Prediction of psychosis using neural oscillations and machine learning in neuroleptic-naïve at-risk patients

Avinash Ramyead1, Erich Studerus1, Michael Kometer2, Martina Uttinger1, Ute Gschwandtner3, Peter Fuhr3 & Anita Riecher-Rössler1

1University of Basel Psychiatric Clinics, Center for Gender Research and Early Detection, Basel, Switzerland, 2Neuropsychopharmacology and Brain Imaging Research Unit, University Hospital of Psychiatry, Zurich, Switzerland, and 3Department of Neurology, University Hospital Basel, Basel, Switzerland

ABSTRACT

Objectives: This study investigates whether abnormal neural oscillations, which have been shown to precede the onset of frank psychosis, could be used towards the individualised prediction of psychosis in clinical high-risk patients. Methods: We assessed the individualised prediction of psychosis by detecting specific patterns of beta and gamma oscillations using machine-learning algorithms. Prediction models were trained and tested on 53 neuroleptic-naïve patients with a clinical high-risk for psychosis. Of these, 18 later transitioned to psychosis. All patients were followed up for at least 3 years. For an honest estimation of the generalisation capacity, the predictive performance of the models was assessed in unseen test cases using repeated nested cross-validation. Results: Transition to psychosis could be predicted from current-source density (CSD; area under the curve [AUC] = 0.77), but not from lagged phase synchronicity data (LPS; AUC = 0.56). Combining both modalities did not improve the predictive accuracy (AUC = 0.78). The left superior temporal gyrus, the left inferior parietal lobule and the precuneus most strongly contributed to the prediction of psychosis. Conclusions: Our results suggest that CSD measurements extracted from clinical resting state EEG can help to improve the prediction of psychosis on a single-subject level.

Introduction

Schizophrenic psychoses are increasingly acknowledged as neurodevelopmental disorders whose signs and symptoms can sometimes be observed as early as in childhood (Insel 2010). A delay between the diagnosis and the treatment of these disorders ranges from 1 to 3 years (Riecher-Rössler et al. 2006) and could result in severe negative ramifications such as a worse functional outcome (Insel 2010), loss of grey-matter volume (Fusar-Poli et al. 2011a), higher cognitive deterioration (Amminger et al. 2002), higher dosage of neuroleptics needed (McGorry et al. 1996) and higher overall treatment costs (Moscarelli 1994). By contrast, therapeutic actions in the earliest phases of the disease could considerably improve the prognosis of these individuals (Stafford et al. 2013).

In the last two decades, there has been increased interest in the early detection of psychosis and reliable criteria have been established internationally to detect an at-risk mental state (ARMS) for psychosis. As only about one-third of ARMS patients eventually develop psychosis (Fusar-Poli et al. 2012), and about one-third remit from their risk state (Simon et al. 2013), further risk-stratification is required to identify subgroups with specific needs and response patterns that could improve the cost–benefit ratio of preventive interventions (Ruhrmann et al. 2014). Although individualised prediction models for psychosis based on structural magnetic resonance imaging (MRI) achieved promising predictive accuracies (Koutsouleris et al. 2014), it has not been investigated whether the same could be obtained using more cost-efficient measures, such as clinical resting-state EEG.

Although both an increase and decrease in gamma activity has been noted in patients with schizophrenia (Herrmann and Demiralp 2005), heightened activity has consistently been reported in unmedicated patients suffering from positive symptoms while the opposite has largely been found in those suffering from negative symptoms (Herrmann and Demiralp 2005; Lee et al. 2006).
have been strongly associated with the pathophysiology of schizophrenic psychoses (Uhlhaas and Singer 2013). Furthermore, previous studies using clinical EEG for prediction of psychosis are limited as they included at-risk patients already medicated with antipsychotics (up to about 40% in one instance (van Tricht et al. 2014)). These medications have been shown to change neural oscillations (Centorrino et al. 2002) and are likely to alter the natural trajectory of psychosis, therefore potentially yielding misleading biomarkers.

To overcome these weaknesses, we set out to employ a machine-learning algorithm, the least absolute shrinkage and selection operator (LASSO), that detects multivariate patterns of high-frequency oscillations across different brain regions on the same sample of patients as in our previous study (Ramyead et al. 2014). However, compared to the previous sample, we excluded the patients who were already medicated with neuroleptics due to the reasons mentioned earlier. To make use of three-dimensional CSD and LPS of high-frequencies (beta1, beta2, gamma) oscillations as input variables, we applied the inverse solution technique exact low-resolution electromagnetic tomography (eLORETA), which allows for a reliable source localisation of brain activity analyses at individual frequencies (Pascual-Marqui et al. 2011). Finally, we conducted our analysis on a group of ARMS patients which were followed-up over the course of at least three years to determine whether they later made transition to psychosis (ARMS-T) or not (ARMS-NT). We hypothesised that – based on their specific pattern of CSD and/or LPS in the high frequencies at 19 cortical regions of interests (ROIs) – ARMS-T individuals could be separated from ARMS-NT individuals with good accuracy.

