Original Article

Modeling Brain Functional Magnetic Resonance Imaging Data Using Collective Density Function Estimation Method Based on Directional Statistics for Determining Addiction Patterns

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Abstract

Introduction: Functional Magnetic Resonance Imaging (fMRI) has been recognized as an attractive tool for understanding brain function for the last two decades. Clustering is a statistical method that opens new doors for researchers to identify the subgroups of the patients and to specialize the treatment. A lot of research has been done on the brain activities of healthy people and people with a history of drug addiction in response to drug stimuli, but there is no literature on whether people with different experiences of quitting drugs and different durations of drug use before quitting have identical brain activities in response to drug stimuli or not. Also, there is not enough research on the fact that how long drug use affects brain activities. Thus, this study is to seek the answer to these two questions. **Method:** In this study, 11 subjects, with no history of addiction, and 27 subjects, with different quitting durations and different durations of methamphetamine use before quitting, were evaluated. The images obtained fMRI images were initially analyzed by FSL software, this analysis included pre-processing and implementing GLM model on each subject. In the second step, the values obtained by fitting the GLM model to each voxel were extracted; the extracted parameters were standardized and used as the input for the penalized spline collective density estimator in R software. After estimating the parameters of the collective density function model, the estimated coefficients were applied as an inputs for hierarchical clustering. **Results:** The results of the clustering showed that the brain activities of subjects with different durations of quitting and different durations of drug use before quitting were correlated and four clusters were identified. **Conclusion:** These findings indicated that in fact, three months can be considered a safe point for being committed to quitting drugs. It is worth to note that the reaction to drugs in people with a quitting duration of less than three months is dependent on the duration of using drugs before quitting, so people with a history of drug use of 60 months and over 60 months before quitting have a different reaction to drug stimuli. These outcomes suggest that in order to do therapeutic works on the subjects to be committed to quitting drugs, the duration of using drugs has to be taken into account as well. Our study was a first step toward this research goal and the results can be used as a suggestion for further research and therapeutic works in this area.

Keywords: Addiction, Collective Density Function, Functional Magnetic Resonance Imaging Method

Introduction

Over the past two decades, Functional Magnetic Resonance Imaging (fMRI) has been recognized as an attractive tool for understanding brain functions, and scientists have initially used this tool to identify areas of the brain that were activated by a specific action. The imaging technique has become more prominent and has been used in a variety of areas, including separating healthy people from the patients or categorizing patients at different stages of diseases such as depression, bipolar disorder, Alzheimer, autism, Parkinson, etc. [1, 2]. The more prominent the functionality of functional magnetic resonance imaging technique becomes, the more the need for more appropriate statistical methods to extract information from the obtained images grow. One of the important statistical methods in the field of functional brain image

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analysis is the clustering methods. The main reason for using these methods in medical sciences is that there is a need to discover new structures that are naturally present in the data without the researcher's prior knowledge of the structure of classes or levels. In clustering methods, there may be subgroups of patients who exhibit the same clinical symptoms; however, the way they respond to a particular treatment varies. In functional magnetic resonance imaging data analysis, clustering explores the brain activity obtained from different voxels in the brain and opens new doors in the discovery of specific patient subgroups and tailoring the treatment. Since one of the key issues in clustering and classification is the input given to these algorithms, this input can be the time series received from each voxel, the standardized values of the GLM model fitted to each voxel, and the brain relation, etc. that each of them can be clustered or categorized into algorithms with or without dimensional reduction [3]. This research also focuses on the inputs given to these clustering algorithms. The models investigated in this study are the models introduced in the directional statistics. The reason for using them is that so far in conventional fMRI data clustering and classification methods, the beta coefficients of the GLM model of each voxel have been used, and only thing that was considered was the beta values obtained from the GLM model of each voxel without considering the fact that the beta values of each voxel may be affected by various factors, such as proximity to a major vessel in the brain [4], then the voxels of those areas are mistakenly considered active and these wrong values for the voxels were clustered in Euclidean spaces. But in our proposed method to eliminate the effects such as voxel proximity to the main arteries, these coefficients are standardized. It has been proven that by standardizing data (model coefficients, time series or other variables) the data can be viewed in a spherical non-Euclidean space, in a way that the size of the vectors no longer matters, and their directions are specifically investigated [5]. By doing so, the space is changed from Euclidean space to non-Euclidean space and the methods that are based on directional statistics are applied.

