Classification of Subjective Cognitive Decline in Alzheimer’s Disease Through Resting-State Hemodynamic Response Function

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Abstract. As a super-early stage of Alzheimer's disease (AD), there is no unified structural change in imaging nor significant difference in assessments in the Subjective Cognitive Decline (SCD), lack of effective clinical diagnosis. The hemodynamic response function (HRF), as the basis of functional magnetic resonance imaging (fMRI), represents the tendency of specific cortex voxel over time after specific stimulation, reflecting the sensitivity and activation of neurons. We equalize the spontaneous dynamic change of the cerebral cortex in resting state to equivalent stimulation for activation, extend the application of HRF. The possible lesion is selected through priori knowledge both academically and clinically. The parameters of HRF: peak, time to peak and FWHM were extracted as the basis for classification via support vector machine (SVM). The SCD group was found deactivation in specific frontal, hippocampus, inferior temporal and occipital regions especially. The classification accuracy between the healthy controls (HC) can reach 74%, which could be great referable in clinical pre-diagnosis. It highlights the possible ROI for SCD stage, provides new methods and research materials for pre-diagnosis of early-stage Alzheimer's disease as a typical brain-related disease.

1. Introduction
Alzheimer's disease is a major threat to human health, studies have shown about every 8 people over 65 suffer from the disease, by the age of 70, the morbidity doubles [1-5]. It is estimated that the number of AD patients in China will reach 115 million in 2050[6, 7]. There is no effective clinical treatment in practice. The sooner the disease is diagnosed, the more likely the deterioration can be slowed down or even prevented [2, 5, 8, 9]. Searching for possible imaging methods to inspect and pre-diagnose high-risk groups comes to the top priority of current research.

In 1982, Reisberg, B., Ferris, SH etc. firstly proposed that self-reported memory loss may be the early symptoms of Alzheimer's disease [10]; in October 2012, the Subjective Cognitive Decline (SCD) was confirmed formally as an earlier period of AD than mild cognitive impairment (MCI) with the most obvious symptom of subjective memory decline [11, 12]. Follow-up studies found that nearly 85% of the SCD groups undertake probabilities deteriorating into degenerative neurological disorders, even AD dementia [11, 13, 14]. Feldman et al. proposed a new IWG-2 standard in 2014, compared to the normal aging group, there was no difference in the clinical scores nor imaging data except for the subjective memory loss [15].
In 1995, Biswal et al reported the first resting state fMRI study [16]. After the definition, the resting-state fMRI research has become an indispensable research field of brain science. Specific functional-related networks like the default mode network (DMN), frontoparietal control network, ventral and dorsal attention networks, somatomotor, visual, and language networks were found consistently across studies, known to support different cognitive functions and brain activities [17, 18]. Studies based on AD patients have found the DMN showed deactivation, in addition to hippocampus and its surrounding as well as prefrontal cortex, plus, networks and regions related to basic functions including feeling, perception and emotion, appear significant weakening [19-21]. In order to find effective detection for the SCD, we are concerned about whether these feature areas of Alzheimer's disease and other clinical diseases can be used as effective indicators to estimate and pre-diagnose the disease.

Specific regions of the cerebral cortex will be activated after the stimulus, reflecting a significant change in the MR signal and the standard response curve is called hemodynamic response function (HRF) [22-24], reflects local blood oxygen content of specific cortical neurons over time after stimulation, corresponds microscopic neuronal activity with macroscopic nuclear magnetic resonance signals.

As the basic state of human body, the resting state integrates various basic functions including sensation, perception, memory and emotion, enjoys great importance in clinical practice as well as a meaningful research spot [20, 25, 26]. Considering the typical symptom of decreased memory with decline in cognitive abilities, we hypothesize that the region associated with memory processing and extraction will decrease in neuronal activity and sensitivity, as shown by a drop peak value, prolonged relaxation time and reduced activation in the HRF curve.

However, the discussion of HRF attains a basic presupposition: the type and onset time of the stimulus input shall be explicit. That’s to say, the HRF research of resting state is limited since the lack of a well-defined stimulus input or in usual definition there is no stimulus input indeed. In response to such contradictions, we expect to introduce an equivalent activation to solve the definition efficiency. According to actual signal, it is found that the resting fMRI data is not in a completely irregular mess but a periodic dynamic balance [27-29]. The resting state analysis by numerous data samples and acquisition methods reveals the dynamics of the resting state exhibits a periodic oscillation even when there is no external stimulus input. The entire process also acclaim peak, propagation and positioning information, satisfies the physiological signal propagation of neuronal cells [30, 31]. Based on such facts and theoretical conjectures, we combine all spontaneous activities into an equivalent input called pseudo-event [31-33] so that the resting state BOLD signal can be considered as spontaneous event-related union. The stimulus leads to a similar waveform change in MR signal just like former defined HRF in task-oriented process, which is quite suitable for the dynamic balance of resting state itself. On the other hand, it effectively solves the dilemma that the resting state is not an activating state, expanding the range of applications of the hemodynamic response function.