Methods
Setting and recruitment

The EEG data analysed in this study were collected as part of the Basel Früherkennung von Psychosen (FePsy) project, a prospective multilevel study aiming to improve the early detection of psychosis (Riecher-Rössler et al. 2007; Riecher-Rössler et al. 2009). The study was approved by the ethics committee of the University of Basel. All participants provided written informed consent. Patients recruited for this study were help-seeking consecutive referrals to the FePsy Clinic at the University Psychiatric Clinics Basel, which was specifically set up to identify, assess, and treat individuals in the early stages of psychosis. Most participants were referred to the early detection clinic via the University Psychiatric Outpatient Department of Basel or a psychiatrist in private practice. Some individuals
were also referred from other physicians, including general practitioners, or came on their own.

**Screening procedure**

The Basel Screening Instrument for Psychosis (BSIP; Riecher-Rössler et al. 2008) was applied to identify ARMS individuals. The BSIP is largely based on the PACE inclusion/exclusion criteria (Yung et al. 1998) and has been shown to have a high predictive validity and a good interrater reliability (Riecher-Rössler et al. 2008). Exclusion criteria for patients were age <18 years, insufficient knowledge of German, IQ <70, previous episode of schizophrenic psychosis treated with antipsychotics, psychosis clearly due to organic reasons or substance abuse, or psychotic symptoms within a clearly diagnosed depression or borderline personality disorder. For this study, we included all ARMS patients that were recruited for the FePsy study between March 2000 and August 2012 and had a clinical EEG session of at least 15 min at baseline assessment. They were followed-up at regular intervals in order to distinguish those who later transitioned to frank psychosis (ARMS-T) from those who did not (ARMS-NT). During the first year of the follow-up, ARMS individuals were assessed for transition to psychosis monthly, during the second and third years they were assessed every 3 months, and thereafter annually using the transition criteria of Yung et al. (1998). In this study, individuals were only classified as ARMS-NT if they had a follow-up duration of at least 3 years and did not develop frank psychosis.

**Assessment of positive and negative psychotic symptoms**

The Brief Psychiatric Rating Scale Expanded (BPRS-E; Lukoff et al. 1986; Ventura et al. 1993) was used to assess positive and negative psychotic symptoms. The positive psychotic symptom scale was based on the four items hallucinations, suspiciousness, unusual thought content, and conceptual disorganisation and the negative psychotic symptom scale was based on the items blunted affect, psychomotor retardation and emotional withdrawal, as defined by Velligan et al. (2005).

**EEG recordings**

EEG data were recorded at the University Hospital of Basel. Patients sat in a quiet room in an eyes-closed resting-state condition for about 20 min. Every 3 min, subjects were asked to open their eyes for a period of 5–6 s. At any signs of behavioural and/or EEG drowsiness, the patients were verbally asked to open their eyes. EEG data were sampled at a rate of 250 Hz by 19 gold cup electrodes (Nicolet Biomedical Inc., Madison, Wisconsin) referenced to linked ears. Electrodes impedances were kept below 5 kΩ.

**Artefact rejection**

EEG pre-processing was performed using Brain Vision Analyzer© 2.0 software (Brain Products GmbH, Munich, Germany). We processed each EEG in parallel split into two branches, one filtered at 0.5 Hz and one at 1 Hz. We did so in order to apply the Independent Component Analysis (ICA) matrix from the most stable signal (1 Hz) to the one that conserved the most signal (0.5 Hz). Both branches were handled in the same way up to the step that involved re-referencing to the common average. As a first step, artefact rejection was performed manually, based on visual inspection, to remove epochs containing extreme ocular artefacts, muscles and/or cardiac contamination and bad signals due to random movements. Biased extended Infomax ICA analyses were then performed for the removal of residual eye movements, eye-blinking, muscles and non-biological components contaminated with high gamma frequencies of 50 Hz and above as measured by Fast Fourier Transform (FFT) of the ICA components (resolution at 1 Hz, power µV2, Hanning window length of 10%). After applying the ICA corrected matrix of the data filtered at 1 Hz to the one filtered at 0.5 Hz, we re-referenced the data to common average. Finally, another manual rejection based on visual inspection was performed to exclude remaining artefacts as mentioned earlier.

**CSD analyses**

EEGs were transformed into reference-free CSD estimates achieved by the Laplacian Weighted Minimum Norm algorithm (Pascual-Marqui 2007). Compared to conventional EEGs based on voltage, accumulated evidence have indicated that the use of CSD as a measure of brain activity allows reliable spatial analysis (Michel et al. 2004) by disentangling the EEG signals from various biological and non-biological artefacts, thus yielding measures that more closely represent the neuronal current generators (Tenke et al. 2011).

The electrode montage in the present study has been shown to be an acceptable EEG spatial sampling for the estimation of cortical sources of eyes-closed resting-state EEG rhythms as these oscillatory rhythms are widely characterised across all human cerebral cortex when compared to the demarcated functional topography of event-related EEG changes. Consequently, the oscillatory rhythms acquired during eye-closed
resting-state EEG can properly be sampled with a relatively low number of electrodes, as opposed to the higher density electrode montage required for observing the functional topography of stimuli-related EEG activity (Babiloni et al. 2013). This relatively low-spatial sampling of EEG oscillatory rhythms is robust as LORETA solutions are intrinsically maximally smoothed at source space thanks to its regularisation procedure (Pascual-Marqui et al. 1994; Babiloni et al. 2013).

