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Review

Towards the identification of imaging biomarkers in schizophrenia, using multivariate pattern classification at a single-subject level☆

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ABSTRACT

Standard univariate analyses of brain imaging data have revealed a host of structural and functional brain alterations in schizophrenia. However, these analyses typically involve examining each voxel separately and making inferences at group-level, thus limiting clinical translation of their findings. Taking into account the fact that brain alterations in schizophrenia expand over a widely distributed network of brain regions, univariate analysis methods may not be the most suited choice for imaging data analysis. To address these limitations, the neuroimaging community has turned to machine learning methods both because of their ability to examine voxels jointly and their potential for making inferences at a single-subject level. This article provides a critical overview of the current and foreseeable applications of machine learning, in identifying imaging-based biomarkers that could be used for the diagnosis, early detection and treatment response of schizophrenia, and could, thus, be of high clinical relevance. We discuss promising future research directions and the main difficulties facing machine learning researchers as far as their potential translation into clinical practice is concerned.

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Contents

1. Introduction

Schizophrenia is a highly complex mental disorder characterized by hallucinations, delusions, cognition deficits and emotional disturbances. The diagnosis of schizophrenia primarily relies upon identifying clinical symptoms and the accurate assessment of behavioral signs through interview with a medical specialist. Considering, however, the variety of clinical presentations of the disorder among patients, the symptomatic overlap with other disorders such as Bipolar Disorder (Demirci and Calhoun, 2009) and the subjectivity involved in current psychiatric practice (Lawrie et al., 2011), reliable objective markers for diagnosing schizophrenia and related conditions are highly desirable.

Over the past years, schizophrenia has been intensively studied using neuroimaging techniques, such as structural and functional magnetic

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resonance imaging (sMRI and fMRI respectively) in order to identify the neurobiological processes underlying the disorder, with the ultimate scope of developing new diagnostic and therapeutic initiatives. There are now many sMRI and fMRI studies in schizophrenia which implicate a range of structural and functional brain abnormalities (Dauvermann et al., 2013; Lawrie and Abukmeil, 1998; Olabi et al., 2011; Wright et al., 2000), some of which are evident even before disease onset and are predictive of illness (Lawrie et al., 2008; Moorhead et al., 2013).

The majority of structural MRI studies have employed Region of Interest (ROI) or Voxel-based Morphometry (VBM) methods for the analysis of neuroimaging data, to compare groups of patients and groups of controls, and reported deficits mainly in the temporal and prefrontal lobes (Lawrie and Abukmeil, 1998; Meisenzahl et al., 2008), particularly in the superior temporal gyrus (Honea et al., 2005), the medial temporal lobe (Honea et al., 2005; Wright et al., 2000), including the amygdala and hippocampal complex and the parahippocampal gyrus, as well as enlargement of the lateral ventricles (Shenton et al., 2001). Similar structural abnormalities have been detected in groups of patients in the early stages of schizophrenia (Kubicki et al., 2002; Steen et al., 2006). These are less pronounced compared to the established state, suggesting active disease processes around the time of onset, although genetic factors, substance misuse, antipsychotic drug treatment and other factors may be partly responsible (Meisenzahl et al., 2008; Olabi et al., 2011). There are, similarly, replicated gray matter density changes over time in high-risk individuals as they develop schizophrenia, again particularly in the prefrontal and temporal lobes (Job et al., 2005; Pantelis et al., 2003). Moreover, functional MRI studies have examined differences in function and cognitive ability between schizophrenia and healthy controls, reporting abnormal activation in a network of brain regions, particularly implicating the prefrontal cortex (Meyer-Lindenberg, 2010) and connectivity from it to the rest of the brain (Lawrie et al., 2002).

Despite the fact that the univariate methods used in these analyses have delivered quite consistent and interesting results, they suffer, however, from certain limitations. ROI methods are confined to predefined brain regions and cannot capture distributed patterns of neuroanatomical and neurophysiological abnormality across the brain. VBM and other approaches to computational morphometry, on the other hand, require brain averaging and cannot capture individual deviations from the norm. To this end, the scientific community has turned to machine learning in an effort to detect the MRI correlates of clinical relevance and utility. Machine learning methods have already been applied in the analysis and interpretation of functional and structural MRI data (LaConte et al., 2005; Lemm et al., 2011; Pereira et al., 2009), in 'mind reading' paradigms (Cox and Savoy, 2002; Haynes and Rees, 2006), in the classification of cognitive states (Mitchell et al., 2004; Mourão-Miranda et al., 2005), and in lie detection approaches (Davatzikos et al., 2005a). More recently, classification algorithms have been applied to diagnose neurological and psychiatric disorders (Bray et al., 2009; Klöppel et al., 2011; Orru et al., 2012), such as dementia (Davatzikos et al., 2011; Klöppel et al., 2008a; Klöppel et al., 2008b), depression (Fu et al., 2008; Mourão-Miranda et al., 2011) and schizophrenia (Davatzikos et al., 2005b; Fan et al., 2008b; Koutsouleris et al., 2009; Koutsouleris et al., 2011). Multivariate pattern recognition techniques provide the possibility of making inferences about a subject's health status at an individual level and, thus, are well suited for clinical decision making purposes.

In this paper, we highlight the application of machine learning in the analysis of structural and functional MRI data in diagnosing schizophrenia, particularly for making an early prediction in people at high-risk of developing the disorder. We first give a brief overview of machine learning theory and the common processing steps that almost every machine learning method shares in their image analysis pipelines. Then, we discuss the studies that have employed machine learning in schizophrenia research and finally, we analyze the main practical challenges and limitations that machine learning methods suffer from, in the context of their potential integration into routine clinical practice, before concluding with future research directions.

2. Methods

The standard approach to the analysis of structural and functional MRI data is based on the General Linear Model (Friston et al., 1995), in that neuroimaging data are modeled as a linear combination of variables, potentially confounding parameters and some error. Statistical tests are then performed on each and every voxel independently in order to make inferences about effects of interest at a group-level, limiting the practical value of MRI in clinical settings. Multivariate pattern recognition methods have been used to overcome these limitations, by examining multiple voxels jointly, in order to identify patterns of differentiation between the groups and make inferences at a single-subject level.

