The Prism of Brain Mapping Techniques and the Need for their Translational Researches and Clinical Applications

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Abstract

After few decades of research on versatile neuroimaging techniques, their clinical or daily-life applications are highly expected. There are some major limiting factors in this regard including: the lack of replicability and reliability, confounding factors of main neurophysiological effects, lack of standard methodology, and patient related factors. Whereas meta-analyses and machine learning approaches are likely to reveal the latent fact behind versatile neuroimaging experimental results, standard methodological issues, and clear clinical routines are expected to come from well-defined globally-guided translational neuroscience studies.

Keywords: Brain Mapping; Clinical Application; Translational Neuroscience.

1. Introduction

As a hot research field, cognitive sciences and brain mapping attracted great human and budget resources. Based on the emerging techniques, including fMRI, M/EEG, fNIRS, PET, brain stimulation, etc, researchers conducted thousands of academic research in this area. Many papers published, or presented in scientific gatherings. Thus their clinical applications are highly expected. On the other hand many brain related disorders like schizophrenia, Alzheimer, Multiple Sclerosis, ADHD, MDD, were being studied in clinical researches through above techniques. Clinical application of fMRI is now limited to presurgical mapping, and is not used for diagnosis purpose in these disorders [1]. I try to summarize some main challenges against applicability of brain mapping techniques, and then give some basic possible directions.

2. The Applicability Challenge of Brain Mapping

Several major issues ban the regulation of the outcome of basic and clinical researches for clinical practice. A main concern in this regard is the lack of replicability and reliability and confounding factors of BOLD effect in fMRI. The replicability is a series concern such that human brain mapping organization put it in their agenda through data sharing initiative and replication award [2]. Whereas almost all fMRI studies report some significant finding in population level, a critical ban for clinical use is the lack of significant effect size in subject level. Thus finding biomarkers for a particular set of symptoms in subject level for psychiatric disorders was not successful yet [1].

Another issue for clinical applicability of neuroimaging is the lack of standard methodology [2]. This points to versatile methods of: image acquisition, experiment (task) design, data analysis, and interpretation used in neuroimaging studies performed even on one common subject/question. Although some initiatives (for example COBIDAS) targeted the issue [2], but conclusive and practical guidelines must be available in these aspects for a clinical use. It is noteworthy that for a clinical use minimum set of hardware and accessories must be defined.

Patient related factors are among the most challenging factors that make changes in the neuroimaging signal. Some important factors are: heterogeneity in patient population (due to the spectrum of some disorders), level of attention to the task, mood, sleep duration, age, duration and type of medications, training the task to the patient.

The existing and emerging computational power, recent achievements in the field of deep learning,, and open-access and large neuroimaging databases are promising resources for conducting well-defined meta-analyses in the field of neuroimaging. These analyses are supposed to reveal the latent fact behind the very versatile existing results in the field of neuroimaging (even for a specific disorder and a common task).

In order to connect neuroimaging and clinics for diagnostics and treatments of psychiatric disorder, translational neuroscience plays an effective role through well-defined researches on specific disorder with the aim of concluding the clinical procedures even for a few application. These globally funded projects must be defined and run in the light of extracted facts from the previous studies extracted by meta-analyses studies.

3. Conclusion

Several limiting factors prevented the clinical usage of neuroimaging routines so far. Applied and Global projects in the field of translational neuroscience are highly expected to regulate and customize at least few neuroimaging routines for clinical use by standardizing the methodology, and providing clear circumstances for patient handling, imaging, diagnosis, etc. Toward this goal, meta-analyses and machine learning approaches are promising tools for extracting the latent fact from the existing longitudal and versatile neuroimaging studies and databases in the field.

Acknowledgment

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Time-Frequency Analysis of Electroencephalogram Signals in a Perceptual Decision-Making Task of Random Dot Kinematograms

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Abstract

There are many situations in which one must decide to choose between a number of possible choices using sensory information. This type of decisions remarkably influences adaptive behaviour and is called “Perceptual Decision-making”, which is the basis of this study. In this research, the underlying neural mechanism of these decisions is investigated using a perceptual decision-making Electroencephalogram (EEG) dataset with a speeded perceptual discrimination task. To this end, clean EEG signal was divided into 1.3-second segments (0.3 second before to 1 second after stimulus onset) and averaged for Event-Related Potential (ERP) and Event-Related Spectral Perturbation (ERSP) calculations. According to the results, the amplitude of N200 component in O_2 channel was larger for correct choices than incorrect ones. Furthermore, it was observed that the beta band power in PO_2 channel was higher for correct choices rather than incorrect ones.

Results suggest that these observations may show the role of attention in perceptual decisions.

Keywords: Perceptual Decision-Making; Electroencephalogram; Event-Related Potentials; Event-Related Spectral Perturbation.

Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

Perceptual decision-making is the act of choosing one option from a set of alternatives based on available sensory information for instance, deciding whether crossing the street on a foggy morning, in poor visibility, is safe [1]. The amount of information gathered from the noisy environment and the individual's attention [2] are the main factors which affect the choice confidence [1], and the outcome of a perceptual decision. The aim of this study is to investigate the brain function in a perceptual decision-making task.

2. Materials and Methods

Pre-processed EEG and behavioral data from [3] were used in this study. Participants in [3] performed a speeded perceptual discrimination task while their EEG signal was getting recorded. They were asked to judge the motion direction of random dot kinematograms (left vs. right). This experiment consisted of 2 blocks, each containing 160 trials. The clean EEG signal was segmented into 1.3 seconds (-300, 1000 ms) intervals, time-locked to stimulus onset and averaged for ERP and ERSP calculations. The ERSP provides elements of event-related brain dynamics that are not shown by the ERP average of the same response epochs. The ERSP quantifies the average dynamic alterations in amplitude of the EEG frequency spectrum in time and in relation to the task event.

3. Results

The average of correct and incorrect choices epochs was calculated. Figure 1 depicts the Grand-Average ERP wave for both correct and incorrect choices in the O_2 channel across all participants. The N200 component is evident in about 200 milli-seconds after stimulus onset. It is derived that the amplitude of N200 was larger for correct choices than incorrect ones in most channels.

Furthermore, Figure 2 depicts the ERSP image for both correct and incorrect choices in the PO_2 channel. It can be observed that the beta band power is higher in about 200 milli-seconds for correct choices rather than incorrect ones.

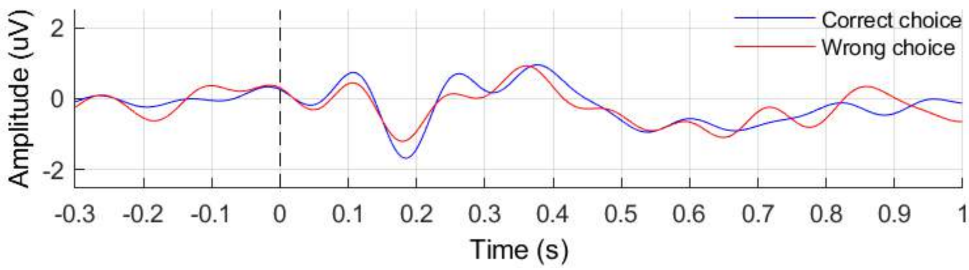
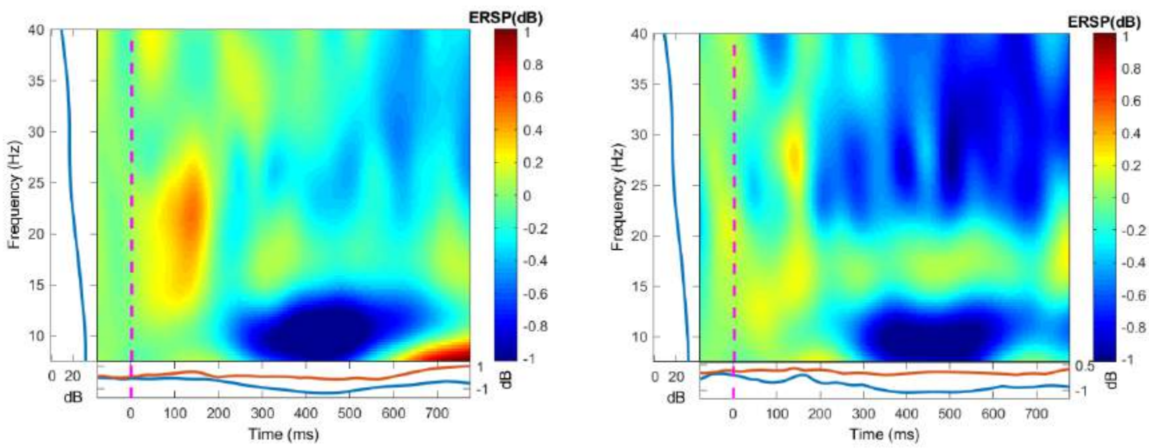


Figure 1. Grand average ERPs for correct and incorrect choices in O_2 channel. N200 amplitude is larger for correct choices



(a) (b)

Figure 2. ERSP images in PO_2 channel for correct (a) and incorrect (b) choices. Beta power is higher in correct ones

4. Conclusion

The present study investigates the ERP and ERSP components of correct and incorrect choices in a random dot kinematogram task. The larger N200 amplitude and the higher beta power for correct choices may be due to more attention on the stimuli.

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Disruption of Resting-State Functional Brain Networks in Children with Attention Deficit/Hyperactivity Disorder: A Resting State EEG Study

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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is a pathological condition with symptoms of inattention and/or impulsivity/hyperactivity. In this study, we evaluated alterations in resting-state Electroencephalography (EEG) source activity and functional connectivity in children with Inattentive ($ADHD_I$) and Combined ($ADHD_C$) ADHD compared to Healthy Controls (HC) using high-density EEG data. The exact Low Resolution Electromagnetic Tomography (eLORETA) was first used to compute Current Source Density (CSD) in different frequency bands. The lagged phase synchronization was then used to examine functional connectivity. Group differences in CSDs and network topological properties were assessed between the ADHD and HC groups. Compared to HC, $ADHD_C$ was characterized with a significant increase in Theta/Beta power Ratio (TBR) due to a global decrease in beta CSD. $ADHD_I$ also exhibited increased TBR in all brain regions with a global increase in theta source power except in posterior areas.

Functional brain networks of both ADHD groups displayed a small-world topology. Compared to HC, $ADHD_I$ was characterized with a global decrease in Lagged Phase Synchronization (LPS) in the delta and beta bands. $ADHD_I$ also showed a tendency for higher and lower network degrees in low and high frequency bands, respectively. $ADHD_C$ displayed increases in LPS in the frontal, central, temporal and posterior areas. Our findings suggest that EEG source analysis can better capture alterations in brain functional connectivity underlying the pathophysiology of ADHD.

Keywords: Electroencephalography; Cortical Source Imaging; Exact Low Resolution Electromagnetic Tomography; Lagged Phase Synchronization; Graph Analysis; Combined and Inattentive Attention Deficit Hyperactivity Disorder.

Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

ADHD is one of the most common neurodevelopmental disorders in children. ADHD children suffer from inattention, impulsivity, and/or hyperactivity. Growing evidence from neuroimaging studies indicates that alterations in brain functional connectivity may play critical roles in the pathophysiology of ADHD. Graph theory analysis has been used in many studies to characterize brain network properties during resting state using network metrics such as clustering and degree describing how efficiently information is exchanged between brain regions [1, 2]. Other metrics like small-worldness can be used to examine the functional balance between network segregation and integration [3]. The main goal of this study is to investigate alterations in resting-state EEG source activity and functional connectivity in children with $ADHD_I$ and $ADHD_C$ ADHD compared to Healthy Controls (HC) using high-density EEG data.

2. Materials and Methods

41 HC and 40 (10 inattentive and 30 combined) ADHD children were included in our study. The ADHD children were diagnosed based on the diagnostic criteria of the DSM-IV TR (4th edition, American Psychiatric Association, 2000) at Public Pediatric Teaching Hospital in Warsaw, Poland [4]. Five-minute resting-state EEG data were recorded from each child using an Electrical Geodesics Incorporated (EGI) 64-channel recoding system (Eugen, OR, United States) with a sampling frequency of 250 Hz and a referential montage referenced to C_z. The EEG source analysis was performed by exact low resolution electromagnetic tomography (eLORETA) on twenty five-second EEG epochs from each subject in four frequency bands, delta (0.5-4 Hz), theta (4.25–8 Hz), alpha (8.25–13 Hz) and beta (13.25–30 Hz). We then explored functional connectivity between 80 AAL regions using the LPS [5] to investigate group differences in functional network topological properties between the ADHD and HC groups using using permutation testing ($p< 0.05$, corrected for multiple comparison).

3. Results

The statistical analysis showed significant differences in CSD between the ADHD subtypes and HC in different frequency bands. Our results revealed a significant diffuse decrease in beta source power, resulting in a global increase in TBR in $ADHD_C$ relative to HC. $ADHD_C$ also exhibited a significant increase in theta CSD in the central, parietal and occipital regions. In this subtype, a significant decrease in delta CSD was found in right frontal areas. In $ADHD_I$, increases and decreases in CSDs were observed in the fronto-central regions in low (delta-theta) and high frequency bands (alpha-beta), respectively. $ADHD_I$ also exhibited an increase in TBR in all brain regions with the exception of the posterior areas. Regardless of the frequency band, all three groups showed a small-world topology. Compared to HC, $ADHD_I$ was characterized with a global decrease in LPS in the delta and beta bands. $ADHD_I$ also showed a tendency for higher and lower network degrees in low and high frequency bands, respectively. $ADHD_C$ displayed increases in LPS in the frontal, central, temporal and posterior areas. $ADHD_C$ was further characterized by declined clustering coefficients in theta and higher global efficiency in delta relative to HC.

4. Conclusion

We assessed differences in EEG cortical source densities and functional connectivity between ADHD and HC children in four frequency bands. Our results revealed altered cortical source densities and functional connectivity in different frequency bands in ADHD children compared to HC. Our findings showed that resting-state functional source connectivity analysis provides an efficient way to identify disruptions in functional brain networks in ADHD children.

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EEG Spectral and Complexity Indices Change during Islamic Praying

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Abstract

There is little information about the effects of Islamic praying (Namaz) on the brain. This study aimed to investigate the change of frequency bands and complexity of the brain signal during and after a four-cycle (rak'at) of Namaz. 80 healthy and Muslim adult participated in this study. Electroencephalography (EEG) recording was taken before, after and during performing a four cycle of the real Namaz. The relative power of frequency bands and nonlinear indices of EEG signals were measured.

The significance level was validated by the False Discovery Rate (FDR) correction. Only an increase in approximate entropy, spectral entropy, and Katz indices were seen in the left hemisphere after Namaz, especially in women and in the eye open state. During the Namaz, in most of the brain regions, the relative power of alpha and beta one bands increased in prostration and decreased in bowing, and the relative power of the other bands consisted of theta, beta 2 and 3, gamma 1 and 2 bands and nonlinear indices in bowing increased and decreased in prostration.

Thus, the brain frequencies and complexity in different positions of Namaz, especially prostration and bowing, undergo specific changes that often return to the pre-Namaz.

Keywords: Electroencephalography; Islam; Praying; Complexity.

1. Introduction

Some studies have been demonstrated the positive effect of Namaz on cases such as immune system disorders, sleep, memory, irregular blood pressure, gastrointestinal infections, and skin diseases [1, 2]. Ms. Rana'i and her colleagues showed that depression was significantly lower students who have a positive attitude toward Namaz [3]. another study showed that the more conscientious group to Namaz had more mental health and were less depressed [4]. Part of these positive effects may be the effect of Namaz on the brain. Unfortunately, there are very few studies in this regard. The research group studies showed that the relationship between the relative power of alpha waves in temporal and occipital channels was significant with an increase in parasympathetic tone during Namaz especially in prostration position [5, 6]. In comparison between actual Namaz and mimic Namaz (i.e., only performing Namaz movements), it was seen that the relative strength of the gamma band in prostration and most areas of the brain, especially the prefrontal and central, and in the bowing state in the prefrontal and frontal regions in real Namaz was more than mimic Namaz [7]. The main error of these limited studies regarding to Namaz, which makes their results unreliable, was not considering of interaction effect of channels that should be removed in statistics. Then a significant level calculated based on FDR correction was used in the current study to remove the interaction effect of channels to each other. In addition, those studies have been limited to the study of alpha and gamma bands. This study aimed to investigate all frequency spectrum of EEG and nonlinear indices before, during, and after a four cycle Namaz. Nonlinear indices are a more accurate interpretation of biological signals [8].

2. Materials and Methods

45 men and 35 women who had inclusion criteria were asked to have a good sleep the night before the test. Do not have severe stress on test day. They were tested between 10 and 14 o'clock. Perform Wudu before the test. The code of ethical research approved by Baqiyatallah University of Medical Sciences is IR.BMSU.REC.1397.190. The EEG recording was taken while sitting on a chair with the eyes open and the eyes closed, 1 minute for each one. Afterward, they were asked to face the Qibla and perform four cycle (rak'ats) of the actual Namaz, at which time the noon. EEG recording was also taken during Namaz. After the Namaz, they returned to sitting on a chair, and again 1 minute of open eyes and one minute of closed eyes were recorded.

To record the EEG signal, a 16-channel EEG device model Liv intelligent technology made in Iran with Resolution: 24 bit. registered channels included: Fp1, Fp2, F3, F4, F7, F8, C3, C4, T5, T6, P3, P4, O1, O2, and the reference electrode was placed on Cz, and the common electrode was placed on Fz. In order to analysis during Namaz, the four segments from each cycle of Namaz were selected for analysis that were standing, bowing, prostration and sitting position and the EEG data for transit situation did not consider. The sampling frequency was 256 samples per second. Preprocessing included signal filtering between the 0.2-48 Hz band, visual inspection of the signal, and removal of motion artifacts, Electromyography (EMG), and flashing removing using the Independent Component Analysis (ICA) algorithm. Spectral indices were: Theta: 4-8 Hz, Alpha 1: 8-10 Hz, Alpha 2: 10-12 Hz, Beta 1: 12-16 Hz, Beta 2: 16-20 Hz, Beta 3: 20-30 Hz, gamma 1: 30-35 Hz and gamma 2: 35-40 Hz [9, 10]. The nonlinear indices were approximate entropy [11] in the time domain ($AppE_n$), spectral entropy of Welch [12] in the frequency domain (S_pE_n), the fractal dimension of Petrosian, and Katz [10], Hurt Exponent and Alpha Detrended Fluctuation Analysis (DFA) [13]. In order to remove the interaction effect of channels to each other, the significance level obtained in the analysis for each index in all channels was placed separately in the FDR correction formula.

3. Results

A significant increase was seen in the $AppE_{nt}$ and Katz, after FDR correction in women in T5, C3, T6, P4, F8, and O1 channels in the open eye after Namaz. A significant difference was seen in fewer channels in the close eye situation. SpecEnt significantly increased after Namaz in women in the open eyes only in the O1 and T5 channels (Figure 1).

During the Namaz, there was no difference in changes between the two sexes. The relative power of the alpha 1, 2 (Figure 2), and beta 1 bands was significantly increased after FDR correction in the prostration position and decreased in the bowing position. At the same time, the relative power of the theta and beta 3 and gamma

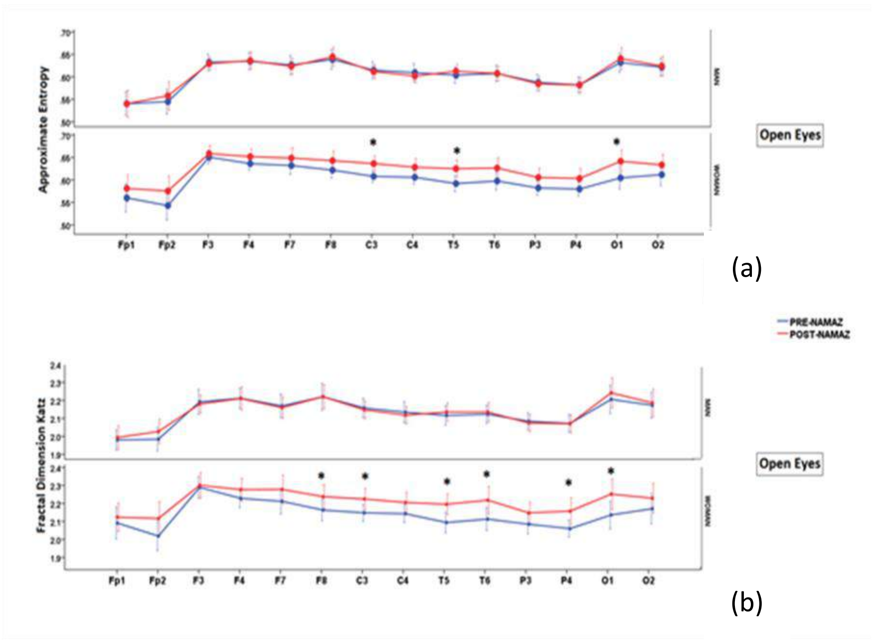

Figure 1. Mean value and 95 CI% of AppEnt (a) and Katz (b) in the open eyes before and after Namaz in women and men. *: Significant difference after FDR correction less than 0.05 between before and after Namaz

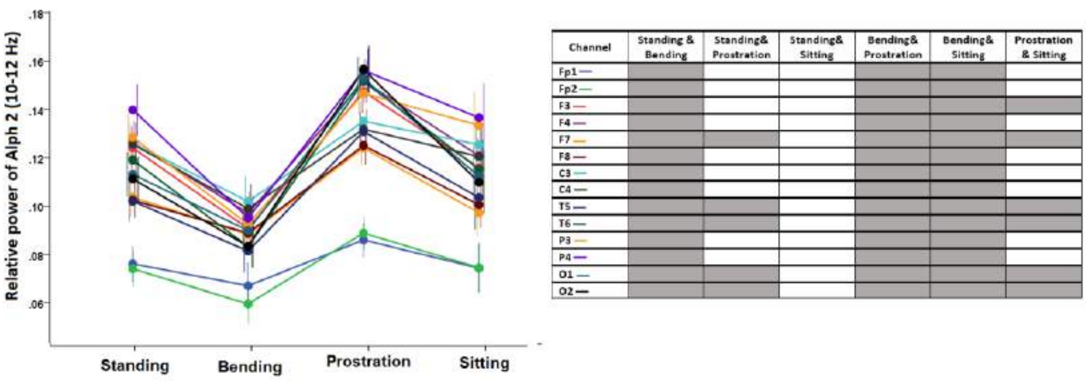

Figure 2. Mean value and 95% CI of the relative power of alpha 2 (10-12 Hz) in 4 positions of standing, bowing, prostration, and sitting in 4 rak'at of Namaz is on the left, and their comparison table with FDR correction p-value between different positions is on the right side of the figure. The significant comparison is shown as the gray color cell

1 and 2 bands and complexity indices (Figure 3) was significantly increased after FDR correction in the bowing position and decreased in the prostration position. There was no difference between sitting and standing in any of the indicators. Some areas, such as the occipital area, showed the most differences and the prefrontal area the least.