To compute the intracortical CSD of neural oscillations, we used eLORETA (Pascual-Marqui et al. 2011) on EEG data segmented into 2-s epochs (671 epochs on average, and groups did not significantly differ in the number of segments). eLORETA is a neurophysiological imaging technique based on weighted minimum norm inverse solution procedures allowing for the 3D modelling of the EEG CSD with an exact localisation performance, with a high correlation of neural sources that are in close proximity. Numerous studies based on neuroimaging tools, such as functional (Mulert et al. 2004) and structural MRI (Worrell et al. 2000), positron emission tomography (PET; Zumsteg et al. 2005) and intracranial EEG recordings (Zumsteg et al. 2006) have validated LORETA as an efficient and reliable tool to study brain activity. Compared to the first version of LORETA (Pascual-Marqui et al. 1994), the most recent version, namely, eLORETA has no localisation bias in the presence of structured noise (Pascual-Marqui 2007).

In eLORETA, a three-shell spherical head model (brain, scalp and skull compartments) is assumed and the solution space is restricted to the cortical grey-matter and the hippocampus. In total, the solution space comprises 6239 voxels of 5 × 5 × 5 mm each. The head model for computing the lead field is based on the Montreal Neurological Institute (MNI) brain MRI average model for computing the lead field is based on the MNI coordinates of the cortical voxel (Pascual-Marqui et al. 1994), the most recent version, which is highly contaminated by the instantaneous artifactual component, is defined as:

\[ \varphi_{x,y}^2(\omega) = \frac{[f_{x,y}(\omega)]^2}{[\text{Re}[f_{x,y}(\omega)]]^2 + [\text{Im}[f_{x,y}(\omega)]]^2} \]  

with:

\[ f_{x,y}(\omega) = \frac{1}{N_R} \sum_{k=1}^{N_R} \left[ \frac{x_k(\omega)}{\text{Re}[x_k(\omega)]} \right] \left[ \frac{y_k(\omega)}{\text{Im}[y_k(\omega)]} \right] \]

Where \( x_k(\omega) \) and \( y_k(\omega) \) correspond to the discrete Fourier transforms of the two signals of interest \( x \) and \( y \) at frequency \( \omega \) for the \( k \)th EEG, \( \text{Re}[C] \) and \( \text{Im}[C] \) denote the real and imaginary parts of a complex number \( C \); the latter explains the cycle of \( C \); and the superscript “∗”, denotes a complex conjugate. The instantaneous (zero-lag) connectivity component is closely related to the real part of the phase synchronisation. LPS, which statistically partials out the instantaneous component of the total connectivity, is defined as:

\[ \varphi_{x,y}^2(\omega) = \frac{[\text{Im}[f_{x,y}(\omega)]]^2}{[\text{Re}[f_{x,y}(\omega)]]^2} \]

In order to calculate the slope between LPS and distances, a linear model was created for all the 171 pairs, which included LPS values as dependent variable and the distance between each of the 19 ROIs as independent variable. Therefore, for each individual, three LPS values (beta1, beta2 and gamma) were extracted. These values correspond to the slope of the linear model which summarises the relationship between LPS at increasing distances between the 19 ROIs. These LPS values were then standardised before feeding them into the LASSO.
Defining the ROIs

For all analyses, we defined ROIs based on the MNI coordinates of the cortical voxel at 19 sites (Canuet et al. 2012) (Supplemental Table 1 available online). For each ROI, we calculated activity at the centroid voxel. We did so as expanding to neighbouring voxels could potentially bias the analysis due to the potential correlation amongst them.

Prediction of transition to psychosis

All multivariate classification analyses were conducted using the R statistical environment (R Core Team 2014). As classification algorithm, we used the L1 regularised version of the logistic regression model, that is, the so-called LASSO, as implemented in the R add-on package liblinear (Helleputte 2013). We chose the LASSO because it performs variable selection and regression coefficient estimation simultaneously and thereby gives rise to models that are sparse and easy to interpret and at the same time still have very good predictive performance. The LASSO selects the most important variables by shrinking the regression coefficient of unimportant variables to zero. It has been demonstrated that the LASSO is more stable and accurate than traditional variable selection methods, such as backward elimination and best subset selection (Tibshirani 1996). Thus, it is highly suitable for high-dimensional data problems (i.e., small event per variable ratio). Another advantage of the LASSO model is that it can easily be summarised by a regression function, whereas most other machine-learning methods, such as for instance support vector machines, lack an intuitive understanding and thus are much more difficult to communicate and validate.

To avoid optimistically biased estimates of performance and to protect against overfitting, we strictly separated the processes of training and testing the classifier. Specifically, we applied nested cross-validation with 10 folds and 10 repetitions both in the inner and the outer loop using the R add-on package MLR (Bischl et al. 2015). The inner loop was used to search for the optimal tuning parameter lambda, whereas the outer loop was used to evaluate the predictive performance of the model. For tuning the model, we performed a grid search over a sequence of the 10 different values of lambda between 0.5 and 15. That is, for each value of lambda the cross-validated balanced accuracy (BAC) was estimated using 10-fold cross validation with 10 repetitions and the lambda value with the highest performance was picked. Since this was repeated at each iteration of the outer loop, the number of times a LASSO model was fitted amounted to $10 \times 10 \times 10 \times 10 = 100,000$. To mitigate problems of class imbalance, we gave more weight to the ARMS-T class than to the ARMS-NT class during model fitting. Specifically, ARMS-T observations were given weights of 1.94, which is the number of ARMS-NT divided by the number of ARMS-T, and ARMS-NT observations were given weights of 1.

