Clinical Neurophysiology 126 (2015) 721–730

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

A machine learning approach using auditory odd-ball responses to investigate the effect of Clozapine therapy

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ARTICLE INFO

Article history:
Accepted 7 July 2014
Available online 27 August 2014

Keywords:
Brain source localization
EEG signals
Odd-ball auditory evoked potentials
Machine learning
Schizophrenia
Clozapine treatment

HIGHLIGHTS

- A machine learning algorithm is used to identify a set of "features", from odd-ball auditory evoked potentials, that can simultaneously discriminate between clinically important conditions.
- This discrimination capability concludes that the brain function associated with these features normalizes in responding patients as a result of Clozapine treatment.
- The proposed approach can help in our understanding of the changes in brain behavior due to Clozapine and its therapeutic effect in schizophrenia.

ABSTRACT

Objective: To develop a machine learning (ML) methodology based on features extracted from odd-ball auditory evoked potentials to identify neurophysiologic changes induced by Clozapine (CLZ) treatment in responding schizophrenic (SCZ) subjects. This objective is of particular interest because CLZ, though a potentially dangerous drug, can be uniquely effective for otherwise medication-resistant SCZ subjects. We wish to determine whether ML methods can be used to identify a set of EEG-based discriminating features that can simultaneously (1) distinguish all the SCZ subjects before treatment (BT) from healthy volunteer (HV) subjects, (2) distinguish EEGs collected before CLZ treatment (BT) vs. those collected after treatment (AT) for those subjects most responsive to CLZ, (3) discriminate least responsive subjects from HV AT, and (4) no longer discriminate most responsive subjects from HVs AT. If a set of EEG-derived features satisfy these four conditions, then it may be concluded that these features *normalize* in responsive subjects as a result of CLZ treatment, and therefore potentially provide insight into the functioning of the drug on the SCZ brain.
Methods: Odd-ball auditory evoked potentials of 66 HVs and 47 SCZ adults both BT and AT with CLZ were derived from EEG recordings. Treatment outcome, after at least one year follow-up, was assessed through clinical rating scores assigned by an experienced clinician, blind to EEG results. Using a criterion of at least 35% improvement after CLZ treatment, subjects were divided into "most-responsive" (MR) and "least-responsive" (LR) groups. As a first step, a brain source localization (BSL) procedure was employed on the EEG signals to extract source waveforms from specified brain regions. ML methods were then applied to these source waveform signals to determine whether a set of features satisfying the four conditions outlined above could be discovered.
Results: A set of cross-power spectral density (CPSD) features meeting these criteria was identified. These CPSD features, consisting of a combination of brain regional source activity and connectivity measures, significantly overlap with the default mode network (DMN). All decrease with CLZ treatment in responding SCZs.
Conclusions: A set of EEG-derived discriminating features which normalize as a result of CLZ treatment was identified. These discriminating features define a network that shares significant commonality with

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http://dx.doi.org/10.1016/j.clinph.2014.07.017

the DMN. Our findings are consistent with those of previous literature, which suggest that regions of the DMN are hyperactive and hyperconnected in SCZ subjects. Our study shows that these discriminating features decrease after treatment, consistent with portions of the DMN normalizing with CLZ therapy in responsive subjects.

Significance: Machine learning is proposed as a potentially powerful tool for analysis of the effect of medication on psychiatric illness. If replicated, the proposed approach could be used to gain some improved understanding of the effect of neuroleptic medications in treating psychotic illness. These results may also be useful in the development of new pharmaceuticals, since a new drug which induces changes in brain electrophysiology similar to those seen after CLZ could also have powerful antipsychotic properties.

1. Introduction

Schizophrenia is a severe psychotic disorder affecting approximately 1% of the world's population (Kelly, 2006). Among the many anti-psychotic drugs used in the treatment of schizophrenia, Clozapine (CLZ) is recognized to have superior therapeutic effectiveness in the treatment of chronic, medication-resistant syndromes, commonly estimated to constitute at least one-third of all cases (e.g., Essali et al., 2009). However, CLZ is potentially toxic, producing agranulocytosis, adverse metabolic changes and myocarditis in some patients (Schulte, 2003; Meltzer, 2012). Studies investigating the neuro-physiological actions of CLZ and other agents are of particular interest as they may provide clues to both underlying pathophysiology and mechanism of action of this exceptionally effective drug.