4. Conclusion

The findings showed that the nonlinear indices of EEG were more sensitive to changes after and during Namaz than spectral indices and the rhythmical changes of complexity was similar high band frequency of EEG. Changes in frequency bands of brain signal and its complexity indices between different position of Namaz, especially in bowing and prostration compared to standing and sitting positions, were quite clear and significant. The low and high frequencies of the brain, except theta band, behaved in the reversed pattern. The bowing position increased the high band frequency (16-40 Hz) due to involvement of more postural stability strategies and motor activity [14]. But the prostration increased the low band frequency (7-16 Hz) due to stimulation of baroreceptors and parasympathetic tone [15, 16], that increases attention and relaxation. Then several factors such as posture and working memory during Namaz changed the brain activity. But several interacted factors should be evaluated in the future studies.

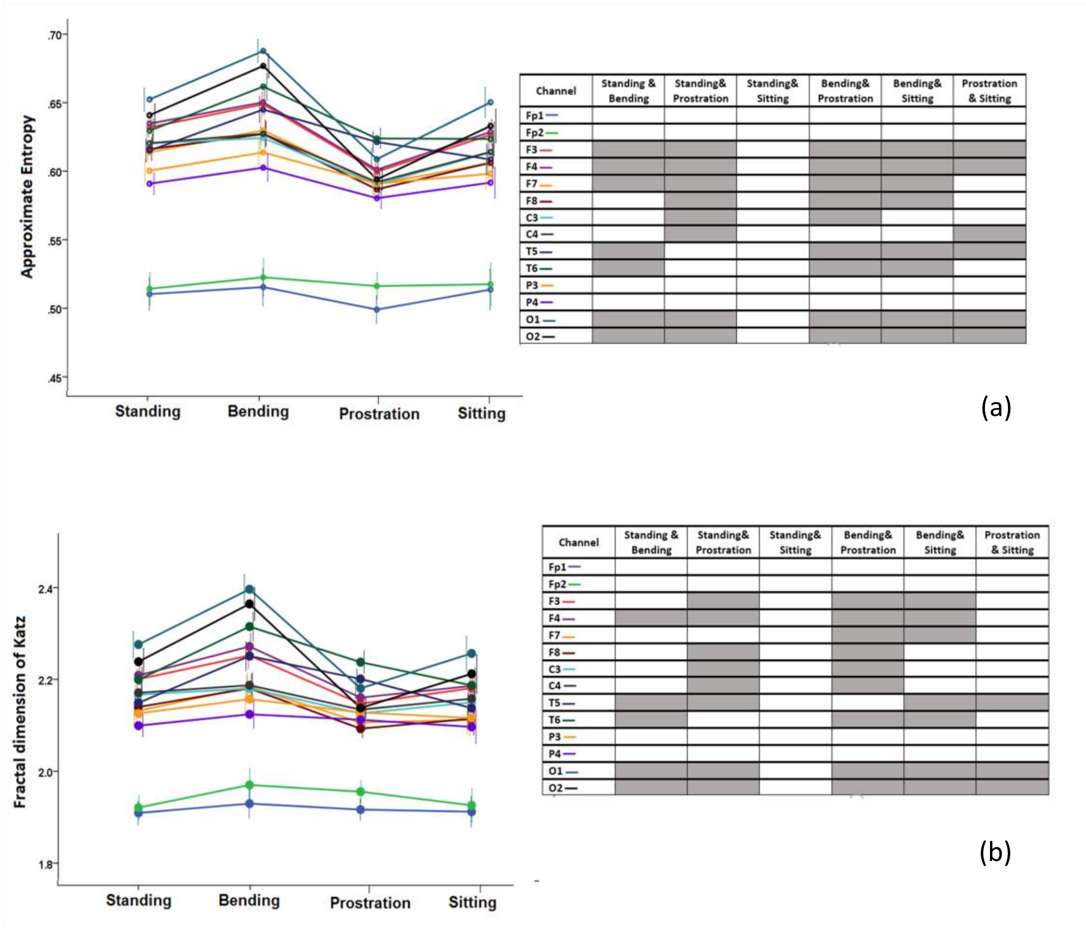

Figure 3. Mean value and 95% CI of approximate entropy index (a) and Katz index (b) in 4 standing, bowing, prostration and sitting positions in 4 rak'at of Namaz is on the left and the results comparison table with FDR p-value between positions is on the right side of figure. Significant amount is shown as gray-colored cell in the recorded channels

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The Influence of Odors on Time Perception

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Abstract

In this paper, we focus on time perception in odor types and music as a perception of duration. Time perception is closely tied to our experience of the world, but specifically relevant in experiences that we enjoy. This study aims at the effect of odor types on time perception. 10 BA students participated in the study. The results show that there is a significant relationship between the pleasant and unpleasant odor and time perception.

Keywords: Odors; Time Perception; Music.

Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

Events and actions constitute an important fact of human behavior that come into existence in time and space. For event sequencing and rate estimation, amount and pace of an object, time plays a significant role. Therefore, time is a primary element of intelligent behavior. Time perception or the experience of temporal intervals has received prevalent focus from varied points of view [1]. Time estimation is regarded as the concrete form of time perception and it plays an important role in everyday activities.

This subjective perception of time can be somehow different from the actual duration. The effect of different elements on this internal clock has been comprehensively researched. The two effects that have absorbed a lot of attention are that subjective duration is dependent upon attention dedicated to time (for reviews: [2, 3, 4, 5, 6], and arousal level [6, 7, 8, 9]). It has been suggested that arousal level would have an effect on the pacemaker rate. A rising level of arousal would expedite the pacemaker rate making for a larger quantity of accumulated pulses and, as a result, in overestimated durations. On the other hand, attention has an effect on the accumulation of pulses. Each time attentional resources are diverged from the time parameters, pulses are lost, resulting in a reduction of the number of pulses piled up, and causing shorter estimated durations. However, if the duration is paid more attention, more pulses will be piled up and duration will be estimated as longer.

A number of studies show that a duration of waiting is estimated shorter when there is concomitant music than when there is no music (e.g. [10, 11, 12, 13]) and that this subjective shortening of time appears to be larger when the subjects listen and enjoy this concomitant music [14, 15, 16, 17].

The creativity and originality of the current study is to use an olfactory stimulus as an external factor and to research how it affects time perception of neutral stimuli (i.e., music). Odors can already have an impact on emotional states in different contexts with little cognitive mediations ([18, 19]; for reviews). Indeed, hedonic valence seems to be the most immediate and significant known feature of any olfactory stimulation [20, 21, 22]. As it appears from literature review, there is only one study done previously on time perception using odors as an external factor. Schreuder [23] utilized environmental odors to measure the arousal conditions of the subjects. Participants had to produce three time intervals (1.33, 1.58, and 2.17 min) when they felt either an arousing odor (rosemary), a relaxing odor (peppermint) or no odor (control condition). When participants sensed rosemary odor, they produced importantly shorter intervals than in the no odor condition. Consequently, this effect could not be gleaned by an increase of arousal but rather by other effects due to exposure to odors. We could note that the odors used in this study were both regarded as pleasant by the participants.

2. Materials and Methods

The research participants were 10 B.A. students between 20 to 30 years old with the average of 24/8 years old. All the participant were psychologically and physiologically normal and were not afflicted by Coronavirus disease (COVID 19) and had normal olfactory sense. All the 10 subjects had been trained for time perception in two intervals of 2:30 minutes and 1 minute and 50 seconds. The training consisted of every individual listening three times to a pieces of music with a duration of 1 minute and 50 seconds and three times to another piece with the duration of 2 minutes and 30 seconds in order to become familiar with rhythm and time measurement. The pieces from both intervals were vocal pop songs.

The participants were placed in a room with no windows and clocks without any possibility for them to tell the time. The room was filled with Eucalyptus incense. The participants were required to have a seat and listen to the instrumental music being played at the time and finally estimate its duration. After a day, the participants were again seated in a room filled with rose water incense. 5 of the participants were in the exact opposite situation. The music in the experiment consisted of two instrumental pieces with monotonous rhythm and their duration was 2:20 minutes and 3:05 minutes respectively. For five of the participants the shorter piece was played in a room filled with Eucalyptus incense and the longer piece was played in a room filled with rose water incense. The situation was exactly vice versa for the other five participants.

The participants were awarded 250,000 Rails per day (totally 500,000 Rails awarded to each individual) and they were asked to sign a consent form (In the consent form, we mentioned that the results would be used in research studies without the mentioning of individual names).

3. Results

The research results show that the participants that listened to the shorter piece in the room filled with Eucalyptus incense estimated the duration of the music piece 3:05 minutes. They estimate the longer piece 3:01 minutes in the rose water incense filled room. The participants in the second group that listened to the longer piece in Eucalyptus incense filled room, estimated its duration 4:12. They estimated 1:50 minutes for the shorter piece in rose incense filled room.

The results showed that the difference in time estimation regarding the type of odor being smelled is significant and unpleasant odors increase time perception.

Table 1. Results of T- Test

Music	Group	M	SD	T	Sig
Long	Rose Water	3.01	0.12	1.43	0.18
Short	Eucalyptus	3.05	0.17		
Long	Eucalyptus	4.12		3.29	0.02
Short	Rose Water	1.50			

4. Conclusion

All the results put together revealed that ambient odor influences time perception.

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Improving the Classification of Real-World SSVEP Data in Brain-Computer Interface Speller Systems Using Deep Convolutional Neural Networks

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Abstract

Noise and artifacts in Electroencephalogram (EEG) data are one of the most important issues for target detection in Brain Computer Interface (BCI) systems. It is critical to provide procedures that operate well in the presence of noises. In this study, an attempt has been made to improve the classification performance of Deep Convolution Neural Network (DCNN) by training on a subset of data and retraining on single-subject data from the BETA SSVEP database, which is recorded outside the electromagnetic shielding room.

The results showed that after retraining, accuracy and Information Transfer Rate (ITR) increased (p-value<0.05) for all selected participants with low performance (based on the accuracy of Canonical Correlation Analysis (CCA) approach). The improved accuracy and ITR averages are 25.72% and 43.10 bits per minute, respectively.

Keywords: Brain Computer Interface Speller; Steady State Visual Evoked Potentials; Deep Convolutional Neural Network; Electroencephalogram.

Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

BCI Speller systems based on Steady-State Visual Evoked Potentials (SSVEP) are used to rehabilitate and assist people with mobility impairments. In this system, as the user stares at targets that flicker at a specific frequency, an activity with the stimulation frequency and its harmonics is evoked in his\her brain. By identifying the stimulus frequency in the user`s brain signal, his\her command can be determined [1]. One of the main challenges in processing EEG signals is to reduce the destructive effect of noise and artifacts. There are several reasons for the appearance of noise and artifacts in EEG signals (e.g., participants' movement, electrode displacement, poor electrode connection, blinking, eye movement, ECG and EMG effect). In addition, signal recording environments are often contaminated by the effects of high-current cables, Wi-Fi, wireless signals, and other electrical equipments [2]. Therefore, there is a need for methods that provide good results in the mentioned environments.

2. Materials and Methods

In this study, the BETA database containing EEG signals from 70 participants (42 males, age: 9 to 64 years) was used [3]. This database is collected outside the laboratory and without any electromagnetic shield. The BETA database contains real-world data properties due to its out-of-laboratory recording. There are 40 stimulus frequencies in this database, set from 8 Hz to 15.8 Hz with a distance of 0.2 Hz. The task is designed in 4 blocks with 40 trials corresponding to 40 targets in each block. The stimulation period is 2 seconds for the first to the fifteenth participant and 3 seconds for the other participants. To equalize trial length, the 3-second epochs were shortened to 2 seconds. At this step, 9 low-quality participants were identified from the other 70 participants in the BETA database. Low-quality participants were chosen based on the results of the CCA approach, which performs poorly against noise (participants with accuracy below 15% were selected) [4].

PODNet is a Deep Convolution Neural Network processing approach that was utilized to identify the targets. Joshua *et al.* were the first to propose this network [5]. Due to the length of the trials (2 seconds), this network was created in 4 separate PODs (with a few modifications) using the Keras library (Tensorflow Backend). Each POD includes Convolutional, Drop-out (50%), Batch Normalization, Rectified Linear Unit (RELU) and MaxPooling layers. In addition, following the last POD, there is a dense layer that is eventually transferred to the softmax operation. The design details of this network are shown in Figure 1.

3. Results

The PODNet was trained on 61 participants (except nine low-quality participants). Out of 61 participants, 43 participants were randomly selected for training, 9 participants for validation and 9 participants for testing. The accuracy and ITR acquired from this training are 72.29% and 90.17 bits per minute for validation data, and 73.19% and 91.89 bits per minute

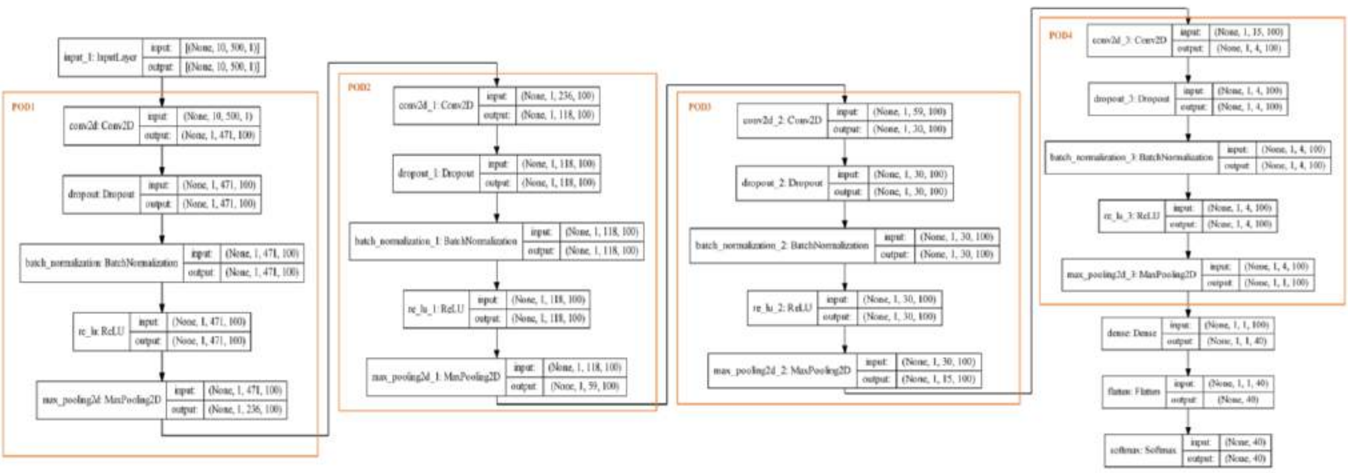

Figure 1. The details of the PODNet network structure

for test data, respectively. This model is then used separately in two different conditions for each of the 9 participants (with low quality). The first condition is without model retraining (only in the test block) and the second condition is with model retraining. In each participant, two blocks were selected for training, one block for validation and one block for testing. The test block is the same between the two conditions. The results demonstrated that after retraining the PODNet, the accuracy and ITR on low-quality participants improved (Wilcoxon rank sum test, p value<0.05). The results are shown in Figure 2. According to the findings, the network appears to be capable of performing efficiently in real-world data by learning the specific features of the data in its deep layers.

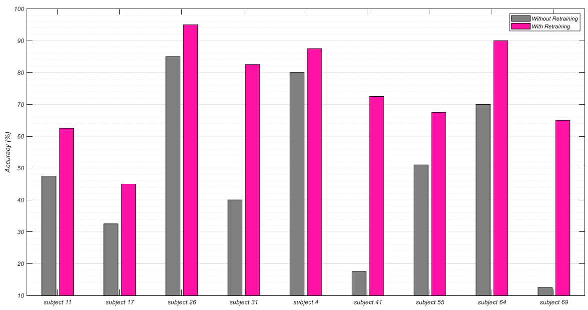

Figure 2. Accuracy (in percentage) in low-quality participants for both cases with and without PODNet retraining

4. Conclusion

According to the findings, PODNet seems to learn specific data attributes in its layers after being trained in two training blocks. As it learns proprietary features, the network's ability to classify stimulus frequencies in low-quality data increases. In other words, by retraining the network on a subset of the data (training blocks), the noise effect for other subsets of the same data can be reduced (validation and test blocks).

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Machine Learning Techniques and Nonlinear Features of EEG Signal to Predict Treatment Response to rTMS in Depression

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Abstract

Repetitive Transcranial Magnetic Stimulation (rTMS) can effectively excite the brain neurons and increase the brain plasticity which come particularly useful in psychiatric and neurological fields. The aim of our study was to investigate a novel non-linear index of resting state EEG activity as a predictor of clinical outcome, and compare its predictive capacity to traditional frequency-based indices. Electroencephalography (EEG) was recorded from 9 patients with Treatment Resistant Depression (TRD) and 5 Healthy Control (HC) subjects. TRD patients were treated with excitatory rTMS to the Dorsolateral Prefrontal Cortex (DLPFC) for 4 to 6 weeks. EEG signals were first decomposed using the ICA algorithm and the extracted components were then processed by non-linear analysis.

The results demonstrated 78%, 74% and 82% accuracy for Artificial Neural Network (ANN), K-Nearest Neighbor (KNN) and Support Vector Machine (SVM) classifiers respectively, indicating the superiority of the proposed method to those mentioned in similar studies. Our findings warrant further investigation of EEG-based biomarkers in depression.

Keywords: Repetitive Transcranial Magnetic Stimulation; Brain Stimulation; Treatment Resistant Depression; Electroencephalography; Non-Linear Analysis.

1. Introduction

rTMS is a safe and effective treatment for TRD with 50–55% response and 30–35% remission rates [1], and rTMS is considered a first-line treatment option for TRD [2]. The prescription of rTMS, similar to antidepressant medication prescription, is currently based on clinical assessment and a process of trial and error. Identification of effective biomarkers that can inform clinical decisions is lacking, and this absence may contribute to higher health-care costs [3]. Developing reliable biomarkers may have profound implications for clinical practice as it would shift the prescription process to a more precise and personalized approach that would further improve clinical outcomes and efficiency during treatment initiation [4]. The purpose of this study is to examine EEG features as predictors of treatment response in the TRD patients receiving excitatory rTMS to the Left Dorsolateral Prefrontal Cortex (L-DLPFC). We hypothesized that EEG-decomposed components will hold different energies for different patients and that these would differentiate responders (RP) from Non-Responders (NR). Furthermore, we hypothesized that non-linear methods would be more efficient predictors of rTMS treatment response compared to traditional linear frequency-band metrics.

2. Materials and Methods

The neurophysiology dataset was part of two randomized, single blinded trials in which patients with TRD were assigned to receive either intermittent Theta Burst Stimulation (iTBS) or High Frequency Left (HFL) rTMS protocols to the left DLPFC. Patients received a 4–6 weeks course of rTMS. A dataset with a total of 14 participants was used in this study, including 9 TRD patients and 5 HC. The patients were referred to the Neuraly Clinical Neuroscience Centre, Tehran, Iran, and depression diagnosis for them was made by a psychiatrist based on Diagnostic and Statistical Manual-IV (DSM-IV) criteria. Participants were also assessed by Hamilton Rating Scale for Depression (HRSD), and Beck Depression Inventory (BDI II) and all had the HRSD score ≥12 and BDI-II score≥15.

2.1. Stimulation Technique and Clinical Measures

A MagPro X100 stimulator with a Cool- B70 fluid-cooled coil was used to deliver rTMS for all patients (Magventure, Farum, Denmark). Resting motor threshold was determined by visual inspection of right interpolicis brevis muscle contraction with the aid of the TMS motor threshold assessment tool. All treatments were delivered at 110% resting motor threshold. Primary clinical outcome was measured using HDRS. For each patient, HDRS scores were collected at baseline and at the end of the rTMS course. Interviewers were blinded to patient treatment allocation. Responders were defined as those having a 50% or greater reduction in HDRS scores between baseline and end of treatment. Out of the 9 patients included in the analysis, there were 6 responders and 3 non-responders to rTMS treatment.

2.2. Pre-Treatment EEG

A 19-channel eWave32 amplifier was used for EEG signal recording which followed the 10-20 convention of electrode placement on the scalp. The amplifier, produced by ScienceBeam (http://www.sciencebeam.com/), provided a sampling rate of 1K samples. The digitalized data were down-sampled to 250 Hz and band-pass filtered with two-way least-squares FIR filtering using: low-pass filtering with cut-off frequency at 60 Hz and high-pass filtering with cut-off frequency at 1 Hz.

2.3. Feature Extraction and Classification

After EEG data preparation, the next step in the prediction of treatment response to rTMS is extracting features. In this paper, we studied a total of 21 features categorized into four groups including nonlinear, spectral, bispectral, and cordance measures. These measures are extracted from the baseline EEG of both groups of RP and NR, and each feature (except cordance measures) was computed for all EEG channels. For each measure, this yields a feature set of 19 features corresponding to the 19 EEG channels. We used three classifiers, KNN, SVM, and MLP to differentiate between EEG of RP and NR before and after treatment. To evaluate the performance of the classifiers, a leave-one-out cross-validation method was applied on account of the input data limitation.

3. Results

The results denote noticeable capacity of the proposed methods in classifying the two classes using the mentioned features and classifiers. To optimize learning cost and prediction performance, the SVM classifier parameters and kernel width must be chosen with caution. The proposed methodology based on SVM classifier presents better results than the other existing approaches. The obtained accuracy, sensitivity, specificity, and precision of the proposed methods are shown in Table 1.

4. Conclusion

In this study, we proposed a method for prediction of rTMS treatment outcome by applying KNN, SVM, and MLP classifiers to several measures of pretreatment EEG including non-linear features. The results of the proposed classification suggest the potential of applying this method in clinical applications. Our results suggest that the rTMS of the left DLPFC increased the activity in the left DLPFC and other regions functionally connected to this region of the brain.

Table 1. Results of the classifier performance in percentage, for leave-one-out cross validation

Classifier	Accuracy	Sensitivity	Specificity	Precision
SVM	81.43	85.00	74.00	87.75
KNN	73.32	77.24	65.67	79.59
MLP	77.37	81.38	71.83	83.67

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The Effectiveness of rTMS and TBS on Cognitive Functions in Suicide

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Abstract

Cognitive dysfunction is common in individuals with depression and these cognitive deficits may be associated with a risk of suicide. Therefore, the identification of the cognitive functions of depressed patients and the introduction of effective interventions on these factors are highly important. This study aimed to compare the effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS) and Theta Burst Stimulation (TBS) to improve on selective attention, working memory and response time of depressed individuals with and without a history of suicide.

This applied quasi-experimental was conducted based on a pretest-posttest design. The population included 40 depressed patients referring to the clinics of Mashhad, Iran, in 2020. The samples were divided into four groups, namely individuals with a history of suicide subjected to treatment with rTMS, without a history of suicide receiving treatment with rTMS, with a history of suicide undergoing treatment with TBS, and without a history of suicide administered with TBS (n=10 each). Data were collected using the Stroop Color and Word Test, Corsi block test, and reaction time tests and statistically analyzed using multivariate analysis of covariance.