To investigate the contribution of each EEG modality (i.e., CSD and LPS), we trained and tested three different classifiers. The first was based on the 57 CSD measures (three frequencies at 19 ROIs), the second was based on the three LPS measures, and the third was based on CSD and LPS measures combined. For the latter, we applied a meta-learner that learned from the predictions of the CSD and LPS based learners. As classification algorithm for the meta-learner, the same method was applied as for the base learners (i.e., LASSO tuned with grid search and 10-fold cross-validation with 10 repetitions).

We restricted potential predictors to those frequencies consistently found to be altered in the resting-state psychosis literature. This procedure is in accordance with text books on clinical prediction modelling (Steyerberg 2009) which recommend to select candidate predictor variables based on the literature, especially in small samples.

Results

Sample description

From March 2000 to August 2012 a total of 134 ARMS patients were recruited into the FePsy study. Of these, 53 ARMS had at least 15 min of EEG data, were antipsychotic-naïve and had sufficient follow-up data to be included in the present study. Eighteen of the included ARMS patients made a transition to psychosis (ARMS-T) during the follow-up and 35 did not (ARMS-NT). None of those who made a transition converted to affective psychosis. The 60 ARMS individuals that were excluded from this study did not differ from the included ARMS individuals with regard to age, gender, sex, years of education, and BPRS total and positive symptoms scores. The clinical characteristics and demographics of the ARMS-T and ARMS-NT groups are shown in Table I. The only overall difference in ARMS-T patients was a slightly higher positive symptoms score ($P = 0.035$).

Prediction of transition to psychosis

The predictive performances in unseen test cases of the classifiers based on CSD, LPS, and both combined (stacked learner) are summarised in Table II and their
corresponding receiver operating characteristic (ROC) curves are displayed in Figure 1. The best predictive performance in terms of AUC was achieved by the stacked learner (AUC = 0.78), followed by the CSD alone (AUC = 0.77) and LPS alone (AUC = 0.56). For all classifiers, performances were much higher in the training than in the testing data sets (Supplemental Table 2 and Figure S1 available online).

The LASSO regularisation paths for the CSD and LPS classifiers, which show the size of the regression coefficients at different values of the shrinkage parameter lambda, are shown in Figure 2. The contribution of each CSD measurement in the tuned CSD classifier is displayed in Figure 3. Twenty-one out of 57 predictor variables had non-zero regression coefficients and thus contributed to the prediction of psychosis. Nine, six and six non-zero coefficients belonged to the gamma, beta1 and beta2 oscillations, respectively. In the gamma band, the three highest contributors were the left inferior parietal lobule (IPL) ($\beta = 3.34$), the precuneus ($\beta = -3.16$) and the right posterior temporal cortex (PPC) ($\beta = -2.44$). In the beta1 band, the highest contributors were the left superior temporal gyrus (STG) ($\beta = 3.79$) followed by the precuneus ($\beta = -3.29$) and the right STG ($\beta = -2.04$). In the beta2 band, the three highest contributors were the left IPL ($\beta = 2.30$), the left superior frontal gyrus ($\beta = 2.12$) and the right frontopolar cortex ($\beta = -1.76$). In the tuned LPS classifier, beta1 contributed the most to the prediction of psychosis ($\beta = 0.62$) followed by beta2 ($\beta = -0.33$) and gamma ($\beta = 0.25$).

**Discussion**

The main purpose of this study was to investigate whether neurophysiological measurements could help to predict the clinical outcome of patients at-risk for psychosis. In particular, we assessed whether CSD distribution and LPS of neural oscillations across various brain areas could be predictive of a transition to psychosis. This was achieved by submitting CSD and LPS values to the LASSO machine-learning algorithm to identify multivariate patterns of brain activity that predict transition. The model was internally validated using nested 10-fold cross-validation with 10 repetitions to allow honest estimation of the generalisation capacity of the prediction model. In ARMS patients, transition to psychosis.

