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1-norm Support Vector Machine on Single-trial EEG and ECG Data to Identify Neural Oscillatory Features in the Ketamine Model for Schizophrenia

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Abstract

Ketamine provides a useful model for studying the physiopathology of schizophrenia as it induces and exacerbates schizophrenic symptoms in healthy individuals and patients, respectively. However, it remains unclear how ketamine affects neural oscillations across frequency bands and the extent to which changes in cortical firing are independent from ketamine's cardiovascular effects. The present study used 1-norm support vector machine (SVM) as a classification approach to determine sources of psychophysiological signal, considering both EEG and ECG, characterizing primary effects of ketamine administration. EEG and ECG recordings of 11 participants were collected before (saline) and after the ketamine (0.5 mg/kg) intravenous infusion The 1-norm SVM model built on EEG and ECG in combination successfully differentiated the two sessions and identified prominent EEG features associated with neuronal oscillation alternation between sessions, which includes beta, delta frequency bands from both F3 and F4. However, SVM models based on EEG or ECG, taken alone, performed only slightly above chance. 1-norm SVM models suggest that machine learning methods could successfully distinguish saline and ketamine sessions, but only when both EEG and ECG single trial data were considered. Our findings show concurrent cardiac and brain effects of ketamine that may resemble alterations in the prodromal phase of schizophrenia.

Keywords: Ketamine, NMDA antagonist, GABA/glutamate, neural oscillations, schizophrenia

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Introduction

Ketamine is commonly used as a dissociative anesthetic. As a noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist, it inhibits glutamate activity and can transiently induce psychosis symptoms and cognitive deficits (Javitt & Zukin, 1991; Lahti, Weiler, Michaelidis, Parwani, & Tamminga, 2001). Experiments in human and animal subjects show that ketamine can induce both positive and negative schizophrenic symptoms. In experiments with healthy adults, subjects experience schizophrenic symptoms such as altered sensory perceptions, bizarre and impoverished thoughts and speech, impaired attention, and disrupted memory (Krystal et al., 1994). Therefore, ketamine infusion offers a useful pharmacological model for studying schizophrenia and has led to a paradigm shift from dopaminergic to glutamatergic dysfunction.

Although the ketamine model has strong explanatory and epistemic values, there have been questions about the validity of the ketamine model for schizophrenia. One of the main weaknesses of the ketamine model is that neuronal oscillations induced by ketamine do not seem to reflect oscillatory abnormalities found in schizophrenia. EEG studies revealed that abnormal oscillatory activity in schizophrenia is particularly at the gamma band (30-80 Hz) (Kehrer, Maziashvili, Dugladze, & Gloveli, 2008; Roopun et al., 2008; Uhlhaas, 2013; Uhlhaas & Singer, 2011). Reduced oscillations at gamma band were found in Schizophrenia patients in several studies (Kehrer et al., 2008; Roopun et al., 2008; Uhlhass and Singer, 2011), however, increases at gamma band were also observed (Bucci, Mucci, Merlotti, Volpe, & Galderisi, 2007). It is widely believed that abnormalities in gamma band neuronal oscillation are due to fast-spiking

GABAergic interneurons (Gloveli et al., 2005; Hájos et al., 2004), which should be affected by ketamine infusion. However, compared with EEG findings in schizophrenia patients, EEG studies on ketamine's effect on neuronal oscillation yielded to diverse, even opposite results. Animal studies showed that ketamine does not affect gamma rhythms in neocortex and hippocampus (Cunningham et al., 2006; Roopun et al., 2008). Another study on clinical population showed that ketamine administration increases the amplitude of the 40 Hz EEG signal (Plourde, Baribeau, & Bonhomme, 1997), whereas in schizophrenia patients, the amplitude of 40Hz EEG signal is instead reduced (Hamm, Gilmore, Picchetti, Sponheim, & Clementz, 2011). The gamma band is not the only frequency band with abnormal oscillatory activity in schizophrenia. Various abnormalities have been observed in high beta (20-29) band as well. One study found that schizophrenic patients with auditory hallucinations show an increase in resting beta power in parietal and frontal cortices (Sponheim, Clementz, Iacono, & Beiser, 2000). Although some studies found that ketamine has similar effect on beta band oscillations (Lee et al., 2006; Mulert, Kirsch, Pascual-Marqui, McCarley, & Spencer, 2011), null results were also reported (L. E. Hong et al., 2010).