The results confirmed the effectiveness of the intervention on the congruent reaction time, incongruent reaction time, working memory, simple reaction time, and selective reaction time in all four study groups ($P<0.05$). The results of multivariate analysis of covariance showed that the group had a significant effect on the variables of congruent reaction time, simple reaction time, and selective reaction time ($P<0.05$); however, it had no significant effect on the variables of incongruent reaction time and working memory ($P>0.05$).

Compared to the rTMS method, the TBS had a greater effect on the variables of congruent reaction time, simple reaction time, and selective reaction time.

Keywords: Transcranial Magnetic Stimulation; Theta Burst Stimulation; Cognitive Function; Suicide.

Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

Suicide, which is often associated with mental disorders, is one of the major concerns of mental health professionals [1]. One of the areas directly related to suicide attempt is depression [2]. About two-thirds of depressed patients think about suicide, and 10 to 15 percent of them end their lives this way. Therefore, identifying effective treatments to reduce depression is very important [3]. Studies that have examined the relationship between depression and executive functions have shown that depression is associated with deficits in executive functions such as attention, processing speed, and impaired working memory [4]. About 35 to 40 percent of depressed people do not respond to antidepressants. rTMS is used as a relatively new technique in the treatment of drug-resistant depression [5]. It is a safe and non-invasive method that improves brain function by altering glucose levels and the activity of neurotransmitters. However, this treatment can be associated with side effects such as headache, fatigue, and pain / discomfort at the site of stimulation. Also, the effects of this treatment are usually short-lived [6]. Therefore, the need for a more effective paradigm design than rTMS seems to be essential in the treatment of depression. TBS therapy is a new therapy that is able to focus energy and power waves three times normal, which creates strong and stable changes compared to traditional rTMS and causes long-term excitatory and inhibitory changes in It becomes the cerebral cortex. the brain. Another advantage of TBS over rTMS is its shorter time [7]. Considering the increasing growth of depression and suicide attempts, as well as the adverse psychological, social and physical effects of this disease, identifying the factors affecting the mental state of patients with depression and providing remedial interventions on these factors is of great importance. Therefore, the aim of this study was to compare the effectiveness of repeated transcranial magnetic stimulation and tetanus magnetic stimulation on improving the selective attention, working memory and response time of depressed individuals with and without a history of suicide.

2. Materials and Methods

The present study was a quasi-experimental applied research (pre-test, post-test) which was performed on 18-50 year olds referring to clinics in Mashhad in 2020. Inclusion criteria were definitive diagnosis of depressive disorder according to Beck Depression Scale, age range between 18 and 50 years and history of suicide attempt. History of seizures, history of head surgery, presence of any implants in the head, neck and upper body, having or having a heart pacemaker, history of drug use and addiction to alcohol and smoking or any other type of drug, pregnancy, lack of normal vision (Colour blindness or other eye diseases), schizophrenia, schizoaffective disorder, schizophrenic form disorder, hallucination disorder or psychotic symptoms were the exclusion criteria.

2.1. Research Tools

Stroop test: This test was used to measure the need for selection and cognitive flexibility. In this test, 48 matching colour words and 48 inconsistent colour words with red, blue, yellow and green colours were displayed [9].

Corsi block test: This test is designed to evaluate and measure the capacity of short-term spatial memory and spatial working memory, which can be measured in both age groups of children and adults and the time required to perform it is between 10 to 15 minutes [10].

Reaction time test: In this test, reaction times with light and sound stimuli are determined by choosing red, yellow or white [11].

In this study, sampling was done in a targeted and accessible way; As a result, 40 people were selected from the volunteers. Twenty of these individuals had a history of suicide who were randomly divided into two experimental groups (treated with theta burst) and (treated with rTMS). Also, 20 people without a history of suicide were selected as the control group, who were treated with theta burst and rTMS in two groups. The Beck Depression Inventory was used to assess depression. Subjects were assessed for cognitive function before performing rTMS and TBS. In the method of repeated transcranial magnetic stimulation, a Magestim device was used, which creates excitations in the desired position of the brain by creating magnetic fields. In this study, the frequency of stimulation was 10 Hz, with intensity 120% Resting Motor Threshold (RMT) This mechanism was performed on the left Dorsolateral Prefrontal Cortex (DLPFC) for 4 weeks and three sessions of 38 minutes each week. In the TBS method, participants received frequencies of 50 and 5 Hz with coils of 8 Magestim device for 12 sessions (3 sessions per week for 4 weeks) in the LDLPFC area. The stimulation intensity was 80% of the patient's motor threshold. The duration of each session was 3.3 minutes One week after the end of the intervention period, the Tower of London tests, corsi block and reaction time were performed and scored in two groups. Finally, the post-test and pre-test data were compared. Prior to the study, the conditions were fully explained to the patients and they were assured that their information would remain confidential.

Data were entered into SPSS software version 19 and then statistically analyzed. Descriptive data were explained using mean and frequency. The normality of the data was assessed using Kolmogorov-Smirnov. Finally, the data were analysed using chi-square, paired t-test and multivariate analysis of covariance. The confidence level was considered less than 0.05.

3. Results

Based on the findings obtained from the frequency of demographic variables, there was no significant difference between the four groups in terms of any of the demographic variables including age, education, gender and marriage ($P > 0.05$). The results of correlated t-test to evaluate the effectiveness of intervention methods on each of the cognitive function variables of depressed people showed that the effects of consonant reaction time, maladaptive reaction time, working memory, simple reaction time and selective reaction time on depression in all four groups ($P < 0.05$).The results of univariate analysis of covariance in the context of multivariate analysis of covariance to determine the effectiveness of intervention methods on each of the dependent variables showed that the group had a significant effect on consistent variables. Reaction time and simple reaction time and selective reaction time ($P < 0.05$), but had no significant effect on the variables of maladaptive reaction time and working memory ($P < 0.05$).

The results of Bonferroni experiment to compare the effectiveness of intervention methods on consonant reaction time, simple reaction time and selective reaction time showed that consonant reaction time and simple reaction time were reduced in non-suicidal individuals. TBS group compared to TBS group Suicide and reduction of consonant reaction time and simple reaction time in TBS group Suicide compared to non-suicidal rTMS groups and rTMS suicide group. Also, the data showed the effectiveness of non-suicidal rTMS group in reducing consonant reaction time and simple reaction time compared to suicidal rTMS group ($P < 0.05$). In reducing the selective reaction time, the effectiveness of the non-suicidal TBS group was lower than the suicidal TBS and suicidal rTMS groups. Also, the effectiveness of the non-suicidal rTMS group in reducing the selective reaction time was less than the suicidal rTMS group ($P < 0.05$).

4. Discussion

According to the findings, in all groups, the intervention reduced the fixed reaction time, simple reaction time and selective reaction time in depressed individuals. However, no significant effect was observed on the variables of maladaptive reaction time and working memory. To reduce consonant reaction time, simple reaction time and selective reaction time, TBS intervention was more effective than rTMS in both groups with and without a history of suicide. Also, TBS resulted in a greater reduction in matching time and simple reaction time in people without a history of suicide than in those with a history of suicide treated with rTMS. In both TBS and rTMS, concurrent response time, reduced simple reaction time, and selective response time were lower in those without a history of suicide than in those with a history of suicide. To increase cognitive activity in depressed patients, various therapies such as medication, electric shock and intracranial magnetic stimulation are used. Some findings have shown that cranial magnetic stimulation in the cortex has the same effect as antidepressants [12]. Our study showed that frequent magnetic stimulation of the skull is effective in improving the cognitive functions of depressed people who attempt suicide and do not. The use of this method led to a reduction in consonant reaction time, maladaptive reaction time, simple reaction time and selective reaction time, and increased working memory in depressed individuals with and without a history of suicide. The effectiveness of rTMS on reducing reaction time is consistent with the results of other studies [13, 14]. Also, the effectiveness of transcranial magnetic stimulation on reducing simple and selective reaction time as well as working memory has been confirmed by other similar studies [18-14]. In this regard, a study was conducted by Kazemi *et al*. In Iran, the effectiveness of bilateral cranial magnetic stimulation on cognitive function in patients with bipolar depression showed that the results show improved executive function and verbal memory. While no change in selective and verbal attention was observed [19]. In explaining this issue, we can point to the differences of the research community. This study focused on patients with bipolar depression, while the present study was performed on patients with major depression or unipolar depression. It is possible that this method will be more effective as the number of repetitive sessions of bipolar magnetic stimulation increases in people with bipolar disorder, which requires further research.

Other results of this study indicate the usefulness of theta stimulation in improving cognitive functions of consonant reaction time, maladaptive reaction time, working memory, simple reaction time, and selective reaction time of depressed individuals with and without a history of suicide. The results of other similar studies in the field of theta explosion stimulation during reaction, matching, and working memory confirm the findings of the present study [25]. In general, both theta stimulation and transcranial magnetic stimulation are safe and non-invasive methods that have been confirmed in various studies. However, the theta stimulation method is shorter and more effective in improving cognitive function than repetitive cranial magnetic stimulation. To date, no study has compared the effects of these two methods on improving cognitive function. However, two studies were conducted by Mendelitz *et al*. And Bolto *et al*. Confirm the effectiveness of these two methods in reducing depression [26]. Due to the lower cost and time required in the theta stimulation method, it seems to be more cost-effective than recurrent transcranial magnetic stimulation.

5. Conclusion

In summary, both methods, repeated transcranial magnetic stimulation and theta stimulation in both depressed groups with and without suicidal history, improved cognitive functions of consonant reaction time, inconsistent reaction time, simple reaction time, and selective reaction time and working memory. Compared with the repeated transcranial magnetic stimulation method, the theta-burst stimulation method had a greater effect on the variables of consonant reaction time, simple reaction time and selective reaction time. But in terms of inconsistent reaction time and working memory variables, no difference was observed between the two methods.

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The Relationship Between Brain Wave Quantitative Patterns with the Dimensions of Posttraumatic Growth in Persons with a History of Hospitalization Because of COVID-19

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Abstract

The aim of the present study was to investigate the quantitative pattern of brain waves with post-traumatic growth dimensions in patients admitted due to Coronavirus disease (COVID-19) disease. Post-traumatic growth is the mental experience of positive psychological changes caused by the individual as a result of coping with challenging situations. In this study, 66 individuals with COVID-19 who were admitted to Baharloo Hospital in Tehran as a stressful event were selected by convenience sampling and completed a post-traumatic growth inventory and their brain waves were in rest was recorded. The results showed that brain components are a good predictor of post-traumatic growth components. According to the results, it can be said that more objective instruments such as Electroencephalography (EEG) have good predictive power in complex psychological and multidimensional cases such as post-traumatic growth.

Keywords: Electroencephalography; Posttraumatic Growth; Trauma; Coronavirus Disease.

1. Introduction

Trauma exposure can have pathological effects such as post-traumatic stress disorder and behavioral problems such as suicide [1]. It is time to understand the Coronavirus disease (COVID-19) pandemic crisis as a new type of trauma. Although the majority of people are not affected by disease, media coverage and possibility of infection cause a lot of stress [2]. Some people go a step further psychologically after experiencing a traumatic event and report symptoms that are now known as post-traumatic growth [3] which is the experience of positive personal change as a result of coping with trauma, which does not neutralize the psychological experience of the traumatic but allows the individual to find new meaning in life, despite the traumatic experiences of the event. Find and achieve positive personal change in areas such as improving self-concept, interpersonal relationships and philosophy of life [4]. Post-traumatic growth occurs in five areas; Identifying new competencies (finding opportunities to do things I could not do), improving relationships with others (understanding how people might be useful), Increased personal strength (I can handle big problems), value of life (I enjoy each day more than the day before), and spiritual change (I have increased my belief in God) [5].

Despite evidence of brain function patterns and cognitive impairments following stress and post-traumatic stress disorder, these dimensions of post-traumatic growth have not yet been studied in detail. Accordingly, the present study intends to use Electroencephalography (EEG) instruments to assess whether individuals' brain function is related to growth components? Answering the above questions in conjunction with studies of the effectiveness of neurofeedback protocols or psychotherapy and counseling interventions, can provide good guidelines for the effectiveness of increasing people's awareness of stress on changing and modifying the function of their brain waves; Finally, on the other hand, considering the shortcomings in the tools of the special questionnaire for measuring growth after traumatic [6] to propose the EEG as a tool in this field.

2. Materials and Methods

The present study is fundamental and in terms of method of initial quantitative studies and a correlation study with the aim of prediction. This study includes people aged 25 to 75 years with a history of hospitalization due to COVID-19 during the last 3 months as an experience of stressful events. 66 people were selected by available method and after completing the post-traumatic growth inventory, EEG recording was taken at rest. This research with the code of ethics IR.UT.PSYEDU.REC.1399.019 was approved by the ethics committee.

The Post-Traumatic Growth Inventory (PTGI) consists of 21 Likert-scale expressions ranging from zero to five. This inventory has 5 subscales: new ways, in relation to others, personal strength, life value and spiritual change. The translation and evaluation of the validity and reliability of this tool in Iran has been examined [7].

EEG, standard 10-20, was used. The device used in the present study was "NrSign3840" (NrSign Inc., Vancouver, Canada) which had 19 channels, database-2 assembly type, notch filter 45-55, 50Hz highpass filter and 0.3Hz lowpass filter and rate Sampling was 500 Hz. For EEG analysis, the relative power of theta, alpha and SMR bands and asymmetry on the F3, F4, Fz, Cz and Pz were compared. EEG data were processed using MATLAB software. Then descriptive calculations and ridge regression analysis were performed using R statistical software, LISREL 10 version 8.8 and SPSS version 20.

3. Results

In this study, 29 females (46.8%) and 33 males (53.2%) with a mean age of about 50 years, right-handed (90.3%) and left-handed (9.7%), with a history of disease Mental (17.7%) and without a history of mental illness (82.3%), with a history of substance use (22.6%) and without a history of substance use (77.4%), without any previous history of head injury that Their recovery from Covid-19 disease was an average of 4 weeks. Due to the data conditions such as limited sample size and many predictor variables, ridge regression method was used to analyze the data. Alpha-parietal components, F3-SMR and asymmetry predicted new possibilities component, alpha-F3 and asymmetry predicted relating to others component, F4-SMR predicted spiritual change component and asymmetry significantly predicted the total post-traumatic growth score. Also, Quantitative Electroencephalogram (QEEG) components did not significantly predict the value of life and personal strength component.

4. Conclusion

The increased power of beta 1 (SMR) waves under stress is observed in patients with post-traumatic stress disorder, especially in the forehead areas in the F3 channel [8, 9]. In this regard, in the present study, SMR-F3 predicted the component of new possibilities and SMR-F4 predicted the component of spiritual change. Also, under stressful conditions, the power of alpha waves decreases, which indicates a change in response to stressful conditions, and the results of the present study showed that the alpha-parietal component for new possibilities and the alpha-F3 component for the relating with others are predicted. Forehead asymmetry, an EEG biomarker, has long been considered a promising indicator of psychological resilience. Post-traumatic growth represents an element of psychological well-being [10]. In the present study, it was also observed that the relative asymmetry of the brain predicts well the components of the new possibilities, relating with others, and the overall post-traumatic growth score. This may enhance the mental recognition of the positive changes experienced in the aftermath of traumatic events such as severe COVID-19 disease. The results of this study confirm the hypothesis that post-traumatic growth may reflect a process of active struggle to achieve new goals and perspectives. In contrast, the dimension of life values and personal strength components were not predicted by brain components; these two components were slightly more abstract than the others and may lead to more or less neural network activity, which is more detectable in functional Magnetic Resonance Imaging (fMRI) and may Is to control a higher cognitive structure than growth after trauma or to deliver it to a higher power. EEG is limited to recording activity in areas involved in emotion regulation and Post-Traumatic Stress Disorder (PTSD), such as the amygdala, hippocampus, and frontal cortex. Studies using better spatial resolution neural imaging techniques are needed to better understand the brain structures involved in Posttraumatic Growth (PTG). This was the first study to measure brain function in relation to post-traumatic growth in Iran and patients with COVID-19. Relative activation of the left frontal cortex with higher growth rates after trauma was shown to occur in a sample of COVID-19 recoveries. We hypothesize that the left hemisphere's self-regulatory system, which mediates the approach and positive effect, facilitates growth. The results showed that alpha EEG asymmetry may be useful in differentiating different dimensions of post-traumatic growth. This study has some limitations, including the fact that according to studies of the effect of COVID-19 disease on the nervous system, especially the brain in a percentage of people, it was useful to use structural tests of the brain, including Computed Tomography (CT) scan along with this functional EEG test to evaluate brain effects of this disease was used.

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Functional Connectivity Analysis in EEG Source Space during Deception

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Abstract

Deception is described as a conscious, intentional attempt to mislead others. In this research, to investigate the cognitive processes associated with deception, Electroencephalography (EEG) data was collected from 17 participants during a deception task in which they had to classify the target stimuli deceptively while responding truthfully to other stimuli (non-targets). In order to survey functional connectivity in source space, EEG source localization and EEG connectivity analysis were employed. The results revealed that deception was associated with significantly greater connectivity between distant regions including frontal- occipital and frontal- parietal connectivity. In addition, Anterior Cingulate Cortex (ACC) demonstrated greater significant connectivity with regions of the frontal and occipital lobes. Besides, deception was accompanied by high number of strong connectivity between the left parietal and frontal lobes.

Keywords: Deception; Electroencephalography; Source Localization; Low Resolution Brain Electromagnetic Tomography; Functional Connectivity.

1. Introduction

Deception needs more cognitive demands than truth telling. In fact, liars have to prepare a credible response while they inhibit the truth which requires to keep active in working memory [1].

So far, various neuroimaging studies have been accomplished to identify active areas of the brain during deception. Some meta-analysis researches on deception revealed that deception is accompanied by the eminent activation of Dorsolateral Prefrontal Cortex (DLPFC) and ACC areas which are associated with executive function [2, 3]. Finding potential interaction between the active regions of the brain in deceptive responses can play a substantial role in better understanding the brain function during deception and differentiating it from telling the truth. Functional connectivity analysis is one of the appealing methods for investigating cognitive processes like deception in EEG researches since it gives instructional information about the connectivity between brain areas [4]. Some former studies illustrated that deception enlists several brain networks involving the anterior cingulate cortex, middle frontal gyrus, prefrontal cortex, temporal gyrus and posterior cortical regions [5, 6], which interact with one another in order to form deception.

In the functional connectivity studies using EEG, most connectivity criteria are sensitive to the effect of volume conduction. Therefore, in order to alleviate this effect, functional connectivity in source space was investigated in this study with the goal of identifying significant differences between the brain networks of deception and truthfulness.

2. Materials and Methods

In this study, 17-participant EEG dataset is utilized which was recorded during the conduction of a task with deception content described in our previous study [7]. Stimuli included pictures of five animals and five plants. Participants were instructed to misclassify two pictures (target stimuli) which they had seen prior to the task while responding truthfully to other pictures (non-target stimuli). After preprocessing, in order to investigate the functional connectivity among brain sources in deception and truthfulness states, at first group Independent Component Analysis (ICA) [8] was used. Group ICA enables the identification of identical sources from both states (deception and truthfulness). Corrmap algorithm [9] was used to identify clusters containing representatives of both groups. Low resolution electromagnetic tomography (LORETA) [10] was used for source reconstruction. Functional connectivity (FC) was calculated using the coherence criterion Equation 1 [11].

$$C_{xy}(f) = \frac{|p_{xy}(f)|^2}{p_{xx}(f)\, p_{yy}(f)} \qquad (1)$$

Where $p_{xx}(f)$, $p_{yy}(f)$ and $p_{xy}(f)$ refer to the spectral density of x and y and the Cross spectral density between x and y respectively. Statistical analysis was performed using the Wilcoxon signed-rank test [12].

Before ICA, all participants' trials were normalized and then placed side by side. Group ICA was implemented in three groups including targets, non-targets and all (target and non-target). Clustering using Corrmap revealed eight clusters with common brain sources from both groups, which were reconstructed using LORETA (by taking each source acquired from group ICA on all as the center of each cluster).

3. Results

The results of source localization showed eight Brodmann areas including anterior cingulate cortex (BA32), medial frontal gyrus (BA8,11), superior frontal gyrus (BA10), postcentral gyrus (BA2), middle temporal gyrus (BA21), cuneus (BA17) and middle occipital gyrus (BA18). For each participant, the functional connectivity matrices (8×8) was calculated for each target and non-target epoch, and then functional connectivity matrices were averaged separately in each group. Finally, two functional connectivity matrices (target and non-target) were obtained for each participant. For each pair of sources, statistical analysis was performed between the values of connectivity. Figure 1 demonstrates the source connectivity which show significant difference ($p < 0.05$) between two groups (target and non-target). Results demonstrate that all significant connectivity were stronger during deception than telling the truth (targets > non-targets).

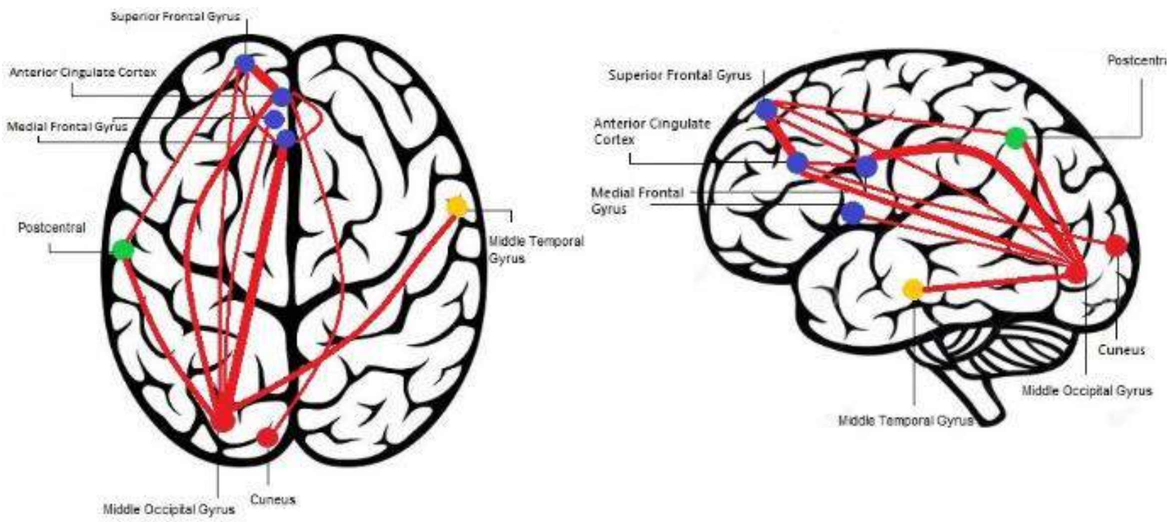

Figure 1. Significant connectivity (P<0.05) between target and non-target groups. The thickness of the lines expresses the p-values (narrow lines: p<0.05, medium lines: p<0.005, wide lines: p<0.0005)

In order to examine the strongest connectivity between brain sources in each of the target and non-target groups, after identifying all brain sources of each group, functional connectivity between each pair of sources using coherence criterion was calculated. Then, the top 15 percent of the connectivity in each group were identified, and the localization of each source was performed using LORETA. Figure 2 shows the top 15 percent of the connectivity between the sources in each group from top and sagittal views. The location of each source is specified using the corresponding color and name in the figure guidance. It is noteworthy that in the top 15 percent of the target group, a considerable number of connectivity are observed between the frontal and left parietal, frontal and left temporal and between the ACC and frontal, temporal and parietal lobes.