We propose to extract the HRF from those pseudo-events. According to the balloon model and neurophysiological phenomena, the HRF reflects the activity of cerebral cortical neurons in voxels, coming from the volume change of vessel and resuming velocity of the blood oxygen [34-36]. We extract the peak, relaxation time (time to peak) and full width half max (FWHM) to represent the activity, sensitivity, and activation capacity of neuronal cells respectively [36].

Support Vector Machine (SVM) is the most widely used, most concise and accurate supervised learning model in the field of machine learning, especially in the data classification problem [37, 38]. Based on the existing research, we extract three parameters as listed as the input of the support vector machine (SVM) to perform the two-class classification from the specific activation regions based on the anatomical structure and the functional network. We expect to find the areas changed associated closely with brain function in SCD phase to early detect and predict the group with high risk of AD.
2. Material and Methods

2.1. Participants and data collection
The participants were divided into experimental group (SCD) and healthy control (HC) group. The population with SCD was collected and confirmed by Department of Neurology, Xuan Wu Hospital. A total of 32 SCD patients and 45 healthy controls were included, right-handed, with no other related diseases. There was no significant difference (p>0.05) in sex, age, education nor the score in clinical examination: Mini-mental State Examination (MMSE), CDT test and etc., all details show as in Table 1.

|                          | Subjective Cognitive Decline | Healthy Controls | P value |
|--------------------------|-----------------------------|-----------------|---------|
| Gender (Female/Male)     | 19/13                       | 29/16           | 0.66    |
| Age (years)              | 64.69±8.22                  | 62.82±8.92      | 0.36    |
| Education (years)        | 11.91±3.90                  | 12.6±4.69       | 0.50    |
| NMSE                     | 27.88±1.63                  | 28.47±2.22      | 0.21    |
| CDT                      | 2.72±0.57                   | 2.84±0.47       | 0.32    |

Clinical BOLD fMRI data were scanned by the Siemens 3T TrioTim magnetic resonance system. The T1 weighted image was obtained by fast gradient echo of 3D pre-magnetization with the following parameters: Slices = 176, TR = 1900 ms, TE = 2.2 ms, inversion time (TI) = 900 ms, FA = 90°, field of view (FOV) = 256×256 mm, the matrix is 256×256, and the thickness is 1 mm. The functional phase parameters are as follows: Slice=239, TR=2000ms, TE=40ms, FA=90°, field of view (FOV) = 64×64 mm, the obtained matrix is 64×64, the layer thickness is 4 mm, and the layer spacing is 4 mm.

2.2. Maintaining the Integrity of the Specifications
Preprocessing of resting-state images was performed using the Statistical Parametric Mapping software (SPM12, https://www.fil.ion.ucl.ac.uk/spm/). The acquired data was first applied with slice timing and realignment to remove noise and artifacts, improve the signal-to-noise ratio; then normalize the individual brain to the standard MNI space, after spatial smoothing and covariate removal to improve data quality for subsequent processing.

![Figure 1](image.png)

**Figure 1.** the processing procedure for raw BOLD signal includes:1) the usual preprocessing to Normalized MNI space date;2) point process analysis to sample and filter the signal for a model rebuilding;3) cycling simulation to a best-fit HRF model;4) Parameter extraction and SVM classification.
2.3. **Point process analysis for equivalent stimulus**

The point process analysis preserves the signal band by sampling and filtering the resting state BOLD signal exceeding the threshold. New waveform reserved amplifies the change of the BOLD signal compared to the original sequence [31]. The point process analysis does not cause information loss other than phase change, the network reconstructed is basically the same as the network obtained from the original signal. The phase delay is reflected in the onset of the activation but there is no mis-locating nor mis-transmission in the activation propagation area [30, 31, 33].

These periodic dynamic fluctuations are treated as equivalent resting state spontaneous stimuli and the localization and propagation of the activation region are well-preserved without loss. The corresponding hemodynamic response function is further obtained by extracting the equivalent stimulus in this procedure [32, 35].

