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Classification of schizophrenia with spectro-temporo-spatial MEG patterns in working memory

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ABSTRACT

Objective: To investigate whether temporo-spatial patterns of brain oscillations extracted from multi-channel magnetoencephalogram (MEG) recordings in a working memory task can be used successfully as a biometric marker to discriminate between healthy control subjects and patients with schizophrenia.
Methods: Five letters appearing sequentially on a screen had to be memorized. The letters constituted a word in one condition and a pronounceable non-word in the other. Power changes of 248 channel MEG data were extracted in frequency sub-bands and a two-step filter and search algorithm was used to select informative features that discriminated patients and controls.
Results: The discrimination between patients and controls was greater in the word condition than in the non-word condition. Furthermore, in the word condition, the most discriminant patterns were extracted in delta (1–4 Hz), alpha (12–16 Hz) and beta (16–24 Hz) frequency bands. These features were located in the left dorso-frontal, occipital and left fronto-temporal, respectively.
Conclusion: The analysis of the oscillatory patterns of MEG recordings in the working memory task provided a high level of correct classification of patients and controls.
Significance: We show, using a newly developed algorithm, that the temporo-spatial patterns of brain oscillations can be used as biometric marker that discriminate schizophrenia patients and healthy controls.

1. Introduction

Schizophrenia is a chronic and disabling mental disorder that affects approximately 1% of the adult population in the world (Picinelli and Gomez, 1997). This disorder perturbs multiple cognitive domains such as attention, memory, executive functions and language, and is associated with symptoms such as auditory hallucinations, delusions and emotional dysregulation. These cognitive impairments and symptoms impact significantly the life of patients. To date, the diagnosis of schizophrenia is based on clinical observations and on the patient self-reported experiences. However, because there is no paraclinical test that can support it, the diagnosis remains uncertain. This diagnostic uncertainty confounds the treatment and the research of the underlying mechanisms of this illness.

To address this problem, several methods using measures of brain activity and brain anatomy have been suggested for discriminating schizophrenia patients from healthy control subjects. These methods are based on features extracted from different types of signals such as electroencephalography (EEG) (Saatchi and Jervis, 1991; Jervis et al., 1996; Winterer et al., 2000; Li and Fan, 2006), magnetoencephalography (Georgopoulos et al., 2007) and functional magnetic resonance imaging (fMRI) (Calhoun et al., 2006; Jafri and Calhoun, 2006; Demirci et al., 2008) that were recorded either during rest (Jafri and Calhoun, 2006; Li and Fan, 2006), fixation (Georgopoulos et al., 2007) or execution of a specific task (Saatchi and Jervis, 1991; Jervis et al., 1996; Calhoun et al., 2006). Features of the gray and white matter have also been used for discriminating schizophrenia patients from healthy subjects (Kawasaki et al., 2007).

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Typically, in this type of classification study, the amount of data recorded from each subject is extremely large, whereas the number of groups to discriminate is small (usually two: patient vs. control). As a consequence, the discrimination algorithms are very likely to over-learn, that is to find spurious differences between the groups. For this reason, it is important to reduce the dimensionality of the data to a small number of features that provide a robust discrimination. The extraction of useful features from a large ensemble of data is computationally complex and algorithms are being developed and refined to this end. Principal component analysis (PCA) (Li and Fan, 2006), factor analysis (FA) and independent component analysis (ICA) (Jafri and Calhoun, 2006; Calhoun et al., 2006; Demirci et al., 2008) have been frequently used in these studies as a pre-processing step to reduce the dimensionality of the feature space. In some cases researchers limited the analysis to a few arbitrary selected EEG or MEG channels to reduce the computational complexity and high dimensionality of the data. Besides projection methods, search strategies such as genetic algorithms have also been used to select a subset of parsimonious features. A summary of the results from the classification studies mentioned above is presented in Table 1.

A number of observations can be made from the studies listed in Table 1. First, studies that used features reflecting functional brain activity reported higher classification accuracy (77–94%) than studies that used features from resting state brain activity (67–76%). This suggests that brain activity associated with functional impairments of schizophrenia patients provides more information than resting state. Second, most studies used sophisticated classifiers as a black box. For this reason, even though high levels of accuracy have been reported, it is difficult to understand the functional basis of the discrimination given the complexity of the classifier. Third, some studies processed single channel event-related averaged waveforms for discrimination (Saatchi and Jervis, 1991; Jervis et al., 1996). However, since brain activity can be examined in spatial, spectral and time domains, these studies used only a limited amount of the information potentially available in the signal. Finally, a caveat that applies to these studies is that they included medicated patients, which is a potential confounding variable. However, there are strong indications that most of the discrimination power results from pathophysiological differences between the groups rather than from side effects of the drugs. For example, although psychotropic drugs affect brain activity, their effect has been found to be small relative to the effect of having schizophrenia (Winterer et al., 2000). In addition, it has been shown that brain oscillatory activity, determined from EEG or MEG, differs between unmedicated schizophrenia patients and healthy control subjects (Fehr et al., 2003; Gallinat et al., 2004; Kotini and Aninos, 2002; Merrin et al., 1989; Nagase et al., 1992). This indicates that these techniques are sensitive to the pathophysiology of brain activity in schizophrenia.

On the bases of these considerations, we designed an experimental paradigm and developed an algorithm with the following objectives:

1. Analyze functional state brain activity to obtain a high degree of discrimination between schizophrenia patients and controls.
2. Apply a discrimination procedure based on features that could be interpretable in terms of their functional significance.
3. Use the spatial, temporal and spectral information available in MEG recordings.

With these objectives, we explored the brain activity related to verbal working memory in schizophrenia patients and healthy control subjects. Working memory impairments (Goldman-Rakic, 1999; Stephane and Pellizzer, 2007) and abnormal working memory neural correlates (Cohen et al., 1997) have been reported frequently in schizophrenia patients. Furthermore, verbal working memory resources are required for linguistic operations and language dysfunction has been closely associated with schizophrenia (Crow, 1997; Stephane et al., 2006). In this study, the memorized information could be processed either phonetically (non-word condition) or both phonetically and semantically (word condition). Consequently, verbal working memory operations and the interaction of these operations with linguistic processes can be evaluated. We predicted that the comprehensive evaluation of brain activity associated with an impaired cognitive function – working memory – in schizophrenia would improve the classification of patients vs. controls. In addition, we developed a two-step filter and search algorithm that extracts features from space, time and frequency for patient/control discrimination. To our knowledge, this is the first time that such a comprehensive approach is used for this purpose. In addition, rather than using a black box strategy in the classification module, our proposed approach provides information about the spatial, temporal and spectral content of the most discriminant neural activity patterns. In this scheme, the proposed approach not only provides patient/control discrimination but also serves as an exploratory tool of the neural bases of the discrimination.

In summary, we obtained multichannel MEG recordings of brain activity associated with verbal working memory. Second, we extracted spectro-temporo-spatial features from MEG recordings to construct a rich feature set. These features reflect power changes during the encoding and memorization period relative to the immediately preceding baseline period. This provides a control for any additive effect of medication on MEG recording as this effect would be present during both the baseline and memorization periods. In addition, in order to select the most informative features for the final classification, we implemented a subset selection procedure that does not require any prior knowledge of the relevant frequency bands, temporal location

Table 1
Summary of classification studies. Schizophrenia patients correctly classified (P_S). Healthy subjects correctly classified (P_H). Overall correct classification (P_{Avg}). Auditory discrimination (AD). Number of Groups (NG). The cells with X indicate that these results were not available.

