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Machine learning fMRI classifier delineates subgroups of schizophrenia patients

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ABSTRACT

Background: The search for a validated neuroimaging-based brain marker in psychiatry has thus far been fraught with both clinical and methodological difficulties. The present study aimed to apply a novel data-driven machine-learning approach to functional Magnetic Resonance Imaging (fMRI) data obtained during a cognitive task in order to delineate the neural mechanisms involved in two schizophrenia subgroups: schizophrenia patients with and without Obsessive–Compulsive Disorder (OCD).
Methods: 16 schizophrenia patients with OCD ("schizo-obsessive"), 17 pure schizophrenia patients, and 20 healthy controls underwent fMRI while performing a working memory task. A whole brain search for activation clusters of cognitive load was performed using a recently developed data-driven multi-voxel pattern analysis (MVPA) approach, termed Searchlight Based Feature Extraction (SBFE), and which yields a robust fMRI-based classifier.
Results: The SBFE successfully classified the two schizophrenia groups with 91% accuracy based on activations in the right intraparietal sulcus (r-IPS), which further correlated with reduced symptom severity among schizo-obsessive patients.
Conclusions: The results indicate that this novel SBFE approach can successfully delineate between symptom dimensions in the context of complex psychiatric morbidity.

1. Introduction

The search for neuroimaging based brain markers in psychiatry has faced two major methodological hurdles. The first is that a region-of-interest (ROI) approach requires a neuro-anatomical hypothesis, whose pathophysiological validity isn't always evident and which provides a limited scope of findings. The second is that in whole brain data-driven approach sensitivity is compromised by the large number of multiple comparisons (Hendler et al., 2014).

Further complicating this effort is the fact that current clinical diagnostic systems are category-based and not symptom-domain specific. Thus, schizophrenia and Obsessive–Compulsive Disorder (OCD) have traditionally been viewed as two distinct psychopathologies with differing underlying pathophysiologies (Kurokawa et al., 2000). Nevertheless, there is compelling evidence for the co-occurrence of obsessive–compulsive symptoms (OCS) in a substantial proportion of schizophrenia patients (roughly 25%) (Poyurovsky et al., 2012), termed "schizo-obsessive" when there is frank OCD. Schizo-obsessive patients appear to have a more deteriorative course, with poorer prognosis and treatment responses, as compared to their non-OCD schizophrenia counterparts (Poyurovsky et al., 2012). In terms of neuroimaging findings, while there is vast literature regarding the neural mechanisms (structural and functional) involved in schizophrenia and in OCD separately, there is scarce data regarding the functional neurobiological substrates involved in schizophrenia-OCD co-morbidity.

Hypofrontality, expressed as reduced neural activation in the dorsolateral prefrontal cortex (DLPFC) (Callicott, 2003), is the most replicated functional brain imaging finding in SCH patients. Therefore, in order to characterize some of the abnormalities in functional brain circuits in schizo-obsessive patients, we previously used fMRI during a working memory task, namely, the N-back task, in which schizophrenia (SCH) patients are known to display abnormal brain processing (Bleich-

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Cohen et al., 2014). Applying region-oriented analyses focusing on the right DLPFC and the right Caudate we demonstrated that schizo-obsessive patients exhibit remarkably similar brain activation patterns as their pure schizophrenia counterparts. Moreover, whole-brain analyses did not produce significant differences between the groups as well.

To further examine possible dissimilarities between these two schizophrenia groups in a data-driven manner, we chose to further apply a whole brain classification based on multi-voxel pattern analysis (MVPA) during the N-back task. MVPA approaches (Mur et al., 2009; Pereira et al., 2009; Orrù et al., 2012) utilize machine-learning algorithms that combine several different markers for classification and robust statistical analysis of the results. Current MVPA methods rely on either a small number of ROIs (Eger et al., 2007) or whole-brain activity (Mourão-Miranda et al., 2005; Fu et al., 2008). However, both approaches have major drawbacks: regional MVPA may achieve better classification accuracy than whole brain MVPA, but remains limited to hypothesis-driven assumptions, while whole brain MVPA may have difficulty achieving significant accuracy rates (Chu et al., 2012) and does not necessarily produce neuroscientifically interpretable results. To tackle this issue of neurological interpretability, some whole-brain studies use weights assigned by the classifier to the different markers in an attempt to produce an interpretation (Mourão-Miranda et al., 2005; Fu et al., 2008). However, this approach can lead to two equally important neural markers receiving substantially different weights, resulting in misleading interpretations (Lee et al., 2010). To overcome these limitations, we used a modified MVPA approach termed as Searchlight Based Feature Extraction (SBFE), which combines a data-driven ROI search with whole-brain classification (Jamshy et al., 2012). The goal of the present fMRI study was to evaluate whether SBFE can distinguish between these two schizophrenia subgroups and delineate the neurobiological substrates involved.