**Table I. Demographic and clinical characteristics at EEG assessment.**

|                      | ARMS-NT ($N = 35$) | ARMS-T ($N = 18$) | $P$ value |
|----------------------|--------------------|-------------------|-----------|
| Gender               |                    |                   |           |
| Women                | 12 (34.3%)         | 8 (44.4%)         | 0.672     |
| Men                  | 23 (65.7%)         | 10 (55.6%)        |           |
| Age                  | 25.8 (7.36)        | 26.7 (7.64)       | 0.687     |
| Years of education   | 11.3 (3.24)        | 11.0 (2.27)       | 0.684     |
| Antidepressants      |                    |                   | 1.000     |
| No                   | 26 (74.3%)         | 14 (77.8%)        |           |
| Yes                  | 9 (25.7%)          | 4 (22.2%)         |           |
| Antipsychotics       |                    |                   |           |
| No                   | 35 (100%)          | 18 (100%)         |           |
| Yes                  | 0 (0.00%)          | 2 (13.3%)         |           |
| Mood stabiliser      |                    |                   | 0.340     |
| No                   | 35 (100%)          | 17 (94.4%)        |           |
| Yes                  | 0 (0.00%)          | 1 (5.6%)          |           |
| Tranquilizer         |                    |                   | 0.469     |
| No                   | 30 (85.7%)         | 14 (77.8%)        |           |
| Yes                  | 5 (14.3%)          | 4 (22.2%)         |           |
| Substance use disorders |             |                   | 1.000     |
| No                   | 29 (87.9%)         | 13 (86.7%)        |           |
| Yes                  | 4 (12.1%)          | 2 (13.3%)         |           |
| Mood disorder        |                    |                   | 0.099     |
| No                   | 25 (75.8%)         | 7 (46.7%)         |           |
| Yes                  | 8 (24.2%)          | 8 (53.3%)         |           |
| Anxiety disorders    |                    |                   | 1.000     |
| No                   | 27 (81.8%)         | 13 (86.7%)        |           |
| Yes                  | 6 (18.2%)          | 2 (13.3%)         |           |
| BPRS Positive symptoms | 6.39 (2.33)       | 7.83 (2.18)       | 0.035     |
| BPRS Negative symptoms| 5.65 (2.52)       | 5.41 (2.90)       | 0.782     |
| BPRS total score     | 37.9 (11.0)        | 40.2 (9.86)       | 0.462     |

ARMS-NT, at-risk mental state patients without later transition to psychosis; ARMS-T, at-risk mental state patients with later transition to psychosis; BPRS, Brief Psychiatric Rating Scale. Categorical and continuous variables were compared by Pearson’s $\chi^2$ (or Fisher’s exact tests if any expected cell frequencies were <5) and ANOVAs, respectively. Numbers in brackets indicate mean and SD for continuous variables and absolute numbers and percentages for categorical variables.

**Table II. The summary of the predictive performances.**

| Learner        | BAC   | AUC test | AUC train | Sensitivity | Specificity |
|----------------|-------|----------|-----------|-------------|-------------|
| LPS            | 0.57  | 0.66     | 0.47      | 0.47        | 0.67        |
| CSD            | 0.69  | 0.77     | 0.63      | 0.76        | 0.76        |
| Stacked        | 0.70  | 0.78     | 0.58      | 0.83        | 0.83        |

BAC, balanced accuracy; AUC, area under the receiver operating curve; LPS, lagged phase synchronisation; CSD, current-source density; Stacked, CSD and LPS combined.
Figure 2. The LASSO regularisation paths for the CSD and LPS classifiers showing the size of the regression coefficients at different values of the shrinkage parameter lambda.
psychosis could be predicted with good accuracy from CSD but not from the spatial slope of LPS data. Combining both measures did not improve the predictive accuracy relative to a model that was based on CSD alone. Since ARMS-T and ARMS-NT could not be differentiated in terms of CSD using an univariate approach in our previous study, the findings of this study suggest that whole patterns of CSD have to be taken into account to successfully differentiate these groups. The present study reveals that CSD activity in the left STG, and to a lower extent the right STG in all frequency bands, are important for predicting transition to psychosis. This is in line with previous structural MRI studies showing that predominantly the left STG grey-matter volume is significantly decreased in schizophrenic psychoses (Kasai et al. 2003) and that a decrease in both the left and right STG at baseline, i.e., during the at-risk state, is associated with a later transition to psychosis (Fusar-Poli et al. 2011a). This decrease in grey-matter volume could be the cause of abnormal high frequency oscillations identified in the present study (Uhlhaas and Singer 2010).

The next important ROI identified in our model is the left IPL, whose CSD in both the beta2 and gamma frequency bands are substantially predictive for transition to psychosis. The IPL is a complex brain region involved in attention, time and space integration (Assmus et al. 2003), language, and action processing (Caspers et al. 2013). The IPL has been shown to be a prime candidate in the schizophrenia network disorder and belongs to the cortical regions most affected by disease progression (Torrey 2007). In line with this finding, while an overall decrease in grey-matter volume in IPL has been associated with increased symptoms severity (Wilke et al. 2001), a decrease in the left IPL has mostly been revealed in male patients (Frederikse et al. 2000). These results suggest that patients prone to a later transition could already have abnormal IPL volumes, causing aberrant CSD generation specifically within this cortical region.

Finally, the LASSO algorithm has also identified beta1 oscillations within the precuneus as important predictors. The precuneus is a crucial part of the default-mode network (see Gusnard and Raichle 2001 for review) and has been implicated in a broad spectrum of integrative processes such as self-consciousness, visuo-spatial imagery and social cognition (Cavanna and Trimble 2006). Interestingly, all these processes are known to be impaired in schizophrenic psychoses (Kuhn and Gallinat 2013), which fits well with the hypoactivation and reduction of the precuneus observed in schizophrenic psychoses (Shapleske et al. 2002). Most importantly, grey-matter volumes of the precuneus has also been found to be reduced in ARMS patients with later transition to psychosis (Borgwardt et al. 2008), potentially explaining the here revealed CSD abnormalities of beta1 oscillations in converters.

The three predictors identified in our model could be cortical areas belonging to a particular network already impaired at the risk-state. Interestingly, converging
evidence has revealed that the STG (Salisbury et al. 1998), the IPL (Fusar-Poli et al. 2011b) and the precuneus (Mulert et al. 2004) are all important areas for the generation of the P300 which is an event-related potential component elicited during stimulus evaluation and/or categorisation (van Tricht et al. 2010). Therefore, an alteration of this network could potentially explain why ARMS patients have been shown to have an altered P300 component, a promising biomarker in predicting the progression to full-blown psychosis (van Tricht et al. 2010; van Tricht et al. 2014).