Study	Signal	Method	Task	NG	P_S (%)	P_H (%)	P_{Avg} (%)
Calhoun et al. (2006)	fMRI	ICA, Euclidean distance	AD	3	92	95	89
Demirci et al. (2008)	fMRI	ICA, Projection Pursuit	AD	2	94	94	94
Georgopoulos et al. (2007)	MEG	Genetic Search, LDA	Fixation	7	X	X	79
Jafri and Calhoun (2006)	fMRI	ICA, NN	Rest	2	X	X	76
Jervis et al. (1996)	EEG	NN	AD	2	X	X	94.6
Kawasaki et al. (2007)	MRI	PCA	–	2	75	75	75
Li and Fan (2006)	EEG	PCA, LDA	Rest	3	60	80	67
Saatchi and Jervis (1991)	EEG	NN	AD	2	92.9	X	X
Shi et al. (2007)	fMRI	Penalized-LDA	–	2	83	74	80
Winterer et al. (2000)	EEG	FA, LDA	AD	2	76	78	77

ICA, independent component analysis; LDA, linear discriminant analysis; NN, neural network; PCA, principal component analysis; FA, factor analysis.

or cortical areas. To this end, a regularization procedure is necessary to avoid algorithm over-learning which could result in finding spurious patterns from the high-dimensional space of the data. Finally, a leave-one out method was used to evaluate the reproducibility of the results.

2. Methods

2.1. Subjects

MEG recordings were obtained from 15 patients (12 males and 3 females) that met the DSM IV diagnostic criteria for schizophrenia and 23 healthy control subjects (14 males and 9 females). The patients were recruited from the outpatient clinic of the Minneapolis VA Medical Center, whereas the control subjects were recruited through flyers placed in the VA Medical Center. The control subjects did not have any history of Axis I diagnosis. All subjects did not have a history of neurological disease or major medical problems or active substance abuse. All subjects gave an informed consent before their participation in the study. The experimental protocol was approved by the Institutional Review Boards of the VA Medical Center and of the University of Minnesota.

The two groups of subjects did not differ significantly in age (mean ± standard deviation: controls = 47 ± 10 years, patients = 40 ± 14 years, t-test $p = 0.107$), in the proportion of male and female subjects (Fisher's exact test, $p = 0.294$), in the personal (patients = 10 ± 7 years, controls = 11 ± 5 years, t-test $p = 0.556$) or average parental education level (patients = 13 ± 3 years, controls = 13 ± 2 years, t-test $p = 0.726$), or in premorbid level of intellectual functioning (patients = 47 ± 7, controls = 51 ± 5, t-test $p = 0.177$), which was evaluated using the Wide Range Ability Test (Wilkinson, 1993). The groups did not differ significantly with respect to the reported daily tobacco use (patients = 7.4 ± 10.5 cigarettes, controls = 0), however the difference was marginally significant for caffeine consumption (patients = 2.6 ± 1.7 cups, controls = 0.9 ± 0.9 cups, $p = 0.05$). The patients were medicated with non-conventional antipsychotic medications but were still symptomatic. Their mean chlorpromazine equivalent daily dose of medication was 260 ± 228 mg. The severity of the illness was evaluated with the Brief Psychiatric Rating Scale (Overall and Gorham, 1962), the Scale for the Assessment of Negative Symptoms (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (Andreasen, 1984) with scores of 44 ± 12, 8 ± 4 and 8 ± 5, respectively. The mean duration of illness was 26 ± 11 years.

2.2. Task

A modified Sternberg task (Sternberg, 1966) was used to assess verbal working memory (see Fig. 1). Five letters were presented sequentially on a computer screen in 1 s. We will call this time segment the "*encode stage*" in the rest of the article. Each letter appeared for 150 ms followed by a 50-ms blank screen. The letters constituted either a word (50% of the trials) or a pronounceable non-word. Two seconds after the last letter a probe letter appeared on the screen. We will use the term "*maintain stage*" for this two second time period following the letters presentation. There was a 50% probability that the probe letter was one of the previously shown letters. The subjects were asked to decide whether the probe letter was one of the previously shown letters ('in') or not ('out'). The response was provided by a button press (left button for 'in' and right button for 'out'). Word vs. non-word and 'in' vs. 'out' trials were randomized with equal probability. Sixty trials were recorded for each word/non-word condition.

2.3. MEG recordings

MEG data were recorded during the task from 248 axial gradiometers with a 1 kHz sampling frequency (Magnes 3600WH, 4D Neuroimaging, San Diego, CA). The subjects lay supine in the MEG shielded room. Their head was supported by a headrest, which was padded for comfort and to restrain head motion. The subjects were informed of the importance of remaining still during the task. To monitor unwanted subject motion, five signal coils placed on the subjects head were digitized prior to MEG acquisition and consecutively activated before and after data acquisition, thereby locating the head in relation to the sensors. In addition, the subjects were monitored for motion with a video camera during the whole recording session. No subject showed body motion during the task and the localization of the head coils at the end of the task never exceeded 4 mm from the initial localization. In parallel, electrocardiogram (ECG) and electrooculogram recordings were also obtained for artifact correction. Principal component analysis was used to remove ECG and eye movement artifact from the MEG data (Ille et al., 2002). Trials with residual artifact activity were visually inspected. Then, the successful trials were bandpass filtered between 1 and 64 Hz and down sampled to 250 Hz. All artifact rejection and data pre-processing steps were accomplished using BESA™, then the data were exported into ASCII files for further analysis using Matlab™. Activity maps were created using the EEG-ToolBox of Delorme and Makeig (2004).

2.4. ERD/ERS patterns

The oscillatory electrical activity of the brain can be modulated in a time locked manner relative to an event. When the event causes an amplitude decrease in the rhythmic activity, it is called "Event Related Desynchronization" (ERD) (Pfurtscheller and Lopes da Silva, 1999; Neuper and Pfurtscheller, 2001). Conversely, when the event causes an amplitude increase in the rhythmic activity, it is called "Event Related Synchronization" (ERS) (Pfurtscheller and Lopes da Silva, 1999; Neuper and Pfurtscheller, 2001). In this study we used ERD and ERS patterns to quantify activated cortical areas (Pfurtscheller and Lopes da Silva, 1999). Rather than focusing on a fixed frequency interval, the MEG activity was decomposed into 8 frequency sub-bands by using a second order Butterworth filter. The bandwidth of each sub-band was set at 4 Hz for the 1–16 Hz range and at 8 Hz for the 16–48 Hz range. Prior to obtaining the ERD/ERS values in each band, the power data in each trial were smoothed with a 250 ms long Gaussian kernel. Then the mean power was estimated in 250 ms windows with 125 ms overlaps to reduce the number of time points for the ERD/ERS calculation.

