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Single-subject classification of schizophrenia patients based on a combination of oddball and mismatch evoked potential paradigms

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ABSTRACT

Objective: The diagnostic process for schizophrenia is mainly clinical and has to be performed by an experienced psychiatrist, relying primarily on clinical signs and symptoms. Current neurophysiological measurements can distinguish groups of healthy controls and groups of schizophrenia patients. Individual classification based on neurophysiological measurements mostly shows moderate accuracy.
We wanted to examine whether it is possible to distinguish controls and patients individually with a good accuracy. To this end we used a combination of features extracted from the auditory and visual P300 paradigms and the mismatch negativity paradigm.
Methods: We selected 54 patients and 54 controls, matched for age and gender, from the data available at the UPC Kortenberg. The EEG-data were high- and low-pass filtered, epoched and averaged. Features (latencies and amplitudes of component peaks) were extracted from the averaged signals. The resulting dataset was used to train and test classification algorithms. First on separate paradigms and then on all combinations, we applied Naïve Bayes, Support Vector Machine and Decision Tree, with two of its improvements: Adaboost and Random Forest.
Results: For at least two classifiers the performance increased significantly by combining paradigms compared to single paradigms. The classification accuracy increased from at best 79.8% when trained on features from single paradigms, to 84.7% when trained on features from all three paradigms.
Conclusion: A combination of features originating from three evoked potential paradigms allowed us to accurately classify individual subjects as either control or patient. Classification accuracy was mostly above 80% for the machine learners evaluated in this study and close to 85% at best.

1. Introduction

Schizophrenia is a complex psychiatric disorder. The diagnostic process is mainly clinical and has to be performed by an experienced psychiatrist, who relies to a large extent on clinical signs and symptoms. Clinicians and patients would benefit from biomarkers that can help distinguish schizophrenia from normal controls.

Current neurophysiological measurements can distinguish between groups of healthy controls and groups of schizophrenia patients. Mismatch Negativity (MMN) amplitude is reduced in schizophrenia patients compared to healthy controls [1]. A reduction in MMN amplitude was also shown in people experiencing very early stages of a psychotic illness and those in an at-risk mental state [2]. Overall, reduction in MMN amplitude is one of the most consistent findings in schizophrenia [2].

In the evaluation of potential biomarkers, individual classification value is more important than group level effects. Individual classification based on neurophysiological measurements only shows moderate accuracy. Greenstein et al. applied the Random Forest machine learner on data from 74 anatomic brain MRI subregions obtained from 98 childhood onset schizophrenia patients and 99 age, sex and ethnicity-matched healthy controls [3]. Patients and controls were classified on a combination of brain regions with an accuracy of 73.7%. Johannesen et al. investigated classification of healthy controls and schizophrenia- and bipolar disorder patients based on different sets of features: (1) P50 suppression, P300 latency and P300 amplitude; (2) N100 amplitude; (3) evoked spectral power and (4) P50 and P300 hemisphere asymmetry [4]. They achieved 71% accuracy when classifying schizophrenia patients and healthy controls with the P50 and P300 endophenotypes.

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Using the N100 and spectral power improved the accuracy to 79% for classification of subjects as either patient or control.

In this study, we wanted to examine whether it is possible to distinguish between schizophrenia patients and normal controls at the individual level with a good accuracy, using machine classifiers. To this end we used a combination of features from the mismatch negativity paradigm, the auditory- and the visual P300 paradigm.

2. Methods

2.1. Participants

Fifty-four patients with schizophrenia or schizoaffective disorder ('Schizo'; 36 male; age: 40.5 ± 10.1) and 54 healthy non-medicated control participants ('Norm'; 36 male; age: 37.6 ± 14.1) were recruited, matched for age and gender. Patients were recruited in the UPC (University Psychiatric Centre KULeuven, campus Kortenberg), where they were diagnosed by a semi-structured interview (OPCRIT v4.0). All participants have given written informed consent. Detailed demographic data can be found in Table 1.

2.2. Recording conditions

EEGs were recorded using a 64-channel ANT digital EEG measure station (ANT, The Netherlands). Ag-AgCl electrodes were arranged in an electrode cap using the international 10/10 system. Signals were digitised at a sampling frequency of 256 Hz and stored for offline analysis.

2.3. Paradigms and procedures

The P300 paradigms are attention related, requiring a response to their "target" stimulus. The MMN is similar but requires no directed attention since it is performed passively. The grand averages for both groups and for the different stimuli are shown in Fig. 1.