One possible explanation of the diverse results from EEG studies is the lack of objectivity and reliability in conventional EEG data analysis. First, the analysis of EEG data often involves different levels of subjective data preprocessing, such as removing artifacts and selecting event time windows, and thus leaving a large portion of the EEG record discarded from further analysis. Also, for group level analysis, conventional method uses averaged waveforms of all participants' time-frequency data. By doing so, we may lose important information since individuals' neural activities generated endogenously are not captured in averaged waveforms. In addition, having a priori hypothesis sets limits on potentials findings from the datasets, and may

lead to omission of other information the datasets could tell. Finally, the conventional procedure of averaging trials can result in a multiple testing errors. The analysis of EEG data usually involves univariate mean group comparisons, such as comparing responses between a clinical and a control group. Group differences are commonly assessed for several amplitudes and latencies at several locations (single electrodes or averages of a set of electrodes), which either causes an increase of family-wise type I error due to multiple testing, or a decrease of power if the alpha error level is adjusted for multiple testing using Bonferroni or similar methods (Stahl, Pickles, Elsabbagh, Johnson, & Team, 2012). Therefore, it would be desirable to have methods that improve the statistical power and avoid subjective judgments in the analysis of EEG studies.

Another potential limitation of traditional EEG data analysis is that the ECG data collected along with EEG data ware often neglected and discarded. ECG data can be a good reflection of autonomic nervous system (ANS) activities as it produces patterns of oscillation that correspond to heart rate variability (HRV) (Heathers, 2014). HRV is related with psychological arousal and is a potential diagnostic and prognostic biomarker in psychiatric disorders including depressive disorders (Chang, Chang, Kuo, & Huang, 2015; Munoz et al., 2015) and bipolar disorder (Eckberg, 2000; Hage et al., 2017).

To address these potential problems in EEG data analysis, here we propose applying a machine learning classification method on both EEG and ECG data to study the ketamine's effect on neuronal oscillations. Machine learning encompasses a body of approaches that can be used for analyzing data through mathematical modeling. Different from traditional null hypothesis significance testing method, machine learning method does not set a priori hypothesis. Instead, it allows the program to adjust the model accordingly to new information until it reaches the optimal result. Machine learning method often employs a multi-fold cross

validation method. The validation process allows machine-learning methods to have good validity despite relative small sample size. Given these advantages, Machine Learning methods have been successfully applied to a variety of fields that deal with high-dimensional data, often accompanied by small sample sizes (Bishop, Aamodt-Leeper, Creswell, McGurk, & Skuse, 2001).

From a machine learning point of view, identifying ketamine-induced neuronal oscillations can be seen as a feature selection problem. Classification algorithm can identify and select most significant oscillatory features that can be used to distinguish before and after ketamine infusion status. Features we are interested in were defined as neuronal oscillatory characteristics, namely the five frequency bands (theta, alpha, beta, delta, and gamma) by neural signal measures (EEG and ECG). Support vector machine (SVM) is one of the most commonly used classification algorithm. It is a supervised learning algorithm that uses a discriminant hyperplane to separate different classes. The advantage of SVM is that it selects a hyperplane that maximized the margins. This particular hyperplane maximizes the prediction accuracy of the classification of previously unseen cases. However, SVM often produces complex models with too many features since it uses the l_2 regluarization, in which redundant features are not punished. In our analysis, we adopted a novel algorithm based SVM that uses the l_1-norm regularizer because this regularizer enforces sparsity of the weight vector, meaning that only a small portion of the features will be used by the classifier. This strategy, named 1-norm SVM, has been proven to be a good combination of avoiding overfitting models and allowing feature selection (Zhu, Rosset, Hastie, & Tibshirani, 2003).

In our study, we used EEG collected from bilateral frontal, central, and occipital brain, along with ECG data, to build classification models and evaluated the performance of the

models. We also utilized the 1-norm SVM algorithm to select the most significant features that differentiate before and after ketamine infusion status. The selected features are the frequency bands that have the most significant neuronal oscillatory changes under ketamine administration.