2.5. Discrimination between healthy control subjects and schizophrenia patients

In order to discriminate patients from control subjects, a feature set was formed by using the ERD/ERS values from all 248 channels, 8 frequency bands and 24 time points starting from the onset of the first letter stimulus and extending to the end of the maintain stage. This constituted a predictor space of $N = 47{,}616$ values per condition. Since the dimensionality of the feature set is very high, a two-step dimension reduction procedure was implemented through a filter and search strategy, as indicated in Fig. 2. The goal of the first step was to select a subset of features that had high discrimination power and to filter out the features with little discrimination information. For this purpose, we used the area under the receiver operating characteristic curve (AUC) which quantifies the discrimination power of a feature (Duda et al., 2000). The receiver operating characteristic (ROC) corresponds to the fraction of true positive (TP) rate versus false positive (FP) rate. In this study

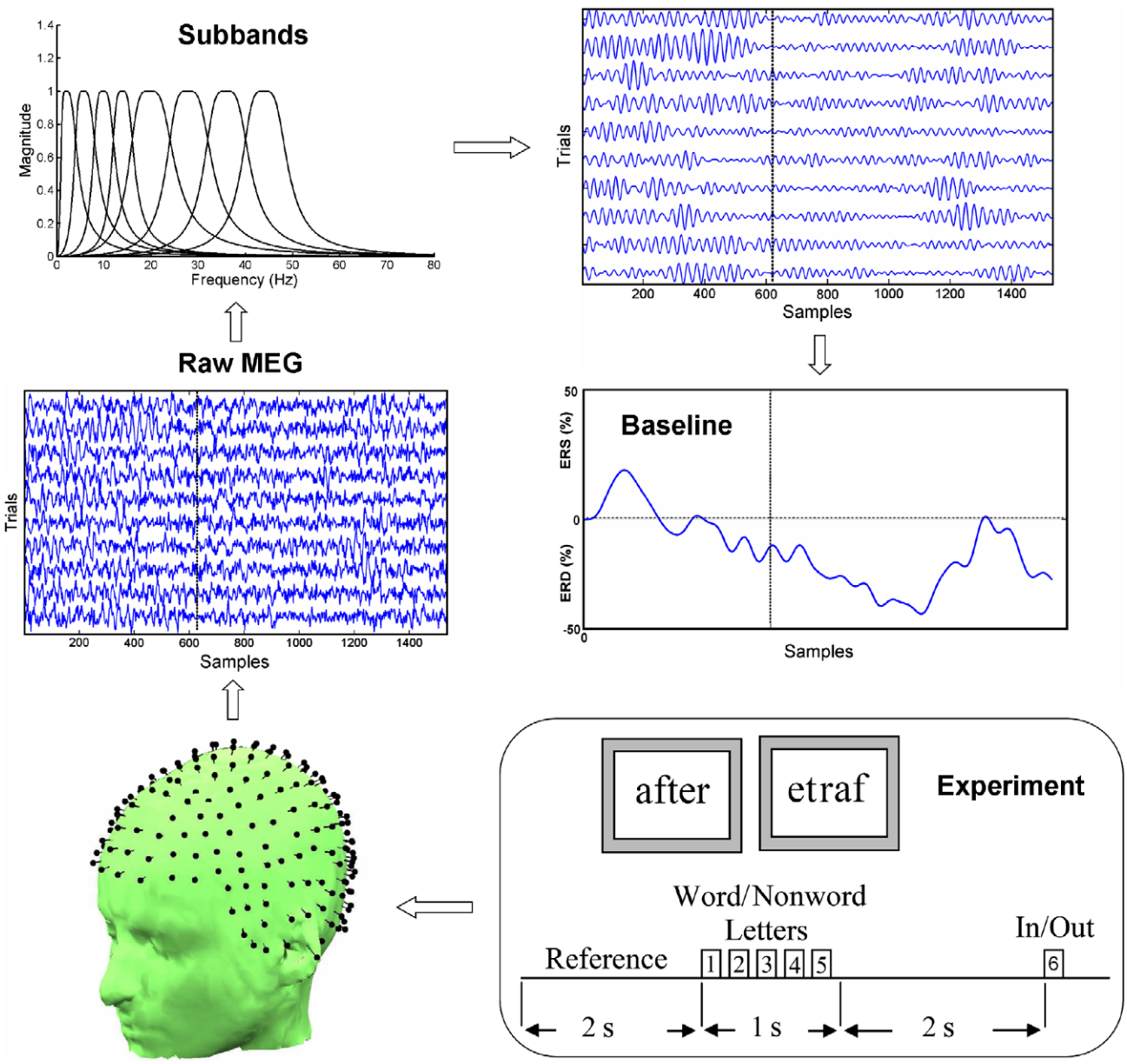

Fig. 1. Timing diagram of the working memory task and proposed signal processing steps to extract ERD/ERS waveforms from oscillatory brain activity. In the task five letters were presented sequentially on the screen. The letters formed either a word or a pronounceable non-word. Each letter appeared for only 150 ms on the screen. Related MEG activity was decomposed into several sub-bands and converted to ERD/ERS values. These energy changes relative to the reference period were used in the final classification step. The vertical line in MEG data plots represents the onset of letters presentation.

the true positive rate corresponds to the fraction of controls classified as controls, whereas the false positive rate represents the fraction of controls that are classified as patients. The ROC curve for each feature was determined by systematically varying the threshold determining the boundary between the cases classified as controls and those classified as patients. In other words, this filtering step gave priority to the features with high TP rate and low FP rate.

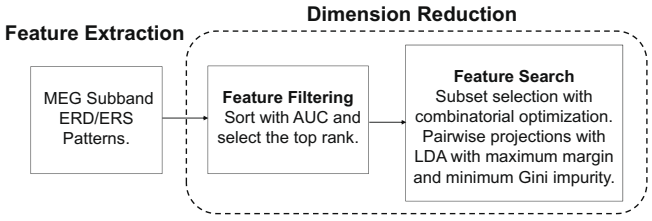

Fig. 2. Block diagram of feature extraction and two-step dimension reduction algorithm.

After sorting the entire feature set of corresponding AUC values in descending order, the top 200 features were kept for the second step of the dimension reduction process. Although the sorting procedure eliminated most of the irrelevant features, the dimensionality was still high. Furthermore, the first step did not consider the potential usefulness of combining features. For these reasons, a second step based on Fisher's linear discriminant analysis (LDA) was used to project pair-wise combinations of features and find, by using an exhaustive search of all possible pairs, those that provided the lowest Gini impurity criterion (Duda et al., 2000) and maximum margin between classes (see Fig. 3 for a schematic illustration). In detail, the procedure works as follows: after projecting the pair-wise features with LDA, the projected data were split into

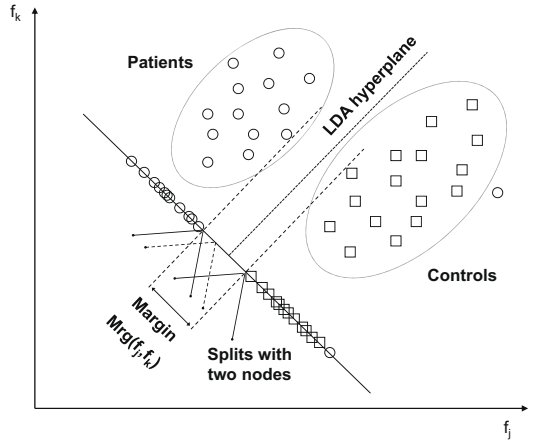

Fig. 3. Search step of the dimension reduction algorithm. The selection of pair-wise features was implemented using an exhaustive search in the reduced features set ($n = 200$) after AUC based feature ranking. The pair-wise MEG features of patients and controls were projected onto a single dimension by using LDA. For each projection the margin was calculated for the region where the Gini impurity was minimum. Features providing maximum margin and minimum Gini impurity were selected for final decision on the test set.