Our study also highlights the importance of internal validation performed to prevent overoptimistic estimates of predictive performance. If we had not cross-validated our model, we would have revealed a near perfect classification with an AUC of 0.99, which, after going through rigorous repeated cross-validations, was decreased to 0.77 (Supplemental Figure S1, training and testing for the CSD analyses, respectively, available online). Unfortunately, in the field of prediction of psychosis, most studies have not applied internal or external cross-validation and therefore are subject to over-optimism (Shah et al. 2013). Furthermore, many of those who did internally cross-validate their results did not do it in line with current recommendations (Steyerberg 2009). That is, they only cross-validated the final model and thus did not take into account the uncertainty introduced by the variable selection.

In many early detection centres for psychosis, resting-state clinical EEGs are now routinely used in the clinical diagnosis of patients exhibiting schizophrenia-like symptoms as a way to search for signs of organic brain disorders such as limbic encephalitis or epilepsy. Moreover, it is relatively easy to place without the need of an advanced degree and only about 15 min of eye-closed acquisition is needed. Automated software could be programmed to perform decent EEG data-preprocessing which would be fed into the model. A prediction score could then be obtained in less than an hour. The latter could be helpful in clarifying the differential diagnosis and in determining the prognosis.

Limitations

It is important to note that – relative to the number of considered predictors – the effective sample size is relatively low. However, it should be noted that ARMS patients are a very difficult to recruit patient population because: (1) these patients are relatively rare, (2) many of them only seek help when they have already developed frank psychosis, and (3) even if they visit our early detection clinic early enough, they often cannot be motivated to participate in scientific studies because they are often already quite suspicious due to the onset of the disease. Due to the small event per variable ratio, we took extra care to prevent over-fitting by conducting repeated nested cross-validation. Nevertheless, our results should be considered preliminary and be replicated in bigger samples. Furthermore, we relied on a low-density EEG system which is commonly used in the clinical field for practical reasons. Although several recent studies have shown that resting-state analyses could reliably be performed using such systems (Babiloni et al. 2013; Canuet et al. 2011,2012), all analyses would have been more precise with a greater number of electrodes. Moreover, some patients across both the ARMS-T and ARMS-NT groups relied on medications other than neuroleptics, which could have influenced the recorded brain activity.

Conclusion

These findings provide preliminary evidence that CSD measurements of high frequency oscillations could be used as predictors for the early detection of psychosis. The main ROIs identified in our model are all important cortical areas in the generation of the P300 ERP component which has been found to be an important predictor of psychosis (van Tricht et al. 2010). To our knowledge, this is the first study to investigate the high frequencies present at numerous ROIs distributed across the brain using powerful neurophysiological techniques. All patients were neuroleptic-naïve and all data were acquired using the widely available low resolution clinical EEG equipment. Moreover, our model was validated using repeated cross-validations which have yielded good internal validation; a step beyond previous EEG studies in the field of early detection.

Acknowledgments

This work was supported by the Swiss National Science Foundation (P0BSP1-152074, 3200-057216.99, 3200-0572216.99, PBBSB-106936, 3232BO-119382). The authors would like to thank the patients and volunteers for participating in this study.

Statement of interest

None to declare.

References

Amminger GP, Edwards J, Brewer WJ, Harrigan S, McGorry PD. 2002. Duration of untreated psychosis and cognitive deterioration in first-episode schizophrenia. Schizophr Res 54:223–230.

Assmus A, Marshall JC, Ritzl A, Noth J, Zilles K, Fink GR. 2003. Left inferior parietal cortex integrates time and space during collision judgments. Neuroimage 20 Suppl 1:S82–S88.
Babiloni C, Carducci F, Lizio R, Vecchio F, Baglieri A, Bernardini S, et al. 2013. Resting state cortical electroencephalographic rhythms are related to gray matter volume in subjects with mild cognitive impairment and Alzheimer’s disease. Hum Brain Mapp 34:1427–1446.

Bischl L, Lang M, Richter J, Bossek J, Judt L, Kuehn T, et al. 2015. mlr: Machine Learning in R. R package version 2.4. https://cran.r-project.org/web/packages/mlr/

Borgwardt SJ, McGuirke PK, Aston J, Gschwandtner U, Pfliueger MO, Stieglitz R-D, et al. 2008. Reductions in frontal, temporal and parietal volume associated with the onset of psychosis. Schizophrenia Research 106:108–114.

Canuet L, Ishii R, Pascual-Marqui RD, Iwase M, Kurimoto R, Aoki Y, et al. 2011. Resting-state EEG source localization and functional connectivity in schizophrenia-like psychosis of epilepsy. PloS One 6:e27863.

Canuet L, Tellado I, Couceiro V, Fraile C, Fernandez-Navoia L, Ishii R, et al. 2012. Resting-state network disruption and APOE genotype in Alzheimer’s disease: a lagged functional connectivity study. PloS One 7:e46289.

Caspers S, Schleicher A, Bacha-Trams M, Palomero-Gallagher N, Amunts K, Zilles K. 2013. Organization of the human inferior parietal lobule based on receptor architectonics. Cereb Cortex 23:615–628.