2.4. **Model optimization of Hemodynamic Response Function**

For the shape and parameters of the hemodynamic function, there have been many aspects of simulation exploration, including: 1) the classic SPM built-in model and its variants; 2) finite impulse response model and its variants; 3). The Inverse Logit model, the most widely used one is the classic HRF model used in SPM software [33, 39-41].

\[
 h(t) = A \left( \frac{t^{\alpha_1 - 1} \beta_1^{\alpha_1} e^{-\beta_1 t}}{\Gamma(\alpha_1)} - c \frac{t^{\alpha_2 - 1} \beta_2^{\alpha_2} e^{-\beta_2 t}}{\Gamma(\alpha_2)} \right)
\]

(1)

This function is a mixture of two gamma functions, including six unknown parameters, t represents time, \( \beta_1 = \beta_2 \), simple and intuitive, fits well with the convolution characteristics of HRF. The form of gamma function proposed by Cohen can describe the corresponding ion flow for nerve current [32]. However, the coupling effects between parameters is not considered, the obtained model is not all optimal in accuracy and fitting effect. To solve this problem, we use the combination of parameter sensitivity analysis and genetic algorithm to optimize the global hemodynamic response function [39]. In order to obtain more accurate results, the study introduced corrections in the simulation process, including its time derivative (first derivative) and dispersion derivative (second derivative), on the other hand, we also introduced residuals solution to avoid overfitting. The model is continuously modified for more fitted results in voxel units by controlling the difference between each two round simulations [42, 43].

Through the combination of Latin hypercube sampling and spearman rank correlation analysis theory, the sensitivity of parameter in the model is carried out [42]. The value range is taken as the initial search interval and the global optimal search is performed for each parameter in combination with the genetic algorithm theory. We get the optimized value considering the mutual coupling change of each parameter. The optimized model can better describe and predict the actual HRF, along with a certain improvement in the fitting effect and experimental prediction accuracy compared with ordinary Cohen's model.

2.5. **Binary-classification process based on SVM**

We selected 18 typical region of interest (ROI) as target lesions for classification based on previous studies and clinical experience as listed in Table.1. According to the research on AD and MCI stage, the deactivations were already discovered in hippocampus, posterior cingulate cortex (PCC) and frontal lobe, in other words, these regions could be a potential lesion for SCD population [7, 19, 20, 39-42].

What’s more, the default mode network (DMN) of resting state has been a research spot due to the special link with anatomical structure and functional activities [43, 44]. The graph theory gives out a possible explanation for deactivation that the information flow is weakening and transmission declines in primary functions like vision, motor and sensory, which are directed specific network components mentioned before [18, 20, 45-47]. Research showed some different changes in occipital lobe and temporal lobe.
The clinically relevant areas like were also selected as references. Among the frontal lobe (emotion, feeling and perception mainly), we select a number of possible areas, including fusiform (responsible for face recognition), Superior Frontal Gyrus (language-specific area), upper and back gyrus (motor and sensory). Hippocampus and ParaHippocampus is a key spot for memory processing especially working memory and spatial memory, which is highly related to neurodegenerative disease like AD [41].

The size of each region is 3mm×3mm×3mm, extracting three typical parameters of the region: peak, time to peak and full width half maximum (FWHM) to perform binary classifications using SVM classification package built in the MATLAB.

| Location                  | MNI coordinate | Related research                                                                 |
|---------------------------|----------------|----------------------------------------------------------------------------------|
| Temporal_Pole_Sup_L (aal) | -33 -21        | brodmann area 28 brodmann area 6                                                |
| Temporal_Inf_R (aal)      | 51 39 -51      | Fusiform_R (aal) Limbic Lobe                                                      |
| ParaHippocampal_L (aal)   | 0 33 -48       | brodmann area 28 brodmann area 11                                                |
| Frontal_Inf_Tri_L (aal)   | -42 27 27      | Middle Frontal Gyrus                                                             |
| Occipital Lobe            | 51 -99 6       | Brodmann area 19 Associative Visual Cortex brodmann area 18 Secondary Visual Cortex V2|
| Calcarine_R (aal)         | -9 -90 -12     | brodmann area 18 brodmann area 17                                                |
| Calcarine_L (aal)         | -45 -102 -15   | brodmann area 17 brodmann area 18                                                |
| Superior Frontal Gyrus    | 36 33 9        | Frontal_Sup_Medial_R (aal) Frontal_Sup_Orb (aal)                                |
| Temporal_Mid_L (aal)      | -48 -39 3      |                                                                                  |
| Cerebellum Posterior Lobe | -39 -102 -39   |                                                                                  |
| Temporal_Inf_L (aal)      | -60 -30 -30    | brodmann area 20 brodmann area 37                                                |
| Fusiform_R (aal)          | 33 -21 -30     | brodmann area 20 brodmann area 36                                                |
| Cingulate Gyrus           | 12 6 36        | Limbic Lobe brodmann area 24 brodmann area 9 brodmann area 5 brodmann area 31   |
| Frontal_Mid_L (aal)       | -39 45 33      | brodmann area 9                                                                  |
| Superior Frontal Gyrus    | 0 63 36        | Frontal_Sup_Medial(aal)                                                          |
| Parietal_Inf_R (aal)      | 81 -51 51      | brodmann area 40                                                                 |
| Medial Frontal Gyrus      | 12 78 21       | Frontal_Med_Orb(aal)                                                             |
| Precuneus_R (aal)         | -21 -60 39     | Precuneus brodmann area 7                                                         |