4. Conclusion

In this study, a significant number of long-range connectivity were observed during deceptive responses. In [13], stronger connectivity was observed between distant regions which could be attributed to increased

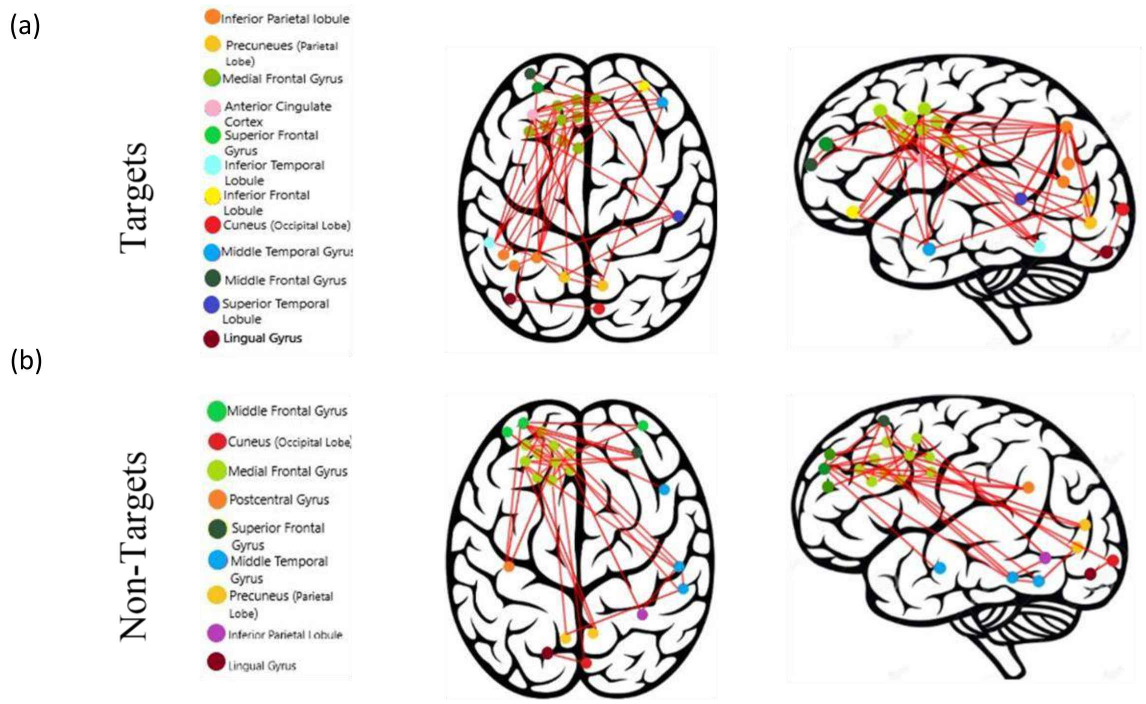

Figure 2. The top 15 percent of the functional connectivity between the sources in a) target and b) non-target group

cognition. Strong connectivity were also observed between ACC and areas of the frontal and occipital lobes, which is in line with [13] indicating that greater connectivity between ACC and occipital lobe could be related to the functions that are most important in performing deception. The results of the strongest connectivity between brain sources in target group showed that deception is associated with high number of strong connectivity between the left parietal and the frontal lobe, which corresponds to [14] demonstrating that left parietal has a key role in the scheming of skillful behaviors.

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Diagnosis of Major Depression Disorder Using 3D Convolutional Neural Networks

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Abstract

Major Depressive Disorder (MDD) is a significant cause of morbidity and unproductivity worldwide. Due to heterogeneity of MDD characteristics, diagnosis based on clinical questionnaires would not be adequate. Previous Magnetic Resonance Imaging (MRI) studies have reported that MDD would be accompanied with changes in cortical and subcortical Gray Matter (GM) structures including the hippocampus, amygdala, anterior cingulate cortex, caudate nucleus, and dorsolateral prefrontal cortex. Hand-crafted Morphological attributes can be identified by Voxel-Based Morphometry (VBM) method. Convolutional Neural Network (CNN) can facilitate the identification of morphological changes in structural MRI for clinical practice. We propose a combination of classic feature extraction and three-Dimensional (3D) CNN model that can extract deep-learned features automatically from cortical hand-crafted VBM attributes. This combination is done by giving the VBM gray matter features as input to model which is able to extract heterogeneous changes. By overcoming the underlining heterogeneity and effectively detecting the abnormalities of GM, accuracy of 86% and specificity of 83% and sensitivity of 89% was achieved for the evaluating of classification between the MDD *vs* the Healthy Control (HC) using REST-meta-MDD Data Sharing Consortium. Our algorithms have the potential to provide an unbiased, and non-invasive assessment of MDD that may allow more efficient treatments.

Keywords: Psychoradiology; Computer Assisted Diagnosis; Gray Matter Volume; Convolutional Neural Networks; Magnetic Resonance Imaging; Major Depression.

Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

MDD is a serious mental disability with high prevalence, recurrence rates, and chronic condition. Thus, efficient diagnosis is critical. Advances in neuroimaging especially MRI have provided progress for characterizing measurable indicators of the brain processes associated with MDD. Fusion of structural MRI and VBM methods have been growingly used to determine neurobiological mechanisms underlying MDD. VBM is a method that enables a voxel-wise estimation of the amount of a specific volume. Most commonly, VBM is used at studying gray matter. A recent analysis of gray matter structural networks discovered existence of global abnormalities that are related with diagnosis of depression. While it is obvious that volumetric GM regional loss appears in MDD, the precise pattern of this loss has not been clearly defined. Existing studies in patients with MDD have manifested loss of GM volume in cortical brain regions, including the medial prefrontal regions of the anterior cingulate cortex and Orbitofrontal Cortex (OFC), the lateral prefrontal cortex, the temporal cortex [1-3], and the pre- and post-central gyri [4-6]. A noticeable point is that these structural biomarkers of pathobiology may be practical as a complementary method of diagnosis in suspected MDD patients. The proposed algorithm in this paper is a novel CAD system based on the recent trend in 3D CNNs [7] to keep the continuity of slices and their joint relations. We proposed an adapted architecture of a 3D CNN for classification of 3D volumes of gray matter of MDD vs HC and combine VBM as classic feature extractor and convolutional layers as automatic feature extractor and provide a fusion of the obtained features as the input to a classifier for diagnosis of subjects. The proposed model was verified on the data from the REST-meta-MDD Data Sharing Consortium for discrimination between MDD and HC. Data was launched in 2019 as a public partnership, led by YAN Chao-Gan in rsfmri.org [8].

2. Materials and Methods

The DICOM images were first converted to 3D NIFTI format by using MRIcron(www.mricro.com), and were preprocessed using VBM8 toolbox (dbm.neuro.uni-jena.de/vbm) in SPM8(www.fil.ion.ucl.ac.uk/spm).The images were then transferred to Montreal Neurological Institute (MNI) stereotactic space. Subsequently, the normalized images were segmented into GM, White Matter (WM), and Cerebrospinal Fluid (CSF). Then, a nonlinear deformation was applied to the segmented GM images. Finally, the GM images were smoothed with a Gaussian kernel and prepared using resizing procedures with Nibable(nipy.org/nibabel/). We proposed a novel CAD system that uses a 3D CNN that is fed by hand crafted features for detecting biomarkers of MDD structural MRI features. Extracted 3D GM volumes of each subject were used as the inputs to the CAD system which classifies the subject as healthy or MDD. To avoid data leakage in training, the data was split into three non-overlapping parts including training, test, and validation data. In this work,900 subjects are selected from the data and we allocate the 600 subjects to train set and 200 subjects for validation set and 100 for test set. Also both of the healthy and MDD subjects are equal and dataset is balanced. The architecture of the proposed model is shown in Figure 1 [9].

The simulation as performed on the keras (keras.io).

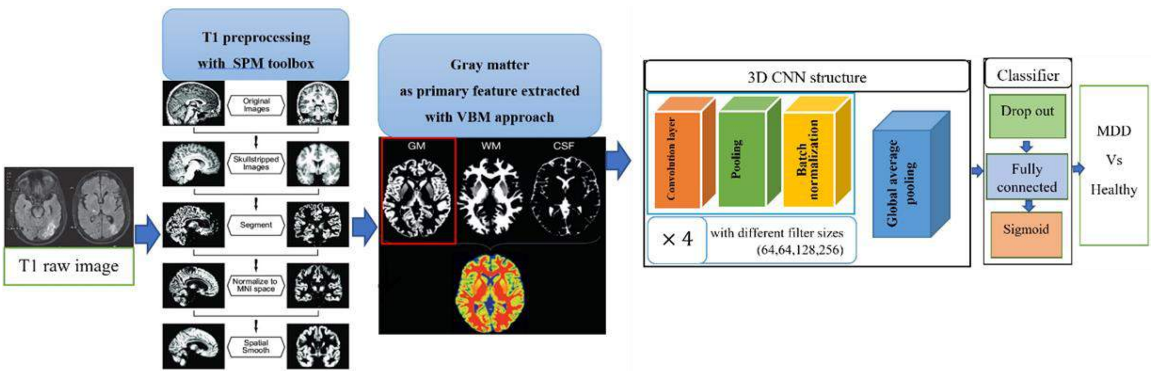

Figure 1. Architecture of the proposed model. At the 3D CNN structure, we use 4 blocks of convolutional layer with different filter size and a average pooling block. Gray matter attributes are given to 3d CNN and finally a fully connected classifies the automatically extracted feature maps. Due to two states of the dataset a nonlinearity block of sigmoid is used

3. Results

The classifier achieved a classification accuracy of 86% with a specificity of 83% and sensitivity of 89% in classifying MDD versus HC. The features that contributed to the classification were gray matter volume and deep-learned results of convolution layers. Figure 2 illustrates the confusion matrix for the classification. The achieved classification accuracy is above the reported accuracy rates by literature focusing on MRI based diagnosis of MDD [10]. Also, code is available in https://github.com/miladalipour99.

4. Conclusion

Using a 3D CNN applied on 3D gray matter volumes and fusing different features, we achieved an accuracy of 86%. The promising results indicates that 3D CNN - based classification can be used for real-world CAD systems in large cohort screening.

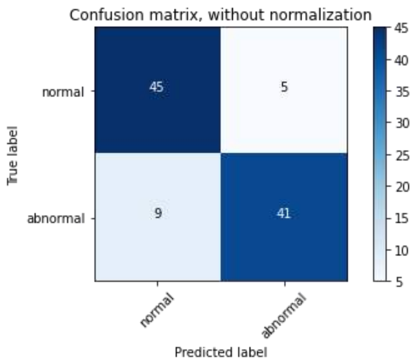

Figure 2. confusion matrix of classification

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A Meta Analysis of the Effects of Repetitive Transcranial Magnetic Stimulation on Aphasia Rehabilitation in Stroke Patients

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Abstract

Aphasia is a complex language and communication disorder that can occur after a stroke as a result of damage to the language centres of the brain. Evidence suggests repetitive Transcranial Magnetic Stimulation (rTMS) can significantly improve language outcomes in patients with aphasia. In this study, we conducted a systematic review and meta-analyses of rTMS treatment studies in patients with aphasia. Eight electronic databases (PubMed, Medline, Embase, Scopus, ScienceDirect, Cochrane Central Register of Controlled Trials, Journals@Ovid, and clinicaltrials.gov) were searched for articles. Relevant studies were further evaluated and studies met inclusion criteria were reviewed. We included studies if were: randomized controlled blinded clinical trials, meta-analyses or crossover designs of rTMS alone or with speech therapy or any other therapy tested with rTMS. Standard mean difference for changes in picture naming accuracy was estimated. Literature search yielded 423 studies. Fifty articles were further evaluated to be included. Eleven met all inclusion criteria and were chosen for review. Eleven eligible studies involving 242 stroke patients were identified in this meta-analysis. Further analyses demonstrated prominent effects for the naming subtest (SMD = 1.26, 95% CI = 0.80 to 1.71, P=0.01), with heterogeneity (I2 = 69.101%). The meta-analysis continued to show that there was a statistically significant effect of rTMS compared with sham rTMS on the severity of aphasia. None of the patients from the 11 included articles reported adverse effects from rTMS.

There are some strong studies evaluating the efficacy of rTMS in stroke patients but further research is required to fully establish the usefulness of this treatment. This meta-analysis indicates a clinically positive effect of rTMS with or without speech and language therapy for patients with aphasia following stroke in overall language function. Moreover, the treatment of low-frequency (1 Hz) rTMS for patients with aphasia after stroke was safe.

Keywords: repetitive Transcranial Magnetic Stimulation; Neurorehabilitation; Stroke; Aphasia; Language Recovery.

1. Introduction

In recent years, advances in cognitive neuroscience, neurorehabilitation research, and neuroimaging have led to dramatic advances in our understanding of how the brain reorganizes in the setting of stroke and other forms of focal brain injury. These discoveries have, in turn, paved the way for the use of noninvasive neuromodulation technologies, such as Transcranial Magnetic Stimulation (TMS), which can potentially be employed to create focal, persistent neuroplastic changes in brain activity. Stroke-related aphasia is one of the most common consequences of cerebrovascular diseases and occurs in one-third of acute or subacute stroke patients [1]. Aphasia can incapacitate all modes of human communication, including language production, language comprehension, reading, and writing. Aphasia is a frequent sequel of stroke with serious effects on the patient's autonomy and quality of life and requires speech and language therapy by which significant improvements of language and communication deficits can be achieved if administered intensively and for prolonged periods [2,3].

Studies in patients with aphasia involving TMS have reported improvement in a variety of language functions, ranging from better accuracy in picture naming [4-8] to self-perceived improvement among patients in the ability to communicate after TMS [9,10]. This article presents an overview of repetitive transcranial magnetic stimulation (rTMS) where this new technology is explained in relationship to treatment of aphasia. The present systematic review and meta-analysis study aimed to investigate the efficacy of rTMS on aphasia rehabilitation in aphasic patients with stroke.

2. Materials and Methods

One reviewer (MGH) carried out independent literature searches to identify potential treatment studies of rTMS in post-stroke aphasia. The following databases were used to conduct electronic searches to identify relevant studies: PubMed, Medline, Embase, Scopus, ScienceDirect, Cochrane Central Register of Controlled Trials, Journals@Ovid, and clinicaltrials.gov. The search terms were "aphasia OR language disorders OR anomia OR linguistic disorders AND stroke AND transcranial magnetic stimulation". The searches were limited to human studies written in English and published between January 1960 and January 2020.

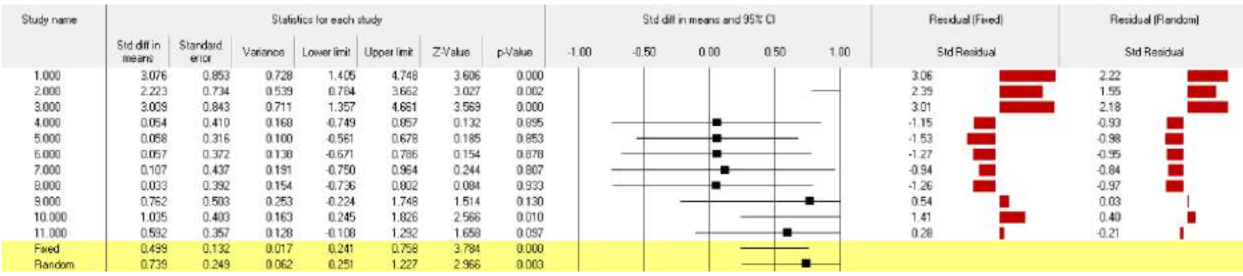
We included all studies that carried out treatment using rTMS in stroke patients with aphasia, regardless of the trial (or experimental) design of the study. Studies that implemented between-subject or Randomized Controlled (RCT) design, cross-over trials, and within-subject or pre-post trials were all included. Since picture naming is one of the most frequently used batteries for assessing improvement in language abilities after treatment with rTMS [11], we included studies that reported raw scores or changes in picture naming accuracy. Picture naming accuracy reflects the number of correctly articulated names of objects, displayed to patients as line drawings [12]. In cross-over trials, the same subjects undergo both the sham and the real treatment and changes in accuracy relative to baseline are compared between conditions. In incomplete crossover studies, a subset of subjects receives only real stimulation, while a subset receives sham stimulation first followed with real stimulation. The comparison is within-subject in the former subset (i.e., assessing post-stimulation performance relative to subject's baseline performance). The comparison in the latter subset is also within-subject but it is relative to subject's performance after the sham stimulation. Comprehensive MetaAnalysis (CMA) Software version 3 (Biostat Inc., USA) was used to conduct this meta-analysis.

3. Results

3.1. Characteristics of the Included Studies

We identified 423 unique records from the database searches. After screening the titles and abstracts, we excluded records and obtained the full texts of the remaining 29 articles. After further assessment, 11 studies [4,8,13-21] fulfilled the inclusion criteria (Figure 1). Some studies have been completed but have not been published, and some of them are ongoing, but we have been unable to obtain unpublished data. Eleven studies involving a total of 301 participants were included. All studies investigated the effect of rTMS versus sham rTMS. Six trials explored the effect of rTMS combined with speech and language therapy. A total of 301 participants were randomized across eleven randomized comparisons that contrasted real rTMS with sham rTMS. The mean patient age reported in the eleven trials was 63.13 years. All participants suffered from ischemic infarct within the left or right middle cerebral artery territory. Some of patients were right-handed and some of them were left-handed.

Trials indicated the length of time elapsed since the participants had experienced the onset of their aphasia; the widest time range post-onset was 24 to 72 months [22]. The shortest mean length of time since the onset of the participants' aphasia was 28 days.



Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Residual (Fixed) Std Residual	Residual (Random) Std Residual
1.000	3.076	0.853	0.728	1.405	4.748	3.606	0.000	3.06	2.22
2.000	2.223	0.734	0.539	0.784	3.662	3.027	0.002	2.39	1.55
3.000	3.009	0.843	0.711	1.357	4.661	3.569	0.000	3.01	2.18
4.000	0.054	0.410	0.168	-0.749	0.857	0.132	0.895	-1.15	-0.93
5.000	0.058	0.316	0.100	-0.561	0.678	0.185	0.853	-1.53	-0.98
6.000	0.057	0.372	0.138	-0.671	0.786	0.154	0.878	-1.27	-0.95
7.000	0.107	0.437	0.191	-0.750	0.964	0.244	0.807	-0.94	-0.84
8.000	0.033	0.392	0.154	-0.736	0.802	0.084	0.933	-1.26	-0.97
9.000	0.762	0.503	0.253	-0.224	1.748	1.514	0.130	0.54	0.03
10.000	1.035	0.403	0.163	0.245	1.826	2.566	0.010	1.41	0.40
11.000	0.592	0.357	0.128	-0.108	1.292	1.658	0.097	0.28	-0.21
Fixed	0.499	0.132	0.017	0.241	0.758	3.784	0.000		
Random	0.739	0.249	0.062	0.251	1.227	2.966	0.003		

Figure 1. Meta-analysis of the eleven articles

Using the 6-point Aphasia Severity Rating Scale (ASRS), the severity of aphasia was reported by 3 trials. The therapeutic procedures used in five trials consisted of rTMS sessions and specific language training. In these trials, immediately after finishing the rTMS treatment, both the experimental and control participants underwent speech and language therapy sessions for 45 minutes. The patients of the other study were only treated with real rTMS or sham rTMS sessions. In all trials, rTMS was performed with a Magstim Rapid stimulator (Magstim Company, Whitland, UK) equipped with an air-cooled figure-of-eight coil (each loop measured 70 mm in diameter). All trials used 1 Hz rTMS with an intensity equaling 90% of the daily defined individual resting motor threshold.

The treatment and sham stimulation sessions of eleven trials were conducted 20 min per day, for 10 days a 2-week period, whereas those of two trials were performed for a 3-week period. All included trials targeted the triangular part of the right Inferior Frontal Gyrus (IFG). The sham stimulation condition of three studies was performed with an air-cooled sham coil that looks and sounds similar to the discharge of real TMS coil. The sham coil was placed at the same site on the scalp and with the same stimulation parameters used for the real rTMS procedure. The other eight studies used the same coil used the real rTMS placed over the vertex. All trials measured language outcomes. In those cases in which the data for this comparison were available, they are presented below in relation to the expressive language.

3.2. Primary Outcomes Severity of Aphasia Impairment

All trials compared the active rTMS group with a group that received sham rTMS by measuring the severity of each participant's aphasia impairment. The language assessment batteries included the Aachen Aphasia Test (AAT) global scores and the Boston Diagnostic Aphasia Examination (BDAE). We obtained statistical summary data suitable for inclusion within a metaanalysis from these eleven trials.

The Standardized Mean Difference (SMD) measure of effect is used when studies report efficacy in terms of a continuous measurement, such as a score on a pain-intensity rating scale. The SMD is also known as Cohen's d. The SMD is sometimes used interchangeably with the term "effect size." Generally, the comparator is a placebo, but a similar calculation can be used if the comparator is an alternative active treatment.

Pooling the available data using SMDs, we observed heterogeneity (I 2= 69.101 %, P= 0.001). The data were pooled using a fixed and random -effects model. There was a significant difference between the real rTMS groups and sham rTMS groups

(SMD = 1.26, 95% CI = 0.80 to 1.71, P=0.01). Sensitivity analyses were conducted after omitting Heiss WD's study, which has an unclear risk of allocation concealment bias and a high risk of incomplete outcome bias (SMD = 1.04, 95% CI = 0.52 to 1.56, P=0.01). The meta-analysis continued to show that there was a statistically significant effect of rTMS compared with sham rTMS on the severity of aphasia.

3.3. Secondary Outcomes

Adverse effects: None of the eleven trials reported any adverse effects.

4. Conclusion

This meta-analysis indicates a clinically positive effect of rTMS with or without Speech and Language Therapy (SLT) for patients with aphasia following stroke in overall language function and expressive language, including naming, repetition, writing, and comprehension. Low-frequency (1 Hz) rTMS over the unaffected hemisphere is effective and compatible with the concept of interhemispheric inhibition. Moreover, the treatment of 1 Hz rTMS for patients with aphasia after stroke was safe. No adverse effects were observed in patients in all eleven trials. However, further well-designed studies are necessary to determine the effect duration and long-term impact.

