibitory neurons and schizophrenia. *Nature Reviews Neuroscience*, *6*(4), 312–324. doi:nrn1648 [pii]. https://doi.org/10.1038/nrn1648

MacQueen, G. M., Young, L. T., Galway, T. M., & Joffe, R. T. (2001). Backward masking task performance in stable, euthymic out-patients with bipolar disorder. *Psychological Medicine*, *31*(7), 1269–1277.

Malach, R. (2012). Targeting the functional properties of cortical neurons using fMR-adaptation. *NeuroImage*, *62*(2), 1163–1169. https://doi.org/10.1016/j.neuroimage.2012.01.002

Manelis, A., Wheeler, M. E., Paynter, C. A., Storey, L., & Reder, L. M. (2011). Opposing patterns of neural priming in same-exemplar vs. different-exemplar repetition predict subsequent memory. *NeuroImage*, *55*(2), 763–772. https://doi.org/10.1016/j.neuroimage.2010.12.034

Mruczek, R. E., & Sheinberg, D. L. (2007). Activity of inferior temporal cortical neurons predicts recognition choice behavior and recognition time during visual search. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *27*(11), 2825–2836. https://doi.org/10.1523/JNEUROSCI.4102-06.2007

Ollinger, J. M., Corbetta, M., & Shulman, G. L. (2001). Separating processes within a trial in event-related functional MRI. *NeuroImage*, *13*(1), 218–229.

Ollinger, J. M., Shulman, G. L., & Corbetta, M. (2001). Separating processes within a trial in event-related functional MRI. *NeuroImage*, *13*(1), 210–217.

Passeri, A., Capotosto, P., & Di Matteo, R. (2015). The right hemisphere contribution to semantic categorization: A TMS study. *Cortex*, *64*, 318–326. https://doi.org/10.1016/j.cortex.2014.11.014

Pizzagalli, D. A., Goetz, E., Ostacher, M., Iosifescu, D. V., & Perlis, R. H. (2008). Euthymic patients with bipolar disorder show decreased reward learning in a probabilistic reward task. *Biological Psychiatry*, *64*(2), 162–168. https://doi.org/10.1016/j.biopsych.2007.12.001

Pourtois, G., Schwartz, S., Spiridon, M., Martuzzi, R., & Vuilleumier, P. (2009). Object representations for multiple visual categories overlap in lateral occipital and medial fusiform cortex. *Cerebral Cortex*, *19*(8), 1806–1819. doi: bhn210[pii]. https://doi.org/10.1093/cercor/bhn210

Reavis, E. A., Lee, J., Wynn, J. K., Engel, S. A., Cohen, M. S., Nuechterlein, K. H., … Green, M. F. (2017). Assessing neural tuning for object perception in schizophrenia and bipolar disorder with multivariate pattern analysis of fMRI data. *Neuroimage: Clinical*, *16*, 491–497.

Reavis, E. A., Lee, J., Wynn, J. K., Engel, S. A., Jimenez, A. M., & Green, M. F. (2017). Cortical thickness of functionally defined visual areas in schizophrenia and bipolar disorder. *Cerebral Cortex*, *27*(5), 2984–2993. https://doi.org/10.1093/cercor/bhw151

Rokem, A., Yoon, J. H., Ooms, R. E., Maddock, R. J., Minzenberg, M. J., & Silver, M. A. (2011). Broader visual orientation tuning in patients with schizophrenia. *Frontiers in Human Neuroscience*, *5*, 127. https://doi.org/10.3389/fnhum.2011.00127

Sapountzis, P., Schluppeck, D., Bowtell, R., & Peirce, J. W. (2010). A comparison of fMRI adaptation and multivariate pattern classification analysis in visual cortex. *NeuroImage*, *49*(2), 1632–1640. https://doi.org/10.1016/j.neuroimage.2009.09.066

Sayres, R., & Grill-Spector, K. (2006). Object-selective cortex exhibits performance-independent repetition suppression. *Journal of Neurophysiology*, *95*(2), 995–1007. https://doi.org/10.1152/jn.00500.2005

Schallmo, M. P., Sponheim, S. R., & Olman, C. A. (2013). Abnormal contextual modulation of visual contour detection in patients with schizophrenia. *PLoS One*, *8*(6), e68090. https://doi.org/10.1371/journal.pone.0068090

Segaert, K., Weber, K., de Lange, F. P., Petersson, K. M., & Hagoort, P. (2013). The suppression of repetition enhancement: A review of fMRI studies. *Neuropsychologia*, *51*(1), 59–66. https://doi.org/10.1016/j.neuropsychologia.2012.11.006