3. Results
The neuronal activity within the unit voxel is consistent in definition and the activities are performed in an all-or-nothing manner. The HRF directly reflects the activation of neurons after stimulation, the change in blood oxygen flow result in a consistent regional response in voxel size. The superposition of blood
oxygen flow is linear and the calculation of the same signal superposition requires a convolution formula[22].

Using the extracted parameters; peak, time to peak and FWHM, the 18 selected ROI are respectively classified by SVM standard package. The accuracy of specific regions can reach 73.3%. We regard the results over 60% as potential possible reference in clinical, about 1/3 single-parameter classification achieve the requirement. For binary classification using all three parameters, the result can be up to 77.8%, all regions appeared a better classification ability. The specific results are shown in the following table:

| Location                     | Single-Parameter Classification | 3-Parameter Classification |
|------------------------------|--------------------------------|-----------------------------|
|                              | Fwhm  | Peak  | Time to peak | Fwhm  | Peak  | Time to peak |
| Temporal_Pole_Sup_L (aal)    | 55.6% | 57.8% | 62.2%        | 57.8% |
| Temporal_Inf_R (aal)         | 57.8% | 57.8% | 55.6%        | 60.0% |
| ParaHippocampal_L (aal)      | 55.6% | 66.7% | 66.7%        | 68.9% |
| Frontal_Inf_Tri_L (aal)      | 55.6% | 73.3% | 57.8%        | 77.8% |
| Occipital Lobe               | 55.6% | 55.6% | 66.7%        | 64.4% |
| Calcarine_R (aal)            | 60.0% | 62.2% | 60.0%        | 64.4% |
| Calcarine_L (aal)            | 62.2% | 62.2% | 64.4%        | 62.2% |
| SuperiorFrontal Gyrus        | 66.7% | 57.8% | 64.4%        | 68.9% |
| Temporal_Mid_L (aal)         | 60.0% | 55.6% | 64.4%        | 71.1% |
| Cerebellum Posterior Lobe    | 60.0% | 60.0% | 55.6%        | 55.6% |
| Temporal_Inf_L (aal)         | 55.6% | 62.2% | 55.6%        | 66.7% |
| Fusiform_R (aal)             | 68.9% | 60.0% | 64.4%        | 73.3% |
| Cingulate Gyrus              | 68.9% | 55.6% | 62.2%        | 73.3% |
| Frontal_Mid_L (aal)          | 55.6% | 57.8% | 62.2%        | 68.9% |
| Superior Frontal Gyrus       | 55.6% | 55.6% | 62.2%        | 62.2% |
| Parietal_Inf_R (aal)         | 71.1% | 60.0% | 55.6%        | 64.4% |
| Medial Frontal Gyrus         | 73.3% | 68.9% | 66.7%        | 71.1% |
| Precuneus_R (aal)            | 57.8% | 55.6% | 57.8%        | 60.0% |

Based on the two-sample T-test of the parameters obtained, regional trends are consistent in the whole brain while some cerebral cortex showed significant change. For the peak, almost all target areas showed a decline compared to the healthy control group. Among them, the right side of the frontal fusiform gyrus and the sacral gyrus (clamping back) were significantly different. In addition, there was a significant difference between the right upper edge (the right lower back) and the central anterior (frontal medial).