2.1. Overview of machine learning

Machine learning (ML) is a term used to describe a set of methods for detecting patterns in data that would enable reliable future predictions. There are two major methodological approaches: supervised and unsupervised machine learning techniques. In supervised learning, the goal is to find a mapping from the data instances x_i to a set of desired outputs y_i, given a set of labeled input–output pairs $D = \{x_i, y_i\}$, for $i = 1 \ldots N$ instances. Here, D is the training set, consisting of feature vectors x_i and their corresponding labels drawn from label set y_i and N is the number of the training instances. If y_i is a categorical or nominal variable drawn from a finite set, for instance $y_i = \{1, 2, \ldots C\}$, then the problem is known as a classification problem. In its simplest form where $C = 2$ (and thus $y_i = \{-1, 1\}$) this is a binary classification problem, whereas if $C > 2$, then there is a multi-class classification problem. On the other hand, if y_i is a real-valued (continuous) variable, the problem is known as regression. In unsupervised learning, on the other hand, the goal is to identify an inherent structure in the data in order to classify given data instances $D = \{x_i\}$ into groups (clustering).

2.2. Classification pipeline

The following steps in the image analysis pipeline are common to most machine learning methods:

2.2.1. Preparation of the training set

The first step in an ML analysis is the creation of the training set. This procedure involves two main processes: i) feature extraction and ii) feature selection. Feature extraction involves the transformation of the original data set into a form that would be meaningful for the classifier to process. In the context of neuroimaging, this procedure entails the extraction of feature vectors corresponding to intensity values of voxels from each subject's scan. Feature selection involves a procedure for selecting those feature vectors that are better at discriminating between the classes and thus could facilitate and speed up the classification process. Feature selection can be performed either with a dimensionality reduction technique (such as Principal Component Analysis) or by constraining the research to specific brain areas for which the research team possesses prior knowledge about their likely involvement in the condition under investigation. Feature extraction is an obligatory step in the classification pipeline, but feature selection approaches are optional.

2.2.2. Model training and testing

In the model training step of the pipeline, the chosen algorithm has to learn the relationship between the training set and the labels associated with it, while trying to optimize the algorithm's parameters in order to maximally discriminate between the groups. In the testing phase, the algorithm tries to predict the class label (in the case of

classification) or the continuous variable (in the case of regression) of previously unseen data instances. It is very important that the algorithm generalizes well to new instances. That is, the testing set should not include instances of the training set to avoid circularity or data overfitting. Cross-validation techniques are a popular way to ensure this. In k-fold cross validation, the original data set is split into k non-overlapping sets and then the algorithm is trained using $k - 1$ subsets and the left-out set is used in the testing phase. The procedure is repeated k times, so that every subgroup is used in the testing phase.

2.2.3. Performance evaluation

The final step is the evaluation of classification performance of the method. This usually includes measures such as sensitivity, specificity and accuracy. Sensitivity refers to the proportion of actual positive cases correctly identified (e.g. the number of schizophrenia patients identified as in the ill group or class) and is computed by the TP / (TP + FN), where TP is the number of true positives and FN is the number of false negatives. Specificity refers to the proportion of the negatives cases correctly classified (e.g. healthy controls correctly identified as being healthy) and is computed by the amount TN / (TN + FP), where TN is the number of true negatives and FP is the number of false positives. Accuracy refers to the overall amount of correct classifications across the groups and is computed by TP + TN / TP + TN + FN + FP, or by the amount of (sensitivity + specificity) / 2, if the classes are balanced. Permutation tests are frequently applied as well, in order to determine the statistical significance of the classifier's performance. In these tests, class labels are randomly assigned between the groups in a certain amount of times, and the cross-validation procedure is repeated. By calculating the number of times that the sensitivity and specificity for the permuted labels are higher than the real ones, and dividing by the number of times one has permuted the labels, one can obtain a p-value for the classification accuracies.

2.3. Machine learning methods explained

A significant number of ML techniques, which have been applied in neuroimaging contexts, include Support Vector Machine (SVM), Support Vector Regression (SVR), Linear Discriminant Analysis (LDA) and Independent Component Analysis (ICA). Below, we briefly discuss the methodology behind each method.

SVM is one of the most popular supervised machine learning methods used in neuroimaging settings, partly because it can deal effectively with high-dimensional data and provide good classification results. The aim of a SVM classifier is to find a decision surface that would optimally distinguish between classes and based on that surface assign new, previously unseen data instances into the groups. In the training phase, the classifier computes the optimal decision surface expressed in the form $f(x) = w \cdot x + b$ only by a subset of the original training set $D = <x_i, y_i>$ called the support vectors. Support vectors are data points that lie closest to the optimal separating hyperplane and hence are the most difficult patterns to classify (see Fig. 1). The optimal hyperplane is determined by maximizing the margin of separation between the two classes (which is equal to $2/||w||$). Equally, the problem of finding the optimal hyperplane, thus, becomes an optimization problem where we need to: $\min ||w||$ subject to $y_i (x_i \cdot w + b) - 1 \geq 0$. The constraint part of the quadratic problem ensures that no data points can lie in the margin.

In the testing phase, the classifier is required to predict the label y_i of new, previously unseen data instances, by evaluating $y = \mathrm{sgn}(w \cdot x + b)$. In case where the data are not linearly separable, kernels are introduced to the machine. Kernels are functions that allow a mapping of the original, non-linearly separable data into a new feature space where the data are linearly separable. Polynomial, Gaussian and radial basis function (RBF) are some of the most commonly used kernels.

Support Vector for Regression (SVR) follows the same principles as SVM, but the goal here is to assign a data sample into a continuous variable rather than a class. SVR aims to find a function that provides the optimum fit between the data samples and their continuous variables, while specifying a tolerance margin of reliable generalization.

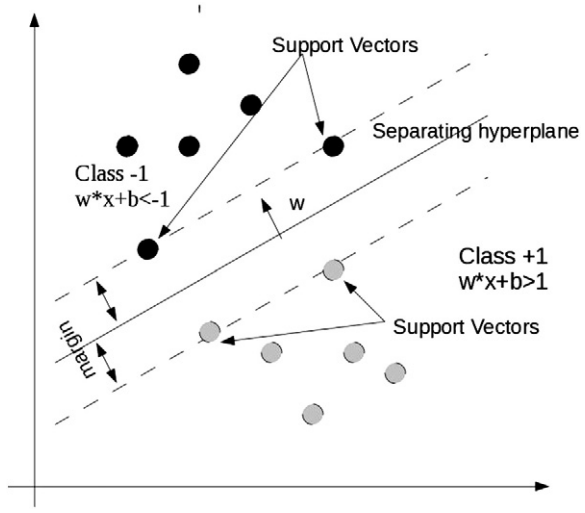

Fig. 1. Representation of a linear, binary SVM classifier. The optimal separating hyperplane is the one with the largest margin of separation between the two groups and is described as a function of $f(x) = w * x + b$, where w is a weight vector that is normal to the hyperplane, b is an offset and $b/||w||$ is the distance from the hyperplane to the origin. Points in the dashed lines represent the support vectors. During the training phase, the SVM classifier computes the optimal decision function f(x) and in the testing phase, this decision boundary is applied to new data instances.