In order to model the directional data parametrically, the well-known models of Von Mises Fisher, Watson, Bingham, Bingham-Mardia, Watson-Fisher and Bingham-Fisher, etc. are used; each of which has different applications [6]. However, besides these parametric methods, there are a wide range of nonparametric methods for estimating the density function, most of which are based on the nuclear density estimator and are used with some changes on the selected nucleation scope of change in directional statistics. In these methods, the estimation of density functions is performed individually [7-10]. In contrast to these methods, it is possible to obtain better accuracy in estimating the density functions of similar subjects using their shared information. For this purpose, Maadooliat et al. (2016) introduced a collective density estimation model for nonparametric estimation of collective density functions. This method assumes that data is distributed through multiple distributions within a common model, and then all distributions are estimated together. In other words, it is considered that the probability density functions have multiple features in common that can be estimated by logarithmic modeling of the density functions [11]. One of the advantages of this method is using the shared information between univariate distributions to estimate the co-distribution leading to a more accurate estimation of a bivariate distribution for cases with low sample numbers. Another advantage is the reduction in the dimension of the parameter space to specify each distribution, because of using a common basis for all of them. In other words, each univariate distribution is specifically determined on the basis of the common coefficients of a set of common foundations that, like principal components, can be used to represent, cluster and classify univariate distributions.

Studies have been conducted on brain activities in response to craving stimuli in substance-dependent subjects [12]. However, there is no literature on whether people with different experiences of quitting drugs and different durations of drug use before quitting have identical brain activities in response to drug stimuli or not. Amphetamine has been found to remain in the urine for 1 to 3 days, over 90 days in hair and for 1 to 2 days in the blood [13, 14], but it has not yet been considered that the brain activities of people with different experiences of quitting drugs and different durations of drug use before quitting have identical brain activities in response to drug stimuli or not. Furthermore, there is not enough research on the fact that how long drug use affects brain activity. In this study, we seek to find the answer to these questions.

For this purpose, we first provided some information on the number of healthy subjects and subjects with different durations of quitting methamphetamine and different durations of methamphetamine use in a completely new statistical method in clustering. Then, the clusters formed were analyzed based on the quitting duration and the duration of using drugs before quitting. In the next step, group analysis of fMRI of each cluster was done and compared.

Methodology

In this study, we used the collective density function method to present a new clustering method in functional magnetic resonance data and obtained a standard linear coefficient probability distribution for all patients' brain voxels collectively and they were analyzed as an input to the clustering algorithm hierarchical with the option of different bonds function and different intervals in R software. Finally, the bond function Ward.2 and Manhatton distance with Rand = 0.90 were chosen as the best clustering. In addition to this model, other models including the mononuclear density function as well as all the obtained beta information from the GLM model were applied as the input of the hierarchical model with the above-mentioned bond function and distance,

and the Rand criterion of 0.75 and 0.74. The results of the clustering done by these two methods and the table of other investigated criteria are provided in the appendix. In the following, the method of collective density function is fully explained.

Collective Estimation of Density Functions

The method of collective collective density estimation was first introduced by Maadooliat et al. (2016) for nonparametric estimation of the density function of two variables in the orientation data. In this method, assuming that the data are distributed from multiple distributions within a common model, the data distribution is estimated as a co-distribution. More precisely, it is assumed that the probability density functions have multiple properties in common that can be estimated using density function logarithmic modeling [11].

For this purpose, suppose that each logarithm of the density function can be written as a linear combination of a common set of basic functions. Specifically, if it is assumed that

$$\log\{f_i(x)\} = w_i(x) - c_i \text{ and}$$

(1)

$$w_i(x) = \sum_{k=1}^{K} \phi_k(x)\alpha_{ik} \qquad i = 1, \dots, m$$
$$c_i = \log\{\int \exp w_i(x)dx\}$$

Then, the estimation of density function of $f_i(x)$ is calculated as

$$f_i(x) = \frac{\exp w_i(x)}{\int \exp w_i(x)dx} = \exp\{\sum_{k=1}^{K} \phi_k(x)\alpha_{ik} - c_i\} i = 1, \dots, m$$

In this method, K is constant but unknown, which can be determined using pebble diagrams in the singular value decomposition estimation method. Since $\varphi_k(x)$ are common basic functions to construct each of the density functions, it is assumed that $\varphi_k(x)$ in a sub-space is constructed with a dimension less than one space covered by fixed basic functions. The construction method is explained as follows:

(2)

$$\phi_k(x) = \sum_{l=1}^{L} b_l(x)\theta_{lk} \qquad k = 1, \dots., k$$

By inserting formula 1 into formula 1 we come to:

$$\omega_i(x) = \phi(x)^T \alpha_i = b(x)^T \Theta \alpha_i i = 1, \dots, m$$

If

$$B = (b(x_1), b(x_2), \dots. b(x_n))^T$$

And

$$A = (\alpha_1, \alpha_2, \dots, \alpha_m)^T$$

$$\Omega = \{\omega_i(x_j)\}^T$$

The following formula can be obtained:

$$\Omega = B\theta A^T$$

So, the parameters of matrices model are (A, $\boldsymbol{\theta}$). Now suppose that the observations x_{ij} , $j = 1, \dots, n_i$ for each of the density functions are fi(x) i=1,…,m; therefore, the logarithm of the likelihood function can be written as follows:

$$l(\theta, A) = \sum_{i=1}^{m}\sum_{j=1}^{n_i}\{\omega_i(X_{ij}) + c_i\}$$

In order to estimate the smooth density function, it is necessary to maximize the logarithm of the likelihood function by considering a penalty criterion, or in other words, minimize the following function based on Green and Silverman [15]:

$$-2l(\theta, A) + \lambda trace(\theta^T D\theta)$$

Where D is a penalty of flexibility and λ >0 is a smooth adjustment parameter. We used the Newton Raphson algorithm to estimate the density function and to estimate λ Akaike criterion was applied which is as follows:

$$AIC(\lambda) = -2l(\theta, A) + 2df(\lambda)$$

Where $df(\lambda)$is calculated as follows:

$$df(\lambda) = \sum_{k=1}^{K} trace\{[\frac{\partial^2 l(\theta, A)}{\partial\theta_k \partial\theta_k^T} + \lambda D]^{-1}[\frac{\partial^2 l(\theta, A)}{\partial\theta_k \partial\theta_k^T}]\}$$

Since the λ parameter estimation is time-consuming to obtain Landa, we used the following formula introduced by Shellasse and Korman (2012) [16].

$$\hat{\lambda}_{i+1}^{-1} = \frac{trance(\widehat{\Theta}_i^t D\widehat{\Theta}_i)}{df(\hat{\lambda}_i) - (m-1)}$$

As our data has an oriented nature, our data space consists of two angles (θ ,τ), and the space of our parameters is as follows:

$$\Omega = \{-\pi \le \theta \le \pi, 0 \le \tau \le \pi\}$$

We applied the tensor multiplication of two sets of trigonometric splines of basic functions to construct the space between the two parameters θ ,τ defined in the space

Ω we considered in this problem. According to Bohr et al., the standard j b-spline of 1+l is defined as

$$B_j^l(x) = \frac{x - \mu_j}{\mu_{j+1} - \mu_j} B_j^{l-1}(x) + \frac{\mu_{j+1,l+1} - x}{\mu_{j+1,l+1} - \mu_{j+1}} B_{j+1}^{l-1}(x)$$

where $B_j = I_{[\mu_j, \mu_{j+1}]}(x)$ and μ_j are $j = 1, .., m$ of nodes. Since τ of the defined angle is on one page and non-periodic, we used these b-spline functions to build the foundations.

Because of the rotational trigonometric splines, these pins were used to construct the pins in the θ variable. These splines are defined as:

Standardized trigonometric splines from υ is with K node $(x_1, x_2, \ldots., x_k)$ and for t is defined between $[x_i, x_{i+\upsilon}]$intervals of spline functions as follows:

$$s_i^1(t) = \{ \begin{matrix} 1 & x_i \le t \le x_{i+1} \\ 0 & o.w \end{matrix} \}$$

$$s_i^{\upsilon}(t) = \frac{\sin\left(\frac{t - x_i}{2}\right)}{\sin\left(\frac{x_{i+\upsilon-1} - x_i}{2}\right)} s_i^{\upsilon-1}(t) + \frac{\sin\left(\frac{x_{i+\upsilon} - t}{2}\right)}{\sin\left(\frac{x_{i+\upsilon} - x_{j+1}}{2}\right)} s_{i+1}^{\upsilon-1}(t)$$

And to cover the Ω space, the tensor multiplication between these trigonometric splines and b-splines was used.

The first k in the construction of each function represents the extent of the contribution after estimating the model parameters. Since the estimated values of A are density, they can be used as a criterion for the input of the clustering and classification algorithms. These values are used as inputs for the hierarchical algorithm.

Testing Method

In this study, the data was collected on 11 subjects with no history of addiction and 27 subjects with different quitting durations and different durations of methamphetamine use before quitting, all of whom had been under abstinence. This information was extracted from the Neuro Imaging and Analysis Group (NIAG) archive of Imam Khomeini Hospital in Tehran. Experiments on these people were done by fMRI and they were asked to press the key if they see an image of a triangle, square or rhombus and not to press the key if they see an image of a circle. These simple geometric shapes were the test stimuli that were on a background; there were four types of backgrounds: simple block, neutral block, negative emotions block, and addiction block. The background varied according to the block. As in the simple block, the background of the page was completely black. The neutral block background had a picture of simple devices that did not produce any emotions in people. In the negative emotions block, images were selected as the background, which produced negative emotions such as disgust or fear. The selected images for the addiction block produced a craving feeling in the addicts. During the test, there were 16 blocks that were evenly divided between the two modes, i.e., 4 blocks per mode. In each block, there were 2 stimuli, of which 18 were go stimuli (a triangle, square or rhombus) and 6 were stop stimuli (a circle). Each stimulus was displayed for one second, and the distance between the two stimuli was semi-randomly selected between zero and one second, applying the gamma distribution functions. There was a rest of 18 seconds between the two blocks, with a positive Persian sign appearing on the black background. And, the whole brain was photographed during the test and the signals related to their blood changes were recorded. Images were initially analyzed by FSL software, which included pre-processing and implementing GLM model on the subjects. In the second stage, the β values obtained by fitting GLM model to each voxel were extracted from the negative emotion block, the addiction block and the neutral block and the extracted parameters were standardized in this step.