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fNIRS Signals Classification with Ensemble Learning Classifiers

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Abstract

Brain-Computer-Interface (BCIs) is designed to interpret brain signals from the brain and communicate between a physical device and the human brain, much like assisting patients with motor disabilities. In this study, fNIRS, a new brain imaging technique based on measuring brain hemodynamic response on the cortical surface used in various neuroscience and neuro-engineering studies, has been used to classify 30 subjects' unilateral finger and foot-tapping in the three classes of left- and right-hand movement and foot tapping. The objective is the classification of the three-class functional Near-Infrared Spectroscopy (fNIRS) signals. We have used the classification methods for each of the three classes one at a time, followed by the voting method as an ensemble learning approach.

The results given in the form of an average for all subjects with no ensemble learning reached 64.9±16.2%, whereas that with the ensemble learning reached 69±15.5%. These results show not only an improvement in the accuracy, but also it shows a decrease in the standard deviation, suggesting that the classification model gets optimal by decreasing the variance of the predictions.

Keywords: Brain-Computer-Interface; Brain-Computer-Interface; Ensemble Learning; Classification functional Near-Infrared Spectroscopy Signal; Support Vector Machine; k Nearest Neighbor; Naïve Bays.

1. Introduction

BCIs are designed to link and communicate between a physical device and the human brain by acquisition and interpret brain signals from the brain in other words like a bypassing and converting system from peripheral nerves and muscles to control commands, for example, BCIs can provide assistance system for patients with motor disabilities [1].

One neuroimaging system's goals are to monitor brain activity achieved by fNIRS, a new brain imaging technique based on measuring brain hemodynamic response on the cortical surface and used in various neuroscience and neuro-engineering studies. It is increasingly being used to measure variations of oxygenated (Hbo) non-invasively and deoxygenates hemoglobin (HbR) changes by optical absorption devices based on modified Beer-Lambert law [2, 3].

Advanced neuroimaging techniques, including EEG and fNIRS, are the most portable, low cost, silent, easy to handle, and compared to fMRI, has higher temporal sampling rate and also spatial resolution [1]. One of the most important advantages compared with other methods like Electroencephalogram (EEG) is that fNIRS has better tolerance to motion artifacts that is less sensitive to head movement and experimental flexibility thus, based on advantages and fewer limitations on subjects, especially allowing variance in motion artifacts it has wide usages in patients' groups like infants and neurological patients unlike inconvenient methods like functional Magnetic Resonance Imaging (fMRI).

fNIRS also has several limitations like depth sensitivity (approximately 1.5cm) and coverage area, and this technology is not suitable for detecting deeper brain structures and cortical neuronal systems and also challenging to determine the cortical region of signal source a coupled or hybrid EEG/fNIRS modalities benefit both systems like higher temporal resolution because of EEG consequently better results in classification and then control commands in BCIs.

1.1. Noises in fNIRS

fNIRS signals contain various types of noise, including instrumental noise due to interfaces in a surrounding environment like external light and devices, experimental noise, motion artifacts, and contact pressure between scalp and optode that would change due to movement and physiological noise [4]. This paper aims to classify fNIRS signals concerning ensemble methods that combine classification models like Support Vector Machines (SVM), Linear Discriminant Analysis (LDA), and k Nearest Neighbor (kNN).

The paper has organized as follow the data collection, preprocessing, classification, and validation procedure.

2. Materials and Methods

The objective of this study is the classification of the three-class fNIRS signals. We proposed a method, as depicted in the flowchart of Figure 1. The proposed

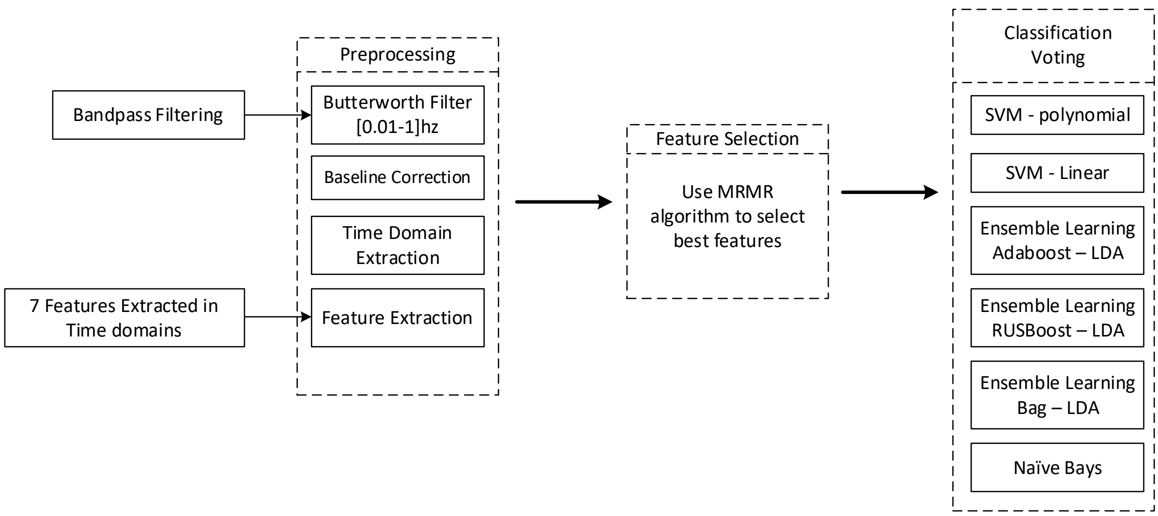

Figure 1. flowchart of proposed method

method consists of preprocessing, feature selection, and classification that uses an ensemble method.

2.1. fNIRS Dataset

A freely available dataset consisting of 30 volunteers (29 right-handed, 17 males in the 23.4±2.5 years old range) participated in this study [5]. No volunteer reported psychiatric or neurological disorders that could affect the experiment [5]. The fNIRS data were recorded by a three-wavelength continuous-time multi-channel fNIRS system consisting of eight light sources (Tx) and eight detectors (Rx). Each of the four Tx and Rx electrodes was placed around the C3 on the left hemisphere, and similarly, the same number of electrodes were placed around the C4 on the right hemisphere. The experiment included three separate sessions with 25 trials for each task, and a trial includes an introduction period (2 sec), a task period (10 sec), and an inter-trial break (17-19 sec). Every trial is related to the Right-Hand filter Tapping (RHT), Left-Hand filter Tapping (LHT), and Foot-Tapping (FT) [5].

2.2. Preprocessing

The fNIRS signal is based on Beer-Lambert law [2] which concerns optical attenuation of biological materials. It consists of oxygenated as well as deoxygenated hemoglobin wavelengths (ΔHbo and ΔHbR, respectively), and to analyze these signals and classification tasks by segmentation thereof, the task is done 1sec before the onset to 4 sec after, and a 3D matrix with time, channels, and trials are obtained [6].

2.3. Signal Filtering

The fNIRS signal consists of both ΔHbO and ΔHbR regarding artifacts and heartbeat and even respiration in trials. For the purpose of signal analysis, a bandpass Butterworth filter with degree 3 and frequency domain [0.01,0.2] has been designed, with every trial filtered with zero phase delay (Figure 2).

2.4. Baseline Correction

An essential part of preprocessing fNIRS signals that must be performed is the baseline correction. If this part is disregarded, a decrease in accuracy in the baseline analysis may result. This preprocessing is performed by contracting the average of the start point of the trial to the onset point, which is applied to every trial after filtering [7].

2.5. Feature Extraction

To extract the signal features, various means of representations exist, such as those of the temporal (time), frequency, and time-frequency, but in the fNIRS signals analysis, only temporal features have been extracted for every trial [8]. Regardless of which class each belongs to, the set of the features extracted are slope, mean, max, kurtosis, and power [9].

2.6. Feature Selection

As extracted Features set is a high dimensional matrix that causes complexity in classification and aims to reach the best subset of features that help better understanding data and effect of the curse of dimensionality [10] should implement a feature selection algorithm.

There are two main feature selection methods, wrapper, and filter method [11], which researches frequently profited by one of these algorithms. Wrapper method analysis is a subset feature combination and is time computation consuming but filter methods, analysis every feature independently, then fast and lower computation consuming as advantages.

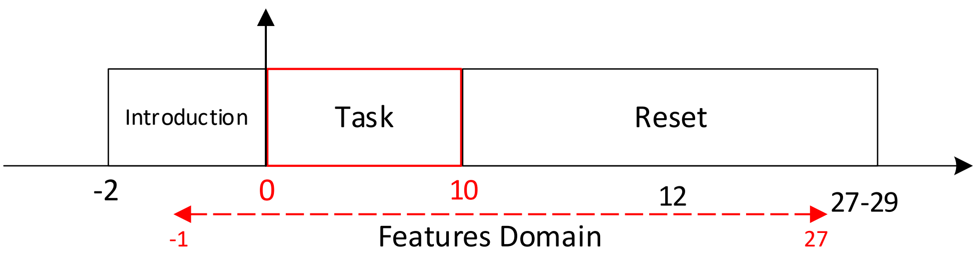

Figure 2. Structure of a single trial

In this study, Minimum Redundancy Maximum Relevance (MRMR) has been implemented to discriminate if a feature in the “feature set” is significant or needs to reject the null hypothesis [12].

2.7. Classification

In this study, voting methods have been implemented, with each trained classifier predicting results, and in the second layer, the most dominant predicts are taken as the final predict win. It is noted that the result from each classifier is based on the overall performance.

In other words, each classifier may have a different weight. The classifier consists of two main layers: the first layer is made up of eight strong learner classifiers, and the second layer possesses a simple, preferably linear classifier such as the logistic regression or single-layer perceptron through a stacking and voting algorithm which selects dominant votes, as a result, also known as the meta classifier [13].

It consists of two main layers: the first layer consists of more than one complex or simple in this study eight classifiers, strong learner, and the second layer a simple, preferably a linear classifier like logistic regression or single-layer perceptron in stacking and in voting an algorithm which selects dominant votes as a result, also called meta classifier.

The first layer employs five classifiers as follows: 1) KNN with k=15, where this classifier itself is trained using Adaboost ensemble classification with 190 models, 2) SVM with the linear and polynomial kernel, 3) LDA with the diagonal kernel trained with AdaBoost, robust boost, and bagging ensemble learning method, 4) naïve Bayes classifier, and 5) decision tree with lp boost. For each of these classifiers, as many as 190 models were used. The results of the two layers have been taken in a voting manner, and the final results were reported as follows. finally, results have been voted, and final results have reported.

3. Results

In classification problems, accuracy as a statistical measurement for classification performance has been proposed, and results in Figure 3 demonstrate that we can achieve higher accuracy within voting ensemble learning.

The average accuracy for the 30 subjects is 64.94 ± 16.2% and 69 ± 15.5% without and with ensemble learning, respectively. This result was evaluated in three classes with 10-fold cross-validation, and the accuracy of each class is higher than the nominal chance-based 33.33%. Moreover, we conclude that classification becomes optimal by a decrease in the standard deviation, especially in BCI systems, leading to much better results.

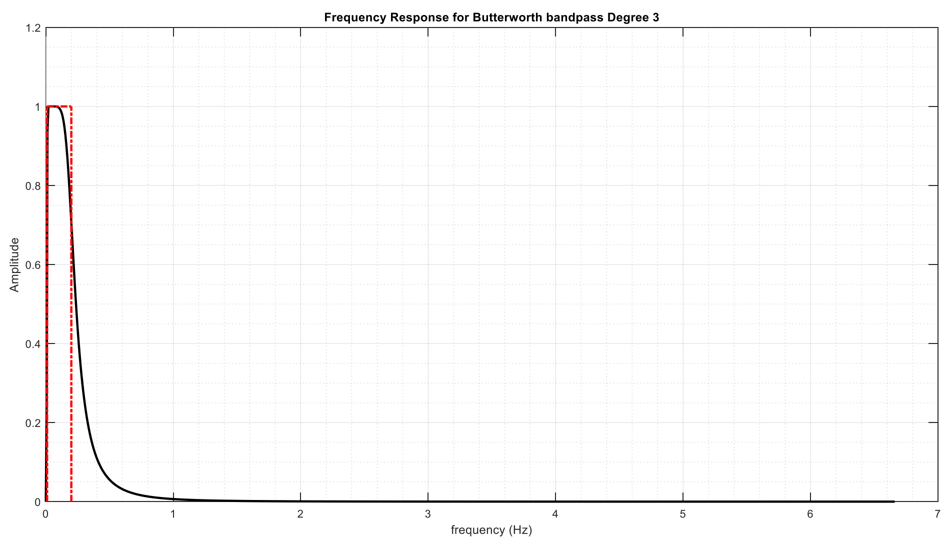

Figure 3. Butterworth designed filter domain: (0.02 0.1) hz, sampling rate: 13.33hz

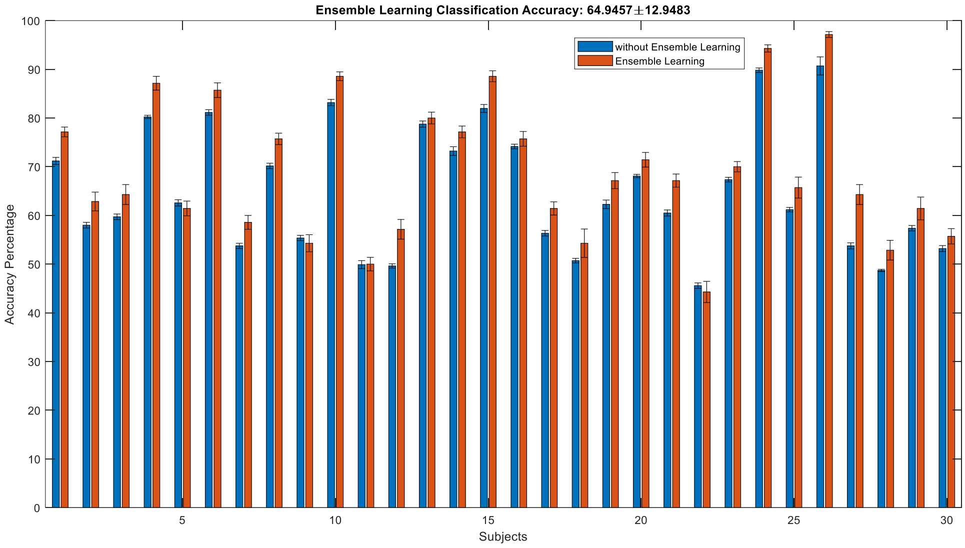

Figure 4. Classification accuracy with or without implementing ensemble learning

4. Conclusion

In this study, to analyze and as a consequence, classification of fNIRS signals a frontier method implements aim to achieve higher classification performance and optimize variance of classification or model robustness and also computation speed which is challenging in real-time BCIs.

Better results in both train and test data that demonstrate the performance of BCI systems, including control of healthy and patient peoples with fNIRS signal, became more effectively stable in both online and offline BCI systems.

Also, as a future study, the hybrid system of EEG and fNIRS system yields higher temporal and spatial resolution and compensates each one's weakness then possibly used in clinical research can detect with better performance in BCIs.

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Detecting ADHD Children Based on Brain Functional Connectivity Using MEG Signals

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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurological disorder in childhood. The apparent symptoms of this disorder include a significant lack of attention, impulsivity, and hyperactivity. As this disorder causes social incompatibility, accurate and early diagnosis can help to control the problems. Magnetoencephalogram (MEG) signals may be an efficient technique for diagnosing ADHD due to being non-invasive and having a high temporal and spatial resolution.

In this paper, we proposed a method to detect ADHD MEG signals recorded in open eyes resting-state condition. Our method measured the Coherence (COH) values between MEG sensors in conventional MEG frequency bands as features. Afterward, the most discriminative features selected by the Neighborhood Component Analysis (NCA) were fed to the Support Vector Machine (SVM) with Radial-Based Function (RBF) as a classifier. Using Leave-One-Subject-Out Cross-Validation (LOSO-CV), The best results using single-band COH values reached the highest accuracy of 91.1% and belonged to delta-band couplings. However, when we used the fusion of COH values of all frequency bands, we got a slight improvement in detection accuracy to 92.7%. The proposed method led to promising performance criteria compared with previous studies on ADHD diagnosis using resting-state MEG data.

Keywords: Computer-Aided Diagnosis System; Attention Deficit Hyperactivity Disorder; Magnetoencephalogram; Resting-State; Coherence.

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1. Introduction

ADHD is the most prevalent neurobehavioral disorder in school-age children [1]. The prevalence of ADHD worldwide in children is estimated at 4% [2]. Impulsivity, inattentiveness, and hyperactivity are the most important symptoms of ADHD. There is no effective biomarker yet to diagnose ADHD accurately. So, the diagnosis is entirely dependent on clinical tests.

Nowadays, using MEG techniques is shown to be beneficial in diagnosing ADHD. The MEG is an efficient functional neuroimaging modality due to being non-invasive and having a high temporal and spatial resolution. MEG records the magnetic fields mainly generated by the cortical activity of the brain. It is worth mentioning that limited research has been done using the MEG signals to detect ADHD, and beyond them, COH has not yet been used for the diagnosis of ADHD using MEG signals.

The objective of the proposed study is to detect ADHD using the straightforward, functional connectivity measure of COH. For this purpose, COH was calculated in conventional MEG frequency bands. We wanted to test whether the COH values of sensor-space MEG signals between two different groups show diagnostic ADHD-related patterns. We did this by feeding the most discriminative coherence values to a classifier.

Recognizing the difference between normal and abnormal brain functional connectivity measured by COH would lead to the identification of ADHD. Our ultimate goal in this paper is to propose a Computer-Aided Diagnosis System (CADS) to detect ADHD.

2. Materials and Methods

2.1. Data Set

In this study, we used the Open MEG Archive (OMEGA), a free MEG dataset provided by the McConnell Brain Imaging Centre of the Montreal Neurological Institute and the Université de Montréal [3]. The data consist of the resting-state MEG signals of 25 healthy participants (age: 20.6 ± 2.35 years; mean ± standard deviation) and 25 patients with ADHD (age: 20.6 ± 3.04 years; mean ± standard deviation), acquired for about 5 minutes at a sampling frequency of 2400 Hz for each subject.

2.2. Proposed Method

At first, for preprocessing the data, a 60 Hz notch filter was applied to eliminate powerline signal contamination. Then physiological artifacts were removed using both visual inspection and Signal-Space Projectors (SSP) [3]. After all, signals were divided into artifact-free epochs of 5s duration (12000 time samples), and an average of 7 epochs was extracted from the MEG signals of each subject. Moreover, COH was used to extract features. It provides information about the degree of coupling between two signals in a specific frequency band [4]. Then Neighborhood Component Analysis (NCA) was used as a nonparametric and supervised feature selection algorithm [5]. After all, to detect ADHD from healthy subjects, the SVM with RBF was used. Furthermore, we used LOSO-CV to evaluate our results which investigate the subject-to-subject variation and eliminate the effect of autocorrelation in time-series data of a single subject. The average performance of all subjects would be reported as the final performance of the proposed method.

3. Results

The proposed method was evaluated on a binary dataset using LOSO-CV. In this paper, we used the COH of 269 MEG channels in conventional MEG frequency bands. First, the COH values of each frequency band were extracted as feature vectors separately. Once more, the fusion of these five feature sets was used in order to achieve probably better performance. In all cases, the most discriminative features were selected using the NCA algorithm. Afterward, the selected features were fed to SVM. In order to evaluate the performance of the classification algorithm, accuracy, sensitivity, and specificity were computed and provided in Table 1.

As seen, we reached the best detection accuracy using the delta band among the other frequency bands in the single-band experiments. It means that ADHD disorganized linear functional couplings in the delta frequency band at a higher level. While concatenating all five feature sets belonging to five different frequency bands, the average accuracy of the algorithm improved

Table 1. Classification performance criteria obtained SVM (kernel function: RBF) as the classifier (mean% ± std%)

Bands (Hz)	Accuracy	Sensitivity	Specificity
δ (0.3-4)	91.1 ± 1.4	94.4 ± 1.1	87.8 ± 1.6
θ (4-8)	78.8 ± 2.1	85.5 ± 1.9	72.4 ± 2
α (8-12)	74.6 ± 2.5	73.9 ± 2	75.2 ± 2.8
β (12-30)	81.7 ± 2.4	79.1 ± 2.6	84.1 ± 2.2
γ (30-50)	86.1 ± 2	89.3 ± 1.7	82.9 ± 2.3
All bands	**92.7 ± 1.6**	**93.6 ± 1.3**	**91.9 ± 1.9**

from 91.1% to 92.7%. The best results reached 92.7% accuracy, 93.6% sensitivity, and 91.9%, which is so better compared to what had been done before. Thus our proposed algorithm may be considered more reliable than the previous methods and seems to be a promising step toward designing an accurate CADS for ADHD.

4. Conclusion

In this paper, the detection of ADHD using MEG signals was performed by computing the Coherence value in sensor space in different frequency bands.

The obtained results showed significant discrimination between ADHD patients and controls, which led to the high accuracy of the detection algorithm. It is noteworthy that fine-tuning in the proposed algorithm may provide us with better results in predicting ADHD. Moreover, different classifiers, feature extraction, and selection methods can be studied to obtain better results.

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Dynamic Functional Connectivity in Major Depressive Disorder with Suicidal Thoughts: An fMRI Study

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Abstract

Precise characterization of psychiatric disorders is a major stream in applied neuroscience. Major Depressive Disorder (MDD) is one of these disorders that may lead to suicide ideation and ends to individual's death. We used functional Magnetic Resonance Imaging (fMRI) in order to study the impairments in the brain functional connectivity of 14 MDD patients with suicide thoughts. Spatial Independent Component Analysis (ICA) (COMBI algorithm) was used to extract independent components and brain networks of resting state fMRI data from these patients. As a measure of functional network connectivity, mutual information was calculated between each pair of resulted spatial maps. Then Independent Vector Analysis (IVA-GL algorithm was applied to the windowed time series and Mountain Standard Time (MST) used as stability measurement. Significant between network connectivity observed in Executive Control Network (ECN), Default Mode Network (DMN), Salience Network (SN), Basal Ganglia and visuospatial networks.

Results are consistent with previous studies about activated networks in MDDs with suicidal thoughts.

Keywords: Functional Connectivity; Independent Vector Analysis; Major Depressive Disorder; Suicidal Thought.

1. Introduction

Major depressive disorder induces dysfunctioning in mood, recognition, psychomotor activity and neurovegetative functions [1]. Suicide ideation among MDD patients leads to suicide attempting with an occurrence rate of 16.6 percent. Single men, students and married women are more vulnerable to such attempts [2]. Resting state functional Magnetic Resonance Imaging (rsfMRI) is a popular approach to study the brain functional organization. Applying ICA analysis on rsfMRI data can separate the brain networks as the sources of Blood Oxygenation Level Dependent (BOLD) signal from noise fluctuations [3]. Despite ICA, IVA can effectively address the permutation problem in group level fMRI analysis [4]. Connectivity calculation with different approaches after applying ICA is common. In connectivity analysis, Dynamic Functional Connectivity (DFC) is better than static functional connectivity to study the brain function. It is illustrated that DFC can demonstrate alterations in macroscopic neural activity that reveals some important aspects of behavior and cognition [5]. DFC was able to distinguish between normal control and patients with schizophrenia [6]. As having knowledge about the recent studies, we decided to find all the independent resting state networks in MDDs with Suicide Ideation (SI) and strength of negative or positive connectivity between them.