Discriminant Function Analysis (DA) is primarily used to predict group membership from a set of continuous variables (features). DA involves two steps: i) evaluating the significance of discriminant functions and of a set of predictors in discriminating the groups and ii) performing the classification by assigning data instances into the groups of interest. In the first step, DA computes the discriminant functions which are given by the equation: $D = v_1X_1 + v_2X_2 + \ldots v_iX_i + a$, where D is the discriminant function, v_i the discriminant coefficient (or weight), X_i the score of the variable i and a is a constant variable. The maximum number of discriminant functions is equal to the degrees of freedom (number of features minus 1), or the number of variables in the analysis, whichever is smaller. In this step, DA automatically determines some optimal combination of variables so that the first discriminant function provides the overall discrimination between groups, the second provides second most and so on. Then, in the second stage classification can be performed. Subjects are classified into the groups in which they had the highest classification scores. In Linear Discriminant Analysis (LDA), the method looks for a linear combination of variables that would best classify data samples into a predefined number of groups. LDA can be used for both classification and feature reduction purposes. In the training stage, LDA computes linear transformations of the features that would provide a more accurate discrimination between the classes y_i, given the training set $<x_i, y_i>$. A transformation function is computed so that the ratio of between-class to within-class variances is maximized (Fisher's LDA). In most cases, there is no transformation that provides complete separation between the classes, so the goal is to find the transformation that minimizes the overlap of the transformed groups (see Fig. 2). Once, the discriminant function is computed and all data instances in the training set are transformed into the new $C - 1$ subspace (where C is the original number of features), classification of new data instances can be performed (second stage of LDA). The discriminant function acts as a classification rule to assigning new data instances into the groups.

Independent Component Analysis (ICA) is a multivariate statistical method, widely applied in problems of image and signal classification,

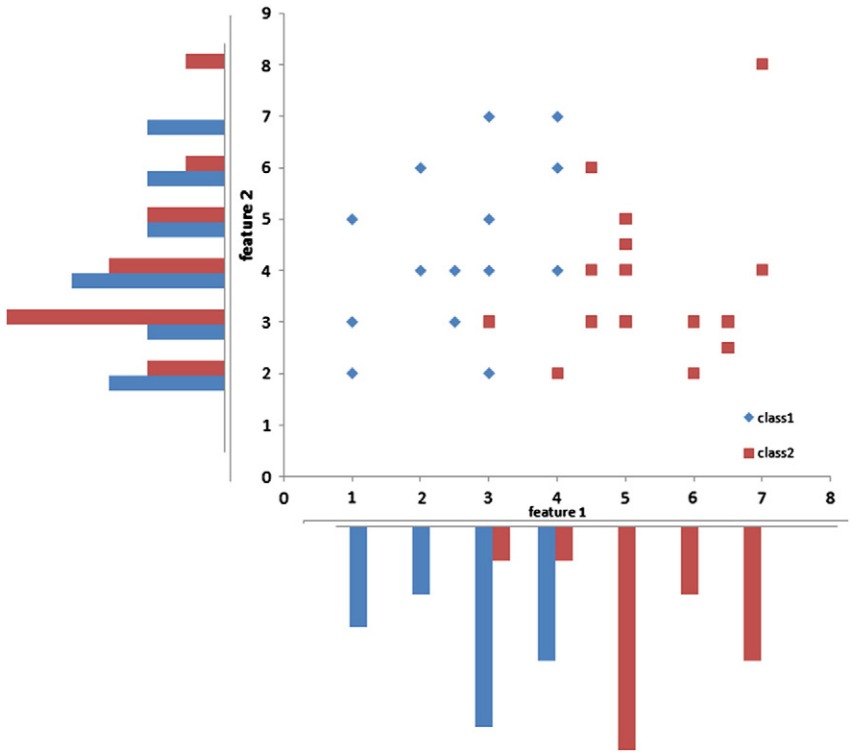

Fig. 2. Representation of LDA for a two-class classification problem based on synthetic two-dimensional data representing measurements in feature 1 and feature 2. As observed, classification is more accurate if the data are projected onto the X dimension, as opposed to the Y dimension where there is substantial overlap between the classes, as shown in the histograms. Once the projection of data instances onto the dimension that fulfills Fisher's criteria is specified, new data instances can be classified based on a threshold (for example, if $X_i < 4$ classify as class 1, otherwise class 2) or a specified metric (e.g. Euclidean distance from the mean of a class).

aiming to decompose a complex data set into independent sub-groups. In brain imaging, ICA is primarily used as a feature extraction and dimensionality reduction technique by decomposing a brain scan into a set of statistically independent components, which correspond to temporally coherent brain networks. ICA makes the assumption that the originally measured data can be expressed as a linear combination of some latent variables, called eigen-images, and aims to map the original high-dimensional data into a linear subspace based on the eigen-images. If X is the original data set, $X = (x_1, x_2, \ldots x_n)^T$ with n data instances and s is a vector of the latent components $S = (s_1, s_2, \ldots s_n)^T$, then X can be written as a linear combination of the form: $X = A_iS_i$, where A is a matrix of elements $A = (a_1, a_2, \ldots a_n)$. In order to find the independent components S, one needs to compute the equation $S = WX$, where W is the inverse of the matrix A. Of note, independent components must be non-Gaussian for ICA to be possible. For a thorough review of this ICA approach, one can refer to Hyvärinen and Oja (2000).