two groups represented by two nodes on a tree by using a threshold, ***th***. Let P_C^n, P_P^n be the percentage of the controls and patients at node ***n***, which are computed using the threshold ***th***. The total Gini impurity (GI) function was defined as:

$$GI(f_j, f_k, th) = \sum_n P_P^n P_C^n p_n, \quad j \neq k \tag{1}$$

where $\boldsymbol{p_n}$ denotes the percentage of the total number of subjects in each node, ***j*** and ***k*** are the indices of paired features. If the split using the threshold ***th*** on the projected data is perfect, then the percentage of the misclassified patients and controls at each node will be zero. High *GI* values indicate poor classification rates. A series of *GI*s was computed by varying the threshold ***th***. Specifically, the projection line was divided into thousand bins between the minimum and maximum values. Then these bins were used as different threshold levels to compute the *GI*. Assume that $Mrg(F)$ denotes the margin between classes which was computed for the threshold where the *GI* was minimum on the projection obtained from features $F_r = \{f_j, f_k\}$. The efficiency of each projection using the features in F_r was estimated by evaluating the quality function *Q*, where

$$Q(F_r) = \frac{Mrg(F_r)}{\min(GI(F_r))^2 + \eta} \tag{2}$$

and $GI(F_r)$ is the impurity of the features, η is a small regularization constant. In this study we empirically set $\eta = 5 \times 10^{-4}$. Although the *GI* vanished to zero for several feature combinations, by using this regularization constant, we could select those features with the maximum margin $Mrg(F_r)$. Basically by evaluating the quality function ***Q*** we extracted the feature combinations that provided low misclassification rates and maximum margin between groups. For each pair-wise classifier the mid point of the margin was used as threshold in the test step. After implementing the exhaustive search, the feature combinations were sorted according to their ***Q*** values and the top $\boldsymbol{m} = 1, 3, 5$, or 7 pairs were selected for final classification of the test data. A simple majority voting procedure was utilized on the outputs of pair-wise classifiers for the final decision. Here odd numbers of pairs (***m***) were used in order to avoid a tie at the majority voting step. Consequently the system always provided either a "control" or a "patient" output. Although more than two features can be combined with LDA, due to the low sample size, we limited the number of features to two in order to prevent overlearning. Furthermore, extracting several pair-wise combinations can provide robustness relative to the inter-subject variability across the alternative pairs. This type of procedure has been widely used in pattern recognition application in order to reduce the variance of the final decision (Breiman, 1996; Kotsiantis and Pintelas 2004). In addition, weak classifiers can be combined to build a strong classifier. With the current data, we also noted that although single features sometimes provided relatively poor classification results, their combination improved noticeably the final classification accuracy.

Finally, in order to assess the efficiency and reproducibility of the classification, a leave-one out method was used. In each step, one subject was used for testing, whereas the other subjects were used for selecting the subset of features and training the pair-wise LDA classifiers. The procedure was repeated until the whole sample was classified. In addition, this procedure was performed separately for the word and non-word conditions to examine the effect of the functional activity in classification performance.

3. Results

3.1. Behavioral results

All control subjects, except one, had 70% or more correct responses. The control subject with less than 70% accuracy was rejected from the analyses. Only the correct trials were used for the analyzes. For the control group, the number of correct trials in word and non-word conditions was 52.4 ± 6.2 and 50.6 ± 6.1, respectively. Whereas for the patient group, the number was 44.2 ± 8.5 and 42.6 ± 8.75, respectively. The repeated-measures ANOVA on the number of correct responses showed a significant effect of Group ($F(1, 35) = 12.039$, $p = 0.001$) and Condition ($F(1, 35) = 6.558$, $p = 0.015$), but not of the interaction Group × Condition ($F(1, 35) = 0.017$, $p = 0.896$). The group of patient did more errors than the group of control subjects. In addition, there were more errors in the non-word condition than in the word condition, but the difference between groups remained the same in the two conditions.

3.2. Classification

The classification accuracies with different number of pairs for both word and non-word conditions are presented in Table 2. The algorithm achieved the highest classification performance in the word condition. In particular the highest classification accuracy was 100% for controls and 86.7% for patients in the word condition by using three pairs of features in majority voting. For the non-word condition the best classification accuracy was 86.4% and 66.7% for controls and patients, respectively. Since the highest classification accuracy was obtained in the word condition, we will discuss mostly the characteristics of the features that were selected in this condition.

3.3. Selected features and their spectral content

In the word condition, four features ($\boldsymbol{f}_{(20,1-4,7)}$, $\boldsymbol{f}_{(95,16-24,21)}$, $\boldsymbol{f}_{(155,16-24,17)}$ and $\boldsymbol{f}_{(186,12-16,20)}$) were most often selected by the

Table 2
Classification accuracy (%) obtained for different number of majority votes in the word and non-word conditions. Schizophrenia patients correctly classified (P_S). Control subjects correctly classified (P_C). Overall correct classification (P_{Avg}).

m	Word			Non-word		
	P_C	P_S	P_{Avg}	P_C	P_S	P_{Avg}
1	95.5	80	89.2	72.7	26.7	54.1
3	**100**	**86.7**	**94.6**	86.4	66.7	78.4
5	95.5	66.7	83.8	77.3	46.7	64.9
7	100	80	91.9	59.1	26.7	46

pair-wise classifiers. Each feature is identified by channel number, frequency band and time point (e.g., $\boldsymbol{f}_{(20,1-4,7)}$ refers to the ERD/ERS value of channel 20 for the sub-band 1–4 Hz at the 7th time point). The most frequently selected pair of features ($\boldsymbol{f}_{(20,1-4,12)}$, $\boldsymbol{f}_{(95,16-24,21)}$) was extracted from the delta (1–4 Hz) and beta (16–24 Hz) frequency bands. Another pair of features ($\boldsymbol{f}_{(186,12-16,20)}$, $\boldsymbol{f}_{(155,16-24,17)}$) that was frequently selected was extracted from the upper alpha (12–16 Hz) and beta (16–24 Hz) bands. The other selected pairs were composed typically by other combinations of these four features or from their neighboring time points. The scatter plot of controls and patients related to the main paired features in the word condition are shown in Fig 4. For the non-word case the selected features were not as robust as in the word case. However, five features were frequently selected by the algorithm in that condition ($\boldsymbol{f}_{(156,24-32,18)}$, $\boldsymbol{f}_{(200,24-32,16)}$, $\boldsymbol{f}_{(137,12-16,17)}$, $\boldsymbol{f}_{(212,1-4,5)}$ and $\boldsymbol{f}_{(37,1-4,5)}$). They were from the upper beta (24–32 Hz), upper alpha (12–16 Hz) and delta (1–4 Hz) bands.

3.4. Topography of the most discriminant features

The locations of the extracted features in the word and non-word conditions are shown in Fig. 5 on 3-D head maps. We can notice that several features that were selected in the word condition where in the left frontal and fronto-temporal areas, which are important areas for language processing. The feature $\boldsymbol{f}_{(20,1-4,7)}$ was located in the dorso-frontal area near the midline. The features $\boldsymbol{f}_{(95,16-24,21)}$, $\boldsymbol{f}_{(155,16-24,17)}$ were located near the left fronto-temporal area. Finally the feature $\boldsymbol{f}_{(186,12-16,20)}$ was located in the occipital area. The locations of most features extracted in the non-word condition were topographically close to those selected in the word condition. However, slightly different frequency bands were selected in some areas across condition.

In addition, the 2D ERD/ERS maps of patients and controls related to the extracted features are presented in Fig. 6 (a better appreciation of the dynamics of the spatio-temporal ERD/ERS patterns of controls and patients can be obtained from 2D movies; see supplementary material). We can notice two things in this figure, one is that the discriminant features were located at or near peaks or valleys of the ERD/ERS maps; and second, that there was greater modulations of ERD/ERS in the control group than in the patient group. In other words, the discrimination between controls and patients resided mainly in the smaller change of brain oscillations in patients relative to controls.

3.5. Timing of the most discriminant features

We present the time-varying ERD/ERS waveforms of the most discriminant features in Fig. 7. The feature $\boldsymbol{f}_{(20,1-4,7)}$ in the dorso-frontal area was extracted from the encode stage of the task, whereas the rest of the features were all selected from the maintain stage.