2. Materials and Methods

2.1. Participants

Participants had major depressive disorder with suicide ideation. 14 females aged between 20 to 50 (30.31 ± 2.42; years old) were referred to this study by Atie Derakhshan Zehn clinic Tehran (https://atiehclinic.com/). In a separate validation the scale for suicide ideation (SSI) and Hamilton were evaluated for these individuals. All participants have the minimum criteria (SSI > 6 and Hamilton > 14).

2.2. Data Acquisition

fMRI data of all subjects were acquired at National Brain Mapping Lab (NMBL) Tehran, Iran. Almost 8 minutes of resting state fMRI data were acquired for each participants using an Echo Planar Imaging (EPI) pulse sequence with TR = 2000ms, TE=30 ms, flip angle= 80 deg, voxel size =3×3×4 mm^3 and Field Of View (FOV) = 240 × 240 mm^2. A set of anatomical T1 weighted images were also acquired for each individual using the Magnetization-Prepared Rapid Acquisition with Gradient Echo (MPRAGE) pulse sequence, with TR = 1810ms, TE = 3.45 ms, TI = 1100 ms, flip angle =7 deg, voxel size = 1×1×1 mm^3 and FOV =264 ×264 mm^2.

2.3. Data Analysis

The Preprocessing pipeline was implemented by DPARSF toolbox [7] (http://rfmri.org/dpabi). We followed the DPARSF usual procedure, although we avoid of filtering and smoothing, in order to get a better ICA analysis at the next stage. After pre-processing the data, we used a powerful toolbox for group ICA and IVA analysis named Group ICA\IVA fMRI Toolbox (GIFT) (https://trendscenter.org/software/gift/) [8]. In this software package the Combi algorithm as a promising method for ICA was employed to separate components efficiently [9]. It is a combination between weights-adjusted second-order blind identification and efficient Fast-ICA. Independent Vector Analysis was applied to time series data after dividing the time series into smaller parts. Then IVA maps from individual subjects were back-reconstructed from the aggregate mixing matrix. At the last stage, mutual information between all possible pairs of spatial components calculated.

3. Results

After applying ICA to the data, 22 of 30 components that extracted form data was chosen by visual inspection the location of component in the brain, power spectrum and fractional Amplitude of Low-Frequency Fluctuations (fALFF) values. Spatial dynamic Functional Network Connectivity (dFNC) hierarchy calculated by information extracted from normal Spatial dFNC and ICA parameters information at the first step. Connectivity between components was meaningfully overlayed with previous studies. The connectivity maps have illustrated in Figure 1. These maps include: Anterior cranial base (S-N), auditory and basal ganglia, in the top row, Dorsal default-Mode Network (DMN), Language and Left Executive Control Network (ECN), in the second row, precuneus, primary visual and right ECN, in

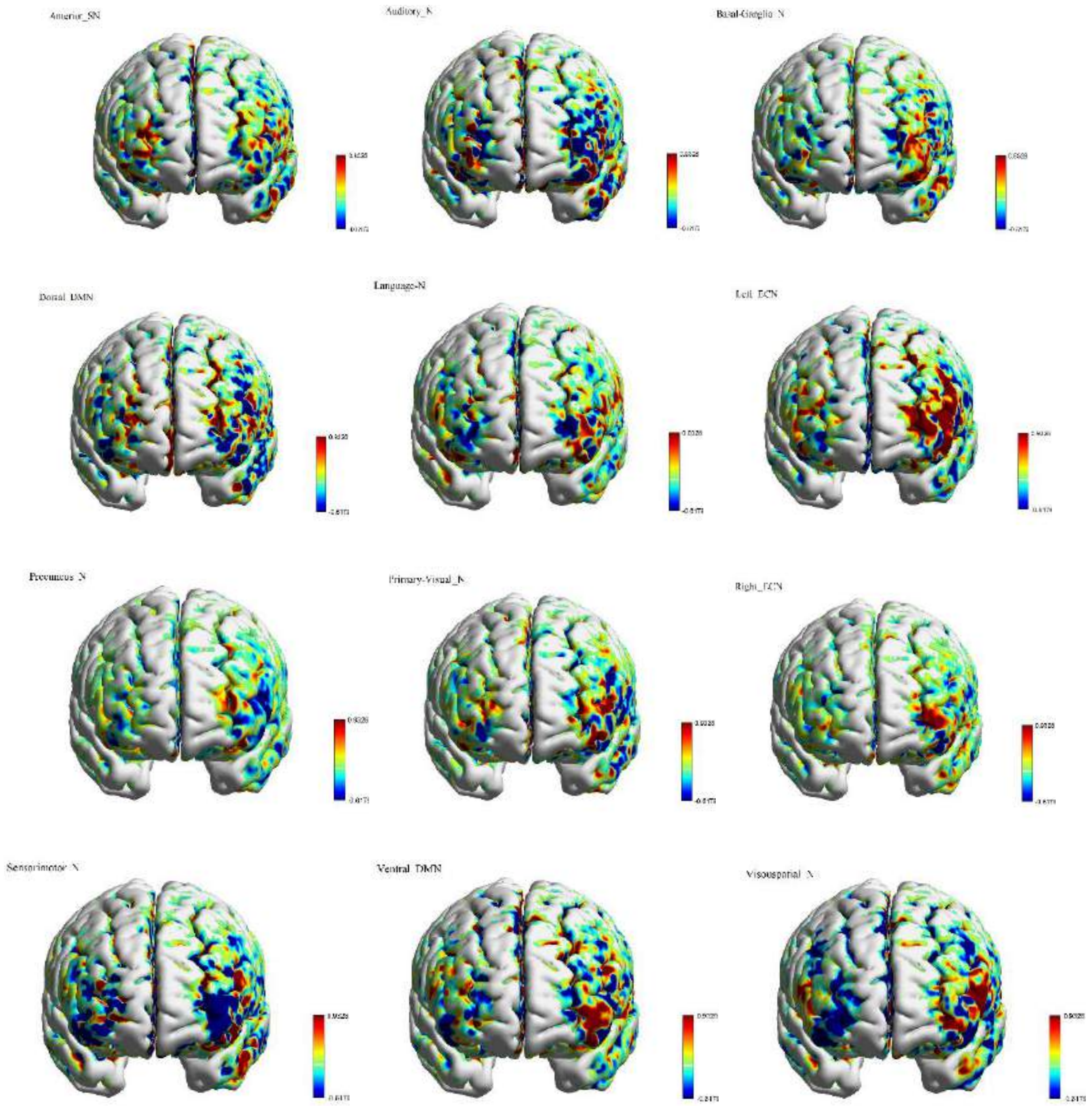

Figure 1. Spatial dynamic connectivity maps for 12 important brain networks that extracted form fMRI data

the third row, also sensorimotor, ventral DMN and visuospatial I the bottom raw of Figure 1. These networks are consistent with previous studies on MDD patients with suicide thoughts [10, 11, 12]. Although Right ECN identified as an important network that has significant information flow to other recognized networks, but hasn't mentioned as crucial area in the brain that has information transition, in previous studies. In another study we compared some connectivity measures and results showed connection between right ECN and some networks that is mentioned below.

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Toward Applicable EEG-Based Drowsiness Detection Systems

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Abstract

Drowsy driving is a serious issue which accounts for a great portion of accidents and has attracted substantial research attention in recent years. Among different measures for Drowsiness Detection (DD), Electroencephalography (EEG) signals are shown to be a reliable measure for human awareness and allow early detection of drowsiness. Unfortunately, there is no comprehensive study showing the applicability of DD systems in real-life scenarios. Therefore, we aimed to investigate the applicability of EEG-based DD systems through the following criteria: being less intrusive, accuracy of detection, and algorithms used for practical implementation.

In this regard, we included 35 documented studies which utilized consumer-grade EEG headsets, namely, Muse, Neurosky, and Emotive, for drowsiness detection. The highest detection accuracy, 99.1%, was achieved by Muse headset, among the studies which reported a detection accuracy. Spectral features were widely used while being relatively simpler than chaotic features for real-time calculations and more informative in comparison to statistical features. This study sheds light on the current status of DD systems and paves the way for future designs of DD systems functional in industry.

Keywords: Drowsiness Detection; Electroencephalography Signals; Consumer-Grade Headsets; Device Intrusiveness.

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1. Introduction

Drowsiness is a transition from alertness towards sleep, causing degradation in performance. Approximately 20 to 40% of total annual accidents in Iran are due to drowsiness, and there are records of up to 60% of accidents being related to drowsiness in one holiday season. Therefore, a drowsiness detection device is vital for safe driving. Based on Iran's five-year development plan, improving the quality of vehicle safety is a necessity. Researchers have attempted to determine driver drowsiness using the following measures: (1) vehicle-based measures (e. g. steering-wheel sensors); (2) behavioral measures (e. g. eye /head-movement patterns) and (3) physiological measures (e. g. brain/heart/skin electrical responses). Among all measures of drowsiness detections, EEG shows the strongest relation with drowsiness and is capable of predicting drowsiness in a timely manner with higher accuracy [1, 2]. Hence, EEG is widely considered as a reliable measure for drowsiness, fatigue, and performance evaluation [1-4]. However, to reduce the cumbersomeness of EEG-based methods for practical usage, a number of solutions, such as taking advantages of EEG headsets, reducing the number of electrodes, and using hybrid methods (i.e., combining EEG with other easily accessible physiological signals), have been suggested in previous studies. Recently, LaRocco *et al.* [5] conducted a systematic review on low-cost EEG headsets to show the reliability of these headsets in drowsiness detection. However, they integrated the results of studies from other categories (e.g., stress, excitement, meditation, physical fatigue, and distraction detection) with drowsiness detection studies in their assessment.

In this research, we intend to investigate EEG-based drowsiness detection methods and provide some insights on developing a drowsiness detection system applicable for real-life scenarios.

2. Materials and Methods

In this research, we targeted the studies under the category of drowsiness detection which adopted an EEG-based approach and were published from 2010 onwards. We investigated the applicability through the following criteria: being less intrusive, accuracy of detection, and algorithms used for practical implementation. In this regard, we focused on studies which utilized consumer-grade EEG headsets, namely, Muse, Neurosky, and Emotive, for drowsiness detection. Figure 1 shows the common methodology used in EEG-based DD studies.

Due to the risks of drowsy driving in real conditions, data acquisition is usually conducted in driving simulators. Drowsiness detection studies have used a variety of measures to induce drowsiness. Inadequate sleep during the night before the test, data recording at times when people normally feel drowsy (after lunch, midnight, and dawn), avoidance of anti-fatigue drinks, etc., are among the most commonly used strategies. EEG signals recorded during driving can be severely affected by different types of artifacts. Therefore, preprocessing is an inseparable part of the detection algorithms. After removing the artifacts, spectral, temporal, or chaotic features are extracted to be fed to a classifier. However, some of the classifiers, such as convolutional neural networks, do not need predefined features and have the ability to extract features from training data. Based on the discriminative features, classifiers decide whether a period of the signal is recorded under alert or drowsy state, and an alarm system warns the driver if necessary.

3. Results

Considering the search methodology, 35 studies [6–40] which utilized consumer-grade EEG headsets were compared in terms of accuracy of detection, features, and classifiers' type (Figure 2). As shown in this figure, the highest detection accuracy, 99.1%, was achieved by Muse headset, and the second-highest accuracy was gained with Neurosky headset. The figure also demonstrates that most of the surveyed studies used spectral features and shallow classifiers (e.g., Support Vector Machine (SVM) and K-Nearest Neighbor (KNN)) to discriminate alert/drowsy states. It is repeatedly reported

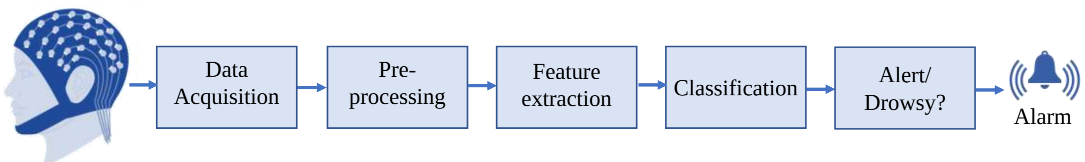

Figure 1. EEG-based drowsiness detection system

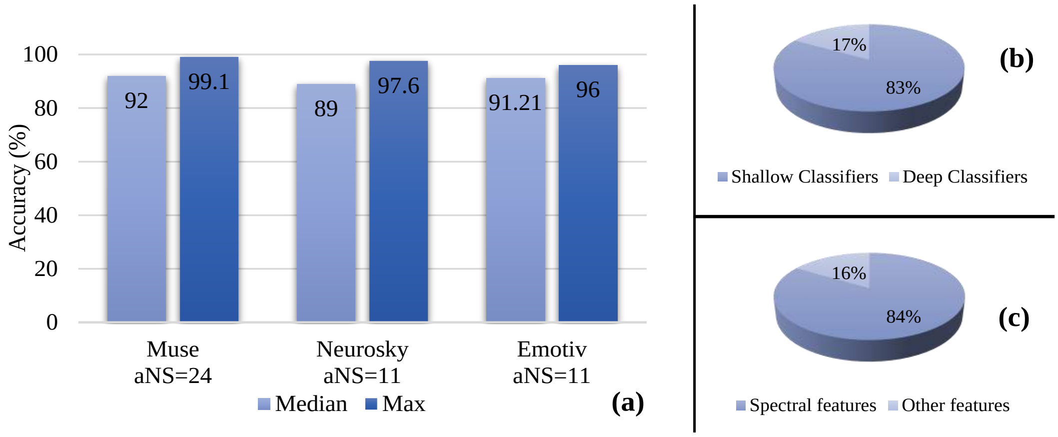

Figure 1. (a) A comparison of performance among three EEG headsets (aNS= average number of subjects), the reported accuracy is based on the studies which reported their detection accuracy: Muse:7/8 (No. of studies which reported accuracy/total no. of studies), Neurosky:7/13, Emotive:8/14; (b) Percentage of studies with shallow and deep classifiers; (c) Percentage of studies using spectral and other features (e.g., chaotic, statistical features, etc.)

that drowsiness is associated with an increase in low-frequency bands power, particularly theta and alpha bands, and a decrease in high-frequency bands, especially beta band; hence these measures are widely used for DD [3, 41– 43].

4. Conclusion

Based on a survey on the previous studies, it can be said that there is a tendency to reduce the cumbersomeness of EEG-based detection systems. In contrast to the earlier studies which were mostly intended to investigate the feasibility of DD with EEG signals and therefore used clinical EEG devices, an increasing number of the recent studies are using consumer-grade EEG headsets for DD.

Although wireless headsets can help increase the applicability of EEG-based systems, significant reduction in the number of electrodes and lower data quality due to improper electrode contact may bring about misleading information, and one should be cautious when using such data. A possible solution for the mentioned limitation is integrating EEG data with other easily accessible physiological signals such as ECG, Photoplethysmogram (PPG), Electromyography (EMG), and ECG Derived Respiration (EDR) (Electrodermal conductivity), some of which are luckily provided in the mentioned headsets.

In summary, using less-intrusive EEG headsets, along with the use of features and classifiers which reduces computational complexity, promises practical implementation of driver drowsiness detection systems.

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Investigating the Effect of Stimulus Type on Electroencephalogram Signal in a Brain-Computer Interface System with Interaction Error

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Abstract

Brain-Computer Interface (BCI) systems can provide a new channel of communication between human thoughts and machines. Although BCI systems exhibit several advantages, they yet have a long road ahead to reach the flawless state. For example, error occurrence is one of the problems in these systems, leading to error-related potentials in the brain signal. In this study, Electroencephalogram (EEG) signals in the condition of system error occurrence are investigated. Since local information of the EEG signal channels alone cannot reveal the secrets of the brain, brain functional connectivity was used as a feature in this research. The findings of this study showed that using brain functional connectivity features along with local features can improve the performance of BCI systems.

Keywords: Electroencephalogram; Brain-Computer Interface; Error-Related Potentials; Brain Functional Connectivity; Statistical Analysis.

1. Introduction

BCI system is regarded as a connective bridge between human thoughts and computers [1, 2]. EEG signals are commonly used in BCI systems, due to their high temporal resolution, simple accessibility and low cost [3]. Today, EEG-based BCI systems can be categorized in three main paradigms including Event-Related Potentials (ERPs)-based BCI, Steady State Visually Evoked Potential (SSVEP)-based BCI and Motor Imagery (MI)-based BCI systems [4]. In Motor Imagery-based BCI Systems (MI-BCI) the participant has to imagine a movement of his\her body limb in a specific direction, and then in the BCI system, depending on the type of motor imagery, a specific command will be executed.

Although a lot of brain information can be obtained via local brain analysis, this information alone cannot reveal all the secrets of the brain. Thus in addition to exploring functional segregation (activation of specific brain areas or local brain regions), functional integration (Coordinated activation of a large number of neural assemblies in various regions of the cerebral cortex on a large scale) must also be considered [5]. In this study, the brain functional connectivity during an MI-based BCI task with 30% of interaction error and different types of stimulation have been studied.

2. Materials and Methods

In this research, brain functional connectivity was studied during a BCI task with interaction error, to this end, 32 channels EEG signals with the sampling frequency of 256 Hz, were recorded from 18 participants while interacting with a BCI system which has interaction error 30% of the time. In this system two types of stimulus were used including visual and tactile ones. Moreover, the Inter-Stimulus-Interval (ISI) was changed during the task in order to assess its effect. More details about this dataset can be found in [6, 7]. Brain connectivity based on magnitude-squared coherence (M-S Coherence) in two conditions was investigated; the first was when there was an error in the system (error case) and the second was when there was no error in the system (correct case). Subsequently, the existence of significant differences in these two cases was investigated using appropriate statistical tests. After detecting the non-normal distribution of the data by the Kolmogorov-Smirnov test, the Wilcoxon signed rank test was used for statistical analysis of M-S Coherence between correct and error classes in the four groups of stimulation type (visual, tactile, tactile- visual (ISI = 3.5) and tactile- visual (ISI = 2).

3. Results

The findings revealed that in tactile stimulation frontal-right temporal connectivity accounts for the majority of the significantly different functional connectivity between correct and error classes (P-value < 0.001). Moreover, in visual stimulation, frontal-occipital connectivity, in visual-tactile (ISI = 3.5) stimulation left temporal-occipital connectivity, and in visual-tactile (ISI = 2) stimulation central-occipital connectivity between correct and error classes comprise the majority of significantly different functional connectivity (P-value < 0.01). These findings are shown in Figure 1.

4. Conclusion

Based on the results of this research, in tactile stimulation, there is a significant difference between correct and error classes in frontal-right- temporal connectivity,

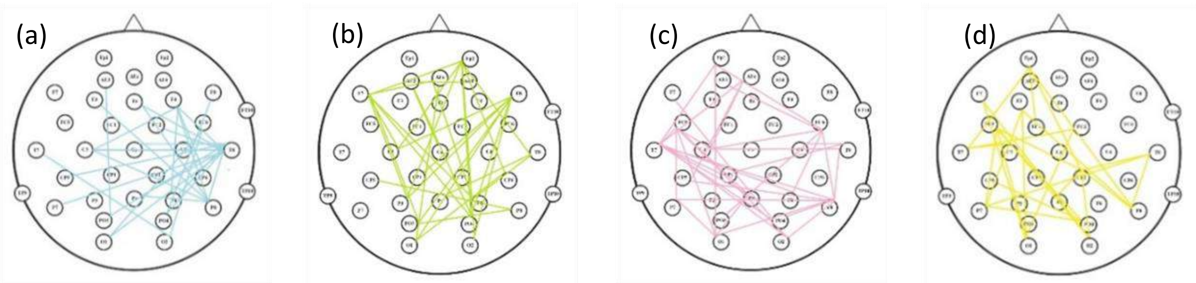

Figure 1. The significantly different brain connectivity between two groups of (a) tactile stimulation- correct case and tactile stimulation- error case; (b) visual stimulation- correct case and visual stimulation- error case; (c) visual-tactile (ISI = 3.5) stimulation- correct case and visual-tactile (ISI = 3.5) stimulation- error case; and (d) visual-tactile (ISI = 2) stimulation-correct case and visual-tactile (ISI = 2) stimulation- error case

and also in visual- tactile (ISI = 3.5) stimulation, there is significant difference between left- temporal with occipital regions and it is in line with the previous study because of involving the temporal lobe [8-10].

Previous studies have shown that visual cortex is located in occipital regions and these part of the brain is mostly activated in response to a visual stimulus [11]. In the visual stimulation of the current research, most significant differences was seen in frontal-occipital connectivity, and also in visual- tactile (ISI = 2) stimulation, there is significant difference between correct and error classes in central-occipital connectivity which is in line with the effect of visual stimulation [8-11]. This study showed that examining functional integration, in addition to examining functional segregation, could help improve brain-computer interface systems performance.

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Brain Stimulation and Prism in Dysgraphia

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Abstract

Objectives: This study aimed to investigate influence of neglect and the effect of Prism Adaptation (PA) combined with continuous Transcranial magnetic Theta Burst Stimulation (cTBS) on the dysgraphia rehabilitation of Persian stroke patients with neglect. Ten patients with neglect and dysgraphia secondary to stroke were randomly assigned to the intervention group and received PA combined with cTBS over the left parietal cortex; the control group received PA combined with sham cTBS for 2 weeks in 10 daily sessions. Patients were assessed for dysgraphia in a spontaneous writing task before and after intervention. Dysgraphia was classified into omission, destruction, tilting, poor handwriting, distance, perseveration, and size errors. Neglect was evaluated using the Star Cancellation Test (SCT) and the Line Bisection task (LBT). Activities of Daily Living disability (ADL) were evaluated using the Catherine Bergego Scale (CBS). All patients showed significant improvement in dysgraphia (measured using a spontaneous writing test), neglect (measured using SCT and LBT), and ADL disability (measured using CBS) ($p < 0.025$). The PA+cTBS user group showed greater improvement in ADL disability compared with the PA+sham cTBS group. Destruction and omission errors were the most frequent errors in dysgraphia. Neglect and rehabilitation influences the writing system in stroke patients. PA combined with cTBS had more beneficial effects on ADL in stroke patients with neglect in compared to the PA. Both approaches improved dysgraphia, ADL disability and neglect symptoms.

Keywords: Rehabilitation; Neglect; Agraphia; Writing; Prism Adaption; Continuous Transcranial Magnetic Theta-Burst Stimulation.