All of the presented machine learning methods have been widely used in neuroimaging-based studies of schizophrenia, producing variable classification results (see the tables). The choice of the machine learning method to be used is directly dependent on the nature of the data set and the classification problem at hand. It is important to note that each machine learning method has its own intrinsic strengths and weaknesses. For instance, SVM is a powerful method in detecting complex and subtle differences between groups due to the fact that only support vectors affect the determination of the decision function. SVMs can also work efficiently with complex, non-linear data whereas LDA can only be applied on groups that can be separated by a linear combination of features. LDA is the optimal classification model when the distributions of the data are Gaussian (parametric method), whereas SVM is a non-parametric classification method and as such, more efficient in handling data that are not regularly distributed or have an unknown distribution. SVM might, therefore, be more appropriate in real-world data sets where the distribution of the data is not always known. On the other hand, LDA is a more simple and straightforward method and does not require any tuning of parameters, whereas SVMs' performance depends on the choice of the kernel and its parameters (Burges, 1998). Therefore, SVMs can be slower and have high computational processing and memory requirements, especially when it comes to large training data sets. Another limitation of LDA is that it is upper-bounded, thus constraining the application of the method in cases where more features are needed, and can only be used for classification, not regression problems.

3. Machine learning in schizophrenia

In the past few years, an increasing number of studies have employed machine learning to investigate the neuroanatomical and neurophysiological correlates of schizophrenia. These studies can be divided into three main categories: (i) studies that examine the diagnostic power of machine learning in distinguishing between healthy controls (HC) and schizophrenia patients (SCHZ), (ii) studies which examine the potential of machine learning to make an early diagnosis of schizophrenia (prediction) by comparing scans at baseline of people at high risk (either for familial or clinical reasons) of making a transition to the disorder and (iii) studies which examine the performance of machine learning in predicting progression of the disease and response to treatment, usually by examining the baseline scans of first-episode (FE) patients with a later known clinical outcome or treatment response. An online search of PUBMED was performed in order to detect suitable papers for inclusion, using the following search words: (machine learning OR pattern recognition) AND (psychosis OR schizophrenia) AND (diagnosis OR early diagnosis OR prediction OR transition to schizophrenia OR disease progression OR treatment response) AND/OR (MRI OR fMRI). Twenty seven studies met our inclusion criteria – of presenting original data about an ML application in patients with formally diagnosed schizophrenia – and are discussed below.

3.1. Diagnostic studies of schizophrenia

The first study to apply a sMRI-based classification method was conducted by Davatzikos et al. (2005b), who tested the performance of Support Vector Machine (SVM) in classifying 69 schizophrenia patients (46 men, 23 women) and 79 matched healthy controls (41 men, 38 women), reaching a 81% classification accuracy via leave-one-out cross-validation. The authors also tested individual men and women classifiers and observed similar classification results (85% accuracy for the male and 82% for the female classifier), possibly implying good generalizability of the MRI-based diagnostic system. In another study by the same group, Fan et al. (2007) achieved an impressive 91.8% and an 90.8% accuracy in distinguishing between the same 23 female SCHZ patients and 38 female HC and 46 male SCHZ patients and 41 male HC respectively. Here, the development of an adaptive regional feature extraction method, that automatically grouped morphological traits of similar classification power, along with a SVM-Recursive Feature Elimination method, that selected features with the highest discriminatory power, may possibly account for what still remains one of the best diagnostic performances observed in chronic schizophrenia diagnostic studies published to date. The researchers achieved this diagnostic performance by using just 39 features for the female and 44 features for the male individual classifiers. This diagnostic result was, however, obtained from a feature set that might be specific to this sample group and the result may well not generalize to other data samples. In the context of examining family members of schizophrenia, only one study has up-to-date investigated the role of genetic factors in the disorder, using MRI-based machine learning (Fan et al., 2008b). Fan et al. (2008b) observed that unaffected family members share similar phenotypic patterns to their affected schizophrenia relatives. Although these initial results are encouraging, longitudinal studies are, however, essential in determining whether this endophenotypic pattern is present before disease onset and how it relates (if so) to transition to schizophrenia in unaffected relatives.

Evaluating a classifier on a totally independent cohort is of course the ideal way of examining the generalizability and robustness of the classifier (Nieuwenhuis et al., 2012). Unfortunately, the consequent need for large data sets makes this endeavor very difficult. In an impressive two-stage study, Kawasaki et al. (2007) observed a 80% classification accuracy using a partial least squares model that was trained on 30 male HC and 30 male SCHZ patients and tested on a new, independent cohort of 16 male controls and 16 SCHZ patients. In a particularly large classification study employing an independent test set, diagnostic accuracy was however only about 70% (Nieuwenhuis et al., 2012), when testing a SVM classifier developed on 239 participants (128 SCHZ) on a completely independent sample of 277 subjects (155 SCHZ). The use of a larger validation set may partly account for the lower diagnostic accuracy, if we take into account the possible inclusion of more variable schizophrenia phenotypes in this larger group.

Several studies have, alternatively, employed fMRI in an attempt to establish the diagnosis in groups of people with schizophrenia and controls (Table 2). These studies have included various cognitive tasks (Costafreda et al., 2011; Yoon et al., 2012) or resting-state fMRI (Calhoun et al., 2006; Shen et al., 2010; Venkataraman et al., 2012), in which the subject is simply instructed to remain still during scanning, not to think of anything in particular and not to fall asleep. In recent fMRI studies, resting-state paradigms are often preferred to task-related approaches, as they are free from task-related confounds and easier for patient populations to perform, although they do have limitations (Morcom and Fletcher, 2007). The diagnostic accuracy of resting-state fMRI-based classification methods ranged from 75% (Jafri and Calhoun, 2006; Venkataraman et al., 2012) to 92%

Table 1
Studies employing machine learning and structural MRI to distinguish patients with schizophrenia from healthy controls.

Author	Sample (N, diagnostic classification)	ML methods and scanner field strength	Classifier's Performance (accuracy %)
Davatzikos et al. (2005b)	HC = 79, SCHZ = 69 DSM-IV	SVM 1.5 T	81.1
Fan et al. (2007)	HC_1 = 38 (females) SCH_1 = 23 (females) HC_2 = 41 (males) SCH_2 = 46 (males) DSM-IV	SVM-RFE 1.5 T	HC_1 vs SCH_1 = 91.8 HC_2 vs SCH_2 = 90.8
Kawasaki et al. (2007)	*Train set*: HC = 30 SCHZ = 30 (males) *Test set*: HC = 16 SCHZ = 16 (males) DSM-IV	DA & MLM 1.5 T	80
Yoon et al. (2007)	HC = 52, SCHZ = 53 DSM-IV	SVM 1.5 T	>90
Sun et al. (2009)	HC = 36, ROS = 36 DSM-IV	SMLR 1.5 T	86.1
Karageorgiou et al. (2011)	HC = 47, ROS = 28 SCID-I for DSM-IV	sMRI & neuropsychological data PCA-LDA 3 T	92
Kasparek et al. (2011)	HC = 39, FE = 39 ICD-10	MLDA 1.5 T	72
Greenstein et al. (2012)	HC = 99, COS = 98 DSM-IIIR/IV	RF 1.5 T	73.7
Nieuwenhuis et al. (2012)	*Train set*: HC = 111 SCHZ = 128 *Test set*: HC = 122 SCHZ = 155 DSM-IV	SVM 1.5 T	70.4
Zanetti et al. (2013)	HC = 62, FE = 62 DSM-IV	SVM 1.5 T	HC vs FE = 73.4
Borgwardt et al. (2012)	HC = 22, FE = 23 ARMS-T = 16 DSM-IIIR	ensemble SVM 1.5 T	HC vs FE = 86.7 HC vs ARMS-T = 80.7 FE vs ARMS-T = 80