The standardization method was to obtain three beta for each voxel, and each of these beta were divided into the vector norm of the beta of that voxel. The obtained values were used as inputs for estimating the collective density function in R software and after estimating the parameters of the collective density function model; the estimated points were used as inputs for hierarchical clustering. After identifying the clusters, the maps of the brain activities of each cluster in two counters (negative feelings > addiction and neutral> neutral) were obtained and the brain activities of subjects in different clusters were compared.

Results

Clustering results indicate that subjects are classified into four different clusters, in which subjects with a history of quitting drugs and a history of drug use before quitting are shown in different colors. The first cluster, all marked in blue, includes people who have no addiction history. The second cluster, all marked in black, includes people who have a history of addiction and they had quit using drugs for less than 3 months. The third cluster, all of the subjects except one are marked in red. Only one person with no history of addiction (blue) is in this cluster and the rest had quit drugs for less than 3 months. The difference between this group and the second cluster was that they had more than 60 months of drug use before quitting, whereas those in the second cluster had all used drugs less than 60 months before quitting.

The fourth cluster, all marked in green, includes people who have a history of addiction and they had quit using drugs for 3 months or longer. It should be noted that all subjects within this cluster had different durations of drug use before

quitting, and their only similarity was the duration of their drug quitting. In this group, there were two subjects with no history of methamphetamine use (blue) and one with less than 3 months of addiction but the duration of using drugs before quitting was less than 60 months.

The results are shown in Figure 1.

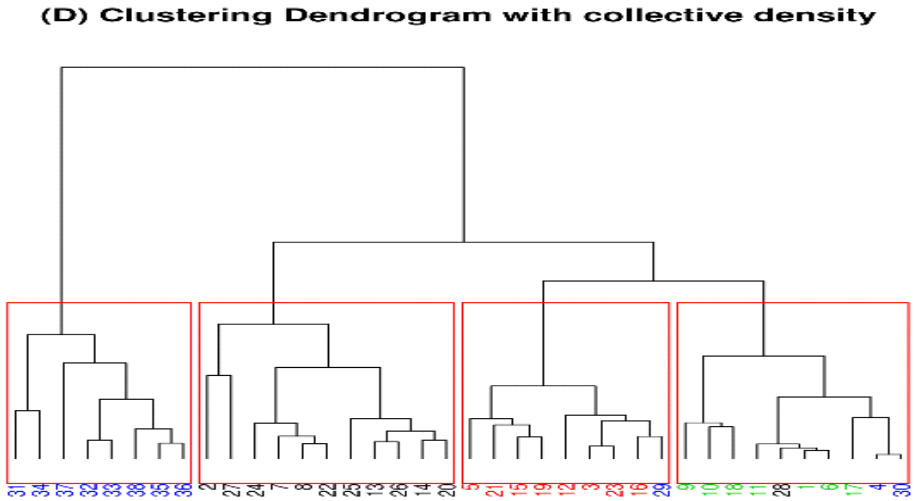

Figure 1: Clustering the subjects using the collective density function

Based on the results, the subjects can be subdivided into the above-mentioned groups. We now turn to group analysis of brain images of each cluster and seek to determine whether these observed differences in clusters are reasonably present in the brain activity maps of the subjects or not. For this purpose, two contrasts (addiction >neutral) and (negative emotions >neutral) are investigated in each cluster.

Investigated contrast (addiction> neutral)