**Figure 2.** The two-sample T-test of the whole brain signal in the HC vs SCD group, the trend in the whole brain range was consistent and the indicators of HRF in the SCD group showed significant decline, and the performance in the local area was obvious;

For the peak of the HRF, the SCD group showed a significant decline in the whole brain scale. Among them, the difference between the left hippocampus and the triangular forehead is more obvious. The classification accuracy is as high as 73.3%. The relaxation time prolonged and there was a significant difference between the left hippocampus and the occipital lobe. The classification accuracy rate remained at 66.7%.
There is a clear difference based on selected parameters in the hippocampus, the left triangular portion and the central front. The classification rate using all three parameters are better and the areas with obvious distinguishing effects increase. The left middle sacral gyrus, the right fusiform gyrus and the left frontal middle gyrus appear higher classification accuracy. Among them, the classification accuracy of Frontal_Inf_Tri_L appears about 80%, which is very referable for the clinical pre-diagnosis of the disease.

4. Discussion
According to the latest standard of ATN, the AD diagnosis needs the confirmation of two pathological markers: amyloid protein (Aβ) and Protein Tau [2]. Clinical examination usually takes PET-CT imaging or lumbar puncture cerebrospinal fluid (CSF). However, the PET-CT is radiative and expensive while the CSF is invasive, causing it difficult to popularize in the SCD group [2, 5]. As a newly established early stage of Alzheimer’s Disease, the conventional imaging methods and neuropsychological test cannot effectively distinguish the SCD and the clinical diagnosis merely rely on doctors’ personal experience with follow-up caring to give out doubt and confirmation. It is badly in need of new methods and parameters for determining target population for early-stage prediction [8, 10, 15].

The activities of human brain in resting state is considered to be an uninterrupted, spontaneous behavior, therefore, we generally think continuous resting-state brain activity closely related to brain electrophysiological activity [17-19, 21]. We regard the preparatory state of basic functions including sensory, perception, motor, language and emotion as cyclical equivalent stimulus to generate the hemodynamic response, thinking the actual characteristic of resting-state BOLD signal. Each round of blood oxygen change caused by neuron activity can lead to a consistent areal responding curve-the Hemodynamic Response Function.

4.1. Hemodynamic Response Function reflects neuron sensitivity and activating ability
HRF is closely related to the metabolism and basic process of neuronal ion channels, reflects the working state of neurons, which are closely related to the information processing flow, the transmission mode and the corresponding explicit memory feelings.

The local peak variation band of the resting state data is amplified and extracted by the point process. After modeling on the basis of the standard SPM-built function, we select and extract the most prominent parameters: peak, time to peak, full width of half maximum to classify patients from healthy controls.

The completely new research of resting-state HRF opens up the connection between microscopic neuron activity and macroscopic clinical manifestation. The peak and the FWHM shows the activation ability represent the activity of neuron cells when exposed to stimuli while the time-to-peak reflects the sensitivity of neurons [22-24].

4.2. The peak value in SCD group decrease apparently in Fusiform and Vision-related area
The decline of peak value focus on the Cuneus and frontal lobe, especially on the left side of frontal lobe. The changing trend between SCD and HC is decreasing in the large scale, indicating the neurons may be less active when appealing to the stimuli.

Among the changing regions in the frontal lobe, there is a significant difference in the Fusiform gyrus, which is associated with the function of face recognition. The clinical symptom of agnostic may also be due to degradation in this area. Psychologically, the existence of self-consciousness and self-cognition is a special indication in human being, it’s a high-grade and complicated issue following with language and high-level understanding [53-55]. The trick is that the weakening in fusiform is discovered in so many brain-related diseases no matter physically or mentally like autism or depression. However, there lacks available examination in direct against the face-recognition function in clinical.

In this study, the triangle of inferior temporal lobe showed a particularly prominent differentiation and the global overall classification accuracy rate reached as high as 77.8%. The area Inf_Tri_L is located in the central sulcus, which is a joint union of multiple Broadman subregions, which means it shall be varied in multiple specific function, broadman8 participate in the eye motion, broadman18 and
broadman19 are responsible for secondary visual processing, like imaginary visual effects and perception. In particular, there is a significant difference in the occipital region while this region is quite rare in previous studies.

According to clinical cases, eyesight efficiency could be a concomitant symptom of Alzheimer and some of the self-reported SCD patients acclaim they suffer from blurred vision as well [52, 56-58]. After confirmation with patients, they do acclaim efficiency in eyesight, however, the controversy is that the secondary visual processing like imaginary visual effect could also give out a similar signal change in these areas even no explicit visual stimulation is pointed cause the vision takes the widest area across almost the whole cortex [57]. It is speculated that the sample size is not too large and a certain type of visual dysfunction in the clinic could be over influenced. It needs further and expanded research for general conclusion in the area of Inf_Tri central sulcus and occipital lobe.