Sehatpour, P., Dias, E. C., Butler, P. D., Revheim, N., Guilfoyle, D. N., Foxe, J. J., & Javitt, D. C. (2010). Impaired visual object processing across an occipital-frontal-hippocampal brain network in schizophrenia: An integrated neuroimaging study. *Archives of General Psychiatry*, *67*(8), 772–782. https://doi.org/10.1001/archgenpsychiatry.2010.85

Silverstein, S. M., Demmin, D. L., & Bednar, J. A. (2017). Computational modeling of contrast sensitivity and orientation tuning in first-episode and chronic schizophrenia. *Computers in Psychiatry*, *1*, 102–131. https://doi.org/10.1162/CPSY_a_00005

Silverstein, S. M., Harms, M. P., Carter, C. S., Gold, J. M., Keane, B. P., MacDonald, A., 3rd, … Barch, D. M. (2015). Cortical contributions to impaired contour integration in schizophrenia. *Neuropsychologia*, *75*, 469–480. https://doi.org/10.1016/j.neuropsychologia.2015.07.003

Sim, M. S., Mohamed, Z., Hatim, A., Rajagopal, V. L., & Habil, M. H. (2010). Association of brain-derived neurotrophic factor (Val66Met) genetic polymorphism with methamphetamine dependence in a Malaysian population. *Brain Research*, *1357*, 91–96. https://doi.org/10.1016/j.brainres.2010.08.053

Simons, J. S., Koutstaal, W., Prince, S., Wagner, A. D., & Schacter, D. L. (2003). Neural mechanisms of visual object priming: Evidence for perceptual and semantic distinctions in fusiform cortex. *NeuroImage*, *19*(3), 613–626.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*, S208–S219.

Soldan, A., Zarahn, E., Hilton, H. J., & Stern, Y. (2008). Global familiarity of visual stimuli affects repetition-related neural plasticity but not repetition priming. *NeuroImage*, *39*(1), 515–526. https://doi.org/10.1016/j.neuroimage.2007.08.011

Solomon, S. G., & Kohn, A. (2014). Moving sensory adaptation beyond suppressive effects in single neurons. *Current Biology*, *24*(20), R1012–R1022. https://doi.org/10.1016/j.cub.2014.09.001

Sponheim, S. R., Sass, S. M., Noukki, A. L., & Hegeman, B. M. (2013). Fragile early visual percepts mark genetic liability specific to schizophrenia. *Schizophrenia Bulletin*, *39*(4), 839–847. https://doi.org/10.1093/schbul/sbs041

Turk-Browne, N. B., Yi, D. J., & Chun, M. M. (2006). Linking implicit and explicit memory: Common encoding factors and shared representations. *Neuron*, *49*(6), 917–927. https://doi.org/10.1016/j.neuron.2006.01.030

Van den Stock, J., de Jong, S. J., Hodiamont, P. P., & de Gelder, B. (2011). Perceiving emotions from bodily expressions and multisensory integration of emotion cues in schizophrenia. *Social Neuroscience*, *6*(5–6), 537–547. https://doi.org/10.1080/17470919.2011.568790

Ventura, J., Lukoff, D., Nuechterlein, K. H., Liberman, R. P., Green, M. F., & Shaner, A. (1993). Brief psychiatric rating scale (BPRS) expanded version: Scales, anchor points, and administration manual. *International Journal of Methods in Psychiatric Research*, *3*, 227–243.

Wang, Y., Fujita, I., & Murayama, Y. (2000). Neuronal mechanisms of selectivity for object features revealed by blocking inhibition in inferotemporal cortex. *Nature Neuroscience*, *3*(8), 807–813. https://doi.org/10.1038/77712

Ward, E. J., Chun, M. M., & Kuhl, B. A. (2013). Repetition suppression and multi-voxel pattern similarity differentially track implicit and explicit visual memory. *Journal of Neuroscience*, *33*(37), 14749–14757. https://doi.org/10.1523/JNEUROSCI.4889-12.2013

Wilkinson, G. S. (1993). *Wide Range Achievement Test* (3rd ed.). Lutz, FL: PAR/Psychological Assessment Resource.

Wynn, J. K., Green, M. F., Engel, S., Korb, A., Lee, J., Glahn, D., … Cohen, M. S. (2008). Increased extent of object-selective cortex in schizophrenia. *Psychiatry Research*, *164*(2), 97–105. https://doi.org/10.1016/j.pscychresns.2008.01.005

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: Reliability, validity and sensitivity. *British Journal of Psychiatry*, *133*, 429–435.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Lee J, Reavis EA, Engel SA, et al. fMRI evidence of aberrant neural adaptation for objects in schizophrenia and bipolar disorder. *Hum Brain Mapp*. 2019;40:1608–1617. https://doi.org/10.1002/hbm.24472