3.6. Differentiation of selected features across conditions and groups

The boxplots of the main features for patients and controls and their related ROC curves in the word and non-word conditions are shown in Fig. 8. The ERD values of controls were significantly lower than those of patients for the feature $\boldsymbol{f}_{(95,16-24,21)}$ (t-test, $p = 0.000091$). Similarly, for the feature $\boldsymbol{f}_{(155,16-24,17)}$, the ERD values of controls were significantly lower than those of patients (t-test, $p = 0.000357$). Previous studies have associated ERD in alpha and beta bands with the activation of cortical areas (Pfurtscheller and Lopes da Silva, 1999), therefore these results suggest that the activation of neural circuits in the left fronto-temporal cortex during the word condition was less pronounced in schizophrenia patients than in controls. In contrast to these features, the mean activity levels of patients and controls had opposite signs for the features $\boldsymbol{f}_{(20,1-4,7)}$ and $\boldsymbol{f}_{(186,12-16,20)}$. For controls these regions were associated with ERS and for patients with ERD levels. The activity levels of patients were significantly lower than those of controls for $\boldsymbol{f}_{(20,1-4,7)}$ (t-test, $p = 0.000086$) and for $\boldsymbol{f}_{(186,12-16,20)}$ (t-test, $p = 0.00016$), as shown in Fig. 7 and Fig. 8. The opposite change of ERD/ERS in the dorso-frontal area during the encode stage and in the occipital areas during the maintain stage for patients relative to controls reveals the dysfunction of these areas in patients during the task.

Although the average classification accuracies were better in the word (94.5%) than in the non-word (78.4%) conditions, there was no significant difference in ERD/ERS pattern between these conditions when the features were analyzed within each group. The reason for this lack of significant difference is that for both controls and patients, the variance of the selected features in the word condition was smaller than the non-word condition. Simi-

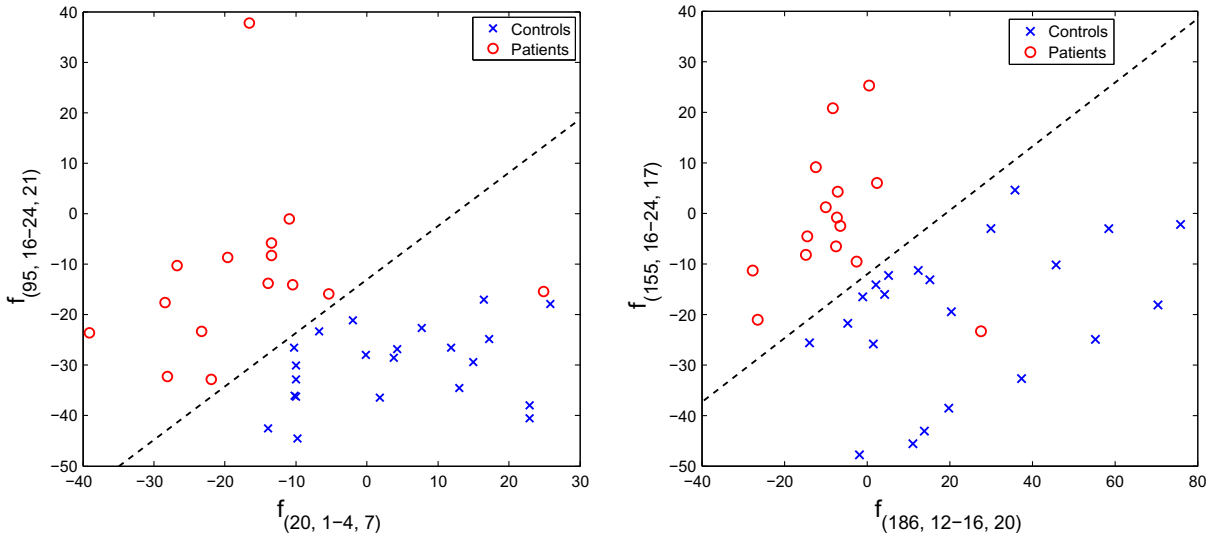

Fig. 4. Scatter plots of the selected features in the word condition. Note that both groups were nearly linearly separable with these combinations of features.

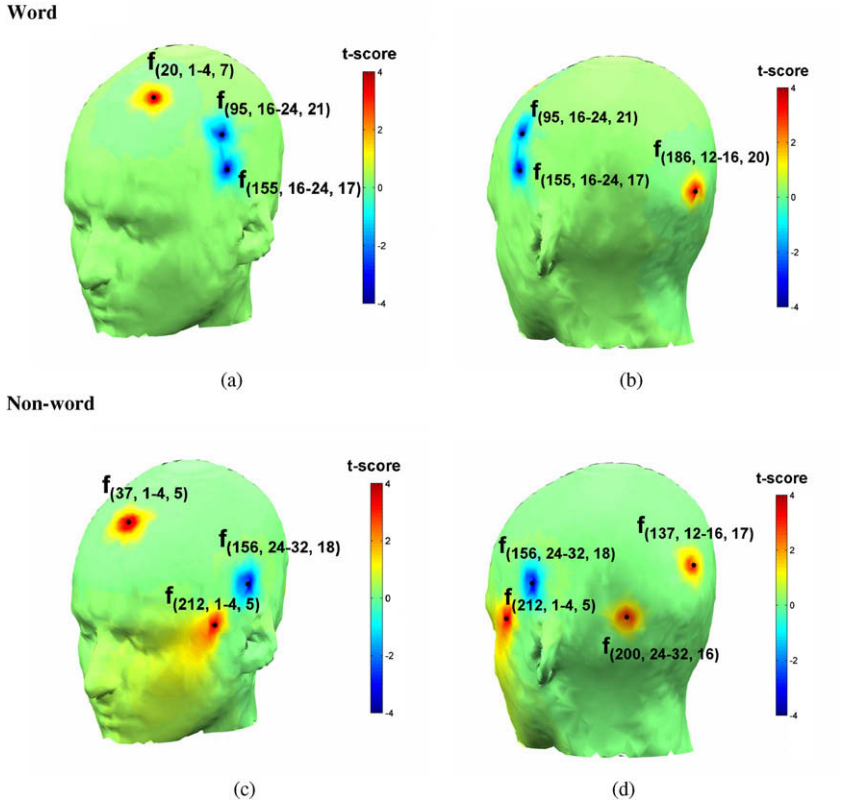

Fig. 5. Sensor locations of the features selected in the word condition (a and b) and in the non-word condition (c and d). Each location was color coded relative to its *t*-score.

larly, the area under the ROC curve, which indicates the discriminability between groups, in the word condition was slightly larger than in the non-word condition for all selected features (see Fig. 8). These results suggest that it is important to analyze combinations of features in order to assess the efficiency of ERD/ERS patterns that differentiates schizophrenia patients and control subjects.

3.7. Time–frequency distribution of discrimination

In order to illustrate the time–frequency content of the discriminatory information, discriminant time–frequency maps were generated for the channels of the features selected in the word condition. These maps are shown in Fig. 9. We note that the classifier integrated information from the late encode and maintain stages and from different frequency sub-bands. The feature $\boldsymbol{f}_{(20,1-4,7)}$ was located towards the end of the sequence of letters in the encode stage. This segment corresponds to the time when the subjects could judge whether the sequence of letters constituted a word or not. The features $\boldsymbol{f}_{(95,16-24,21)}$, $\boldsymbol{f}_{(155,16-24,17)}$ and $\boldsymbol{f}_{(186,12-16,20)}$ were all selected from the maintain stage. These results show that a variety of frequency bands and cortical areas at different times of the process need to be selected to obtain the best discrimination between patients and controls.