Method

Participants

Recruitment was done through advertisements on the Internet (e.g. Craiglist) and posters in New York State Psychiatric Institute. All recruits went through screening where they received a diagnostic interview (Structured Clinical Interview for DSM-5 or Diagnostic Interview for Genetic Studies) and a medical exam. During the screening, participant's blood sample and urine sample were collected for a pregnancy test and toxicological screen. The study included participants who i) were aged 21 to 45; ii) had no history of recreational ketamine and/or PCP use; iii) had no current or past Axis-I psychiatric disorders or history of alcohol/substance abuse; (iv) had no first-degree relative with schizophrenia; (v) had no history of violence; (vi) were not currently taking psychotropic medication; (vii) had no presence or history of significant medical or neurological illness, including high blood pressure (SBP > 140, DBP > 90), cardiac illness, head trauma; (viii) were not pregnant, (ix) had no metallic or other material in the body or medicinal patch that would preclude safe exposure to MRI and EEG, and (x) had ability to provide informed consent. Eleven participants with good quality of EEG data were included in analyses (two female and nine male; average age = 28.9, SD= 5.4). The Institutional Review Boards of the New York State Psychiatric Institute (NYSPI) and Columbia University Medical Center approved this study.

Experimental Procedures

All participants were informed of effects of ketamine and typical reactions after ketamine

infusion. And then all participants read and signed informed consent before the experiment started. During the experiment, each participant was asked to stay still in an MRI scanner and received a sequence of six 13-minute simultaneously EEG and MR scans using a 64-channel MRI-compatible EEG recording system (BrainAmp MR plus amplifier; Brain Products HmbH, Gilching, Germany). The first scan included quantitative MRI structural imaging for optimal segmentation of brain images into gray matter, white matter, and cerebrospinal fluid (CSF). After the first scan (baseline), participants started to receive a slow intravenous infusion of saline solution with 0.5mg/kg of ketamine hydrochloride (Abbott Laboratories, North Chicago, IL). The infusion process was approximately 40 minutes. Both EEG and ECG signals were constantly collected prior to, during, and after the ketamine infusion until the end of the experiment. The whole sequence of six scans, including time intervals, lasted approximately 90 minutes. Blood pressure was monitored and recorded at 5-minute intervals at baseline and throughout the ketamine infusion, and at 10-minute intervals following the end of infusion until the end of the scan (90 minutes post initiation of ketamine infusion). After the experiment, each participant was evaluated by the PI of the study, who is a licensed psychologist and physician, to determine if the participant was safe to be discharged from the study without admission for an overnight stay at the hospital.

Measures

Neuronal oscillations were recorded using a 64-channel MR-compatible EEG system, with direct current BrianAmp MR plus amplifiers (Brain Products HmbH, Gilching, Germany). The 64 channels included 62 EEG channels, an electrooculography (EOG) channel and an echocardiogram (ECG) channel. EEG signals were referenced to the FCz electrode and grounded to the Iz electrode. All signals were hardware-filtered between 0.016 and 250 Hz and sampled at

5000Hz.

Data Analysis

In principle, one might leave the method of resolving the best predictor from the entire raw ERP record to supervised classification methods. However, in practice, it is usually helpful to undertake a preliminary data pre-processing and reduction step to form a set of data features (DeBoer, Scott, & Nelson, 2007; Fujioka, Mourad, He, & Trainor, 2011; Hoehl & Wahl, 2012; Luck, 2005).

EEG signal processing. EEG data was processed offline in BrainVision Analyzer 2.1. We first identified extreme values (2000μV -4000μV range) and then used these extreme values to create a template for artifact removal, using the Template Drift Compensation method (Allen, Josephs, & Turner, 2000; Rosa, Kilner, Blankenburg, Josephs, & Penny, 2010). The DC detrend transform was applied to correct for DC trending in EEG data. Other outliers of scalp EEG were filtered using low-pass filters (with a cutoff frequency of 100 Hz, slope of 24 dB/octave) and high-pass filter (with a cutoff frequency of 0.4 Hz, time constant of 0.398s, slope of 24 dB/octave) to reduce slow drifts in the signal. In addition, a 60 Hz notch was applied (with a bandwidth of 5Hz, symmetric around 60Hz with the edge rise of 24 dB/octave).

The correction of cardiac artifacts often involves removal of the first several principal components that are time locked to QRS waves of the ECG from EEG data. However, this method has been criticized for introducing more artifacts in theta and gamma frequency rage. Cardioballistic (CB) artifacts were instead automatically marked at the Q component of each QRS wave using the following settings of the Cardioballistic Correction Transform (peak detection option, semiautomatic mode, pulse rate [bpm]; min-max: 48-110; pulse rate [ms]; 897.5-352.5, Correlation and Amplitude; Correlation; 0.6, Amplitude; 0.2-0.8, write markers

only), without corrections.

