NeuroImage: Clinical 15 (2017) 264–273

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Auditory prediction errors as individual biomarkers of schizophrenia

J.A. Taylor[a,b], N. Matthews[c], P.T. Michie[d,e], M.J. Rosa[f,g], M.I. Garrido[a,h,i,j,*]

[a] Queensland Brain Institute, The University of Queensland, Australia
[b] School of Information Technology and Electrical Engineering, The University of Queensland, Australia
[c] School of Psychology, The University of Queensland, Australia
[d] School of Psychology, University of Newcastle, Callaghan, New South Wales, Australia
[e] Priority Centre for Brain and Mental Health Research, University of Newcastle, Newcastle, New South Wales, Australia
[f] Max-Planck UCL Centre for Computational Psychiatry and Ageing Research, University College London, UK
[g] Department of Computer Science, University College London, UK
[h] School of Mathematics and Physics, The University of Queensland, Australia
[i] Centre for Advanced Imaging, The University of Queensland, Australia
[j] ARC Centre for Integrative Brain Function, Australia

ARTICLE INFO

Keywords:
Machine learning
Schizophrenia
Mismatch negativity
EEG

ABSTRACT

Schizophrenia is a complex psychiatric disorder, typically diagnosed through symptomatic evidence collected through patient interview. We aim to develop an objective biologically-based computational tool which aids diagnosis and relies on accessible imaging technologies such as electroencephalography (EEG). To achieve this, we used machine learning techniques and a combination of paradigms designed to elicit prediction errors or Mismatch Negativity (MMN) responses. MMN, an EEG component elicited by unpredictable changes in sequences of auditory stimuli, has previously been shown to be reduced in people with schizophrenia and this is arguably one of the most reproducible neurophysiological markers of schizophrenia.

EEG data were acquired from 21 patients with schizophrenia and 22 healthy controls whilst they listened to three auditory oddball paradigms comprising sequences of tones which deviated in 10% of trials from regularly occurring standard tones. Deviant tones shared the same properties as standard tones, except for one physical aspect: 1) duration - the deviant stimulus was twice the duration of the standard; 2) monaural gap - deviants had a silent interval omitted from the standard, or 3) inter-aural timing difference, which caused the deviant location to be perceived as 90° away from the standards.

We used multivariate pattern analysis, a machine learning technique implemented in the Pattern Recognition for Neuroimaging Toolbox (PRoNTo) to classify images generated through statistical parametric mapping (SPM) of spatiotemporal EEG data, i.e. event-related potentials measured on the two-dimensional surface of the scalp over time. Using support vector machine (SVM) and Gaussian processes classifiers (GPC), we were able classify individual patients and controls with balanced accuracies of up to 80.48% (p-values = 0.0326, FDR corrected) and an ROC analysis yielding an AUC of 0.87. Crucially, a GP regression revealed that MMN predicted global assessment of functioning (GAF) scores (correlation = 0.73, R^2 = 0.53, p = 0.0006).

1. Introduction

Schizophrenia is a chronic psychiatric disorder affecting approximately 1% of the population, expressed through cognitive dysfunction and psychotic symptoms such as hallucinations and delusions (Kahn et al., 2015). Schizophrenia is currently diagnosed through symptomatic evidence collected through patient interview. An investigation of current International Classification of Diseases diagnostic criteria (ICD-10, codes F20.0–F20.3 and F20.9) suggests the validity of schizophrenia diagnoses may be of about 89.7% (Uggerby et al., 2013). Whilst reasonably accurate, this method relies on self-report measures and ultimately on a subjective clinical decision. Hence, there is a pressing need to find biomarkers for schizophrenia that can objectively inform diagnosis and prognosis.

A number of potential candidates for schizophrenia biomarkers have been investigated, with the mismatch negativity (MMN), being one of them. The MMN is an event-related potential (ERP) elicited by an occasional unpredicted change (or deviant) in a sequence of predicted auditory events (standards). Indeed, the MMN is known to be robustly attenuated in patients with schizophrenia (Catts et al., 1995; Shelley

* Corresponding author at: The Queensland Brain Institute, The University of Queensland, Building 79, Research Road, St Lucia, 4072 Brisbane, Australia.
E-mail address: m.garrido@uq.edu.au (M.I. Garrido).

http://dx.doi.org/10.1016/j.nicl.2017.04.027
Received 4 February 2017; Received in revised form 24 April 2017; Accepted 26 April 2017
Available online 03 May 2017

et al., 1991; Todd et al., 2013) and is correlated with poor cognitive function (Light and Braff, 2005). MMN reduction is arguably one of the most reproducible neurophysiological markers of schizophrenia (Kaser et al., 2013; Shelley et al., 1991). Remarkably, this reduction is accentuated in people at risk who end up developing schizophrenia, compared to those who do not, even if there are no other behavioural differences at the baseline (Bodatsch et al., 2011; Perez et al., 2014).

While these are exciting findings, they rely on the comparison of group differences. In recent years, however, machine learning has been applied to neuroimaging data in order to provide predictive measures of diagnostic outcomes at the single individual level (Iwabuchi et al., 2013). For example, Gould et al. (2014) used abnormalities found in the neuroanatomical structure through MRI to classify schizophrenia patients and healthy controls with up to 72% accuracy.