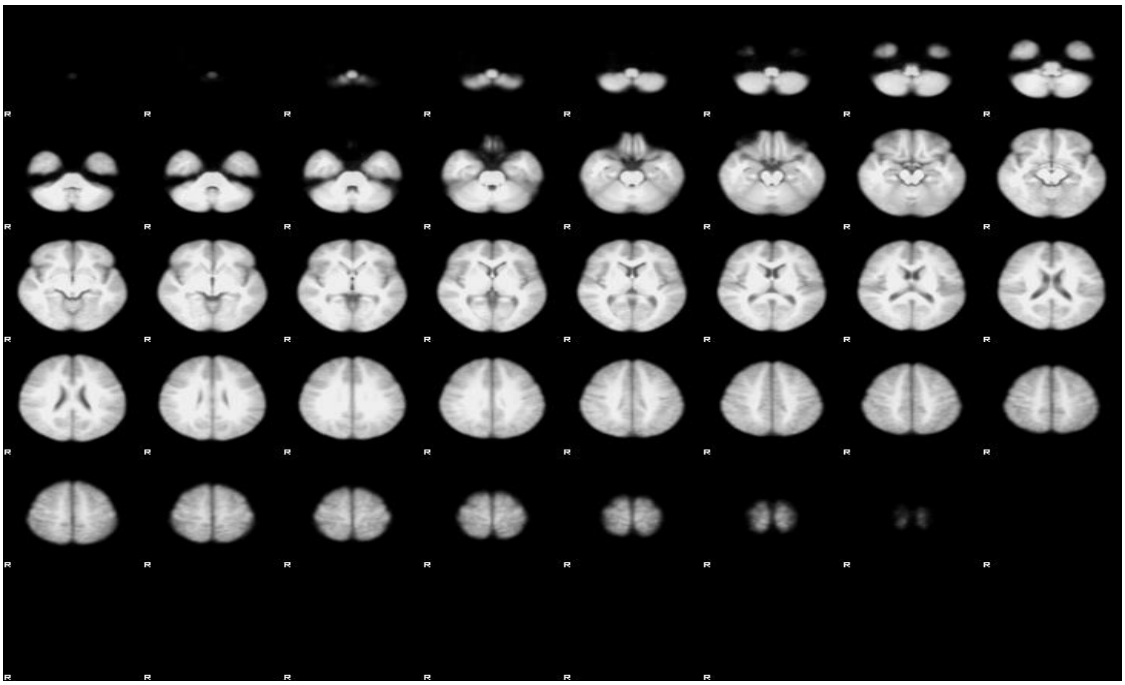

Figure 2: Brain activity in the first cluster (no history of methamphetamine addiction)

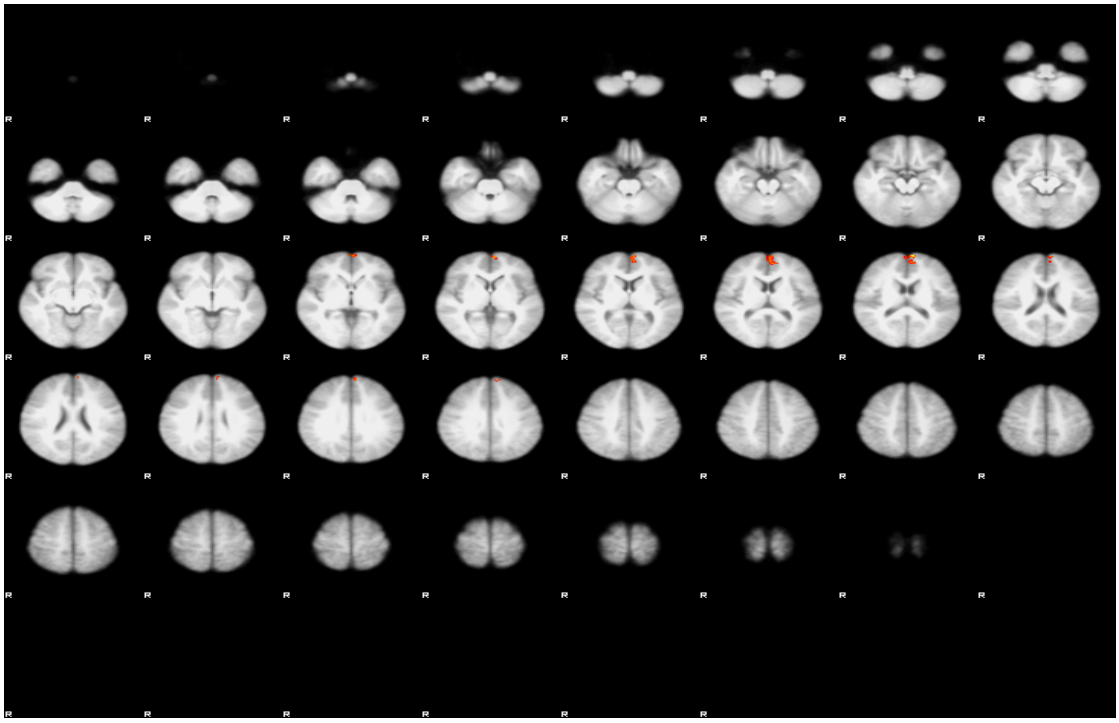

Figure 3: Brain activity in the second cluster (people who have a history of addiction and had quit using drugs for less than 3 months and their drug use before quitting is less than 60 months)

Table 1: Summary of Active Area Information (related to Figure 2)