Time-frequency extraction was applied to single trial data using Morlet continuous wavelet transform. The low cutoff of frequency bands was 0.5 Hz, and the high cutoff was 60 Hz. Time-frequency values were divided into five frequency bands: delta (0.5-4Hz), theta (4-8Hz), alpha (8-12Hz), beta (14-28Hz), and gamma (30-58Hz) (Chen et al., 2014). For each frequency band, trials with outliers that were over two standard deviation from the mean were discarded from analysis. Time frequency values from six regions (bilateral frontal, central, occipital) and two time windows (before infusion and after infusion) were then exported to MATLAB (The MathWorks, Inc., Natick, MA) for further analysis using machine learning algorithm.

1-norm SVM classification and feature selection. Although the current study is based on a relatively small sample (N=11), a large number of EEG and ECG time-frequency data (7810 trials by five frequencies) were used for analysis. For each of the six regions (bilateral frontal, central, and occipital lobes), a 1-norm SVM classification algorithm was used to classify before and after ketamine infusion status. The parameter C in the 1-norm SVM was tuned in a 10-fold cross-validation process, where the whole dataset was divided into ten equal subsets, and for each fold, we used nine of these datasets as training group to develop a classification model, and then test the classification model on the remaining one dataset. Receiver operating characteristics (ROC) curves were used to evaluate the performance of the classifiers. Specifically, the area under the curve (AUC) was reported. We averaged the AUC values over the 10 folds for each choice of C in a range from 0.01 to 10e6 with a step size of 10 times. The value of C was determined based on the best AUC performance. Then the chosen C value was used to train the final classifier using the same SVM model with 10-fold cross-validation. The AUC values were

reported to evaluate the performance of the final models using the chosen C.

Results

Using the EEG data alone, classification models produced by 1-norm SVM did not have good performances (Table 1). All models had classification accuracy around chance level (AUC = 0.5). Using the ECG data alone did not yield meaningful classification model either (AUC = 0.589). After combing EEG and ECG data together to train the models, better overall classification accuracy was achieved. As presented in Table 2 and Figure 1, the SVM model successfully differentiated before and after ketamine infusion status based on EEG and ECG signals, evident by AUC value of 0.82 for left frontal brain (F3) and AUC value of 0.86 for right frontal brain (F4). The 1-norm SVM model also successfully identified prominent features associated with neuronal oscillation alternation between ketamine infusion statuses. At left frontal region, the 1-norm SVM model identified delta activity, beta activity, and ECG activity as the primary features associated with ketamine administration status. At right frontal region, the 1-norm SVM model identified delta activity, beta activity, and ECG activity as the primary EEG features associated with ketamine administration status (Table 3). Additional features used in the models had weightings of .10 or less and were not considered as meaningful for further interpretation.

Power Analysis

Machine learning is different from traditional statistical analysis in the way that machine learning is more exploratory and does not require a priori hypothesis. However, this does not mean that statistical significance level of the present results cannot be calculated. If we understand the analysis using a null hypothesis testing framework, the null hypothesis would be

that the 1-norm SVM cannot predict before and after ketamine administration state better than chance level. Establishing statistical significance is generally done by determining how improbable the observed classification accuracy would be given the null hypothesis is true. The p value in this case is the fraction of the sample that is greater than or equal to the accuracy actually observed when using the correct labels (Pereira, Mitchell, & Botvinick, 2009).

For each SVM model, after testing the model for ten times (10-fold cross-validation), we accurately predict 80% cases out of the total test trials. If the null hypothesis was true and the classifier was operating at chance level, then we would expect an accuracy of 0.5 at average. Thus, we can establish a Bernoulli distribution where for each test trial there is 50% chance to be predicted accurately. The probability of having 80% accuracy rate test trials after a 10-fold cross validation is $C\binom{8}{10}0.5^8 0.5^2 = 0.044$. Therefore, in our analysis, the p value is smaller then 0.044. A power analysis was conducted using the software package, GPower (Erdfelder, Faul, & Buchner, 1996). The sample size of 7810 time-frequency trials was used for the statistical power analyses and the α level used was $p<0.05$. The power analysis revealed the statistical power (1-β) of this study is 1, indicating that our finding has a very strong statistical power.

