NeuroImage 145 (2017) 238–245

Contents lists available at ScienceDirect

NeuroImage

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

# Classification of first-episode psychosis in a large cohort of patients using support vector machine and multiple kernel learning techniques

Letizia Squarcina [a,b], Umberto Castellani [c], Marcella Bellani [a,b], Cinzia Perlini [b,d], Antonio Lasalvia [a], Nicola Dusi [a,b], Chiara Bonetto [e], Doriana Cristofalo [e], Sarah Tosato [e], Gianluca Rambaldelli [b,e], Franco Alessandrini [f], Giada Zoccatelli [f], Roberto Pozzi-Mucelli [g], Dario Lamonaca [h], Enrico Ceccato [i], Francesca Pileggi [j], Fausto Mazzi [k], Paolo Santonastaso [l], Mirella Ruggeri [a,e], Paolo Brambilla [m,n,*] The GET UP Group[1]

[a] UOC Psychiatry, Azienda Ospedaliera Universitaria Integrata Verona (AOUI), Italy
[b] InterUniversity Centre for Behavioural Neurosciences (ICBN), University of Verona, Verona, Italy
[c] Department of Informatics, University of Verona, Verona, Italy
[d] Department of Public Health and Community Medicine, Section of Clinical Psychology, University of Verona, Verona, Italy
[e] Section of Psychiatry, Department of Neurological, Biomedical and Movement Sciences, University of Verona, Verona, Italy
[f] Neuroradiology Department, Azienda Ospedaliera Universitaria, Verona, Italy
[g] Department of Radiology, G.B. Rossi Hospital, University of Verona, Verona, Italy
[h] Department of Psychiatry, CSM AULSS 21 Legnago, Verona, Italy
[i] Department of Mental Health, Hospital of Montecchio Maggiore, Vicenza, Italy
[j] Department of Mental Health, Azienda ULSS Bologna, Bologna, Italy
[k] Department of Mental Health, Modena, Italy
[l] Department of Neuroscience, University of Padova, Padova, Italy
[m] Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy
[n] Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center at Houston, TX, USA

ARTICLE INFO

*Article history:*
Received 14 August 2015
Revised 25 November 2015
Accepted 6 December 2015
Available online 12 December 2015

*Keywords:*
Schizophrenia
Affective psychosis
Cortical thickness
MRI
Frontal
Temporal cortex

ABSTRACT

First episode psychosis (FEP) patients are of particular interest for neuroimaging investigations because of the absence of confounding effects due to medications and chronicity. Nonetheless, imaging data are prone to heterogeneity because for example of age, gender or parameter setting differences. With this work, we wanted to take into account possible nuisance effects of age and gender differences across dataset, not correcting the data as a pre-processing step, but including the effect of nuisance covariates in the classification phase. To this aim, we developed a method which, based on multiple kernel learning (MKL), exploits the effect of these confounding variables with a subject-depending kernel weighting procedure. We applied this method to a dataset of cortical thickness obtained from structural magnetic resonance images (MRI) of 127 FEP patients and 127 healthy controls, who underwent either a 3 Tesla (T) or a 1.5 T MRI acquisition. We obtained good accuracies, notably better than those obtained with standard SVM or MKL methods, up to more than 80% for frontal and temporal areas. To our best knowledge, this is the largest classification study in FEP population, showing that fronto-temporal cortical thickness can be used as a potential marker to classify patients with psychosis.



## Introduction

First episode psychosis (FEP) patients are of particular interest for Magnetic Resonance Imaging (MRI) studies because they allow the investigation of neurobiological processes involved in functional psychoses without the confounding effects of medications and chronicity. Several MRI studies have demonstrated changes in brain structure of FEP patients, in particular using the FreeSurfer software package: cortical thinning has been detected especially in frontal and temporal cortex (Gutiérrez-Galve et al., 2010; Price et al. 2010; Peruzzo et al. 2015, Koo et al. 2008, Sun et al. 2009,Janssen et al. 2009, Schultz et al. 2010b), and hippocampal cortex (Mechelli et al. 2011; Schultz et al. 2010a). Differently from voxel-based morphometry (VBM) or volumetric studies, Sprooten et al. (2013) found widespread thickness reduction in the whole gray matter, which could be explained by differences in the