4. Discussion

In this study we show that ERD/ERS patterns associated with working memory operations can be used to discriminate successfully between schizophrenia patients and healthy control subjects. As predicted, the functional state provided better classification accuracy than studies that used resting brain state for discrimination (Jafri and Calhoun, 2006; Li and Fan, 2006). Furthermore, the patient/control discrimination was based on identifiable spectral, spatial and temporal parameters. This means that the method proposed provides the elements for interpreting the pathophysiological bases of the discrimination. However, a potential problem when extracting features from a high-dimensional space is that it is likely that spurious differences that discriminate well patients and controls be found. As a consequence, it is reasonable to question whether the set of features extracted is robust and would generalize to other samples of schizophrenia patients and healthy control subjects. For this reason, we employed the leave-one out method which provides a statistical estimation of the reproducibility of the results. The process consisted in selecting features from the whole sample of patients/controls minus one case and testing the classification using the excluded case, and then the same process was repeated with each case. Since the classifications were always done using cases that were not used to select the features, this process effectively generalizes the selected features to patients/controls not included in the sample.

We found that the discrimination was greater in the word (94.5%) than in the non-word (78.4%) condition. This is likely an effect of the language disorders of schizophrenia patients (Crow, 1997; Stephane et al., 2006). Patients may not use effectively the semantic information associated with the word condition to alleviate working memory load. In addition, the discriminating features were found both in the encoding and maintain phases, which correspond to the verbal working memory subprocesses impairments identified in schizophrenia patients using EEG (Kayser et al., 2006).

The extracted oscillatory features were frequency-specific (delta (1–4 Hz), beta (16–24 Hz) and alpha (12–16 Hz)), area specific (delta (1–4 Hz) in the dorso-frontal, beta (16–24 Hz) in the left fronto-temporal and alpha (12–16 Hz) in the occipital regions) and time specific (delta (1–4 Hz) during the encode phase, alpha (12–16 Hz) and beta (16–24 Hz) during the maintain phase). The

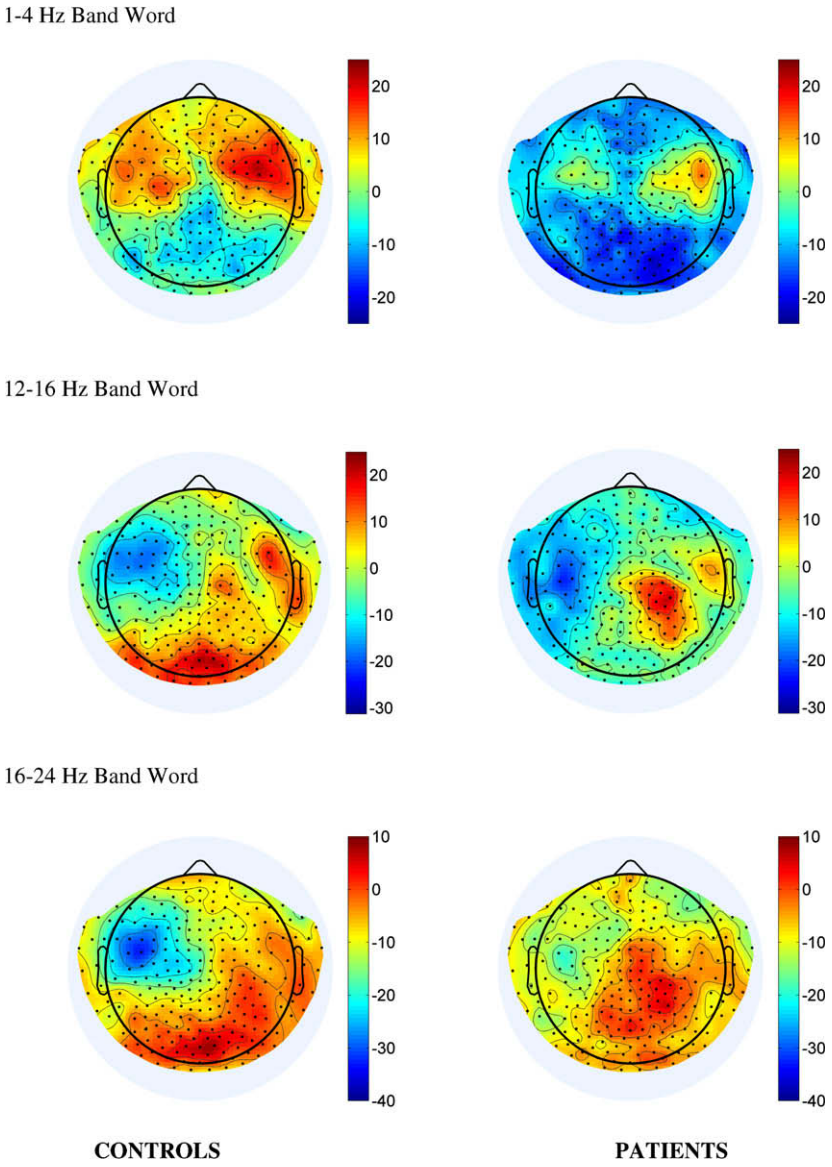

Fig. 6. ERD and ERS contour maps in delta, alpha and beta bands.

features in the left fronto-temporal area ($\boldsymbol{f}_{(95,16-24,21)}$, $\boldsymbol{f}_{(155,16-24,17)}$) showed an ERD during the maintain stage for both patients and controls. ERD in alpha and beta bands is associated with the activation of cortical areas (Pfurtscheller and Lopes da Silva, 1999). Since the ERD was less pronounced for patients than controls, these results suggests that the left fronto-temporal area was hypoactive during the maintain phase of verbal working memory in schizophrenia patients, which is consistent with the reports of linguistic and working memory dysfunction in this illness (Crow, 1997; Stephane et al., 2006; Stephane and Pellizzer, 2007).

In contrast, the features in the dorso-frontal ($\boldsymbol{f}_{(20,1-4,7)}$) and occipital areas, ($\boldsymbol{f}_{(186,12-16,2)}$) showed ERS in controls and ERD in patients. The occipital ERD during the maintain phase in patients could reflect an abnormal recovery from the active state (Pfurtscheller et al., 1996). On the other hand, the pattern of dorso-frontal ERS of the control subjects is consistent with other studies that have shown a pronounced but transient ERS in lower bands during the encoding of stimuli (Klimesch et al., 1996; Asada et al.; 1999; Jensen and Tesche, 2002). Furthermore, working memory has been associated with an increased power in the 2–6 Hz band at frontal and posterior parieto-temporo-occipital sites in healthy controls (Stam et al., 2002). Thus, in these studies, the lower band ERS was linked to stimulus encoding and working memory in healthy subjects. The dorso-frontal ERD anomaly in patients during the encode phase is consistent with the abnormal activation patterns of dorsolateral prefrontal and anterior cingulate regions in schizophrenia patients found during the encoding stage in a fMRI working memory study (Schlösser et al., 2008). As a consequence, these results suggest that the dorso-frontal and occipital areas of schizophrenia patients were dysfunctional.

