# DIAGNOSTIC CLASSIFICATION WITH NEURAL CORRELATES OF VERBAL FLUENCY DISTINGUISHES SCHIZOPHRENIA FROM BIPOLAR DISORDER AND HEALTHY INDIVIDUALS

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*Background*

We sought to examine whether the pattern of brain activation during verbal fluency could be useful in the diagnosis of schizophrenia, as individuals with this disorder show distinct neural correlates during verbal fluency tasks. To approximate a clinically relevant diagnostic challenge, we included as control subjects not only healthy individuals, but also patients with bipolar disorder.

*Methods*

104 right-handed subjects were scanned using fMRI while performing a phonological verbal fluency task with two levels of difficulty. Subjects were 32 patients with schizophrenia, 32 patients with bipolar disorder and 40 healthy volunteers. A support vector machine classification algorithm was applied to each subject's brain activation map, yielding a predicted diagnosis. We compared this computerized diagnostic label with the clinical gold-standard diagnosis produced by consultant psychiatrists following DSM-IV criteria.

*Results*

In the initial two-group analysis, the computerized algorithm produced 90% correct diagnoses when identifying schizophrenia subjects relative to healthy controls, and 75% accuracy when classifying schizophrenia subjects from bipolar disorder. This method also distinguished bipolar disorder subjects from healthy controls with 69% accuracy. In the more complex three-way classification (Table 1), the algorithm produced the correct diagnosis for 71% of all 104 subjects, with better results for patients with schizophrenia than for patients with bipolar disorder, who were often misdiagnosed as healthy controls. The areas that contributed the most to the classification included a fronto-temporal network identified in previous studies on verbal fluency, right precuneus, and thalamus (Figure 1).

*Conclusions*

Accurate differential diagnosis of schizophrenia patients relative to bipolar disorder and healthy controls was achieved with computerized analysis of individual brain activation during verbal fluency. Pattern classification of fMRI measurements may provide a step towards developing neurobiological diagnostic tools for schizophrenia.

**Table 1. Classification results for the 3-group diagnostic classification combining easy and difficult verbal fluency.**

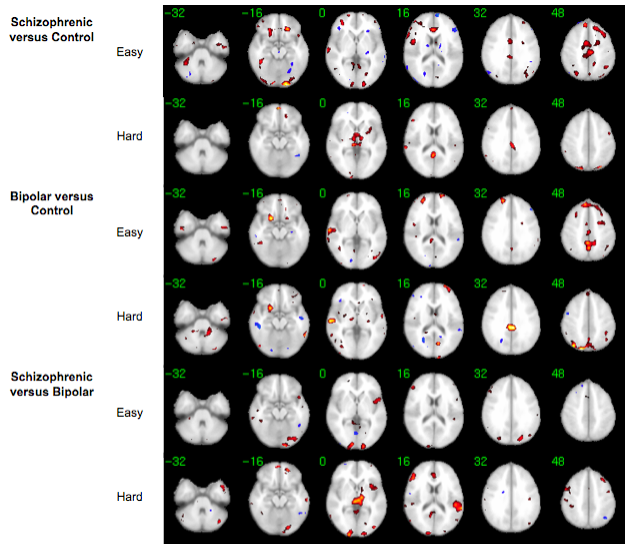
| DSM-IV diagnostic labels | SVM predicted labels: Schizophrenia | Bipolar | Control |
|---|---|---|---|
| Schizophrenia | 27 | 1 | 4 |
| Bipolar | 5 | 12 | 15 |
| Control | 2 | 3 | 35 |

| | Sensitivity | Specificity |
|---|---|---|
| Schizophrenia | 84.4% | 90.3% |
| Bipolar | 37.5% | 94.4% |
| Control | 87.5% | 70.3% |

Overall Classification Accuracy = 71.2% ($p<0.001$)

Note: Classification accuracy corresponds to the proportion out of all subjects correctly classified to their DSM-IV diagnostic group by the suport vector machine procedure, and it was computed using the leave-one-out method. The p-value was obtained by permutation and is applicable to this overall accuracy. Sensitivity and specificity were computed for each group separately. For instance, 27 of 32 (84.38%) of schizophrenic subjects were correctly classified by the algorithm, while 65 of 72 (90.28%) of bipolar and control subjects were correctly classified as non-schizophrenic.

**Fig 1. Discrimination scores for pair-wise classifications.**




Although the classification algorithm was based on the pattern of activity across the whole brain, some areas provided a stronger contribution to the classification decision. Regions colored in red have high discriminative score for the first group in each classification, and regions in blue for the second group (ie. schizophrenia (red) and healthy individuals (blue); bipolar disorder (red) and healthy individuals (blue); and schizophrenia (red) and bipolar disorder (blue)). Higher BOLD response in colored areas at the individual level tipped the diagnostic decision one way or another. Integrating all pair-wise classifications created the 3-way classification algorithm. Transverse brain images are presented in radiological convention with z-coordinates from -32 to + 48.