* Corresponding author at: Dipartimento di Neuroscienze e Salute Mentale, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35, 20122 Milano, Italy. Tel.: +39 02 5032 0312 / 02 5503 2717.
*E-mail address:* paolo.brambilla1@unimi.it (P. Brambilla).
[1] see http://www.psychiatry.univr.it/page_getup/pdf/RESUB_Online_supplementary_Part%206_Ruggeri_GET%20UP_DEC4.pdf for details on the Authors.

http://dx.doi.org/10.1016/j.neuroimage.2015.12.007
1053-8119/

cortical folding of gray matter in subjects with high risk of developing schizophrenia in respect to healthy subjects (Harris et al., 2007). Other causes of cortical thinning could be related to axonal pruning or loss of neuropil (Schultz et al., 2010a).

Recently, there has been great interest towards automatic methods aimed to distinguishing subjects belonging to different groups, called classes, for example healthy subjects and psychotic patients, by using support vector machines (SVMs). The classes are separated on the basis of some characteristics, called features (Veronese et al., 2013). These methods, also referred to as machine learning or "classification methods", have been applied to mental disorders with good accuracies. From a purely clinical point of view, psychiatrists do not need automatic methods to diagnose psychosis or other major disorders. However, from a translational point of view, machine learning could help in understanding the biological basis of psychiatric diseases, highlighting the biological basis of psychosis (Koutsouleris et al., 2015).

A good accuracy has been reached in the case of mental illnesses (Veronese et al., 2013; Perina et al., 2014; Castellani et al., 2012). In a review examining the applications of machine learning to neuroimaging, Klöppel et al. (2012) showed how good accuracies can be reached in the case of mental illness as dementia, schizophrenia and depression. Regarding patients at psychosis onset, promising results have been achieved with accuracies up to 90% when considering deformations in respect to an atlas representing healthy subjects (Pohl and Sabuncu 2009). Other studies (Takayanagi et al., 2011, Borgwardt et al. 2013, Zanetti et al. 2013, Sun et al. 2009) demonstrated how patients can be separated from healthy controls on the basis or gray matter thickness, regional volumes or gray matter density, with accuracies which reached around 85%. In a previous work of our group, we showed how FEP can be differentiated from HC when considering blood perfusion in the brain (Squarcina et al., 2015).

A common problem of clinical datasets is that they are prone to be heterogeneous. Variability in the considered populations, due to confounding factors such as age or gender, could make it difficult to interpret the results (Sederman et al., 2006). In general, these factors, which cause a dispersion of the observed values, are considered as nuisance variables corrupting the acquired data (Sederman et al., 2006). For instance, in brain classification if the cortical thickness reduction is dependent on both the considered disease and normal aging, it may be difficult to discriminate between a young patient and an elderly control. Another common problem in brain data is the integration of data acquired with different MRI systems. The possibility of integrating MRI images acquired with different machines would be very useful, in particular in the case of classification problems, where an increased numerosity of the training set greatly helps in the process (Abdulkadir et al., 2011). We applied our method to images acquired with 1.5 T and 3.0 T, with the aim of distinguishing between the classes, overcoming the difference generated by the difference in the acquisition techniques.

A common approach to deal with data heterogeneity is to introduce a correction based on statistical regression (Takayanagi et al., 2011). For example, General Linear Model (GLM, Peter and Nelder, 1989) can be used to infer the contribution of the nuisance variable, which can then be removed from the data during the pre-processing phase. The most critical hypothesis of this method is that the effect of the variable, thus the association between the considered measures, is modeled as linear, which clearly impacts on the generalizability of this approach. Moreover, GLM needs large samples, which makes it difficult to be used in clinical settings where sample size is usually of few dozens of subjects.