One question regarding the spatial localization of MEG activity using axial gradiometers is that a local brain source is captured better by adjacent sensors, than by a sensor just above the source (note that the direction of the magnetic flux that is important for Event Related Potential studies is not relevant here because we analyzed the power of oscillatory activity which does not have phase (influx, outflux) information). For this reason, axial gradiometers tend to show a more spread activation in sensor space than planar gradiometers. For example, Fig. 6 shows that channels that

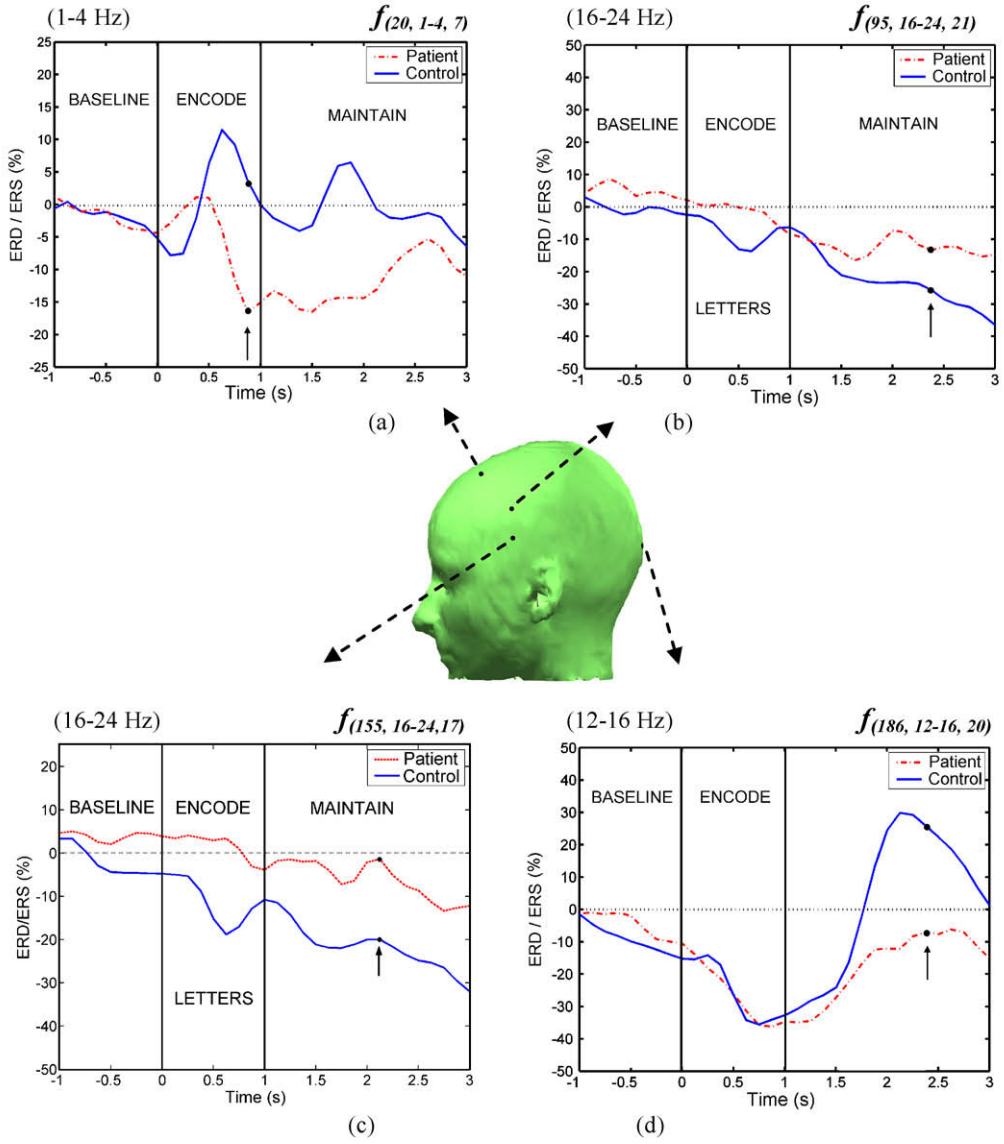

Fig. 7. ERD/ERS time-course for the features selected in the word condition. The time locations of the selected features are marked with black dots.

are close together tend to record similar oscillatory activity. The channels selected by the algorithm come from within a region of channels with similar characteristics, but the ones selected were the ones that provided the best discrimination. It is also important to note that the algorithm selected sensor positions that were consistent across subjects.

The spatial locations of the extracted features are consistent with brain areas found impaired in other studies. The location of $\boldsymbol{f}_{(95,16-24,21)}$ was on the left frontal area, which has been reported as dysfunctional region in schizophrenia in a positron emission tomography study (Schroeder et al., 1994) and in a fMRI study during an auditory working memory paradigm (Menon et al., 2001). The feature $\boldsymbol{f}_{(155,16-24,17)}$ was located near the left fronto-temporal area, which is known to be associated with language production. This area was reported as impaired in schizophrenia in several studies that used fMRI (Cohen et al., 1997) and structural MRI imaging (Wisco et al., 2007). The feature $\boldsymbol{f}_{(186,12-16,20)}$ was extracted from the occipital area. Several studies have provided evidence for abnormalities in early visual processing in the occipital lobe by using the EEG related to gestalt visual stimuli (Spencer et al., 2003). Furthermore a reduction in gray matter volume of this area in schizophrenia patients has been reported in several MRI studies (Zipursky et al., 1992; Davatzikos et al., 2005; Onitsuka et al., 2007). Finally, the feature $\boldsymbol{f}_{(20,1-4,7)}$ was located in the frontal region near the midline, which has been found to be dysfunctional in schizophrenia patients during working memory tasks (Tan et al., 2006).

ERD/ERS levels were computed as power changes during the memorization period with respect to the baseline. In our view this should address the possible confounds in this study, including, medication effect, higher coffee and tobacco consumption in the patient group, and possible drowsiness during the performance of the task. All the above confounds would affect both the baseline and memorization periods and normalization with respect to baseline is expected to remove any additive effect. The difference in classification accuracy related to word and non-word processing provides further evidence that the performance of the system was associated with the cognitive process carried out by the subjects. However, there is still the possibility of an interaction effect of medications that cannot be controlled by the experimental paradigm. Furthermore, the patient database was constituted of 12