4.3. Time-to-peak prolonged reflects deactivation in emotion-related area

The time-to-peak value has close relationship with the neuron sensitivity, it gives out the general acting state of the cortex due to the characteristic of voxel-consistent. As for resting state itself, a preparatory state for potential activating and response, the time-to-peak value shows the relaxation time in loose state towards later activations.

Time-to-peak value in SCD group appears significantly extension and the change area mainly concentrate in the frontal lobe, in addition, the caudate nucleus and thalamus also appeared in the report. These two areas participate in emotion processing mainly [59], especially negative feeling inhibition and basic instinct perception, causing the people more addicted to the down spirits, less positive towards life [56, 60]. Low emotion could be a major symptom along with memory efficiency as well, the Alzheimer could be more like depression disease in the origin period.

The most used behavioral examination in clinical is NMSE and CDT test, however, they are just designed for common and basic cognitive abilities rather than specialized for Alzheimer’s Disease dementia [61]. The finding that negative-emotion related region loose and less preparation for activation may help lead to more directed examination for AD. Usually the test doctors choose mainly focus on the memory processing and decision-making tasks, the findings here highlight another possible changing aspect especially in the very early stage of neurodegenerative dementia. Also, the distinction between AD and normal emotion disorder like depression shall be a necessary research spot.

4.4. FWHM decrease mainly focus in Hippocampus

In the comparison of FWHM, the value appeared obvious decrease in hippocampus and temporal lobe. Both of them involved in the emotion perception and information processing, consistent with the clinical symptoms of Alzheimer's disease.

The hippocampus plays a critical role in the formation, organization, and storage of new memories as well as connecting certain sensations and emotions to these memories, usually take responsibility to working memory/short-term memory.

As a basic component of Limbic system, research has also found that different subregions of the hippocampus itself play important roles in certain types of memory. The rear part of the hippocampus is involved in the processing of spatial memories. Studies of London cab drivers have found that navigating complex mazes of big city streets is linked to the growth of the rear region of the hippocampus [62].

The hippocampus also plays a role in consolidating memories during sleep. Studies suggest that greater hippocampal activity during sleep following some sort of training or learning experience leads to better memory of the material the following day. People get less sleep time and worse sleep quality following with the aging process, causing the hippocampus hard to take in information, register and temporarily store it before it being filed and stored in long-term memory. Damage to the hippocampus can also result from oxygen starvation (hypoxia), encephalitis, or medial temporal lobe epilepsy. People with extensive, bilateral hippocampal damage may experience anterograde amnesia (the inability to form and retain new memories) [46, 63, 64].
In conclusion, the SCD group showed peak decrease, relaxation time extension and a FWHM decrease compared with the HC group, which is highly consistent with the clinical symptoms about the decline of memory ability and emotional abnormally down.

The changing regions are widely distributed, including frontal, temporal, occipital and limbic system. Many of the selected 18 ROIs showed significant differences, especially in the hippocampus and its gyrus, Frontal_Inf_Tri_L of the frontal lobe and the central anterior gyrus, the regional classification accuracy reached over 73%, which it is already a very credible reference for clinical. In previous studies, these areas were typical variants of Alzheimer's disease. Other imaging methods and parameters failed to detect or confirm any obvious signs of disease, especially during the SCD stage.

On the basis of the research, we chose five regions that binary classification over 70% for clinical diagnosis among the 18 original selected ROIs (Frontal_Inf_Tri_L, Temporal_Mid_L, Fusiform_R, Cingulate Gyrus and Medial Frontal Gyrus), thinking to the outstanding results in single-parameter classification, three more regions were added as well: ParaHippocampal_L, Occipital Lobe, Parietal_Inf_R.

The innovation of the study is to combine the advantage of date-oriented model estimation and data-driven classification, we extract the HRF parameters from selected cortex lesions based on the previous research of AD along with the cortex corresponding to clinical symptoms including frontal lobe, occipital lobe, fusiform, default mode network, etc. At the same time, we innovatively introduce the equivalent stimuli to extend the definition and usage of HRF into resting state in consideration of the intrinsic dynamic equilibrium. The point process just work as an extension of the sparse sampling, subtly filters and amplifies the local peaks information, avoiding data loss. The obtained equivalent activation curve is

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