In the case of different MRI machines, previous works (Abdulkadir et al., 2011; Mwangi et al., 2012) integrated acquired data without considering the possible introduction of confounds given by different hardware components, obtaining good classification accuracies.

In this work, we integrated the data correction into the learning phase by defining a classification model that explicitly takes into account the nuisance covariates. With the aim of combining different sources of information, we exploited the multiple kernel learning (MKL) (Gonen et al., 2011), which has already been applied to neuroimaging (Castro et al., 2011, Gönen and Alpaydin, 2011). The MKL methods (Gönen and Alpaydin, 2008; Bach et al., 2004) consider several kernels. Each kernel is associated with a different feature, and an optimal combination is learned, considering the interdependent information of the features. Simultaneously, the classifier is trained.

We wanted to modify the simple MKL formulation (Rakotomamonjy et al., 2008) to enable the correction of the covariate effect in the kernel space instead of the feature space. With our method, we employ a subject-specific kernel weighting scheme where each weight is locally dependent on the subject covariate. A similar strategy is localized kernel learning (Gönen and Alpaydin, 2008; Gönen and Alpaydin, 2011), where different weights are assigned to a kernel in different regions of the input space.

To our best knowledge, this is the largest classification study in FEP population and our aim was to improve the performances to automatically detect psychosis (Kuroki et al., 2006; Tang et al., 2012). We considered age and gender as confounding covariates in the classification, and we also took into consideration the MRI scanners.

## Materials and methods

### *Dataset*

#### *Subjects*

127 patients with a first episode of psychosis (FEP) (mean age +/− S.D. = 30.0 +/− 9.0 years old, 71 males) and 127 healthy controls (HC) (mean age +/− S.D. = 30.8 +/− 5.8 years old, 64 males) were recruited to take part to this study. 62 patients and HC were acquired with a 3.0 Tesla (T) MRI machine and 52 patients and HC with a 1.5 T MRI system. Written consent was obtained for all participants and the study was approved by the local Ethics Committee.

#### *Data acquired at 3.0 Tesla*

Sixty two FEP patients 29.3 +/− 8.9 years old, 35 males) and 62 HC (mean age +/− S.D. = 29.3 +/− 4.3 years old, 29 males) underwent a MRI session with a 3.0 T Siemens Allegra MRI scanner (Siemens Ag). No statistical differences in age were found between patients and controls ($p = 0.05$).

Patients who took part in these acquisitions were recruited in the frame of the GET UP Study (Genetic Endophenotype and Treatment: Understanding early Psychosis, National Coordinator: Professor Mirella Ruggeri, Verona, funded by the Italian Ministry of Health as part of a National Health Care Research Program — Ricerca Sanitaria Finalizzata) (Ruggeri et al., 2012, 2015) in the sub-Project COgnitive Neuroendophenotypes for Treatment and RehAbilitation of psychoses: Brain imaging, InflAmmation and StresS project (CONTRABASS, coordinator: Prof. Paolo Brambilla). Inclusion criteria were based on the screening method adopted in the WHO 10-country study (Ruggeri et al., 2012), and included: (1) age 18–54 years; (2) residence in the catchment area of participating CMHCs; (3) presence of at least one of the following symptoms: hallucinations, delusions, qualitative speech disorder, qualitative psychomotor disorder, bizarre or grossly inappropriate behavior; or at least two of the following symptoms: loss of interest, initiative and drive, social withdrawal, episodic severe excitement, purposeless destructiveness, overwhelming fear, marked self-neglect, as measured by the Screening Schedule for Psychosis (Ruggeri et al., 2012); (4) first lifetime contact with participating CMHCs. Patients had no history of head injury or substance or alcohol abuse in the six months prior to the MRI acquisition.

MRI data were obtained using a Siemens 3.0 T Magnetom Allegra MRI scanner (Siemens Ag). T1-weighted MPRAGE images were acquired with the following acquisition parameters: $256 \times 256 \times 256$ voxels, $1 \times 1 \times 1$ mm$^3$, TR 2060 ms, TE 3.93 ms, flip angle 15°.