Cortical folding and the potential for prognostic neuroimaging in schizophrenia

Shuixia Guo1,6, Sarina Iwabuchi2,3*, Vijender Balain4, Jianfeng Feng5,6, Peter Liddle2,3, Lena Palaniyappan2,3,4.

1College of Mathematics and Computer Science, Key Laboratory of High Performance Computing and Stochastic Information Processing (Ministry of Education of China), Hunan Normal University, Changsha, PR China.
2Division of Psychiatry & Applied Psychology, University of Nottingham, Nottingham, UK.
3Centre for Translational Neuroimaging, Institute of Mental Health, Nottingham, UK.
4Penticton Regional Hospital, 550 Carmi Avenue, Penticton, British Columbia, Canada.
5Shanghai Center for Mathematical Sciences, Fudan University, Shanghai 200433, PR China.
6Department of Computer Science, University of Warwick, Coventry CV4 7AL, UK.

* equal contribution

Key words: gyrification, schizophrenia, prognosis, thickness, severity, pattern classification, support vector machine

Number of words:
Summary: 90
Article (excl. cites): 1166
Figures: 0
Tables: 1

Address correspondence to: Dr. Lena Palaniyappan, Room-09, C Floor, Institute of Mental Health Building, Triumph Road, Nottingham, NG7 2TU, England, United Kingdom. Phone: +44 (115) 823 0407; Fax: 44 (115) 823 0433; E-mail: Lena.Palaniyappan@nottingham.ac.uk

Funding information: This work was funded by the Medical Research Council (UK) Grant Number: G0801442. L Palaniyappan is supported by the Wellcome Trust (Research Training Fellowship WT096002/Z/11).

Conflicts of interest: L Palaniyappan received a travel fellowship sponsored by Eli Lilly in 2011, and support in kind from Magstim Company Ltd for a conference presentation in 2014. In the past five years, P F Liddle has received honoraria for academic presentations from Janssen-Cilag and Bristol Myers Squibb; and has taken part in advisory panels for Bristol Myers Squibb. All other authors declare no conflict of interest. S Guo is supported by the National Natural Science Foundation of China (NSFC) grant (No. 11271121), Program for New Century Excellent Talents in University (NCET-13-0786) grant.
SUMMARY
The use of multivariate classification in objectively discriminating patients with schizophrenia from healthy controls has provided some promising results to date, though the utility of this approach in predicting severity of illness in those with an established diagnosis of schizophrenia remains unknown. We used neuroanatomical information derived from structural imaging to identify patients with more severe illness, characterized by high symptom burden, low processing speed, high degree of illness persistence and lower social and occupational functional capacity. Cortical folding, but not thickness or volume, showed a high discriminatory ability in correctly identifying patients with more severe illness.
To date there are no objectives tests that aid prognostic prediction in schizophrenia. Historically, clinical outcomes have improved considerably for medical disorders where severity can be quantified reliably (e.g. malignancies, asthma). Prognostic prediction, in particular the ability to identify those who will do well in the long term, has proved to be a great challenge in schizophrenia. Neuroimaging offers great promise of providing objective measures of clinical utility in managing psychosis. In recent times, the use of multivariate pattern classification in neuroimaging has enabled diagnostic separation at a single subject level. In this study, we investigated whether this approach can reliably discriminate a patient with less severe illness from one with more severe illness. Given the previous observations that cortical thickness, folding patterns and grey matter volume relate to prognosis in schizophrenia, we employed these surface-based morphometric measures to identify illness severity.

Methods

A sample of 41 patients with DSM-IV diagnosis of schizophrenia or schizoaffective disorder were recruited for this study. This sample is described in detail in our previous studies. The clinical severity was quantified using a composite index derived from symptom burden, functional ability, cognition and persistence of illness as described in our previous work and in the supplement. Using this severity index, 20 subjects were classified to have high severity while the remaining 21 had low severity. The clinical and demographic characteristics of the two groups are presented in the Supplement.

The structural MRI scan obtained from the subjects were processed using Freesurfer (http://surfer.nmr.mgh.harvard.edu/) as previously described. Cortical folding was measured using LGI proposed by Schaer et al. Cortical thickness was estimated using the standard procedures described by Fischl and Dale. The reconstructed brain surfaces were parcellated using the Destrieux atlas to provide 148 brain
regions based on sulcogyral boundaries described by Duvernoy\textsuperscript{13}. For each metric, these 148 values were used as features in the classifier.

We used a linear support vector machine (SVM) proposed by Cortes and Vapnik (14) and implemented by the libsvm toolkit (http://www.csie.ntu.edu.tw/~cjlin/libsvm/). SVM is a statistical discrimination procedure that finds a linear separation surface in the high-dimensional multivariate feature space that maximally separates the training data into two classes as specified by the pre-assigned labels (in this case, high and low severity groups). Based on this separation, the class membership of a new subject (test data) can be predicted, and the accuracy of these predictions quantified. Further details on the statistical procedures are given in the supplement. We computed test performance measures and diagnostic odds ratio using a leave-one-subject-out (LOSO) cross validation approach. The statistical significance of these measures was determined by way of permutation testing ($n=1000$ permutations).