Quantitative electroencephalography (QEEG or EEG) has shown some promise in this regard. QEEG abnormalities in schizophrenic (SCZ) subjects and changes due to CLZ therapy have been the focus of several clinical studies (see e.g., Gunther et al., 1993; Malow et al., 1994; Freudenreich et al., 1997; Hughes and John, 1999; Knott et al., 2000, 2001, 2002; Adler et al., 2002; Gross et al., 2004; Birca et al., 2006; Coburn et al., 2006; Dunki and Dressel, 2006; Oikonomou et al., 2006; Sakkalis et al., 2006; Boutros et al., 2008; MacCrimmon et al., 2012).

Knott et al. (2001) have used conventional statistical analytical methods in a study to determine the effect of chronic and acute CLZ therapy on the SCZ brain. They evaluated coherences (connectivity) from resting EEGs and identified changes in coherence patterns between normal vs. pre-treatment SCZ subjects, and then also between the pre-treatment state and both the acute and chronic post-treatment states after CLZ therapy. Takahashi et al. (2013) used exact low-resolution electromagnetic tomography analysis (eLORETA) (Pascual-Marqui et al., 2006) to identify neural sources of mismatch negativity (MMN) and P3a. They found MMN deficits in SCZ that were associated with reduced activations in discrete medial frontal brain regions. Na et al. (2002) used information theoretic constructs such as average cross mutual information (A-CMI) to characterize connectivity patterns in SCZ subjects. They concluded that SCZ patients were subject to left temporal lobe deficits and inter- and intra-hemispheric over-connectivity.

Although there are numerous such studies identifying and characterizing deficits of schizophrenia, few have identified and characterized aspects of the brain that are *normalized* in subjects who respond to neuroleptic treatment in general, and to CLZ therapy specifically. Our objective is therefore to determine what features if any in the SCZ brain *normalize* as a result of CLZ treatment. We use machine learning (ML) methods to identify EEG-derived features that satisfy the following set of four *discriminating conditions*. That is, we wish to find features that simultaneously

(1) discriminate all before treatment (BT) SCZ from healthy volunteer (HV) subjects,[2]
(2) discriminate the BT condition from the after treatment (AT) condition in most responsive (MR) SCZ subjects,
(3) discriminate AT least responsive (LR) SCZ subjects from HV subjects,
(4) specifically do NOT discriminate AT most responsive (MR) SCZ subjects from HV subjects.

We conclude that a set of features simultaneously satisfying these discriminating conditions *normalizes* as a result of treatment; i.e., that the brain function associated with such a set of features becomes indistinguishable from normal. This study demonstrates that it is indeed possible to identify such a feature set using the methodology explained in this paper.

This finding may be of significant value in the development of new psycho-pharmaceutical agents, since a new drug, which demonstrates this same effect on the brain could have psychotropic properties similar to those of CLZ, potentially without the toxicity.

Machine learning, which includes pattern recognition and dimensionality reduction paradigms, is finding increasing application in psychiatry, particularly when multi-dimensional, noisy, highly complex data or multi-modal data sets are analyzed together, (see e.g., Gallinat and Heinz, 2006). For example, support vector machine (SVM) techniques that select spectro-temporal patterns from multichannel magnetoencephalogram (MEG) data collected during a verbal working memory task have been used to distinguish SCZ from control subjects (Ince et al., 2008). ML algorithms analyzing structural brain magnetic resonance images (MRIs) (Fan et al., 2007), functional MRI (fMRI) data (Guo et al., 2008) and combined genomic and clinical data (Struyf et al., 2008) have been employed to separate SCZ, bipolar and healthy control subjects. Khodayari-Rostamabad et al. (2010, 2013) have used ML methods to predict response to CLZ treatment and SSRI medications for depression. QEEG technology is considerably less expensive and more readily available than genetic analyses, MEG and fMRI.

One of the most reliable brain source localization (BSL) methods to localize the EEG signal is the source montage approach (Scherg et al., 2002; Miller et al., 2007). The source montage approach is a BSL method that localizes the EEG signal and estimates composite brain source activity emanating from predefined low-resolution regions throughout the cortex from the signals received from the scalp electrodes. An important feature of the beamforming class of BSL methods, to which the source montage approach belongs, is that it explicitly incorporates a spatial filtering procedure that suppresses interference from sources in neighboring regions (Ille

[2] This condition implies that the selected features are capable of diagnosing schizophrenia. However, since this capability is not directly related to the objectives of this study (the objectives being the identification of brain changes induced by CLZ treatment), this finding is not discussed any further in this paper.