Cluster Index	Z	x	y	z	
3	1	5.32	-8	66	Left medial frontal lobe

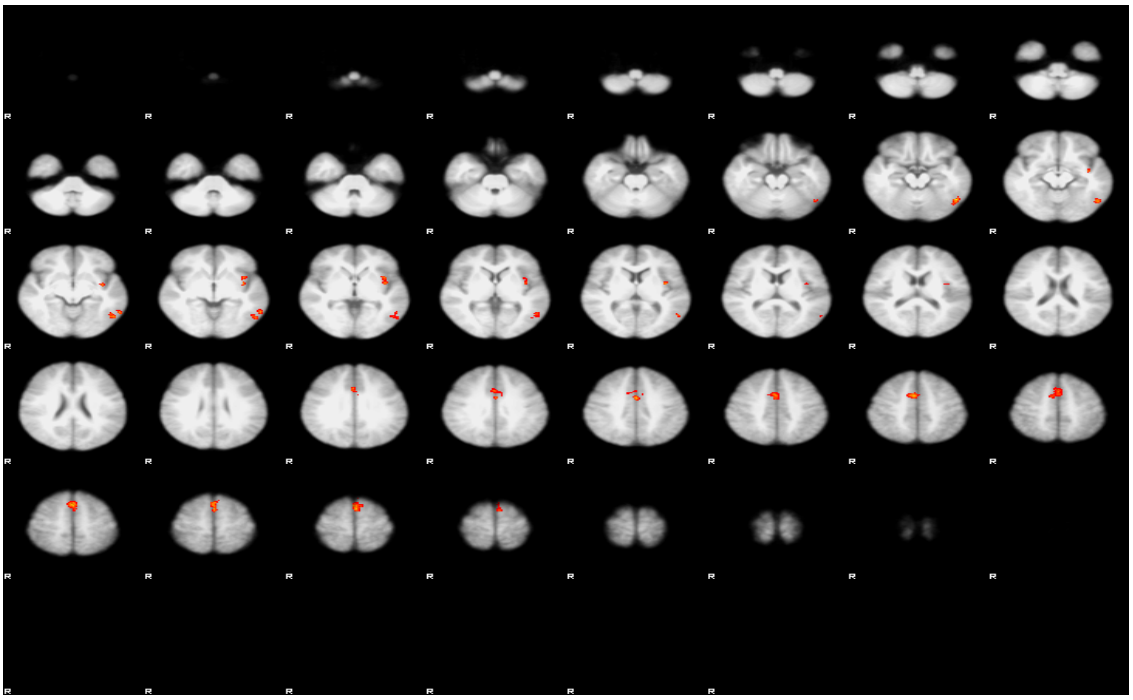

Figure 4: Brain activity in the third cluster (people who have a history of addiction and had quit for less than 3 months and their drug use before quitting was longer than 6 months)

Table 2: Summary of Active Area Information (related to Figure 3)

Cluster Index	Z	x	y	z	
3	4.84	0	16	58	Superior frontal gyrus(SEM)
2	4.91	-50	-60	-16	occipital temporal
1	4.5	-38	10	-2	Left insula

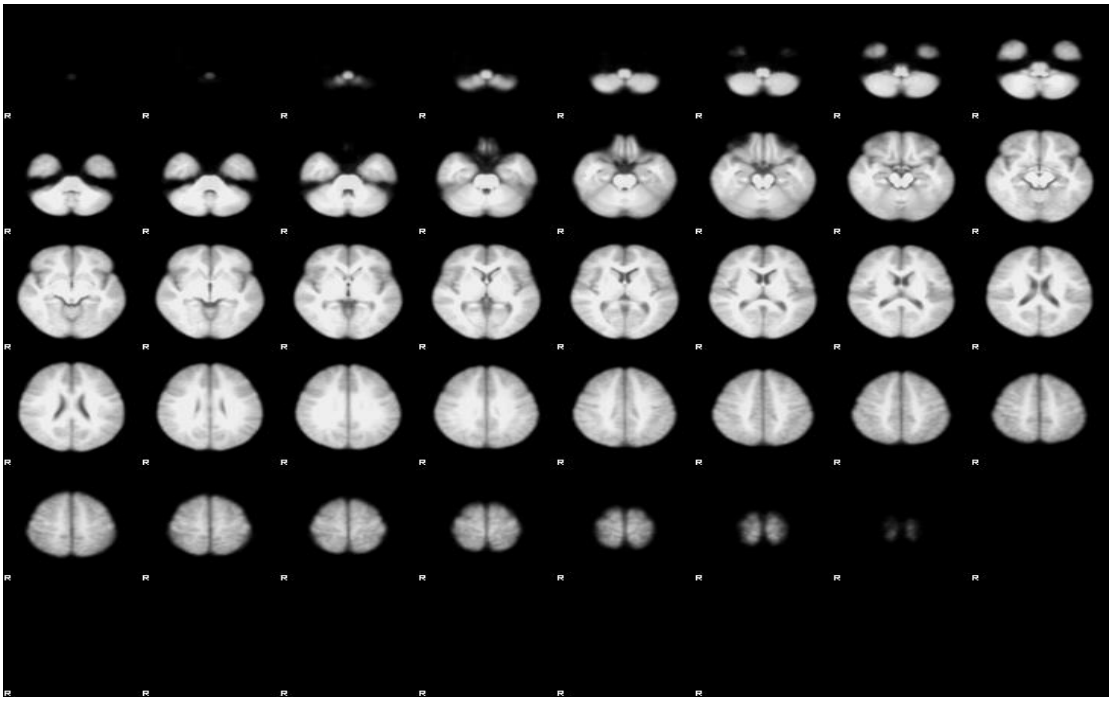

Figure 5: Brain activity in the fourth cluster (people who have a history of addiction and had quit using drugs for more than 3 months