2. Materials and methods

2.1. Subjects

Three groups were evaluated in this study. The study group included sixteen inpatients (10 men, 6 women; mean age 27, range 19–32 years) who met DSM-IV criteria for both schizophrenic disorder and OCD. The comparison group included 17 schizophrenia inpatients (11 men, 6 women; mean age 25, range19–31 years) matched for age, gender and education, who were hospitalized in the same department (Tirat HaCarmel Mental Health Center) during the same time period. The control group included twenty healthy volunteers (12 men, 8 women; mean age 26, range 20–35 years) recruited using an advertisement. All participants were right-handed Hebrew speakers with adequate language comprehension. All participants gave written informed consent, approved by the Institutional Review Boards of both Tirat Carmel Hospital and the Tel Aviv Sourasky Medical Center.

2.2. Patient evaluation

The Structured Clinical Interview for DSM-IV Axis-I disorders, Patient Edition (First et al., 1994) was used for the diagnosis of schizophrenia and OCD. All patients were interviewed after the resolution of acute psychosis. Severity and content of OCS were evaluated using the Yale–Brown Obsessive–Compulsive Scale (Y–BOCS), (Goodman WK et al., 1989). To be included in the schizo-obsessive group, patients had to have typical OCS that are time-consuming (≥1 h a day), distressful obsessions and/or compulsions which significantly interfere with patient's functioning, and present for ≥6 months. Severity of schizophrenia symptoms was assessed using the Schedule for the Assessment of Positive Symptoms (SAPS, (Andreasen, 1984)) and the Schedule for the Assessment of Negative Symptoms (SANS, (Andreasen, 1983)).

2.3. Neurocognitive task

While scanned, subjects performed the N-back task composed of two conditions, 0-back and 2-back, interspersed by periods of no stimuli. The visual stimuli consisted of 60 achromatic numbers with a red fixation point added at the center of the image. Numbers were prepared for presentation with Adobe Photoshop 5.0. The trial consisted of 6 alternating blocks of the two conditions and 8 baseline blocks. Following instructions, conditions were presented as a series of one digit numbers. During the 0-back condition subjects were required to indicate with a gentle finger tap whenever the number 9 appeared. During the 2-back condition subjects were required to indicate whenever a number appeared 2 steps before (e.g. 4 6 8 6 2 3). During the baseline condition subjects were instructed to concentrate on the fixation point in the middle of the screen. Each block consisted of 10 stimuli. Stimuli presentation rate was 2 s (1 s per number interposed with 1 s blank). There were 21 s of no stimuli at the beginning and 6 s at the end of the paradigm. There were 6-s periods of rest between blocks. The stimuli sequences were generated on a PC and projected via an LCD projector (Epson MP 7200) onto a translucent tangent screen located on the head coil in front of the subject's forehead. Subjects viewed the screen through a tilted mirror fixed to the head coil. Prior to the fMRI experiment all participants underwent a preparatory session in which adequate compliance was assured and documented.

During the fMRI experiment the participants were provided with a response box, and were required to press a button with their right hand during the “0-back” condition, and to press a button with their left hand during the “2-back” condition. Participants' reaction time and accuracy were recorded.

2.4. Image acquisition

Imaging was performed on a GE 1.5T Sigma Horizon LX 8.25 echo speed scanner (Milwaukee, WI, USA) with a resonant gradient echoplanar imaging system. All images were acquired using a standard quadrature head coil. The scanning session included anatomical and functional imaging. Anatomical imaging consisted of 27 contiguous axial T1-weighted slices of 4-mm thickness, with 1-mm gaps that were prescribed based on a sagital localizer and covered the whole brain. In addition, a three-dimensional (3D) spoiled gradient echo (SPGR) sequence with high resolution (a slice thickness of 2 mm) was acquired for each subject, in order to allow volume statistical analyses of the functional signal change. Functional imaging included T2*-weighted images that were acquired at the same locations as the spin-echo T1-weighted anatomical images, at runs of 1190 images each (70 images per slice). BOLD contrast was acquired with gradient-echo echo-planar imaging (EPI) sequence (TR/TE/Flip angle = 3000/55/90°; with FOV 24 × 24 cm2; matrix size 80 × 80).

2.5. fMRI analysis

Preprocessing of the functional scans included head movement assessment, high-frequency temporal filtering, removal of linear trends, and transformation into Talairach space. Using brain voyager software, statistical parametric maps of the specific contrast of all visual (o back and 2 back) were calculated, in order to prevent bias and to examine whether patients can discriminate between the two conditions. These statistical parametric maps were calculated separately for each subject and averaged across subjects per group (Bleich-Cohen et al., 2014).

Our SBFE (Jamshy et al., 2012) approach applied MVPA to GLM contrast values to search for spherical regions that best distinguished between the two populations with regard to a specific condition. It