Abbreviations: ARMS-T, at-risk mental state with transition to schizophrenia; COS, child-onset schizophrenia; DA, discriminant analysis; DSM-IV, Diagnostic and Statistical Manual of Mental Disorder *Fourth Edition*; DSM-IIIR, Diagnostic and Statistical Manual of Mental Disorder *Third Edition Revised*; FE, first-episode schizophrenia patients; HC, healthy controls; ICD-10, the International Statistical Classification of Disease and Related Health Problems; LDA, linear discriminant analysis; MLDA, maximum-uncertainty linear discrimination analysis; MLM, multivariate linear model; PCA, principal components analysis; RF, random forests; ROS, recent-onset schizophrenia; SCHZ, schizophrenia patients; SCID-I, Structural Clinical Interview; SMLR, sparse multinomial logistic regression; SVM, Support Vector Machine; SVR, Support Vector Regression; SVM-RFE, Support Vector Machine with Recursive Feature Elimination.

(Costafreda et al., 2011; Shen et al., 2010), suggesting that resting-state fMRI has the potential to be useful in clinical practice. Results should be interpreted with caution, however, since the sample sizes in most cases (Anderson et al., 2010; Shen et al., 2010) are very small and potentially introduce a bias to the classification (Demirci and Calhoun, 2009).

Adequate sample size is an important consideration in the robustness and reliability of the proposed classification system. Classification models based on small sample sizes tend to favor diagnostic performance (Anderson et al., 2010; Fan et al., 2007; Kawasaki et al., 2007; Sun et al., 2009; Yang et al., 2010; Yoon et al., 2007) whereas in studies evaluating larger samples, which possibly include a wider range of phenotypic manifestations of schizophrenia, classification accuracy tends to be worse (Greenstein et al., 2012; Nieuwenhuis et al., 2012; Zanetti et al., 2013). Differences in the image analysis and classification pipelines might, also, partly explain such variation in findings. The introduction of refined feature selection methods can boost classifiers' performance, as was observed in Fan et al. (2007), compared to a previous study of the same group (Davatzikos et al., 2005b). The choice of the machine learning method is another crucial factor in the performance of the diagnostic model as well. Notably, SVMs tend to provide better classification results (Pereira et al., 2009) (see Table 1) than other pattern recognition methods, although, a direct comparison between the machine learning methods used in the presented studies and classification performance cannot be performed due to other differences in the imaging and clinical characteristics of the samples used.

The clinical characteristics of patients may play a significant role in the observed fluctuations in accuracy across diagnostic studies (Greenstein et al., 2012; Zanetti et al., 2013). Machine learning in FE schizophrenia studies seems to deliver worse diagnostic performance (Kasparek et al., 2011; Yoon et al., 2012; Zanetti et al., 2013) than studies of established schizophrenia (see Tables 1 and 2), possibly due to the less pronounced brain alterations in the former group, although diagnostic accuracies can be as high as 92% (see Table 1). It is known that the first-episode stage of schizophrenia is characterized by less marked brain changes than in chronic schizophrenia, and this could partly account for the accuracy fluctuations observed (see Tables 1, 2). In addition, comorbid disorders and patient recruitment procedures may, also, have an effect on the sensitivity of the classifier in detecting disease-specific patterns. For instance, Zanetti et al. (2013) recruited a population-based sample of FE patients with comorbid substance use disorders, using epidemiological methods in order to ensure representativeness of 'real-world' individual cases, and observed just 73.4% accuracy in classifying them against HCs. In childhood-onset schizophrenia (COS), only one study examined the neuroanatomical correlates in 98 COS subjects (all below the age of 13) versus 99 HCs (Greenstein et al., 2012) and observed moderate diagnostic accuracy (73.7%), possibly due to the young age of their patients and the fact that their unconsolidated brain structure may hinder the detection of clear, concrete brain patterns that would facilitate classification. Factors associated with the use of anti-psychotic drug treatment are, also, a serious consideration because medication may have an effect on brain structure (Pantelis et al., 2003) possibly even up to a point that the sensitivity of the classifier to detect morphological abnormalities specifically associated with schizophrenia diagnosis is compromised.

3.2. Early diagnostic studies of schizophrenia

Several recent neuroimaging studies have shown structural and functional abnormalities in subjects at high-risk of developing schizophrenia compared to healthy controls as well as compared to established patients (Lawrie et al., 2008; Mechelli et al., 2011; Smieskova et al.,

Table 2
Studies employing machine learning methods and functional MRI in diagnosing schizophrenia.

Author	Sample (N, diagnostic classification, fMRI paradigm)	ML methods and scanner field strength	Classifier's performance (accuracy %)
Jafri and Calhoun (2006)	HC = 31, SCHZ = 38 DSM-IV Resting-state paradigm	ICA & NN 3 T	76
Calhoun et al. (2008)	HC = 26, SCHZ = 21 DSM-IV AOD task	ICA 1.5 T	*SCHZ* vs *N-SCHZ*: Sensitivity = 92 Specificity = 98 *HC* vs *N-HC*: Sensitivity = 95 Specificity = 88
Shen et al. (2010)	HC = 20, SCHZ = 32 DSM-IV Resting-state paradigm	Unsupervised classifier based on C-means 1.5 T	92.3
Yang et al. (2010)	HC = 20, SCHZ = 20 DSM-IV AOD task	FMRI & genetic data SVM 3 T	87
Anderson et al. (2010)	HC = 6, SCHZ = 14 DSM-IV Resting-state paradigm	ICA & RF 3 T	85
Castro et al. (2011)	HC = 54, SCHZ = 52 DSM-IV AOD task	ICA & composite kernels with RFE 3 T	95
Costafreda et al. (2011)	HC = 40, SCHZ = 32 DSM-IV Verbal fluency task	SVM 1.5 T	SCHZ vs HC: 92
Fan et al. (2011)	HC = 31, SCHZ = 31 DSM-IV Resting-state paradigm	ICA & SVM 1.5 T	85.5
Venkataraman et al. (2012)	HC = 18, SCHZ = 18 DSM-IV Resting-state paradigm	RF 3 T	75
Yoon et al. (2012)	HC = 51, FE = 51 DSM-IV Cognitive control task	LDA 1.5 T	61.8