Investigated contrast (negative> neutral)

In the four groups studied, the only active brain point was the visual cortex and no difference was observed between the groups.

Discussion

The duration of using drugs and quitting drugs is an important factor in controlling cognitive affairs and functional organization of the brain [17]. It is not yet fully understood how brain function changes in response to methamphetamine stimuli in its users. The effect of different durations of drug use and different durations of quitting drugs are also not completely understood. The change in gray matter of the prefrontal cortex in methamphetamine users and its recovery after a long period of quitting has been previously studied [18]. Schwarta et. al. also showed a correlation between subcortical gray area density and the duration of drug use [19]. In addition, prolonged quitting duration can have a significant relationship with the function of the prefrontal cortex. In this research, we also found a similar result between a group with long duration of quitting and a group of people with no history of drug use facing images with drug content. This finding may be indicating the recovery of brain damage to methamphetamine users after prolonged quitting. Similar studies examining the decision-making activity of methamphetamine users have shown that people who were long in quitting had a better performance in decision-making processes than people who had recently quit drugs [20]. It has been proven that exposure to images can increase the craving feeling in users [21]. The present study showed a significant difference in exposure to methamphetamine images among people whose duration of use was different. Activity in ACC and SMA in people with short quitting duration but long duration of drug use may be an indication of a failure in abstinence [22].

Anatomically ACC is associated with the prefrontal areas and has a role in causing the craving feeling [23]. According to a study carried out by Morphy et al [24], the activation of ACC in facing methamphetamine stimuli may also be due to the effort to control the craving feeling. It has also been shown that SMA is a component of the brain's inhibitory network and its activity is related to self-control processes [25]. Activation of mPFC in people who have not used drugs for a short time may also be associated with the craving feeling [26].

Previous observations have also shown that the activity in this area is correlated with the craving feeling [27] as well as the rate and frequency of use [28]. In facing negative feeling images, as expected, only the visual cortex was activated and there was no difference between different groups.

From the statistical point of view, the reason for selecting the cut point of 3 months is that at first glance we examined the clusters and found that one of the four main clusters (marked in blue) consisted of 8 subjects with no history of methamphetamine addiction, and we realized that 3 other subjects with no previous history of drug use were in the other three clusters. So, for investigating other three clusters we first looked at the duration of quitting drugs. The next cluster we examined was the black one. In this cluster all subjects seemed to be alike in one respect, 11 subjects (marked in black) all had a history of drug use and had quit drugs for less than 3 months. In the next group, in red, except for one person with no history of addiction, all had a history of addiction and had quit using drugs for less than 3 months, just like the previous group. With more investigations, it was found that he difference between these two clusters was due to the duration of drug use before quitting, which was less than 60 months in the black group, and more than 60 months in the red one. This cut point, based on the number of months before quitting, indicates the important effect of the duration of using drugs before quitting on the brain activity. As it can be seen, the two groups with a similar history of quitting drugs were not similar in response to the craving stimuli. In the last cluster, out of 10 people, 2 had no history of addiction and one had quit using drugs for less than 3 months and had used drugs for less than 60 months before quitting (subject 28 had a history of drug use for 54 months before quitting and had quit using drugs for 64 days). The rest of the subjects in this group had quit drugs for longer than 3 months, but the duration of drug use varied from 10 months to 120 months. Depending on the results of this clustering, it is possible to examine whether the impact of substance use can be reduced within 3 months and beyond, and in fact, consider these 3 months as a recovering time for the addicts with further studies. Three subjects had no history of addiction and were placed in other cluster; factors such as their family background, their smoking cigarettes or hookah or drinking alcohol led them to fall into a cluster similar to those with a history of quitting for more than three months. Each of these causes requires further investigation, which unfortunately is not possible due to the lack of access to them in this study. One of the limitations of this study may be the case of subject 28 who is expected to be in the second cluster (duration of quitting drugs for less than 3 months and duration of drug use for less than 60 months). One of the factors can be the commitment to treatment and the person's will is that make the person's response to the craving stimuli similar to those with longer than 3 months of quitting.