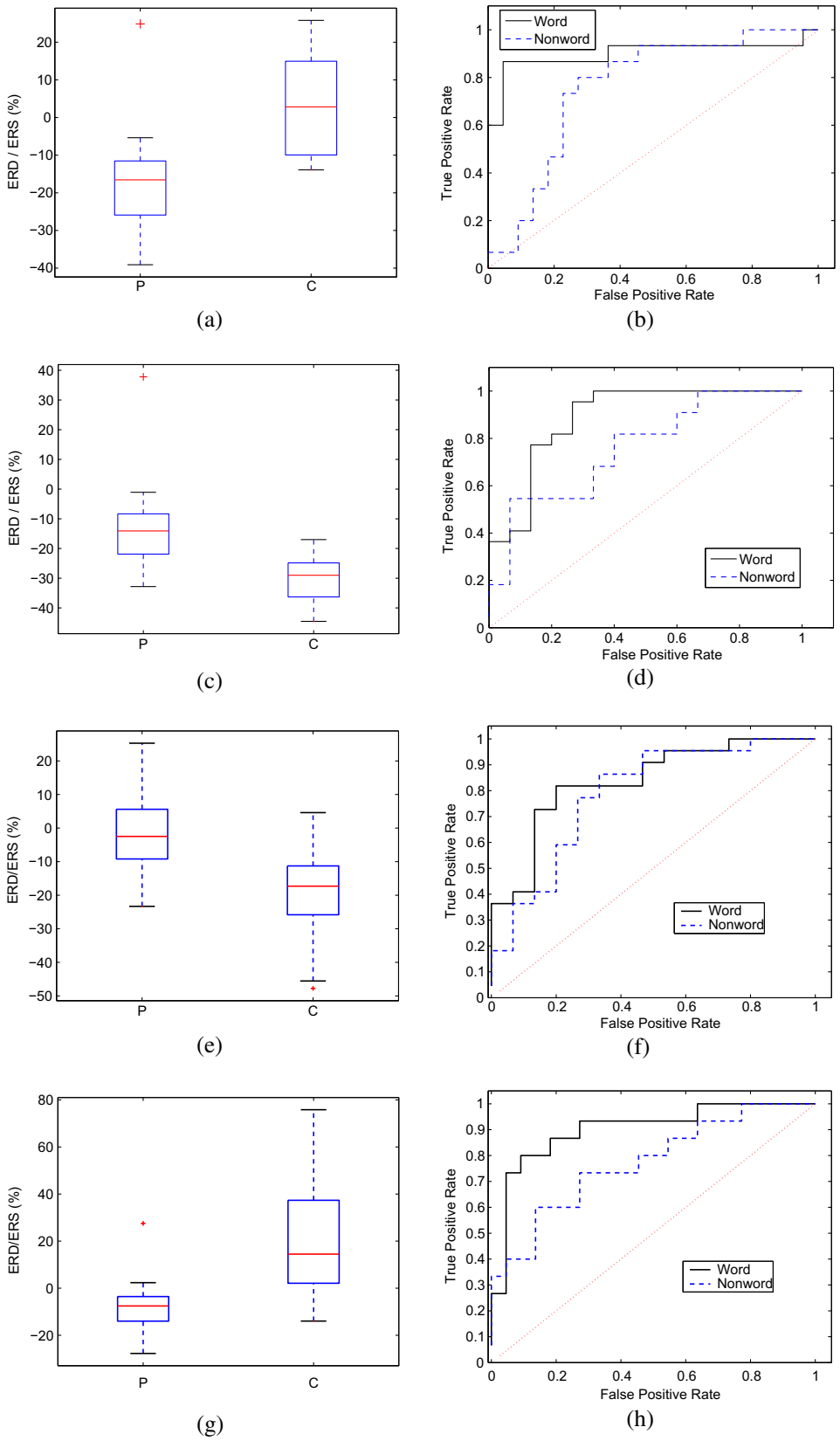

Fig. 8. Box plots for the features ($f_{(20,1-4,7)}$, $f_{(95,16-24,21)}$, $f_{(155,16-24,17)}$ and $f_{(186,12-16,20)}$) are shown in the left column: (a), (c), (e) and (g), respectively. In order to emphasize the difference between word and non-word conditions the ROC curves for both condition estimated from these features are plotted in the right column. Note that the AUC was larger for the word condition than for the non-word condition.

males and 3 females, which raises questions about the generalization of the results to female patients. Further research is needed to assess these potential limitations.

The results indicate that different cortical areas were associated with different frequencies of brain oscillations and at different times during the working memory task. The discriminant

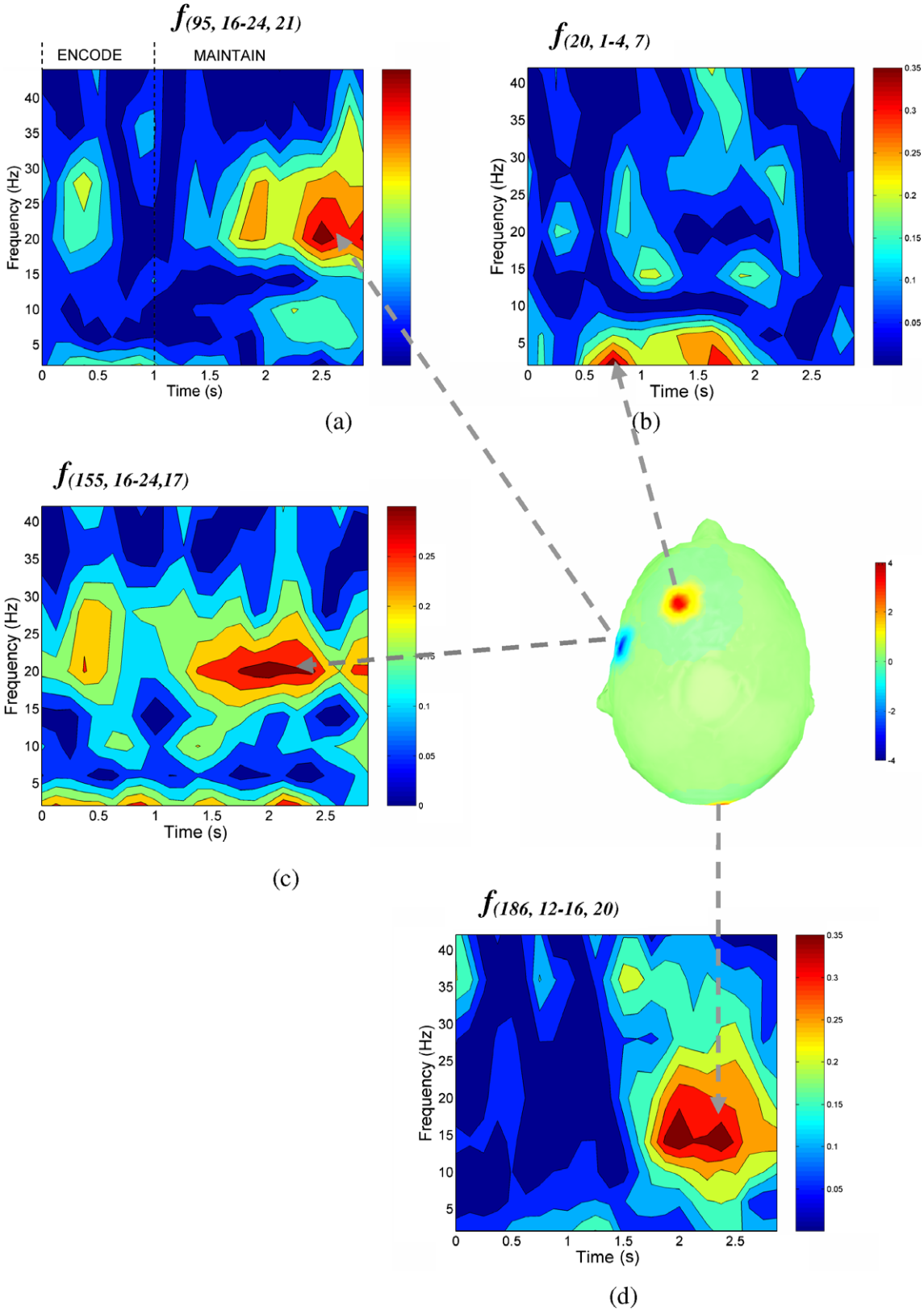

Fig. 9. Discriminant time–frequency maps of the channels with selected features in the word condition. Note that the most discriminant time locations were varied with sensor location. The dorso-frontal feature $f_{(20,1-4,7)}$ was located in the encode stage towards the end of the sequence of letters in the 0–4 Hz band. In the left fronto-temporal area, the features $f_{(95,16-24,21)}$ and $f_{(155,16-24,17)}$ were located in the late and mid maintain stage in the 16–24 Hz band, respectively. In the occipital region the most discriminant feature $f_{(186,12-16,20)}$ was located in the mid maintain stage in 12–16 Hz frequency band.

features were extracted by exploring a wide range of frequency sub-bands, temporal locations and brain regions. The results show that verbal working memory ERD/ERS patterns extracted from MEG can be used successfully as biometric markers for classifying schizophrenia patients vs. healthy control subjects.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clinph.2009.04.008.

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