NeuroImage: Clinical 16 (2017) 491–497

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Assessing neural tuning for object perception in schizophrenia and bipolar disorder with multivariate pattern analysis of fMRI data

Eric A. Reavis[a,b,*], Junghee Lee[a,b], Jonathan K. Wynn[a,b], Stephen A. Engel[c], Mark S. Cohen[a], Keith H. Nuechterlein[a], David C. Glahn[d], Lori L. Altshuler[a,1], Michael F. Green[a,b]

[a] Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, CA 90024; USA
[b] Desert Pacific Mental Illness Research, Education, and Clinical Center, Greater Los Angeles Veterans Affairs Healthcare System, Los Angeles, CA 90073, USA
[c] Department of Psychology, University of Minnesota, Minneapolis, MN 55455; USA
[d] Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06511, USA

ARTICLE INFO

Keywords:
Schizophrenia
Bipolar disorder
fMRI
Multivariate pattern analysis
Visual perception

ABSTRACT

Introduction: Deficits in visual perception are well-established in schizophrenia and are linked to abnormal activity in the lateral occipital complex (LOC). Related deficits may exist in bipolar disorder. LOC contains neurons tuned to object features. It is unknown whether neural tuning in LOC or other visual areas is abnormal in patients, contributing to abnormal perception during visual tasks. This study used multivariate pattern analysis (MVPA) to investigate perceptual tuning for objects in schizophrenia and bipolar disorder.

Methods: Fifty schizophrenia participants, 51 bipolar disorder participants, and 47 matched healthy controls completed five functional magnetic resonance imaging (fMRI) runs of a perceptual task in which they viewed pictures of four different objects and an outdoor scene. We performed classification analyses designed to assess the distinctiveness of activity corresponding to perception of each stimulus in LOC (a functionally localized region of interest). We also performed similar classification analyses throughout the brain using a searchlight technique. We compared classification accuracy and patterns of classification errors across groups.

Results: Stimulus classification accuracy was significantly above chance in all groups in LOC and throughout visual cortex. Classification errors were mostly within-category confusions (e.g., misclassifying one chair as another chair). There were no group differences in classification accuracy or patterns of confusion.

Conclusions: The results show for the first time MVPA can be used successfully to classify individual perceptual stimuli in schizophrenia and bipolar disorder. However, the results do not provide evidence of abnormal neural tuning in schizophrenia and bipolar disorder.

1. Introduction

There is strong evidence that visual perception is abnormal in schizophrenia. People with the disorder exhibit poor performance on tasks involving visual masking, contour integration, motion discrimination, and other tests of perception (Butler et al., 2008; Green et al., 2009a, 2012; Javitt, 2009; Javitt and Freedman, 2015). Performance on such tests predicts functional outcomes in schizophrenia, suggesting that visual dysfunction might have important cascading effects (Green et al., 2012). There is also emerging evidence that similar, related perceptual deficits may exist in bipolar disorder, an illness that shares some phenotypic characteristics and genetic risk factors with schizophrenia (Chen et al., 2005; Chkonia et al., 2012; Jahshan et al., 2014).

Converging evidence suggests that abnormalities in the structure of visual cortex exist in schizophrenia and related disorders. Postmortem histological studies have shown reductions in the thickness or volume of visual cortex in schizophrenia (Dorph-Petersen et al., 2007; Selemon et al., 1995). Similarly, a recent in vivo structural MRI study found thinner visual cortex in schizophrenia than in controls, with intermediate cortical thickness in bipolar disorder (Reavis et al., 2017).

The function of visual cortex also appears to be abnormal in schizophrenia. Evidence from fMRI suggests that the receptive fields of neurons in early- and mid-level visual areas (V1, V2, and V4) have weaker inhibitory surrounds in schizophrenia than in controls (Anderson et al., 2017). There is also evidence of dysfunction in higher visual areas during perceptual tasks on which patients show deficits. In particular, the lateral occipital complex (LOC), an object-selective

* Corresponding author at: 760 Westwood Plaza, Room 27-440, Los Angeles, CA 90024, USA.
E-mail address: ereavis@ucla.edu (E.A. Reavis).
[1] Deceased.

http://dx.doi.org/10.1016/j.nicl.2017.08.023
Received 9 May 2017; Received in revised form 25 August 2017; Accepted 31 August 2017
Available online 01 September 2017

region, shows abnormal activity during visual masking and contour integration tasks (Green et al., 2009b; Silverstein et al., 2015).

A ubiquitous property of perceptually driven neurons is *preferential tuning*. Throughout the visual system, individual neurons respond more or less vigorously to stimuli in their receptive fields depending on the degree to which the features of the stimulus match the preference of the neuron. Neurons in early visual cortex are preferentially tuned to basic perceptual features such as orientation. Thus, a V1 neuron might respond most vigorously to stimuli containing image features at a particular orientation, and gradually less vigorously as the difference between the orientation content of the stimulus and the preferred orientation increases (Hubel and Wiesel, 1959). Similar tuning preferences exist in higher visual areas for more complex stimulus features. For example, converging evidence from human and animal studies suggests that neurons in LOC are tuned to visual objects, responding preferentially to specific object features (DiCarlo et al., 2012). Animal studies show that this type of neural tuning depends on gamma-aminobutyric acid-dependent (GABAergic) inhibitory mechanisms (Isaacson and Scanziani, 2011).