Cavanna AE, Trimble MR. 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129:564–583.

Centorrino F, Price BH, Tuttle M, Bak M, Hennen J, Albert MJ, et al. 2002. EEG abnormalities during treatment with typical and atypical antipsychotics. Am J Psychiatry 159:109–115.

Dua S, Du X. 2011. Data mining and machine learning in cybersecurity. Boca Raton: CRC press.

Frederikse M, Lu A, Aylward E, Barta P, Sharma T, Pearlson G. 2000. Sex differences in inferior parietal lobule volume in schizophrenia. Am J Psychiatry 157:422–427.

Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, et al. 2012. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Archives of General Psychiatry 69:220–229.

Fusar-Poli P, Borgwardt S, Crescini A, Deste G, Kempton MJ, Lawrie S, et al. 2011a. Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. Neurosci Biobehav Rev 35:1175–1185.

Fusar-Poli P, Crossley N, Woolley J, Carletti F, Perez-Iglesias R, Broome M, et al. 2011b. Gray matter alterations related to P300 abnormalities in subjects at high risk for psychosis: Longitudinal MRI-EEG study. Neuroimage 55:320–328.

Gusnard DA, Raichle ME. 2001. Searching for a baseline: functional imaging and the resting human brain. Nature Reviews Neuroscience 2:685–694.

Helleputte T. 2013. LiblineaR: Linear Predictive Models Based On The Liblinear C/C++ Library. R package version 1.80-7 ed. Herrmann CS, Demiralp T. 2005. Human EEG gamma oscillations in neuropsychiatric disorders. Clin Neurophysiol 116:2719–2733.

Insel TR. 2010. Rethinking schizophrenia. Nature 468:187–193.

Kasai K, Shenton ME, Salisbury DF, Hirayasu Y, Lee CU, Ciszewski AA, et al. 2003. Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. Am J Psychiatry 160:156–164.

Kopell N, Ermentrout GB, Whittington MA, Traub RD. 2000. Gamma rhythms and beta rhythms have different synchronization properties. Proc Natl Acad Sci USA 97:1867–1872.

Koutsouleris N, Davatzikos C, Bottlender R, Patschuk-Kliche K, Scheuerrecker J, Decker P, et al. 2012. Early recognition and disease prediction in the at-risk mental states for psychosis using neurocognitive pattern classification. Schizophr Bull 38:1200–1215.

Koutsouleris N, Riecher-Rössler A, Meisenzahl EM, Smieskova R, Studerus E, Kambetz-Illankovic L, et al. 2014. Detecting the Psychosis Prodrome Across High-risk Populations Using Neuroanatomical Biomarkers. Schizophr Bull.

Kuhn S, Gallinat J. 2013. Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. Schizophr Bull 39:358–365.

Lee KH, Williams LM, Breakspear M, Gordon E. 2003. Synchronous gamma activity: a review and contribution to an integrative neuroscience model of schizophrenia. Brain Res Brain Res Rev 41:57–78.

Liu C, Che D, Liu X, Song Y. 2013. Applications of machine learning in genomics and systems biology. Computational and Mathematical Methods in Medicine 2013:

Lukoff D, Nuechterlein K, Ventura J. 1986. Manual for the expanded brief psychiatric rating scale. Schizophr Bull 12:594–602.

McGorry PD, Edwards J, Mihalopoulos C, Harrigan SM, Jackson HJ. 1996. EPPIC: an evolving system of early detection and optimal management. Schizophr Bull 22:305–326.

Michel CM, Murray MM, Lantz G, Gonzalez S, Spinelli L, Grave de Peralta R. 2004. EEG source imaging. Clin Neurophysiol 115:2195–2222.

Morris R, Griffiths O, Le Pelley ME, Weickert TW. 2012. Attention to irrelevant cues is related to positive symptoms in schizophrenia. Schizophrenia Bulletin:br192

Moscarelli M. 1994. Health and economic evaluation in schizophrenia: implications for health policies. Acta Psychiatr Scand Suppl 382:84–88.

Mulert C, Jäger L, Schmitt R, Bussfeld P, Pogarell O, Möller H-J, et al. 2004. Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. Neuroimage 22:83–94.

Pascual-Marqui RD. 2007. Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization. arXiv preprint arXiv:0710.3341.

Pascual-Marqui RD, Lehmann D, Koukkou M, Kochi K, Anderer P, Saletu B, et al. 2011. Assessing interactions in the brain with exact low-resolution electromagnetic tomography. Philos Trans a Math Phys Eng Sci 369:3768–3784.

Pascual-Marqui RD, Michel CM, Lehmann D. 1994. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int J Psychophysiol 18:49–65.

R Core Team. 2014. R: A language and environment for statistical computing.

Ramseyd A, Kometer M, Studerus E, Koranyi S, Ittig S, Gschwandtner U, et al. 2014. aberrant Current Source-Density and Lagged Phase Synchronization of Neural Oscillations as Markers for Emerging Psychosis. Schizophr Bull.
Riecher-Rössler A, Aston J, Ventura J, Merlo M, Borgwardt S, Gschwandtner U, et al. 2008. [The Basel Screening Instrument for Psychosis (BSIP): development, structure, reliability and validity]. Fortschr Neurol Psychiatr 76:207–216.