Results

Table 1 displays the accuracy of the prognostic classification based on the 2 morphometric measures. The highest prediction accuracy was obtained from gyrification measures. The most significant predictors of this classifier are also listed in table 1.
### Table 1: Test performance measures of morphometric multivariate pattern classifiers

<table>
<thead>
<tr>
<th></th>
<th>Accuracy (p values)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Likelihood Ratio (Positive &amp; Negative)</th>
<th>Diagnostic Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regional Thickness</strong></td>
<td>65.9% (0.07)</td>
<td>70%</td>
<td>61.9%</td>
<td>1.84, 0.48</td>
<td>3.79</td>
</tr>
<tr>
<td><strong>Regional Gyrification</strong></td>
<td>79.2% (0.004)</td>
<td>60%</td>
<td>85.7%</td>
<td>4.20, 0.47</td>
<td>9.00</td>
</tr>
<tr>
<td><strong>Regional Volume</strong></td>
<td>51.2% (0.5)</td>
<td>0%</td>
<td>100%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Most significant predictors among regional gyrification values

<table>
<thead>
<tr>
<th>Direction of difference</th>
<th>Mean (SD) in low severity group</th>
<th>Mean (SD) in high severity group</th>
<th>T value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right lateral occipitotemporal sulcus Low&gt;High</td>
<td>2.6867</td>
<td>2.5935</td>
<td>2.8051</td>
<td>0.0078</td>
</tr>
<tr>
<td>Left inferior orbitofrontal gyrus Low&gt;High</td>
<td>3.8257</td>
<td>3.4825</td>
<td>2.4911</td>
<td>0.0171</td>
</tr>
<tr>
<td>Left middle temporal gyrus Low&gt;High</td>
<td>3.2919</td>
<td>3.1235</td>
<td>2.4481</td>
<td>0.0190</td>
</tr>
<tr>
<td>Right inferior temporal gyrus Low&gt;High</td>
<td>2.6367</td>
<td>2.5595</td>
<td>2.3143</td>
<td>0.0260</td>
</tr>
<tr>
<td>Right inferior occipital gyrus and sulcus Low&gt;High</td>
<td>2.6690</td>
<td>2.5765</td>
<td>2.2993</td>
<td>0.0269</td>
</tr>
<tr>
<td>Left inferior temporal sulcus Low&gt;High</td>
<td>2.8695</td>
<td>2.7540</td>
<td>2.2329</td>
<td>0.0314</td>
</tr>
<tr>
<td>Left superior occipital gyrus Low&gt;High</td>
<td>2.7133</td>
<td>2.6060</td>
<td>2.0458</td>
<td>0.0476</td>
</tr>
<tr>
<td>Right posterior midcingulate sulcus and gyrus High&gt;Low</td>
<td>2.0790</td>
<td>2.1530</td>
<td>-2.0377</td>
<td>0.0484</td>
</tr>
</tbody>
</table>

Given that the gender and parental socioeconomic status differed between the two groups, we regressed out the variance explained by these two variables, and repeated the SVM analysis. As shown in the supplement, our results continued to show a superior, statistically significant accuracy for regional gyrification but not for thickness or volume.

**Discussion**
To our knowledge, this is the first study to investigate the prospect of exploiting multivariate neuroanatomical information to predict clinical severity of schizophrenia at the individual level. Using a classifier based on the features of cortical folding, we can identify the degree of illness severity in medicated, community-living patients with clinically stable schizophrenia. This predictive ability appears to be a unique feature of folding patterns, as the classifiers based on cortical thickness and volumetric features do not perform significantly above the chance level when separating the two groups of high and low illness severity.

While the accuracy achieved by the gyrification-based classifier is statistically significant, the performance of this classifier is considerably weaker when compared to the multivariate neuroanatomical classifiers tested in the separation of healthy controls from patients with schizophrenia. While there may be several reasons for this disparity, the use of median split to divide the sample into high and low severity could have contributed to the lack of very strong discriminative features between the two groups. With larger samples, extreme prognostic groups (lying on the rather end of the severity continuum) could be used for training the classifier and improve the accuracy. It is worth noting that in clinical practice, it is rarely necessary to apply a test to differentiate a patient with schizophrenia from a healthy control. The clinical classification of a patients with schizophrenia from a healthy control can already be done with a high degree of confidence, thus even a very highly performing neuroimaging test will have limited clinical utility. On the other hand, at present there are no reliable means of predicting prognostic group membership; even a test that increases the likelihood of identifying prognostic grouping to a moderate extent, could be of significant benefit to the patients and clinicians.

We quantified illness severity on the basis of a number of variables; this approach offered a multidomain metric that reflected symptom burden across the three
syndromes of schizophrenia, in addition to a cognitive function that is most prominently affected in schizophrenia i.e. processing speed, social and functional performance and persistence of illness. Nevertheless, various other metrics relevant for the assessment of severity (e.g. Clinical Global Impression, Quality of Life scales, self-rated recovery measures or assessments of daily living) were not collected in this study. Furthermore, from this cross-sectional study, it is not possible to extrapolate whether a gyrification-based classifier applied at illness onset could prospectively predict later severity. Nevertheless, when compared to cortical thickness and volume, gyrification has been shown to be relatively stable during the adult life\textsuperscript{17}. In addition, a large degree of variance in the cortical folding patterns relates to the neurodevelopmental integrity during the fetal or early neonatal period\textsuperscript{18}. Taken together, these observations suggest that the burden of neurodevelopmental abnormalities in a patient with schizophrenia could be a potential influence on illness severity.

Our results provide preliminary evidence for the utility of cortical folding in single subject-level prognostic imaging in schizophrenia. With larger validation studies that combine high-yield clinical prognostic indicators with gyrification metrics, the predictive value can be further improved, enabling an objective grading of outcome in the management of schizophrenia. This has the promise of assisting targeted service delivery and making personalized recommendations with regard to the required duration of antipsychotic treatment. Most importantly, this approach can be refined to provide accurate information on the chances of a satisfactory clinical recovery and thus potentially empower patients by addressing the uncertainty that surrounds prognosis in psychotic disorders.
REFERENCES