Various seemingly disparate perceptual deficits found in schizophrenia and bipolar disorder could be parsimoniously explained by abnormalities in neural tuning. For example, deficits in contour integration and motion perception could each be related to aberrant neural tuning (in orientation- and motion-tuned cells, respectively). To our knowledge, only one published study has investigated neural tuning in schizophrenia. That study measured orientation tuning psychophysically and found evidence consistent with broadened orientation tuning in early visual cortex, which was linked to reduced GABA in that region (Rokem et al., 2011).

We hypothesized that broadened neural tuning for more complex visual features might also exist in schizophrenia or bipolar disorder. LOC contains object-tuned neurons and activity there is aberrant during various perceptual tasks in schizophrenia. Therefore, we decided to investigate tuning for object stimuli with LOC as a primary region of interest (ROI).

Evidence of perceptual tuning abnormalities in schizophrenia or bipolar disorder could provide new insights into the pathophysiology of the illnesses. The neural mechanisms and properties of tuning are similar across sensory modalities, so identification of tuning deficits in the visual system would suggest the possible presence of tuning deficits in other neural systems. Evidence of abnormal visual tuning would suggest a specific pathophysiological mechanism that might underlie various known visual deficits, which predict functional outcomes in schizophrenia. Thus, improved understanding of visual tuning could lead to innovative treatments in the future, either to ameliorate visual perception deficits specifically or to improve neural tuning more broadly across various neural systems.

In the current study, we used multivariate pattern analysis (MVPA) of fMRI data to investigate tuning for objects in schizophrenia and bipolar disorder. Unlike traditional univariate fMRI analyses, which assess the response of individual voxels in different experimental conditions, MVPA compares *patterns* of activity, spanning many voxels, across experimental conditions (Haxby et al., 2001). In our study, we used machine learning techniques to classify patterns of fMRI activity corresponding to specific visual stimuli: a classification algorithm was trained to distinguish experimental conditions based on patterns of activity among voxels in a selected area of the brain, then tested with unlabeled data held out of the training.

With this approach, classification accuracy depends upon the extent to which particular stimuli reliably evoke a unique pattern of activity in a given region, making it an indirect measure of tuning. Broadly tuned neurons would be expected to respond more similarly to different object images than narrowly tuned neurons would. In turn, these more similar neural responses would produce less distinctive patterns of fMRI activity, which are harder to classify accurately.

We performed two types of classification analyses: an ROI-based analysis of data from LOC, and a whole-brain searchlight analysis, which performs MVPA throughout the brain in a comprehensive set of small, overlapping, spherical regions (Kriegeskorte et al., 2006). While LOC is specifically an object-selective area, and thus the main focus of our analyses, we expected that stimulus classification would also be possible in other visual areas. That is because stimuli containing different object-level features must also contain different low-level features (e.g., orientation and spatial frequency content). These low-level differences are expected to evoke different patterns of activity in visual areas tuned to those features (e.g., early visual cortex). Thus, we expected that classification of the stimuli would be possible not only in LOC but throughout visual cortex, and that classification accuracy in each region would be commensurate to the specificity of neural tuning in that area.

Based on the hypothesis that participants with schizophrenia and bipolar disorder have broader visual tuning than healthy controls, we predicted that multivariate classification of object stimuli in LOC and other areas of visual cortex would be less accurate in patients than controls. We expected that this difference would manifest as a significant effect of group in omnibus tests of significance (ANOVAs). However, because we expected to find impairment in both patient groups, for the main analyses we also performed pairwise tests (*t*-tests) to separately compare each patient group to the control group with maximal statistical power.

2. Methods and materials

2.1. Participants

Participants came from an NIMH-sponsored study of visual processing in major mental illness. In total, 53 schizophrenia patients, 56 bipolar disorder patients, and 53 healthy controls participated in an MRI scan. However, data from a handful of participants in each group were unusable for a variety of reasons (e.g., missing data, excessive motion, or other factors causing data processing to fail). Those subjects were excluded from the analyses, leaving usable samples of 50 schizophrenia patients, 51 bipolar disorder patients, and 47 healthy controls.

All patient participants were clinically stable outpatients with a DSM-IV diagnosis of either schizophrenia or bipolar disorder. Patient participants were on clinically-determined doses of medication and were tested outside of mood episodes. Patients were recruited from outpatient treatment facilities in the Los Angeles area, University of California, Los Angeles (UCLA) outpatient clinics, and mental health clinics at the Veterans Affairs Greater Los Angeles Healthcare System (GLA). Healthy participants were a matched community sample recruited with internet ads. All recruitment methods and experimental procedures were approved by the Institutional Review Boards of GLA and UCLA. All participants provided written informed consent prior to participation.

Selection criteria for all subjects included: a) age 18–65, b) understanding of spoken English sufficient to comprehend testing procedures, c) no evidence of IQ < 70 or developmental disability based on chart review, d) no medical history of clinically significant neurological disease (e.g., epilepsy), e) no history of serious head injury (i.e., loss of consciousness > 1 h, neuropsychological sequelae, cognitive rehabilitation post-head-injury), f) no sedatives or benzodiazepines within 12 h of testing, g) normal or corrected vision, h) no positive urine toxicology screening on day of assessment, i) no known contraindications for MRI scanning, j) no evidence of substance or alcohol dependence in the past three months or of substance or alcohol abuse in the past month, and k) no history of a mood episode in the past two months.

Selection criteria for patient participants included: a) diagnosis of schizophrenia or bipolar disorder based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1997), and