Discussion

It is well known that ketamine induces similar clinical presentations to schizophrenic symptoms, but the underlying mechanism remains debatable. In the present study, we used a machine learning based classification algorithm to explore the neural oscillatory changes induced by ketamine infusion, aiming to better understand the mechanism of ketamine's model for schizophrenia. One purpose of this study is to test a more objective and exploratory way to perform EEG data analysis. The results show that machine learning method not only can solve classification problems, but also provide a mean to identify prominent features from multiple

regressors. The present analysis utilized ten fold cross validation method in machine learning and ensured the result to have considerable statistical power despite the small sample size.

To our surprise, neither EEG nor ECG data alone is sufficient for the algorithm to generate successful classification models (Table 1). Instead, the algorithm can only differentiate before and after ketamine administration statuses by incorporating EEG and ECG data altogether (Figure 1). Within this classification model, the features selected by the 1-norm SVM algorithm includes bilateral frontal delta band. This is consistent with animal studies. Specifically, findings from animal studies showed that ketamine induced decreases in delta power in frontal regions (Kargieman, Santana, Mengod, Celada, & Artigas, 2008). Human studies of ketamine's effect also showed decreases in delta (de la Salle et al., 2016; L. E. Hong et al., 2010) in prefrontal regions. Our findings of decreased delta at rest are also consistent with what observed in patients with schizophrenia (Göder et al., 2006; Keshavan et al., 1998; Sekimoto, Kato, Watanabe, Kajimura, & Takahashi, 2011). Delta wave at the frontal regions is considered to be associated with the process of information consolidation (Huber, Ghilardi, Massimini, & Tononi, 2004), significant changes at delta band might explain working memory deficits elicited by ketamine administration as well as cognitive deficits observed in schizophrenic patients. The features selected also include beta band. Beta band's significance in our 1-norm SVM classification model is compatible with previous research evidences of resting beta oscillations in schizophrenia patients with auditory hallucinations (Lee et al., 2006; Mulert et al., 2011; Roopun et al., 2008). It also maps on the research finding that pathological enhancement of beta-band activity is likely to result in deficits in flexible behavioral and cognitive control (Engel & Fries, 2010) as well as in perception alternation(L. E. Hong, Buchanan, Thaker, Shepard, & Summerfelt, 2008). However, past findings focused on the high beta frequency (e.g. 20-29 Hz)

while in our analysis we did not further divide the beta frequency band. Further analysis is needed to see if it is the high beta band that contributes to the neural oscillatory changes. ECG is also a feature selected by the classification model, indicating that cognitive changes observed in subjects are accompanied by changes in automatic nervous system (e.g. cardiovascular activities).

The fact that the classification algorithm can only generate significant result with the combination of EEG and ECG data indicated that the interaction of ECG and EEG data plays a key role in reflecting ketamine induced physiological changes. The cardiovascular effect of ketamine's data is well studied. It is well established that ketamine has a cardiovascular stimulation effect (Y. Hong & Henry, 1992), and it may due to the ketamine's inhibition of catecholamine reuptake (Reich & Silvay, 1989). For the past decades, researches on ketamine's model for schizophrenia mainly focused on how ketamine affect the brain directly as an NMDAR antagonist and neglected the indirect pathways—the interaction of automatic nervous system and brain functions. Certain studies have attempted to explore how cardiovascular arousal can affect cognitive functions and found that different HRV can predict different performance in a variety of cognitive tasks on executive functioning (Thayer, Hansen, Saus-Rose, & Johnsen, 2009). Other studies suggest that change in cardiac output can lead changes in cerebral blood flow (CBF) (Holcomb, Lahti, Medoff, Weiler, & Tamminga, 2001)(Holcomb et al., 2001; La, 2015; Langsjo et al., 2003; Schwedler, Miletich, & Albrecht, 1982), which can be associated with both positive and negative schizophrenic symptoms (Bouma & Muizelaar, 1990; Liddle et al., 1992). Ketamine's effect on cognition and perception is probably mediated by more mechanisms then we expected. A more comprehensive ketamine model should take its cardiovascular effect and CBF effect into consideration.

Tables and Figures

	Left			Right		
	Frontal	**Central**	**Occipital**	**Frontal**	**Central**	**Occipital**
AUROC	0.523	0.545	0.554	0.546	0.558	0.499

Table 1. Performance statistics of 1-norm SVM model built on EEG data and ECG data separately. AUROC: the Area Under an ROC curve.

	Left			Right		
	Frontal	**Central**	**Occipital**	**Frontal**	**Central**	**Occipital**
AUROC	0.820	0.830	0.849	0.860	0.865	0.828

Table 2. Performance statistics of the models built on EEG and ECG data. AUROC: the Area under an ROC curve.