2.3.1. Auditory P300 (P300a)

The paradigm consists of 't' (target), 'd' (distractor) and 's' (standard) tones. The target and the distractor differ from the standard tone (1000 Hz) respectively by a higher (1500 Hz) and a lower frequency (500 Hz) and all have a duration of 100 ms and a loudness of 70 dB. These stimuli are presented pseudo-randomly, with a distribution of 80% standard, 10% target and 10% distractor and an inter-stimulus interval randomised between 1 and 1.5 seconds. In total 400 tones are provided per test, with a total test time of 540 seconds.

2.3.2. Visual P300 (P300v)

For the visual P300 a target (Square, side 106 pixels), distractor (Circle, diameter 176 pixels) and standard figure (Square, side 158 pixels) are presented in full blue (RGB = 0, 0, 255) in the centre of a black (RGB = 0, 0, 0) background with a resolution of 1024 by 768 pixels. The distribution of the stimuli and the total test time are the same as for the auditory P300.

Table 1
Demographic data.

	Patients	Controls	P
Amount of participants	54	54	
Male	36	36	
Age (years): mean ± std	40.5 ± 10.1	37.6 ± 14.1	0.22
Age (years): range	[22.4, 60.5]	[15.1, 64.4]	
Education (years): mean ± std	12.6 ± 1.80	14.8 ± 2.11	4.84×10^{-5}
Disease duration (years): mean ± std	14.8 ± 9.04	–	
Disease duration (years): range	[1, 40]	–	

2.3.3. MMN

The paradigm consists of 'd' (duration deviant), 'f' (frequency deviant) and 's' (standard) tones. The duration and frequency deviant tones differ from the standard tone (100 ms, 1000 Hz) respectively by a longer duration (250 ms) and a higher frequency (1500 Hz) and all have a loudness of 70 dB. These stimuli are presented in pseudo-random order, with a distribution of 90% standard, 5% duration deviant and 5% frequency deviant and an inter-stimulus interval of 300 ms. In total 1800 tones are provided per test, with a total test time of 733 seconds.

2.4. EEG signal pre-processing

Offline signal processing was done in Matlab [5] using SPM8 [6]. First, three Butterworth filters were applied: a high-pass filter with a cut-off frequency at 0.1 Hz, removing DC, a low-pass filter with a cut-off frequency at 30 Hz followed by a band-stop filter with range of 48 Hz to 52 Hz, removing 50 Hz mains hum.

Then, signals were epoched with a [-200, 800] ms peristimulus interval for the P300 paradigms, and a [-100, 500] ms peristimulus interval for the MMN, after which baseline correction and rereferencing to linked ears were performed.

This was followed by artefact rejection, using three criteria: absolute maximum (>80 μV), peak-to-peak maximum (>120 μV) and flat segment rejection. Then, the epochs were averaged into stimulus specific responses for each individual patient. Subsequently, to remove high frequencies that might have arisen by this averaging, the abovementioned low-pass filter was reapplied and baseline correction was performed.

2.5. Feature detection

We designed an algorithm in Matlab for automatic detection of the latencies and amplitudes of a set of peaks (see Table 2) in channels Fz, Cz and Pz. The parameters that are entered into the algorithm, are the averaged evoked potentials, a time interval in which the peak is to be detected, and the direction of the peak (positive or negative). A peak is defined as a time point that has a higher amplitude than its neighbouring time points, so multiple peaks can be detected in an interval. The latency and amplitude of the peak with the largest absolute value is returned. The possibility exists that no peak is detected at all, e.g. when the interval only contains a rising edge. To handle missing values that might occur when no local maxima are detected, we added a 'force' option to the algorithm. In theory, the derivative of the signal is zero when the signal reaches a local maximum. This option 'force' therefore returns the time point with the smallest derivative in the specified interval.

The choice of the minimum and maximum value for each intervals in which the algorithm should search for the peak, was data-driven. We always started with a [-50, +50] milliseconds interval around the average latency of the peak, measured on the grand averages of the dataset (see Fig. 1). When the deviation of the latency of a peak was larger than 50 milliseconds for at least one subject, which was the case for the P300 peaks in both the auditory and the visual P300 paradigm, this interval was extended as much as necessary to contain correct data from all subjects. The limit to extending the detection interval of a peak was the presence of a larger peak nearby, e.g. N100 and N200, or P200 and P300. Optimisation consisted of extending intervals where necessary whilst ensuring as little overlap as possible between intervals of peaks that point in the same direction. The peaks and their detection intervals are shown in Table 2.

The complete feature set consisted of amplitude and latency of each of these peaks in channels Fz, Cz and Pz, which yielded six features per peak. With four peaks in the target- and in the distract event of the auditory and visual P300 paradigm and two peaks in the frequency- and in the duration deviant event of the mismatch negativity paradigm, 120 features were measured in total for each subject. For both P300