1. Introduction

Agraphia caused by acute right parietal infarction and lesion in the right hemisphere of the brain is often the cause of a non-aphasic disorder of agraphia and writing known as spatial agraphia or dysgraphia (constructive errors in writing) [1-6]. Dysgraphia is defined by inscribing errors which commonly contain missing elements, destruction mistakes, omissions, tilting, and addition errors. These errors have been observed in patients of different languages, such as Spanish [4], Japanese [3]), French [7], English [8], and Korean, with stroke in the right-brain area [9-11]. Dysgraphia due to stroke in the right-brain area has various forms related with the specific writing system of a given language. For instance, Japanese stroke patients demonstrated the disorder associated with ideograms in kanji writing but not with phonograms in kana [3]. However, these language-specific constructive errors of writing are not quite accepted; they may be modified by graphemic systems that need visuospatial processing, have a convened array of letters of the alphabet, and require a rehabilitation strategy of the letters of the alphabet [3, 9, 10, 12-15]. Visuospatial neglect and rehabilitation have been shown to influence dysgraphia [7]. PA as a single nonpharmacological therapeutic approach has been shown to be effective on dysgraphia [7], neglect, and disability in daily activities following stroke [16, 17]. Stroke studies in cognitive neuroscience with transcranial magnetic stimulation have been shown to treat neurological dysfunction and neglect [18]. Prism adaptation is possible to improve rehabilitative effects when combined with brain stimulation. However, the combination of PA with transcranial magnetic stimulation has not been evaluated for dysgraphia, neglect, and disability in daily activities. To examine the effectiveness of transcranial magnetic stimulation combined with prism adaptation in the rehabilitation of dysgraphia, a pilot, randomized, sham-controlled clinical trial of patients with dysgraphia due to stroke-induced neglect was designed and conducted. Accordingly, patterns in constructive errors of writing were detected to improve dysgraphia. The Persian (Farsi) alphabet includes 32 letters and words are located from right to left for spatial structure. Nevertheless, no study to date has examined the relation between dysgraphia and neglect in patients before and after rehabilitation. In this study, it was hypothesized that cTBS would boost prism adaption effects on improving dysgraphia, neglect, and ADL disability test scores.

2. Materials and Methods

This pilot, interventional, sham-controlled, single-blinded, randomized clinical trial was conducted in the Stroke Unit of Tehran Medical Department of Neurology, Shariati Hospital, Iran, from August 2017 to September 2018.

2.1. Subjects

Fifteen individuals enrolled in the study for cTBS rehabilitation on visual neglect. Stroke patients with visuospatial neglect, verified by MRI and clinical examination, were enrolled and provided informed consent for participation. Ten subjects had more than 5 years of grade school education. For this study, a total of 10 patients were assigned using the block randomization method into two groups of 5 participants. All 10 participants were right-handed. The 8 (80%) men and 2 (20%) women were aged between 46 and 77 years, and all had a grade school education between 5 and 16 years. They were tested for dysgraphia (constructive errors of writing) using spontaneous writing. They were also asked to attend 10 sessions over a 2-week period of interventional rehabilitation with prism adaption combined with cTBS or sham cTBS. The assessments were done before and after intervention. No follow-up was performed. The inclusion criteria consisted of neglect due to stroke, dysgraphia (constructive errors of writing), and completion of more than 5 years of grade school education, being right-handed, and having suffered a right-brain stroke. The exclusion criteria were having a previous history of a writing deficit, cerebral edema, epilepsy, brain trauma, implanted heart pacemaker, or pain, and the patients were aged less than 18 and more than 80 years old. In terms of stroke type, 6 (60%) participants had ischemic compared to hemorrhagic cerebral infarction, and stroke onset date was within the 6 months prior to randomization in 4 (40%) patients. There was no difference in age, gender, education level, sex, chronic, acute, stroke type, and health status between both groups (Table 1).

2.2. Assessment of Writing, Neglect, ADL Disability and Measurement Technique

All participants were evaluated for dysgraphia using spontaneous writing [10]. The Star Cancellation Test (SCT) [19], the Line Bisection task [20, 21] for neglect symptoms, and the Catherine Bergego Scale (CBS) [22-24] for ADL disability were utilized. Writing, neglect, and ADL were evaluated before and after treatment. The experimental intervention group underwent PA + cTBS. The control group underwent PA + sham cTBS therapy.

In the writing task, patients were asked to spontaneously write their name, address, and an autobiographical memory including where, what, and when on an A4-sized plain piece of paper before and after the rehabilitation. Only constructive writing errors were assessed as dysgraphia, and semantic linguistic errors were not evaluated. Each error was scored as one.

Previous studies have shown the classification of dysgraphia into tilting and visuospatial omission in accordance with the criteria determined by Yoon *et al.* [10]. In this study, a new suggestion was made for the detection of classification of dysgraphia in the writing system. Dysgraphia patterns were detected and scored, including increased distance between writing lines, increased size writing, omission (meaning that the writer ignores more than 50% of the left side of each writing line and deletes one part of the grapheme), destruction (errors were the creation of a nonexistent form), tilting (meaning that the lines of writing are not straight), poor handwriting style, and perseveration (repetitions and additions in the writing).

The SCT is scored by counting the number of small stars marked by the patients (a total of 100 small and large stars; 50 small stars) on an A4 sheet of paper. The number of stars marked was calculated on the left side of the page. A score between 0 and 46% illustrates unilateral visuospatial neglect.

In the Line Bisection task, patients were asked to complete midpoint straight lines on an A4 sheet of paper, bisect 12 lines on the left side of the page and 18 lines on the middle side of the page, and bisect 10 lines on the right side of the page. Scores range from a deviation of severe neglect (32.10±21.70) to normal range (0.61±0.12).

The CBS test was divided into two sections, an attention item and a motor-exploratory item consisting of real-life conditions such as dressing, mouth cleaning, moving, finding personal belongings, eating, gaze orientation, knowledge of left limbs, grooming, auditory attention, and spatial orientation. The items were scored from 0 to 3, and a total score of 30 was possible for dependency regarding the activities of daily living and neglect [22].

2.3. TMS Intervention

A MagPro X100 machine (Magventure Company, Farum, Denmark) equipped with a commercially available figure 8-coil was used for TMS. Motor Evoked Potentials (MEP) were measured by attaching active electrodes to the Abductor Pollicis Brevis (APB) muscle on the right hand and reference electrodes to the tendon on the right hand. Once the largest motor evoked potentials at the lowest intensity was implicated, it was stimulated ten times, and the minimal intensity of stimulation showing a peak-to-peak amplitude of 50 μV or above at least five times was set as the Resting Motor Threshold (RMT). The intervention group received continuous theta-burst stimulation cTBS. Inhibitory protocol was 801 pulses in 3 bursts at 30 Hz repeated every 100 ms (5 Hz, θ rhythm) with 80% of RMT, and over P3 on the intact parietal cortex, left-side based on the EG 10/20 system in 10 sessions over a 2-week period [25]. Then, prism glasses with a 10º right shift adaption mirror were given to the patients for 20 minutes. The mirror box (35*35*30 cm) was placed vertically. Patients observed the reflection of the movement of the right hand in the mirror. The control group underwent sham magnetic stimulation by tilting the coil vertically (90º) in 10 sessions over 2 weeks. Participants were blind to the type of therapy they received. Stroke patients with neglect tolerated the inhibitory cTBS treatment using 8-coil without any side effects.

2.4. Statistical Analysis

The student's t-test and Fisher exact test were employed to compare the groups (cTBS + PA vs. sham cTBS+ PA) in continuous and dichotomous variables, respectively. Then, repeated ANOVA model was used to compare the pre-rehabilitation and post-rehabilitation status of the groups by time factor and

Table 1. Patient's characteristics†

N/Intervention	Age (yr.)	Sex (M/ F)	Grade school education	Region of stroke: P, T, F, O, IN, TH	Time since the stroke onset: the chronic / sub-acute	Type of the stroke: I/H	writing errors
1) PA	46	F	16	RTH,	S-A	H	Omission
2) PA	63	M	9	RO, RP	S-A	I	Omission, destruction, size, distance, tilting, poor handwriting
3) PA	70	M	16	RT, RF	C	I	Tilting
4) PA	65	M	12	RT	C	I	Omission, destruction, size, distance, tilting
5) PA	67	M	16	RT, RF, RP,TH	C	H	Destruction, perseveration, size. tilting, poor handwriting
1) PA+TMS	62	M	12	RF, RT, RP	S-A	H	Omission, destruction, size, distance, tilting, perseveration, poor handwriting
2) PA+TMS	77	M	5	IN	S-A	I	Omission, destruction, size, distance, tilting, poor handwriting
3) PA+TMS	53	M	12	RP	C	I	Destruction, distance, size, tilting
4) PA+TMS	67	F	12	RT, RF, RP	C	I	Omission, destruction, tilting, perseveration, poor handwriting
5) PA+TMS	70	M	16	RT, RF, RP	C	H	Omission, size, tilting, poor handwriting
PA mean (SD) **PA+ cTBS mean (SD)** **P value†**	60(10) 67(4.5) p=0.09	p=0.77	14.2(2.48) 10.80 (4.08) p=0.42	F: p=0.50 P: p=0.73 T: p=0.73 TH: p=0.7 O: p=0.50 IN: p=0.50	p=0.73	p=0.26	6.80(4.43) 11.60(2.88) p=0.66

†Dichotomous variables are compared with Fisher exact test and quantitative variables with t-test.

Abbreviations: P, Cortex parietal; T, Cortex temporal; F, Cortex Frontal; R, right; IN, internal capsule; TH, thalamus; O, occipital; H, Intracranial hemorrhage; I, Intracranial ischemic; S-A, sub-acute; C, chronic; cTBS, continuous theta-burst transcranial magnetic stimulation; PA, prism adaptation.

differences between the groups using the group × time factor of the repeated ANOVA model. For all statistical analyses, a p-value less than 0.025 (0.05/2) to reject null hypotheses was considered significant after Bonferroni correction was applied [26].

3. Results

3.1. Change in the Dysgraphia Score

Descriptive statistics on the dysgraphia scores before and after the intervention are provided in Table 2. In a repeated ANOVA model of dysgraphia scores, the time factor was significant (F=27.567, p=0.001), indicating that both groups' dysgraphia scores (total error score of spontaneous writing test) improved after treatment. However, the group × time was not significant (F=0.945, p=0.359), indicating no difference between cTBS + PA and PA alone on dysgraphia scores changes. Figure 1 illustrates the mean spontaneous writing test scores in the PA + cTBS and PA alone groups before and after the 10 sessions of rehabilitation.

In dysgraphia, all patients showed, on average, 9 (mean ± SD, 9.1 ±4.53) errors on the spontaneous writing test before rehabilitation compared to only 1 (mean ± SD, 1.00 ±1.49) errors on the spontaneous writing test. Destruction and omission errors were the most common errors committed by stroke patients with neglect in dysgraphia. A reduction was seen in the scores of all classifications of errors in the spontaneous writing test, which suggests rehabilitation was successful in dysgraphia of participants in both groups after treatment (Figure 1). Classification of errors on the spontaneous writing test including: omission error, increase distance, destruction errors, tilting, perseveration (addition), poor handwriting, small size errors were detected to sum of score of errors in the stroke patients at pre- and post-intervention (Examples shown in Figures 1, 2). The results showing significant increased rehabilitation in dysgraphia, ADL disability, and neglect are summarized in Figure 1.

3.2. Change in Neglect and ADL Scores

Descriptive statistics regarding neglect and ADL scores before and after treatment are provided in Table 2. In a repeated ANOVA model with the CBS scores as the outcome variable, the time factor was significant (F=204.988, p<0.001), indicating that CBS scores improved in both groups after rehabilitation. More important, the group × time interaction was also significant (F=22.776, p=0.001), indicating that functional recovery happened more in one group than in the other. Figure 1 shows ADL increased in both groups after treatments, while more improvement was seen in the cTBS user group compared to the PA.

In contrast to ADL, neglect was not improved more with cTBS + PA than the sham stimulation + PA. In a repeated ANOVA model of SCT and LBT scores, the time factor was significant (in SCT, F=27.107, p=0.001; in LBT, F=33.612, p<0.001), indicating that the SCT scores of both groups improved after treatment. However, the group × time was not

Table 2. Dysgraphia, activities of daily living disability, and visuospatial neglect measurement before and after the rehabilitation.

Outcome	Before intervention; mean (SD)		After intervention; mean (SD)		Repeated ANOVA	
	CTBS+PA	PA	CTBS+PA	PA	Time	Time*group
SWT	10.4±(4.0)	7.8±(5.0)	0.8±(1.3)	1.2±(1.7)	P=0.001*	P=0.359
CBS	22.2 ±(4.6)	13.6± (3.9)	4.6± (4.4)	4.8± (4.2)	P<0.001*	P=0.001**
SCT	20.8±(7.9)	15.4±(13.5)	0.8±(1.7)	1.0±(1.7)	P=0.001*	P=0.421
LBT	30.5± (11.9)	24.5± (9.6)	4.6 ±(12.1)	4.9± (6.8)	P<0.001*	P=0.464

NOTE. Values are mean ± SD. * Significant difference between pre-rehabilitation and post-rehabilitation of group at p<0.025 by repeated ANOVA model, time factor. **Significant difference between groups at p<0.025 by repeated ANOVA model, the group × time factor.

Abbreviations: LBT, line bisection test; SCT, star cancellation test; CBS, Catherine Bergego Scale; cTBS, continuous theta-burst transcranial magnetic stimulation; PA, prism adaptation; SWT, total score spontaneous writing test errors.

significant (in SCT, F=0.718, p=0.421; in LBT, F=0.651, p=0.464), indicating no difference between true and sham cTBS stimulation on changes to SCT and LBT scores (Figure 1).

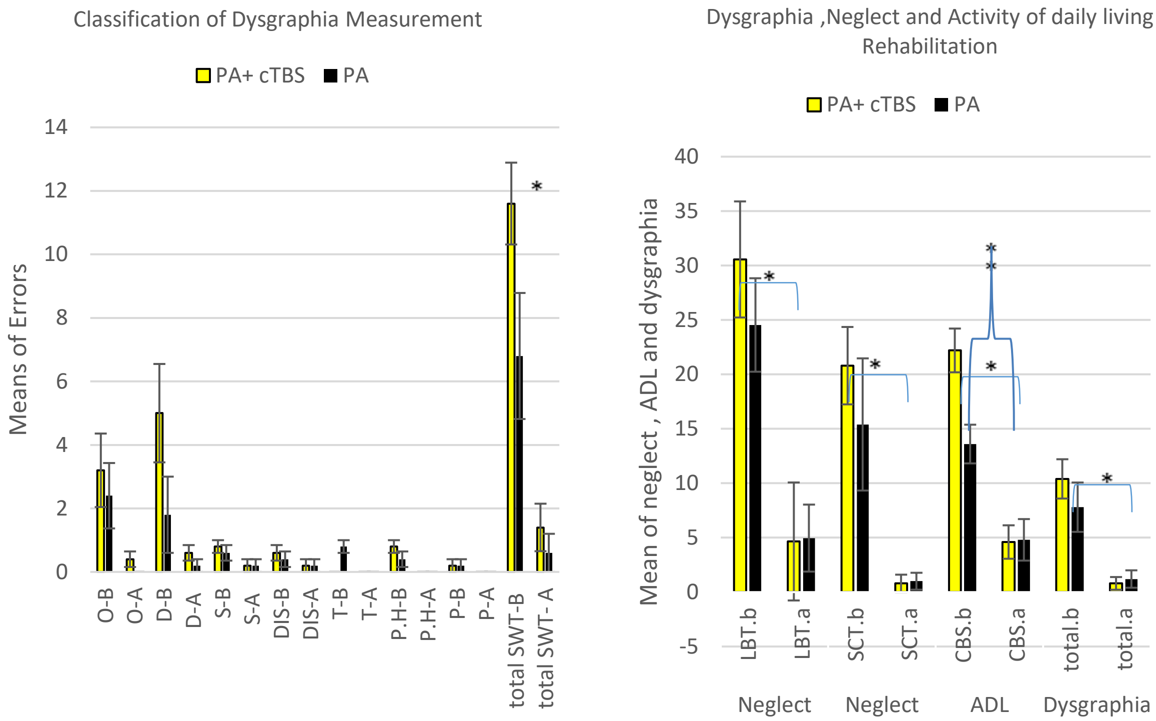

Figure 1. Figure on the left side shows patients with classification of dysgraphia in the spontaneous writing test of rehabilitation without writing practice before and after 10 sessions. Figure on the right side shows stroke patients' scores in LBT, SCT, CBS and Spontaneous writing test (total errore) of rehabilitation without writing practice before and after 10 sessions. All patients show to rehabilitation significantly in dysgraphia (measured using total errors of spontaneous writing test), neglect (measured using LBT and SCT) and disability in activities of daily living (measured using CBS). The PA+ cTBS group shows to significant greater improve in the activities of daily living measured by CBS compared to the PA. Asterisks indicate results that were significant using repeated ANOVA model, time factor: *P<0.025, the group × time factor: **P<0.025

Abbreviations: O-B, omission errors before rehabilitation; O-A, omission errors after rehabilitation; D-B, destruction errors before rehabilitation; D-A, destruction errors after rehabilitation; S-B, size errors before rehabilitation; S-A, size errors after rehabilitation; DIS-B,distance errors before rehabilitation; DIS-A,distance errors after rehabilitation; T-B, tilting errors before rehabilitation; T-A, tilting errors after rehabilitation; P.H-B, poor handwriting style before rehabilitation; P.H-A, poor handwriting style after rehabilitation; P-B, perseveration errors before rehabilitation; P-A, perseveration errors after rehabilitation; total SWT-B, total score spontaneous writing test errors before rehabilitation; total SWT-A, total score spontaneous writing test errors after rehabilitation; cTBS, continuous Theta-Burst Transcranial Magnetic Stimulation; PA, prism adaptation; LBT, the Line Bisection Test; SCT, Star Cancellation Test; CBS, the Catherine Bergego Scale; ADL, activity of daily living.

4. Discussion

The current pilot clinical trial showed that, in all stroke patients with dysgraphia, visuospatial neglect and disability in activities of daily living were improved after 10 sessions of rehabilitation with PA + cTBS and with PA + sham cTBS. The PA combined with cTBS group showed a significantly greater improvement in ADL compared with the group receiving PA alone.

Dysgraphia was assessed in Persian stroke patients with neglect. Dysgraphia was classified into omission, destruction, tilting, poor handwriting style, distance, perseveration, and size errors. The most frequent errors were destruction and omission errors.

There is limited research into rehabilitation approaches for adults with dysgraphia acquired after

Figure 2. The classification of dysgraphia used in this study. Figure on the left side of columns shows examples of the response of the neglect patients with dysgraphia at before intervention. Those on the right side of columns examples of the response of the neglect patients with dysgraphia of rehabilitation after 10 sessions without writing practice

stroke. Non-pharmacological approaches like PA and cTBS were useful for dysgraphia in few clinical trials [7, 27]. PA and cTBS have been shown to rehabilitate visuospatial unilateral neglect and ADL disabilities in some clinical trials [18, 28].

PA in the single case has been designed to improve stroke-related neglect, and the result of rehabilitation was improvement in dysgraphia and neglect symptoms [7]. Improved neglect symptoms as a result of rehabilitation may translate to improved dysgraphia. Some trials used PA therapy for visuospatial neglect and disabilities in the activities of daily living with variable success rates. It was useful for unilateral neglect and motor function disability in some clinical trials [16, 17], yet PA therapy was not useful in some other clinical trials [29, 30]. Differences in the trials include different designs of lenses creating an optical right shift of 6º prism compared to the 10º prism in the current study, and the characteristics of the recruited stroke patients with neglect can explain this disparity. No additional improvement in dysgraphia and neglect-associated test scores was found by coupling cTBS with our rehabilitation techniques. One possible explanation is the near complete rehabilitation effect of the dysgraphia and neglect tests in both groups. All patients showed, on average, 9 errors in dysgraphia before rehabilitation compared to only 1 error in dysgraphia after rehabilitation. Another explanation is the fact that in the present study, the sham control group and the experimental group at base received PA treatment.

In contrast to PA, cTBS over intact parietal cortex was found to be an effective non-pharmacologic therapeutic approach in the treatment of unilateral neglect [31-36]. Rehabilitation in disabilities in activities of daily living and visuospatial unilateral neglect is a result that was not generally found in previous studies on neglect treatment with continuous theta-burst stimulation. However, no functional disability assessment was reported in some clinical trials of neglect therapy [32, 37], and some trials showed rehabilitation in disabilities in activities of daily living with targeted treatment of unilateral neglect [38-42]. In a randomized trial with three groups of conventional rehabilitation, repetitive TMS alone, and rTMS + sensory cueing, stroke patients who received TMS therapy were better at neglect during therapy compared with the conventional rehabilitation group. Recovery from ADL was seen in all patients across the three groups [38]. More improvement in disabilities in activities of daily living was seen in the present study compared with Yang *et al*. (2017). This result is possibly due to differences in the combination of treatments (cTBS + PA compared to rTMS + sensory cueing), the trials' designs due to usage of the cTBS protocol instead of repetitive TMS, and differences in the employed assessment measures of the recruited patients. The combination of rTMS and intensive speech therapy in four stroke patients has been explored for aphasia with the aim of improving speech deficit. The result of rehabilitation was improvement in the degrees of aphasia and dysgraphia with writing exercises [27]. The near complete rehabilitation of dysgraphia in the current study compared to Kakuda *et al.* (2011) is possibly due to usage of the cTBS protocol over the parietal cortex instead of rTMS over the frontal cortex, a more precise test, difference in the employed evaluation measures, and the combination of PA and cTBS instead of rTMS and speech therapy.

In this study, it was hypothesized that the rehabilitation combination stimulated and employed more networks of the brain, which might improve dysgraphia, neglect, and neurological function disability in stroke patients. More studies are needed with functional neuroimaging to verify this hypothesis. In fact, previous studies have shown the correlation between changes in functional connectivity in the dorsal attention network, recalibration of target position of eye and hand, spatial realignment of various sensory-motor in PA [43, 44], promotion of the front-parietal attention network, and reduction in pathological hyperexcitability to have pivotal roles in the visuospatial neglect in cTBS [32, 36, 45]. Changes in functional connectivity in the brain network and the new mechanism of combined rehabilitation may explain the implicit recovery effect seen in stroke-induced dysgraphia, neglect, and the greater improvement in ADL in the current study. In contrast with the implicit recovery (without practice) in dysgraphia, previous studies have been based on writing, copying, spelling, and relearning with practices in writing for errors in writing [12, 15].