Abbreviations: AOD, auditory oddball discrimination; BD, bipolar disorder; DSM-IV, Diagnostic and Statistical Manual of Mental Disorder *Fourth Edition*; FE, first-episode schizophrenia patients; HC, healthy controls; ICA, independent component analysis; LDA, linear discriminant analysis; NN, neural networks; N-BD, non-bipolar subjects; N-HC, non-healthy controls; N-SCHZ, non-schizophrenia subjects; RF, random forests; SCHZ, schizophrenia patients; SVM, Support Vector Machine.

2010). To date, there are no biological markers for the identification of emerging psychosis, which is currently identified by clinical symptomatology. The early identification of those high-risk individuals who are most likely to develop psychosis is of high potential clinical value, as early intervention and treatment planning could alleviate symptoms burden or even prevent disease onset (Marshall and Loockwood, 2006; Riecher-Rossler et al., 2006). Job et al. (2005) were the first to assess the predictive value of gray matter reductions in genetic high-risk subjects regarding the possible transition to schizophrenia but they used univariate analysis methods, with their known limitations. More recently, machine learning has been applied in the context of making an early diagnosis of schizophrenia and even to predict disease transition at individual level (see Table 2), by identifying the neuroanatomical correlates of vulnerability to psychosis in individuals at high-risk of developing the disorder mainly due to clinical reasons.

Koutsouleris et al. (2009) were the first to apply multivariate pattern recognition to evaluate individual vulnerability to psychosis and predict disease onset. In their work, a SVM classifier was built upon structural MRI data of individuals in early (ARMS-E, n = 20) and late at-risk mental state of psychosis (ARMS-L, n = 25) and a group of matched healthy controls (HC_1, n = 25). The performance of the classifier was validated by distinguishing sMRI data derived from baseline scans of individuals with subsequent transition to schizophrenia (ARMS-T, n = 15), those who did not make the transition (ARMS-NT, n = 18) and matched healthy controls (HC_2, n = 17). Three group and pairwise classifiers were constructed, all achieving classification performance above 80% (with the exception for the binary classifier HC_1 vs ARMS-L = 78%). In the most critical in terms of clinical utility, the ARMS-T vs ARMS-NT pairwise classifier achieved an accuracy of 82%, suggesting the potential of a MRI-based system in predicting transition to schizophrenia. In a follow-up study, Koutsouleris et al. (2011) emphasized on the predictive potential of SVMs in classifying an independent cohort of 22 HC, 16 ARMS-T and 21 ARMS-NT subjects. The authors, here, constructed a robust classification method, based on SVM ensemble classifiers that performed feature selection, model learning and predictive ensemble learning wrapped in a nested cross-validation framework. The critical ARMS-T vs ARMS-NT pairwise classifier showed slightly improved classification results compared to that of Koutsouleris et al. (2009), whereas diagnostic performance was lower in the pairwise HC vs ARMS-NT classifier (66.9% accuracy as opposed to 86% in Koutsouleris et al. (2009)), possibly due to greater heterogeneity in the control sample.

Despite the fact that neuroanatomical pattern classification methods provide very encouraging results in the context of prediction of disease transition, there is, however, some way to go before demonstrating their clinical utility. The small sample size in these studies limits the statistical power of the MRI-based system proposed, so replication of the results to larger data sets is crucial. Another consideration is that the at-risk mental state sample in those studies involved symptomatic, help-seeking individuals (Koutsouleris et al., 2011) and it is therefore unclear if these classification results could generalize to asymptomatic high-risk groups as well.

3.3. Predicting disease progression and treatment response

Prediction of disease progression is also of interest and potential clinical utility in established cases of schizophrenia, with a view to establishing the prognostic context and/or therapeutic responsivity of the psychosis. Based on neuroanatomical pattern classification methods, studies reported poor to modest diagnostic performance (Table 3) in predicting the outcome of psychosis in FE schizophrenia patients at baseline. In this context, Mourao-Miranda et al. (2012) used a linear SVM to predict clinical outcome from baseline sMRI scans of 100 FE psychosis individuals, who at 6-year follow-up were classified as having a continuous, episodic or intermediate course and a group of 91 matched HCs. Although classification accuracy was less than 75% in all contrasts (see Table 3), this result serves as a promising starting point in predicting subsequent course type at the individual level. In another study, Zanetti et al. (2013) failed to predict 1-year outcome of FE schizophrenia patients. Despite the fact that the authors presented a robust method for feature generation and feature selection, their SVM

Table 3
Studies using machine learning to predict transition, progression and treatment response in schizophrenia.

Author	Sample(N, diagnostic classification)	ML methods and scanner field strength	Classifier's performance (accuracy %)
Koutsouleris et al. (2009)	HC_1 = 25, HC_2 = 17 ARMS-E = 20, ARMS-L = 25, ARMS-T = 15, ARMS-NT = 18 At inclusion: DSM-IV At follow-up: ICD-10	Structural MRI SVM 1.5 T	HC_1 vs ARMS-E vs ARMS-L = 81 HC_2 vs ARMS-T vs ARMS-NT = 82
Khodayari-Rostamabad et al. (2010)	*Train set*: SCHZ = 23 R = 12, NR = 11 *Test set*: SCHZ = 14 At inclusion: DSM-IV Post-treatment evaluation: PANSS	EEG kernel PLSR	R vs NR = 85
Koutsouleris et al. (2010)	HC = 28,ARMS = 25 ARMS-T = 12, ARMS-NT = 13 At inclusion: DSM-IV At follow-up: ICD	Structural MRI SVR 1.5 T	HC vs ARMS: r = 0.83 HC vs ARMS-T vs ARMS-NT: r = 0.83
Koutsouleris et al. (2011)	HC = 22, ARMS-T = 16, ARMS-NT = 21 At inclusion: APS, BLIPS At follow-up: classification criteria by Yung et al. (1998)	Structural MRI ensemble SVM 1.5 T	HC vs ARMS-T = 92.3 HC vs ARMS-NT = 66.9 ARMS-T vs ARMS-NT = 84.2
Mourao-Miranda et al. (2012)	HC = 28, EP-PS = 28 CON-PS = 28, INT-PS = 32 At inclusion: ICD-10 At follow-up: WHO Life Chart	Structural MRI SVM 1.5 T	EP-PS vs CON-PS = 70 CON-PS vs HC = 67 EP-PS vs HC = 54
Zanetti et al. (2013)	R-FE = 15, NRsub-FE = 21 At inclusion: DSM-IV (SCID) At follow-up: DSM-IV	Structural MRI SVM 1.5 T	R-FE vs NRsub-FE = 58.3 HCsub vs NR-FE = 64.3