	Left			Right		
	Frontal	**Central**	**Occipital**	**Frontal**	**Central**	**Occipital**
Features	Beta	Beta	Beta	Beta		
	Delta	Delta		Delta		
	ECG		Alpha	ECG		Gamma

Table 3. Features selected by 1-norm SVM models. Alpha: 8-12 Hz, Beta: 14-29 Hz, Delta 0.5-5Hz, Gamma: 30-50Hz.

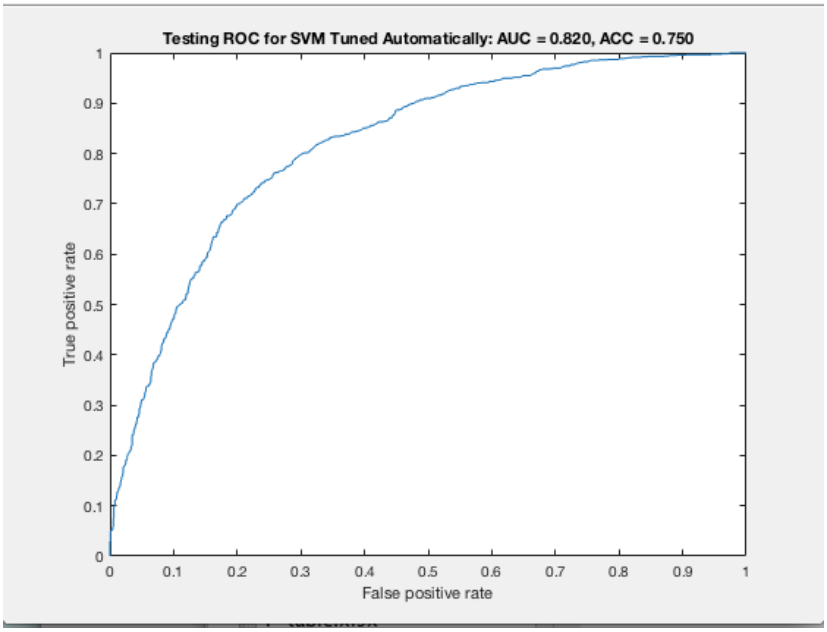

Figure 1(a). ROC curve for the classification model generated by using EEG data and ECG data from the left frontal area (F3) as training dataset. AUC: area under the curve; ACC: accuracy.

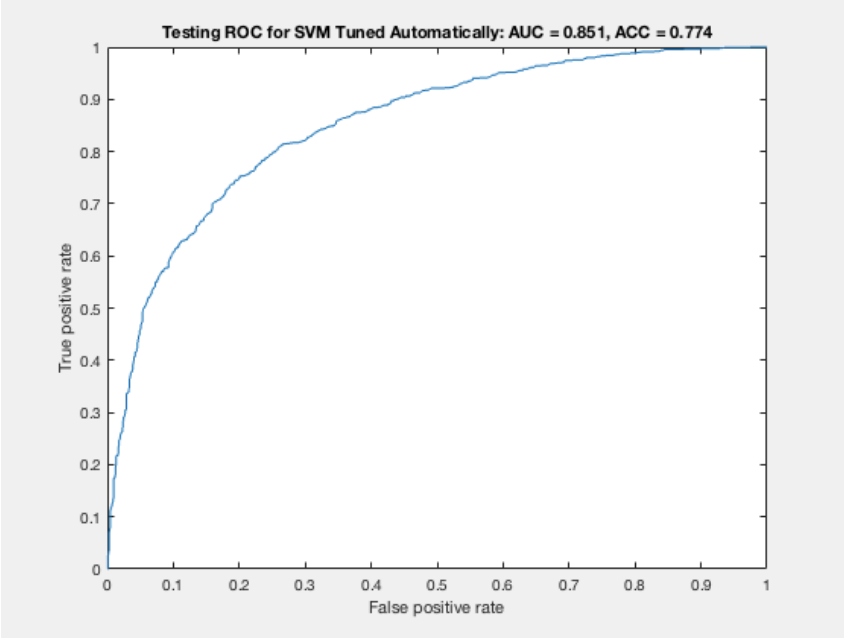

Figure 1(b). ROC curve for the classification model generated by using EEG data and ECG data from the right frontal area (F4) as training dataset. AUC: area under the curve; ACC: accuracy.

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