Findings regarding the classification of constructive errors in writing showed that destruction and omission errors were the most common in Persian stroke patients, and the result regarding omission errors was consistent with a study of Korean patients [9, 10]. Likewise, constructive errors, such as left space omission, in writing have been reported in people of various languages, including Japanese [3], French [7], Korean [10], and Spanish [4]. In contrast, right omission was reported in left-handed patients with neglect due to stroke involving damage to the left parietal cortex instead of right-brain damage as in the current study [8]. Previous studies, including that of Dae-Hyun Jang *et al*., have reported right space omission [9] (in the Persian graphic system it is written from right to left and in Korean it begins with a consonant on the left side), and the patients have been educated to keep the strictly defined position for the graphic system. This pattern of right space omission could be specific to the Korean language. The results regarding destruction error were consistent with studies on Japanese in ideogram kanji writing [3], Spanish [4], and Korean patients [1, 9, 10]. Duplication (perseveration) results were consistent with studies on Spanish in Roman alphabetic systems, Japanese in Kanji, Chinese characters in Kana, and Korean Han-geul letters. Frontal-brain stroke patients showed mostly perseveration (adding) errors [3, 4, 9, 10]. The brain processing of neglect patients has been disturbed in estimating distance as a result of neglect-related cognitive impairment, which may translate to disturbance in distance, size, poor handwriting, and tilting errors [1, 10, 46].

The present pilot study had a relatively small sample size in only a single center with no follow up. Although small sample size has been shown in all previous study on dysgraphia [7, 12, 15, 27]. Characters of dictation and copy were not used for the writing tests. Moreover, 40% of patients with neglect in the current study were sub-acute after stroke. There was no statistically significant difference between the 2 groups (PA + cTBS and PA) in baselines of time since onset of chronic and acute phases after stroke (Table 1). Likewise, TMS was used for sub-acute stroke patients [36, 38-40]. The absence of a group of patients undergoing continuous theta-burst stimulation alone for comparison was one limitation of the present study, although cTBS alone has been done in a previous study on neglect and ADL disability [41]. More research is needed to replicate the current findings in a larger sampling size of stroke patients with dysgraphia, neglect, and ADL.

The current study was the first clinical trial of PA combined with cTBS therapy for dysgraphia, neglect, and ADL.

In future, studies with larger sampling sizes and embedded functional neuroimaging will help verify more explicitly the results of the current study.

5. Conclusion

An influence was found between dysgraphia and unilateral neglect in stroke patients. Dysgraphia patterns were determined to improve increased distance, increased size, omission, destruction, tilting, poor handwriting style, and perseveration (addition). The current results showed that dysgraphia and neglect may be affected by rehabilitation and educational strategies. In addition, neglect appears to specifically affect the writing systems of stroke patients. The novel c TBS+PA method and PA alone could be potentially useful tools for rehabilitating patients with stroke-induced dysgraphia, unilateral neglect, and disabilities in performing activities of daily living. The cTBS + PA users showed greater improvement in ADL disability compared with patients receiving PA alone. The cTBS enhances the effect of PA for ADL in stroke patients.

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The present study was approved by the Ethics Committee of Iran University of Medical Sciences. Written informed consent forms were obtained from all eligible stroke patients with neglect [IR.IUMS.REC.1396.93012334]. This study was registered at the Iranian Registry of Clinical Trials [IRCT20170423033606N3]. This work was supported by the Iran Cognitive Sciences and Technologies Council (Grant no.1446508).

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Evaluating the Effect of Increasing Working Memory Load on EEG-Based Functional Brain Networks

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Abstract

Working Memory (WM) plays a crucial role in many cognitive functions of the human brain. Examining how the characteristics of functional brain networks modulate with increasing WM load can help us have a more precise understanding of the WM. To investigate the effect of increasing WM load on the functional network characteristics, we used Electroencephalogram (EEG) data recorded from 21 healthy participants during a WM task with three load levels (0-back, 2-back, and 3-back). The networks were constructed based on the weighted Phase Lag Index (wPLI) in theta, alpha, and beta frequency bands. After identifying the significant wPLI values, graph-theory metrics consisting of mean clustering coefficient, characteristic path length, and node strength were analyzed by statistical tests. We revealed that in the 2-back and 3-back compared with 0-back, the alpha-band functional integration and segregation were reduced. Moreover, node strength of channels located in the frontal, parietal and occipital regions were decreased in the alpha-band.

These results indicate that analysis of topological properties of the alpha-band network can be an appropriate way to explore task difficulty-related changes in the cortical regions of the human brain.

Keywords: Electroencephalogram; Working Memory; Functional Connectivity; Weighted Phase Lag Index; Graph Theory.

Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

WM refers to a short-term memory system that enables temporary storage, retrieval, and manipulation of information. WM plays a vital role in the complex cognitive functions of the human brain, such as reasoning, language comprehension, and learning [1]. Increasing the difficulty level of WM-related tasks can increase the amount of load imposed on the WM system. Most previous studies on WM have focused on the effects of the presence of or change in WM load on the activation of brain regions using various imaging modalities and have identified specific regions of the prefrontal and parietal cortices that are activated during WM tasks [2]. Although brain activation-based analysis provides valuable information, a more precise comprehension of the WM system would not be attainable without brain connectivity analysis. Functional connectivity is generally defined as the temporal dependency of signals from different anatomical regions [3]. The tools provided by graph theory can be used to describe the properties of the reconstructed functional networks [4].

In this study, we use EEG, phase-based connectivity analysis, and graph theoretical measures to investigate the effect of increasing WM load on the characteristics of functional cortical networks during a WM task with three load levels.

2. Materials and Methods

EEG data were collected by Shin *et al.* [5]. A total of 28 electrodes were placed on the entire scalp according to the 5–10 system with a sampling rate of 1000 Hz for 21 healthy participants during three n-back task conditions (0-back, 2-back, and 3-back). The preprocessing of the EEG data was done using EEGLAB toolbox.

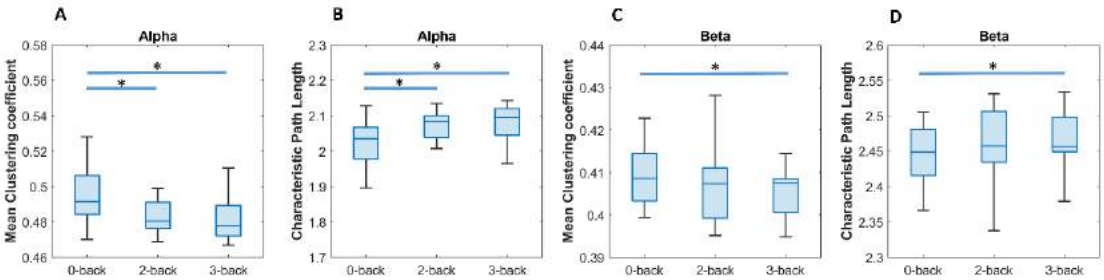

Figure 1. Significant task difficulty-related alterations in global network metrics

The wPLI between every pair of channels was computed in theta (4-8 Hz), alpha (9-14 Hz), and beta (15-30 Hz) frequency bands. To identify statistically significant wPLI values, we applied non-parametric permutation testing with 500 iterations. Therefore, weighted undirected networks were constructed by significant wPLI values and non-significant values were set to zero. After network construction, characteristic path length and mean clustering coefficient were estimated to reflect global integration and segregation of functional networks. In addition, we calculated the local nodal connection strength, which is the sum of weights of links connected to the node. Then, the effect of task difficulty on network measures was assessed using Friedman's non-parametric test ($p < 0.05$). Paired Wilcoxon signed-rank tests were used for post hoc pairwise comparisons with Bonferroni correction ($p < 0.05$) for global measures and False Discovery Rate (FDR) adjustment ($q < 0.01$) for the local measure of networks.

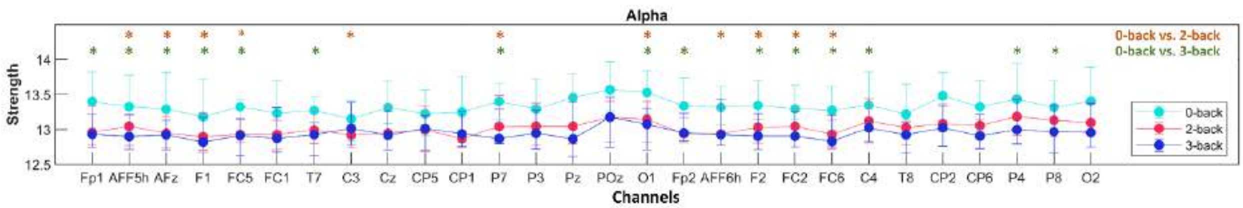

Figure 2. Significant task difficulty-related changes in node strength

3. Results

Significant task difficulty-related alterations in global network metrics are shown in Figure 1. In the alpha-band network, in the 2- and 3-back tasks compared with the 0-back task, the mean clustering coefficient, which is a measure of functional segregation, decreased significantly (Figure 1A), while the characteristic path length, which is a measure that is inversely related to functional integration., exhibited a statistically significant increase (Figure 1B). In the beta-band network, the mean clustering coefficient decreased significantly in the 3-back task compared with the 0-back task (Figure 1C), while the characteristic path length exhibited a significant increase (Figure 1D).

Significant task difficulty-related changes in node strength are shown in Figure 2. In the alpha-band, node strength decreased during increased mental workload in most of the channels. However, these differences were significant only in the 0-back vs. 2-back and 0-back vs. 3-back for channels specified in Figure 2.

These results indicate that analysis of topological characteristics of alpha-band network based on graph theory seems to be an appropriate way to explore task difficulty-related changes in the cortical regions of the human brain. Also, an effective combination of these global and local metrics (particularly in the frontal cortex) in the alpha-band network can be explored as novel features for future BCI studies on improving working memory capacity.

4. Conclusion

In this study, we constructed theta, alpha, and beta-band wPLI networks and applied a graph-theoretical approach to investigate the topological alterations of the brain network during a WM task with three load levels. Statistical analysis revealed that in the 2-back and 3-back tasks compared with the 0-back task, the alpha-band functional integration and segregation were decreased, and the node strength of different channels located in the frontal, parietal and occipital regions were reduced in the alpha-band. These findings demonstrate that alpha-band wPLI network metrics have the potential of providing a more precise understanding of the WM system.

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Predicting Mini-Mental State Examination Scores Using EEG Signal Features

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Abstract

The purpose of this study is to use linear and non-linear features extracted from Electroencephalography (EEG) signal to predict the Mini-Mental State Examination (MMSE) test score by machine learning algorithms. First, the MMSE test was taken from 20 subjects that were referred with the initial diagnosis of dementia. Then the brain activity of subjects was recorded via EEG signal. After preprocessing this signal, various linear and non-linear features are extracted from it that are used as input to machine learning algorithms to predict MMSE test scores in three levels. Based on the experiments, the best classification result is related to the Long Short-Term Memory (LSTM) network with 68% accuracy. Findings show that by using machine learning algorithms and features extracted from EEG signal the MMSE scores is predicted in three levels. Although deep neural networks require a lot of data for training, the LSTM network has been able to achieve the best performance. By increasing the number of subjects, it is expected that the classification results will also be increased.

Keywords: Mini-Mental State Examination; Electroencephalography Signal; Electroencephalography Feature Extraction; Machine Learning Algorithms.

1. Introduction

Cognitive impairment is a spectrum that ranges from subjective cognitive decline to dementia [1]. Dementia is a clinical syndrome that includes a group of disorders related to cognitive decline that influence language, presentation, memory, social abilities, etc. [2]. In 2013, the World Health Organization (WHO) study [3] estimated the top 20 leading causes of death in 2030 showing that non-communicable diseases such as dementia will become the major threats to human lives. Diagnosing dementia involves cognitive assessment of brain functions, such as attention, memory, problem-solving, thinking, and many other mental abilities [4]. Cognitive assessments are usually performed using veiled clinical tests [5]. One of these tests is the MMSE test [6], which is widely used in clinical and research studies to measure the severity and progression of cognitive disorders. Although this test can be used to follow the cognitive changes over time, so it is an effective way to document the response to treatment. This test consists of questions in five different areas including orientation, memory, attention, naming, follow verbal and written commands, write a sentence spontaneously, and copy a complex polygon [6], the answer to which leads to a score between 0 (greatest cognitive decline) to 30 (no cognitive decline). The MMSE is the most widely used screening tool for cognitive health but the manual operation of this test restricts its screening within primary care facilities [7]. This test is considered to be too complicated, time-consuming, relatively costly for certain clinical settings, and often requiring a trained neuropsychologist or physician to administer the test in a clinical setting [8]. Also, it can overestimate impairments in those older than the age of 60 years and in with fewer education subjects [9]. To overcome the above limitations, automated methods can be used to predict the MMSE score.

Recently, machine learning has been used to produce an automatic prediction model. These algorithms have been used to model information based on causal and/or statistical data, explore hidden dependencies between factors and diseases in a big data environment, and detect various diseases such as liver malfunction, coronary artery disease, and select genes for cancer detection. Recently, machine learning techniques have been studied for diagnosing dementia. For this aim, the algorithm is trained using various cognitive impairment biomarkers to learn the relationship between the input data and the corresponding output variable (clinical diagnosis). Once the learning process is completed, the algorithm can yield predictions or classifications or with new data. Farzana *et al.* [5] employ a set of automatically-extracted psycholinguistic, discourse-based, lexicosyntactic, and acoustic features for predicting clinical MMSE scores using several machine learning techniques. Yancheva *et al.* [8] use a set of semantic, lexical, syntactic, and acoustic features extracted from speech samples to predict MMSE scores by a bivariate dynamic Bayes net. Youn *et al.* [9] were developed a machine learning algorithm for the detection of cognitive impairment based on the MMSE and Korean Dementia Screening Questionnaire (KDSQ). They trained a logistic regression using 24 variables including education duration, sex, diabetes mellitus, age, etc. based on the training dataset and then calculated its accuracy using the test dataset. The author in [10] proposes a method for diagnosis dementia by predicting MMSE scores using finger-tapping measurement and a machine learning pipeline. This method first selects finger-tapping attributes such as the number of taps and standard deviation of the inter-tapping interval with copula entropy and then predicts MMSE scores from the selected attributes by predictive models. Authors in [11] build a machine learning-based model for predicting cognitive impairment among elderly people using MMSE score. In this research, several machine learning algorithms including random forest, naive Bayes, logistic regression, and XGBoost were used to assess the 3-year risk of developing cognitive impairment.

EEG is a neurodynamic time-sensitive biomarker that helps in detecting cortical abnormalities associated with cognitive decline and shows good performance in diagnosing dementia [12-14]. EEG is also widely available and faster to use than other imaging devices. According to this, the purpose of this study is to use linear and nonlinear features extracted from EEG signals to predict the MMSE score by various machine learning algorithms.

The rest of the paper is organized as follows: In section 2, steps of recording and preprocessing of EEG data, feature extraction from them, and machine learning algorithms are explained. In section 3, the results of the classification using various algorithms are described. And in section 4, the conclusion is presented.

2. Materials and Methods

2.1. Data Collection and Preprocessing

To predict the MMSE scores, first, the MMSE test was taken from 20 subjects that referred with the initial diagnosis of dementia. Based on the results of this test the subjects were classified as T3 (MMSE: 28-30), T2 (MMSE: 24-27) or T1 (MMSE < 24) groups [15]. Then, the brain activity of subjects was recorded via EEG according to the international 10-20 system using Mitsar 19 channel system. All the EEG electrode contact impedances were maintained below 5 kΩ. To remove interferences from EEG signals, a high-pass filter with a cut-off frequency of 0.1 Hz, a low-pass filter with a cut-off frequency of 50 Hz, and a Notch filter with cut-off frequencies of 45 and 55 Hz were used. Independent Component Analysis (ICA) algorithm has also been used to remove blinking, eye movements and muscles artifacts.

2.2. Feature Extraction

After pre-processing the EEG signals, various linear and non-linear features including kurtosis, skewness, Interquartile Range (IQR), median, range, covariance, entropy, coherence, and image coherence in the delta, theta, alpha, beta, and gamma frequency bands, delta/theta, delta/alpha, delta/beta, delta/gamma, theta/alpha, theta/beta, theta/gamma, alpha/beta, alpha/gamma, and beta/gamma power ratios, theta, alpha, beta, gamma, Alpha rhythm Frequency (AF), and broadband central frequencies, absolute and relative powers, alpha and alpha AF spectral peaks, Individual Alpha spectral Frequency (IAF) are extracted from them. A summary of the features extracted from the EEG signal are shown in Table 1. In addition to the features extracted from the EEG signal, due to the relationship between cognitive decline and age, the age of the subjects is also used as a feature. The combination of features described above is used as input to the machine learning algorithms. In order to create a hybrid feature, each feature is placed in a row of the matrix as shown in Figure 1.

2.3. Machine Learning Algorithms

Machine learning algorithms are trained using the extracted features for the training dataset to detect the MMSE scores of the test dataset. These algorithms include Support Vector Machine (SVM), multi-layer perceptron (MLP), Convolutional Neural Network (CNN), Long Short-Term Memory (LSTM), and logistic regression which are discussed below.

Table 1. Features extracted from the EEG signal

- Kurtosis, Skewness, IQR, median, range, covariance, entropy, coherence, and image coherence in the delta, theta, alpha, beta, and gamma frequency bands.
- Delta / theta, delta / alpha, delta / beta, delta / gamma, theta / alpha, theta / beta, theta / gamma, alpha / beta, alpha / gamma and beta / gamma power ratios.
- Theta, alpha, AF, beta, gamma and broadband central frequencies.
- Theta, alpha, alpha AF, beta, gamma and broadband absolute powers.
- Theta, alpha, alpha AF, beta, gamma and broadband relative powers.
- Alpha and alpha AF spectral peaks.
- IAF

$$\begin{bmatrix} \text{Kurtosis in delta frequency band} \\ \text{Kurtosis in theta frequency band} \\ \vdots \\ \text{Skewness in delta frequency band} \\ \text{Skewness in theta ferequency band} \\ \vdots \\ \text{Individual alpha frequency band} \\ \text{Subjects age} \end{bmatrix}$$

Figure 1. The procedure of the combine different features to obtain a hybrid feature matrix

2.3.1. SVM

SVM is one of the supervised learning methods. In the simplest type of this classifier, the training data set can be categorized linearly with at least one hyper-plane. Linear classifiers are inefficient for real problems that have a nonlinear structure. One of the abilities of SVM is to be converted to a non-linear learner, which is done by mapping the features to a higher-dimensional space [16]. The SVM used in this research is nonlinear with a cubic kernel.

2.3.2. MLP

An artificial neural network is a mathematical computational model that models the operation of biological neural systems. In 1958, Rosenblatt [17] introduced the first neural network called perceptron. Perceptron is the basic unit of the concept of deep learning and an artificial neuron that, when combined with other components, is able to solve complex problems in accordance with human function. Perceptron can be considered as a binary classification algorithm that can be used to divide a set of input signals into two categories, 0 and 1. Unlike other common classification algorithms, this algorithm is inspired by the basic processing unit of the human brain (neuron) and has the ability to learn and solve complex problems. When several perceptrons combine in layers, an artificial neural network called the MLP is created. The MLP network that used in this research consists of a hidden layer with 60 neurons.

2.3.3. LSTM

LSTM is an artificial recurrent neural network that used in the field of deep learning. This network has feedback connection thus it can process not only single data points, but also entire sequences of data [18]. In the LSTM network used in this research, after the input layer, there are a dropout layer with a probability of 0.3, LSTM layer with 70 neurons, a dropout layer with a probability of 0.2, and fully connected, softmax, and classification layers.

2.3.4. CNN

CNN is a class of artificial neural networks that is designed to adaptively learn spatial hierarchies of features through backpropagation by using multiple blocks, such as convolution, pooling, and fully connected layers [19]. In the CNN used in this work, after the input layer, there are convolutional layer with filter size 5, batch normalization, max pooling, dropout with a probability of 0.5, fully connected, softmax, and classification layers.

2.3.5. Logistic Regression

Regression methods describe the relationship between a response variable and one or more explanatory variables. The logistic regression model is the most frequently used regression model for the analysis of data. The goal of an analysis using this model is to find the best fitting to describe the relationship between a dependent or response variable and a set of independent or predictor variables [20].

3. Results

Machine learning algorithms are trained using hybrid features extracted from the EEG signals of 15 subjects (training phase) to recognize the MMSE scores of 5 other subjects (testing phase) using 5-fold validation method.

Criteria for evaluating classification results are accuracy, sensitivity, and specificity. The accuracy of a machine learning classification algorithm is one way to measure how the algorithm classifies a data point correctly. According to Equation 1, accuracy is the number of correctly predicted data points out of all the data points.

$$ACC = \frac{TP + TN}{TP + TN + FP + FN} \tag{1}$$

In this Equation, TP, TN, FP, and FN are respectively show true positive, true negative, false positive and false negative values.

According to Equation 2, sensitivity is the metric that evaluates a model's ability to predict the true positives of each available category.

$$TPR = \frac{TP}{TP + FN} \tag{2}$$

Based on Equation 3, specificity is the metric that evaluates a model's ability to predict the true negatives of each available category.

$$TNR = \frac{TN}{TN + FP} \tag{3}$$

The classification accuracy, specificity, and sensitivity using different classifiers are shown in Figure 2. Based on this figure, the best classification result is related to the LSTM network with 68% accuracy. Sensitivity and specificity are also in acceptable range in all classifiers.

4. Conclusion

In this research, by training and testing different machine learning algorithms using linear and nonlinear features extracted from EEG signals and a

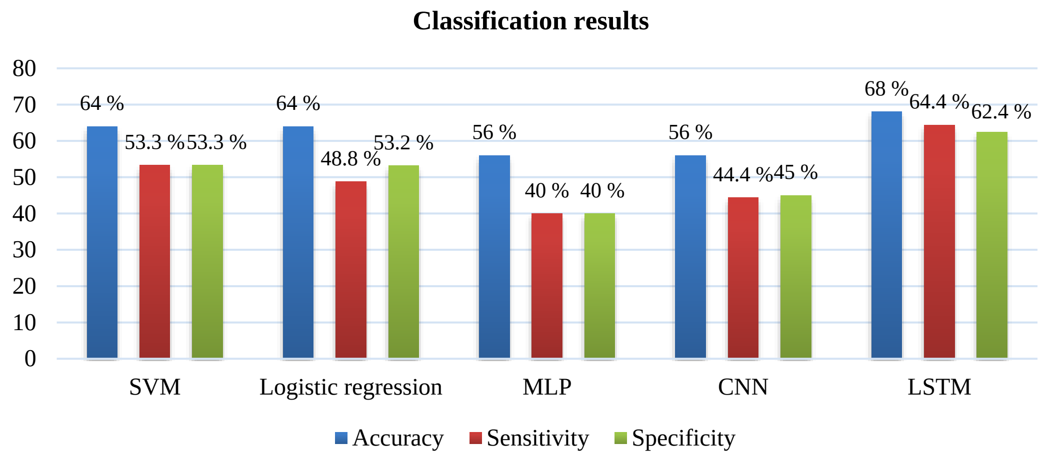

Figure 2. MMSE scores classification results using different machine learning algorithms

combination of them with subject's age, the MMSE score is predicted in three levels. Although deep neural networks require a lot of data for training, in this work, the LSTM neural network, which is suitable for processing time series with a limited amount of data, has been able to achieve the best performance with 68% accuracy. By increasing the number of subjects, it is expected that the classification results will also increase.

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