Abbreviations: ARMS, at-risk mental state; ARMS-E, at-risk mental state early; ARMS-L, at-risk mental state late; ARMS-T, at-risk mental state with Transition to schizophrenia; ARMS-NT, at-risk mental state without transition to schizophrenia; APS, Attenuated Psychotic Symptoms; BLIPS, brief limited intermittent psychotic symptoms; CON-PS, continuous psychotic; DSM-IV, Diagnostic and Statistical Manual of Mental Disorder *Fourth Edition*; EP-PS, episodic psychotic; HC, healthy controls; ICD-10, the International Statistical Classification of Disease and Related Health Problems; INT-PS, intermediate psychotic; NR, non-responders; NRsub-FE, subgroup of non-remittent first-episodes; partial least squares regression; PANSS, positive and negative syndrome scale; PSLR, partial least squares regression; R, responders; R-FE, remittent fist-episodes; SCHZ, schizophrenia patients; SCID, Structured Clinical Interview; SVM, Support Vector Machine; SVR, Support Vector Regression; WHO, World Health Organization.

classifier (based on the method proposed in Fan et al. (2007)), achieved an 58.3% accuracy in predicting clinical outcome of 15 FE patients with a subsequent remitting course versus 21 first-episodes with a subsequent non-remitting course. Differences in data samples (and/or data sample selection procedures) and in the duration of follow-up study might partly explain the accuracy discrepancies observed between the two studies.

A key determinant of prognosis in psychosis is diagnosis, both because schizophrenia tends to have a worse outcome than bipolar disorder, and because these conditions tend to respond differently to treatments. Early studies have shown the possibility of distinguishing group activation patterns on fMRI in schizophrenia and bipolar disorder (McIntosh et al., 2008), but little SVM work has thus far been done in this vein, especially at first presentation when it might be most valuable. In the context of predicting response to treatment in schizophrenia, only one study that we are aware of has thus far employed machine learning to do so. Khodayari-Rostamabad et al. (2010) used kernel partial least squares regression in order to predict response to clozapine in chronic schizophrenia subjects, based on pre-treatment electroencephalography (EEG) data, providing 85% accuracy in identifying responders and non-responders to the medicine.

The really useful thing to do, for clinicians, patients, their families, and society more widely, would be to determine likely therapeutic response to different treatments in individual patients to facilitate the timely and effective application of particular treatments to patients who need them. In someone with psychotic symptoms, in early intervention or general adult services, it would be very useful to know, for example, who needs treatment because spontaneous resolution is unlikely or would take too long or, who needs ongoing treatment to avoid relapse and/or optimize day-to-day function. It would also be helpful to be able to identify those who are likely to be treatment-resistant who will need treatments like clozapine or intensive rehabilitation at an early stage in treatment. These goals remain aspirational at the moment, and may well require the inclusion of multiple data sources for successful implementation.

4. Discussion

In this review, we have presented an overview of machine learning methods in clinical studies and a detailed consideration of studies employing them in schizophrenia research. Studies published so far demonstrate promising leads for the development of neuroimaging machine learning-based tools that could assist in establishing the diagnosis and prognosis of schizophrenia and therefore be useful in clinical practice. Machine learning methods are advantageous compared to standard univariate statistical methods, in that they have the potential to make inferences about effects of interest at a single-subject level and can detect subtle and widespread neuroanatomical and functional differences that span over large networks of brain regions, by virtue of their multivariate nature.

The development of a MRI-based machine learning system could well aid in the identification of objective biological markers for schizophrenia, and could thus help overcome the subjectivity in traditional clinical assessments. There are, however, significant hurdles to be overcome before their integration of machine learning into clinical practice is possible. The classifiers' performance is a key element for the potential integration of machine learning into clinical decision making. As a general observation, diagnostic classification performance in psychiatry may not supersede clinical expertise in the foreseeable future, no matter the techniques employed, since training a classifier requires prior knowledge of a subject's clinical status (Orru et al., 2012). Where imaging and machine learning could seriously impact upon clinical practice is where future diagnosis, outcome and treatment response are difficult to predict. The identification of high-risk individuals, likely to convert to schizophrenia is of high clinical value as a means to inform early treatment strategies that could have better outcome for the patients. It is, however, evident from the early diagnosis studies thus far (see Tables 1–3) that classification accuracy in the early detection of schizophrenia and predicting clinical course is not as high as in diagnostic schemes. This is probably explained by the fact that in the diagnosis of established groups of patients from controls, neuroanatomical and functional patterns of differentiation are more clearly and strongly established than in same group subjects who do or do not go on to show an outcome of interest and therefore present a more difficult classification problem.

It should be borne in mind that a classifier with high sensitivity and high specificity is desirable, and that overall accuracy is important, but the relative value of high and low sensitivity and specificity could have different implications in patients' clinical management, in different clinical scenarios, depending on the availability of treatment and the seriousness and frequency of adverse effects. Moreover, for an individualized patient high positive/negative predictive power is the most critical consideration (Lawrie et al., 2011). Furthermore, classification performance is primarily affected by the sample size. The limited number and nature of patient populations in SVM neuroimaging-based studies mean that these encouraging early results may not generalize well to other patient groups. Recruiting patients for research studies can be difficult and patients with co-morbid conditions are often excluded, resulting in a limited representation of the various phenotypes across the spectrum of schizophrenia. Despite the fact that several machine learning methods can deal effectively with small sample size (Pereira et al., 2009), a limited number of data samples can cause model overfitting, resulting in poor generalization of the method to independent data sets. In such cases, cross-validation frameworks are often employed, to partition the original data set. However, cross-validation schemes should be performed and interpreted with caution, because there is a serious danger of biasing classifier's performance, especially in cases where data samples in the validation set are also present in the testing set. As a general rule, the greater the complexity of a method, the higher is the risk for overfitting the data (Mourao-Miranda et al., 2012). Ideally, data for validation should be derived from completely independent cohorts from the training population, as the case in a few model studies thus far (Kawasaki et al., 2007; Nieuwenhuis et al., 2012) in order to ensure the robustness and reliability of the system.