Riecher-Rössler A, Gschwandtner U, Aston J, Borgwardt S, Drewe M, Fuhr P, et al. 2007. The Basel early-detection-of-psychosis (FEPSY)-study-design and preliminary results. Acta Psychiatria Scandinavica 115:114–125.

Riecher-Rössler A, Gschwandtner U, Borgwardt S, Aston J, Pfueger M, Rossler W. 2006. Early detection and treatment of schizophrenia: how early? Acta Psychiatr Scand 113 Suppl:73–80.

Riecher-Rössler A, Pfueger MO, Aston J, Borgwardt SJ, Brewer WJ, Gschwandtner U, et al. 2009. Efficacy of using cognitive status in predicting psychosis: a 7-year follow-up. Biol Psychiatry 66:1023–1030.

Ruhmann S, Schultz-Lutter F, Schmidt SJ, Kaiser N, Klosterkötter J. 2014. Prediction and prevention of psychosis: current progress and future tasks. Eur Arch Psychiatry Clin Neurosci 264 Suppl 1:9–16.

Salisbury DF, Shenton ME, Sherwood AR, et al. 1998. First-episode schizophrenic psychosis differs from first-episode affective psychosis and controls in p300 amplitude over left temporal lobe. Archives of General Psychiatry 55:173–180.

Shah JL, Tandon N, Keshavan MS. 2013. Psychosis prediction and clinical utility in familial high-risk studies: selective review, synthesis, and implications for early detection and intervention. Early Intervention in Psychiatry 7:345–360.

Shapleske J, Rossell SL, Chitnis XA, Sukling J, Simmons A, Bullmore ET, et al. 2002. A computational morphometric MRI study of schizophrenia: effects of hallucinations. Cereb Cortex 12:1331–1341.

Simon AE, Borgwardt S, Riecher-Rössler A, Velthorst E, de Haan L, Fusar-Poli P. 2013. Moving beyond transition outcomes: meta-analysis of remission rates in individuals at high clinical risk for psychosis. Psychiatry Res 209:266–272.

Stafford MR, Jackson H, Mayo-Wilson E, Morrison AP, Kendall T. 2013. Early interventions to prevent psychosis: systematic review and meta-analysis. BMJ: British Medical Journal 346.

Steyerberg EW. 2009. Clinical prediction models a practical approach to development, validation, and updating. New York, NY: Springer.

Tenke CE, Kayser J, Mann C, Fekri S, Kroppmann CJ, Schaller JD, et al. 2011. Current source density measures of electroencephalographic alpha predict antidepressant treatment response. Biol Psychiatry 70:388–394.

Tibshirani R. 1996. Regression shrinkage and selection via the lasso. Journal of the Royal Statistical Society. Series B (Methodological) 267–288.

Torrey EF. 2007. Schizophrenia and the inferior parietal lobule. Schizophr Res 97:215–225.

Uhlhaas PJ, Singer W. 2010. Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci 11:100–113.

Uhlhaas PJ, Singer W. 2013. High-frequency oscillations and the neurobiology of schizophrenia. Dialogues Clin Neurosci 15:301–313.

van Tricht MJ, Nieman DH, Koelman JH, van der Meer JN, Bour LJ, de Haan L, et al. 2010. Reduced parietal P300 amplitude is associated with an increased risk for a first psychotic episode. Biol Psychiatry 68:642–648.

van Tricht MJ, Ruhmann S, Arns M, Müller R, Bodatsch M, Velthorst E, et al. 2014. Can quantitative EEG measures predict clinical outcome in subjects at Clinical High Risk for psychosis? A prospective multicenter study. Schizophrenia Research 153:42–47.

Velligan D, Prihoda T, Dennehy E, Biggs M, Shores-Wilson K, Crismon ML, et al. 2005. Brief psychiatric rating scale expanded version: How do new items affect factor structure? Psychiatry Research 135:217–228.

Ventura J, Green MF, Shaner A, Liberman RP. 1993. Training and quality assurance with the Brief Psychiatric Rating Scale: “the drift busters.”. International Journal of Methods in Psychiatric Research.

Wilke M, Kaufmann C, Grabner A, Putz B, Wetter TC, Auer DP. 2001. Gray matter changes and correlates of disease severity in schizophrenia: a statistical parametric mapping study. Neuroimage 13:814–824.

Worrell GA, Lagerlund TD, Sharbrough FW, Brinkmann BH, Busacker NE, Cicora KM, et al. 2000. Localization of the epileptic focus by low-resolution electromagnetic tomography in patients with a lesion demonstrated by MRI. Brain Topography 12:273–282.

Yung AR, Phillips LJ, McGorry PD, McFarlane CA, Fraceoy S, Harrigan S, et al. 1998. Prediction of psychosis. A step towards indicated prevention of schizophrenia. Br J Psychiatry 172:14–20.

Zumsteg D, Lozano AM, Wennberg RA. 2006. Depth electrode recorded cerebral responses with deep brain stimulation of the anterior thalamus for epilepsy. Clin Neurophysiol 117:1602–1609.

Zumsteg D, Wenneberg R, Treyer V, Buck A, Wieser H. 2005. H2(15)O or 13NH3 PET and electromagnetic tomography (LORETA) during partial status epilepticus. Neurology 65:1657–1660.