Previous studies on EEG-based classification of schizophrenia via machine learning have primarily coupled auditory components of the ERP with visual attentional measures as discriminatory features. Neuhaus et al. (2014) measured the visual P300 response to unexpected sequences of letters, and the auditory P300 and MMN responses to a frequency oddball paradigm. In that study, they achieved an accuracy of 72.4% using the standard visual response at two electrode locations and nearest neighbour classification. Similarly, Laton et al. (2014) measured the visual P300 response to sequences of shapes, as well as the auditory P300 and MMN responses to a combined frequency and duration stimulus paradigm, achieving accuracies of up to 84.7% for a combination of all three paradigms, and up to 75% for MMN alone. However, it appears that these accuracy levels may potentially be inflated through the use of both model training and testing data for feature selection, rather than the training dataset alone. This and other studies, such as Neuhaus et al. (2011), are also limited to specific peak components (MMN and P300) as features, extracted through pre-processing in pre-defined time windows from discrete electrode locations.

The aim for this study was to develop a predictive model which aids schizophrenia diagnosis, based on objective biological quantities, measured through widely accessible imaging technologies such as EEG, and a simple task suitable for patients. Instead of using predefined time windows and electrodes, we used a whole spatiotemporal approach by considering all the electrodes and the whole peristimulus window as potential features. We assessed the performance of multivariate pattern recognition in classification of schizophrenia patients and healthy controls, using three different auditory oddball paradigms. Moreover, we compared the performance of different classification algorithms (SVM vs. GPC), responses (standards, deviants, and MMN difference wave), feature selection (with and without an a priori defined temporal mask), and data normalisation operations.

2. Methods

2.1. Participants

Twenty-one individuals with schizophrenia (age 20–52 years, M = 39.7 years, SD = 9.0, 15 male) were recruited from outpatient sources, including a volunteer register managed by the Schizophrenia Research Institute and the Inner North Brisbane Mental Health Services of the Royal Brisbane Hospital. A healthy comparison group (N = 22) was recruited from students of the University of Newcastle and community volunteers. Control participants were similar to the schizophrenia patients in both age and sex (age 23–53 years, M = 39.1 years, SD = 9.4, 14 male). Controls recruited from the University of Newcastle received course credit for participation; all other participants were reimbursed for travel costs and expenses. All participants gave written informed consent in accordance with the guidelines of the University of Newcastle and the University of Queensland's ethical committees.

2.2. Cognitive and clinical characterisation

Pre-morbid verbal IQ differed significantly between control (M = 117.5, SD = 6.8) and patient (M = 110.2, SD = 10.2) groups (p = 0.0078), based on the National Adult Reading Test (NART, Nelson, 1982). All participants were right handed, as assessed by the Edinburgh handedness inventory (Oldfield, 1971).

Participants were excluded if screening revealed a history of major head injury, epilepsy, hearing loss, or a recent history of substance abuse. Additionally, healthy controls were excluded if there was a personal history of mental illness, or a history of schizophrenia in first-degree relatives. Audiometric testing confirmed that detection thresholds were normal for all participants across frequencies of 500–2000 Hz.

Diagnoses for individuals within the patient group were made using Diagnostic Interview for Psychosis (DIP, Castle et al., 2006). The same interview was administered to the healthy comparison group to exclude significant psychopathology. All patients included in this study received an ICD-10 diagnosis within the schizophrenia spectrum. Ratings of current symptomatology for patients were obtained on the Scale for Assessment of Positive Symptoms (SAPS, Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS, Andreasen, 1982), summarised in Table 1. All patients were prescribed typical antipsychotic medication at the time of testing, except for one participant who was not receiving medication.

The participants' overall level of functioning, across psychological, social and occupational domains, was assessed using the Global Assessment of Functioning Scale (GAF, American Psychiatric Association, 2000), a numeric scale scored from 1 to 100 and divided into 10 associated levels of functioning and symptom severity. The GAF ratings ranged from 32 to 85 (M = 55.43, SD = 14.93) in patients and 73–90 (M = 83.8, SD = 5.3) in healthy controls.

2.3. Experimental design

In an encephalographic auditory-oddball experiment, participants listened to sequences of short audio stimuli repeating at 500 ms intervals presented via headphones whilst watching a silent movie. Three different stimulus variations (Fig. 1), each with specific tonal properties, were tested in separate blocks. For each paradigm, approximately a small percentage trials deviated from the standard stimulus in some physical aspect (8% for duration, 12% for left and right gap, and 10% for left and right inter-aural time difference deviants), occurring in a pseudo-random, non-consecutive order. These deviations were all expected to elicit the MMN signal.

The first paradigm employed duration deviants (DUR, Fig. 1a), where standard stimuli were binaural 1 kHz sinusoidal tones, 50 ms in duration, with deviant stimuli lasting 100 ms; i.e. twice the standard

Table 1
Summary of schizophrenia patient symptom scores. Table shows group means and standard deviation for each measure of the SAPS and SANS (absent to severe, scale 0–5), and GAF (extremely high to severely impaired function, scale 1–100).

	Measure	Mean	SD
SAPS	Hallucinations	2.20	1.74
	Delusions	2.10	1.71
	Bizarre Behaviour	1.05	1.19
	Positive Formal Thought Disorder	0.75	1.16
	Summary SAPS Score	6.10	3.92
SANS	Affective Flattening	2.00	1.17
	Alogia	1.35	1.27
	Avolition	2.55	1.00
	Anhedonia	2.40	1.05
	Attention	1.95	1.23
	Summary SANS Score	10.25	4.67
GAF		55.43	14.93