The need for large data sets could be addressed with pooling data from multiple research centers (Mechelli et al., 2011). The existence of a well-validated training dataset to be shared between neuroimaging centers is likely to be of importance for standardizing classification accuracy across laboratories. In addition, future multi-site studies could provide the possibility for encompassing more heterogeneous clinical populations, demonstrating a range of clinical manifestations of a disorder (Borgwardt and Fusar-Poli, 2012), for example subjects with various transition rates to psychosis or subjects of lower diagnostic certainty, which could thus provide a more realistic mirroring of everyday psychiatric practice. Data sharing among research centers faces, however, its own difficulties. Different scanners, imaging parameters and protocols result in varying image intensity and susceptibility profiles that will require careful consideration and compatibility solutions. One promising approach is however to generate metrics from individual scans that can then be compared to reference data sets (Tijms et al., 2011).

It is a priority that future studies also address the challenge and opportunity of fusing neuroimaging data from various imaging modalities, along with genetic and clinical information, that seem likely to interact in determining the development and outcome in schizophrenia (Lawrie et al., 2011). It would be reasonable to assume that the introduction of neurocognitive and other clinical measures could possibly enhance diagnostic power of the classifier. Just as a clinician takes a detailed report of symptoms and other clinical measures to diagnose a patient with schizophrenia, so might the integration of symptom severity measures and other neurocognitive scores, along with MRI scans aid to the classification process. Early studies have already shown that classification performance might well be improved (Sui et al., 2012; Yang et al., 2010), as in Karageorgiou et al. (2011) where Karageorgiou et al.

observed a 92% accuracy in classifying recent-onset schizophrenia when structural MRI data and neuropsychological variables (NP) were combined than when employing either quantitative measure alone (86.7% when only NP data were used and 70.7% with sMRI data alone). Other neuroimaging technologies such as arterial spin labeling (ASL) perfusion MRI and diffusion tensor imaging (DTI) have shown very promising leads in unraveling the neurobiological substrate of several psychiatric and neurological disorders (Pinkham et al., 2011; Sussmann et al., 2009; Van Essen et al., 2012), and might as well be combined with MRI methods in schizophrenia research. The interpretability of such data is not, however, necessarily straightforward and, as a general rule, each additional diagnostic variable increases sensitivity at the expense of specificity. It is overdue, though, that combined features, such as symptoms, duration of illness, genomics and proteomics along with various brain imaging modalities are incorporated into imaging and other evaluations in clinical research studies, with the scope of making more reliable and objective judgements about the diagnosis of schizophrenia and to classifying patients into more homogenous subgroups (Lawrie et al., 2011).

Equally important, future studies should test the efficacy of machine learning in making a diagnosis of psychiatric disorders apart from schizophrenia, such as bipolar disorder, borderline personality disorder, depression and autism. Initial studies have already used machine learning to diagnose schizophrenia and bipolar disorder versus HC subjects (or in a one-vs-all rationale), providing very encouraging results (Calhoun et al., 2008; Costafreda et al., 2011). However, replication of these early findings in studies that include larger samples and more cases across a putative psychosis spectrum is necessary in order to identify patterns that differentiate between these psychiatric disorders.

From a methodological point of view, novel methods for feature selection and decision making of the classifiers could be introduced in order to improve diagnostic power in schizophrenia studies. For example, ensemble learning methods could be introduced in order to improve the generalization ability of a classifier. Ensemble classifiers can achieve better predictive performance than single classifiers, by combining multiple weak learning models that decide upon the classification of a new instance through majority voting (Polikar, 2006). Some well-known ensemble learning methods, such as bagging and random subspace methods have already been used in neuroimaging settings to identify biological markers for prodromal Alzheimer's disease (Fan et al., 2008a; Liu et al., 2012), reporting excellent diagnostic results. Ensemble learning could be a useful approach in data fusion studies as well, where a single classifier could be built and trained for each imaging modality and/or clinical measures (such as neurocognitive measures) separately and outputs from each classifier could be combined to classify new instances. An example of this approach is the study of Yang et al. (2010), who developed SVM-based ensemble classifiers of genetic and fMRI data and combined them to a single module that decided upon classification of testing samples via majority voting, achieving better diagnostic accuracy than either SVM ensembles alone (87% for the combined module, 74% for the genetic data classifier and 83% for the fMRI classifier). Future studies could, also, possibly address the problem of 'tuning' a machine learning method to fit into neuroimaging settings. Refinements in the SVM method, for example, already exist. The SVM-Recursive Feature Elimination (SVM-RFE), a very popular method that performs feature selection during training and recursively removes data instances, and has already been successfully employed in cancer classification (Guyon et al., 2002), and SVM-Sequential Minimal Optimization (SVM-SMO) which facilitates and speeds up the classifier's training, are methods yet to be validated for their efficacy in neuroimaging settings. Finally, probabilistic machine learning might also be a promising tool in neuroimaging-based schizophrenia research. More specifically, probabilistic machine learning can be used to quantify a degree of uncertainty in the prediction and could thus be applied in the context of predicting transition to psychosis or future clinical outcome, indicating for example a percentage of confidence for classification into one group or another (e.g. 75% risk transition to schizophrenia and 25% not making a transition.).

The application of machine learning methods for the purposes of diagnosing or making a prognosis in schizophrenia has already demonstrated very encouraging results. The main advantage of machine learning methods, over standard univariate ways of analyzing and interpreting neuroimaging data, is that they may allow inferences to be made at subject-level, a feature essential in clinical practice. There are however, important difficulties yet to be fully considered and overcome, before their translation into routine clinical practice. The optimal means of multi-center analyses, fusing imaging modalities and integrating various sources of information are critical considerations. Finally, once suitable techniques have been developed, they will ideally need to be tested, preferably in randomized control trials to ensure that they are acceptable and useful to clinicians and patients.

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