Conclusion

The results of this study suggest that in order to make people committed to quitting, the duration of their quitting should be considered, especially in those who have quit using drugs for less than three months. Another point that should be taken into account in is the duration of using drugs before quitting, and then regarding their active brain area, the therapeutic works should be done. This study has taken the first steps in understanding the hidden layers of the impact of quitting drugs. By increasing the sample size, it is possible to increase the accuracy of this study and use its results for cases where the actual status of subjects (duration of drug use before quitting and duration of quitting) is unclear. Through looking at active images in the identified clusters, the status of subjects in terms of the duration of quitting and duration of drug use before quitting can be realized and the therapeutic works can be done according to the existing circumstances.

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Attachment

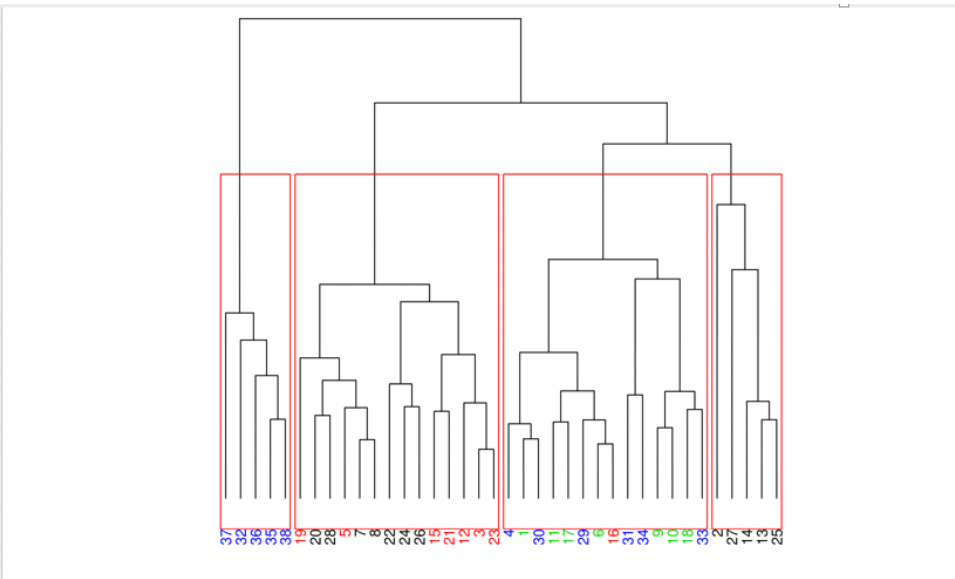

Figure 6: Clustering the subjects using the kernal density function

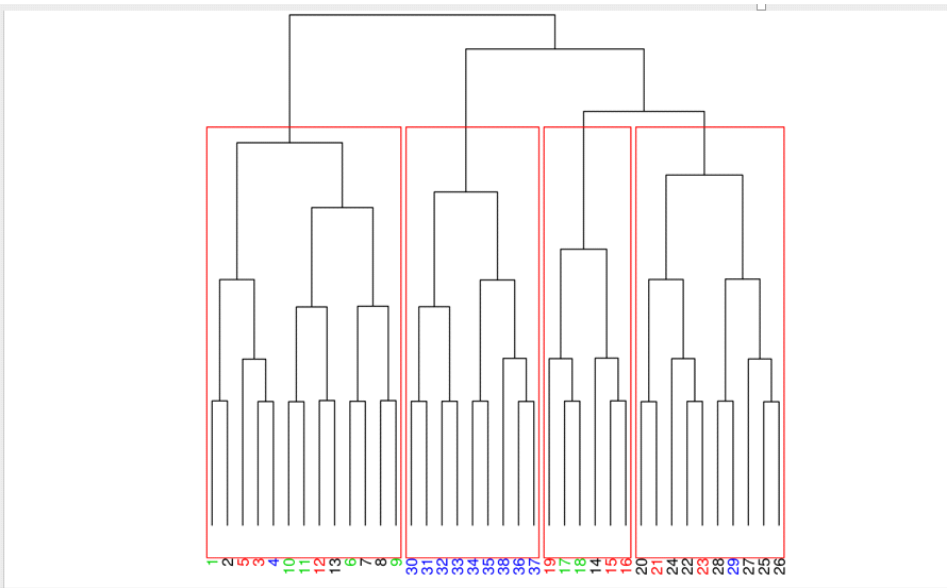

Figure 7: Clustering the subjects using beta coefficients (beta vector for block of neutral images, negative images and addiction related images) obtained from GLM model

Table 3: Comparison of different indices in hierarchical clustering with different inputs

Input	Rand	HA	MA	FM	Jaccard	NMI
Collectivedensity points	0.90	0.73	0.75	0.79	0.66	0.77
Collective Score	0. 75	0.36	0. 4	0. 53	0.36	0.52
Kernel	0.75	0.36	0.4	0.53	0.36	0.57
Raw Parameters	0.74	0.3	0.35	0.47	0.31	0.41