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A Study of Subjective Cognitive Decline and Subclinical Depression Based on Dynamic Network Connectivity of Cerebral fMRI Data

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Abstract: A certain number of fMRI studies on subjective cognitive decline (SCD) have been widely debated. They mainly focus on the differences in brain structure and function between SCD and normal people, while more studies focus on objective cognitive decline. The relationship between psychological factors and SCD via cerebral fMRI data in the elderly is rarely discussed. In this study, we included 66 SCD patients and 63 normal controls (NC) to investigate the neural processes amid the psychological aspects of those with subclinical depression and SCD using dynamic network connectivity and to provide theoretical support for neuroimaging for improved Alzheimer's disease prevention and therapy. We calculated temporal flexibility and spatiotemporal diversity via fMRI data using Shen's 268 brain template and No. 74 brain region was selected by t-test and correlation analysis. In the NC group, no significant correlation was observed in temporal flexibility value of No. 74–SCD and Hamilton depression scale HAMD–SCD, whereas No. 74–HAMD showed a significant correlation. In the SCD group, all of the three parameters exhibited significant correlation. Mediation analysis obtained the mediation model of No. 74 brain region, subclinical depression, and subjective cognitive decline (No. 74→HAMD→SCD). The results show that visual system plays an important role in subclinical depression, and subclinical depression increases the risk of SCD.

Keywords: Subjective Cognitive Decline, Subclinical Depression, Dynamic Network Connectivity, Temporal Flexibility, fMRI

1. Introduction

Subjective cognitive decline (SCD) is a condition in which older adults show persistent concerns about their cognition and a subjective decline compared to their usual baseline cognitive ability [1]. Some common diseases, including neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease, cerebrovascular diseases, inflammatory encephalopathy, and craniocerebral trauma, can trigger subjective cognitive decline in patients. Substance abuse or other drugs (e.g., sedatives, anticholinergics, opioids, and corticosteroids) can also affect cognition. Emotional factors, such as anxiety and depression, complicate the question of whether SCD is predictive. Sinoff et al. proposed that anxiety is inextricably associated with subjective memory decline and that anxiety may be a strong predictor of future cognitive decline [2]. Subsequently, Jessen et al. also found that depression and anxiety may aggravate the occurrence of SCD, and SCD may also promote the development of both [3]. The study by Hill et al. verified the above conclusion and found that there was a positive correlation between SCD and depressive symptoms. At the same time, individuals with SCD would be more worried about cognitive impairment, resulting in anxiety [4], so SCD is also closely related to anxiety. This suggests caution when exploring the relationship between SCD and MCI and AD, because even subjective cognitive decline is

likely to be due to emotional factors such as depression or anxiety, or to personality factors.

Functional magnetic resonance imaging (fMRI) can detect the activity status of neurons and evaluate whether there are functional abnormalities by comparing the blood oxygenation-dependent signals caused by neuronal activity. Studies on AD pedigree have found that there are differences in cognitive performance, regional gray matter atrophy pattern, and functional connectivity among SCD, mild cognitive impairment (MCI), and AD, and there is an association between cognitive domain score and regional atrophy and networking-specific functional connectivity [5]. Wang et al. [6] found in their study that the amplitude of low frequency fluctuation (ALFF) in the lingual gyrus and superior frontal gyrus of patients with SCD and MCI increased, and they had similar abnormal activation. SCD patients have low average functional connectivity in various regions of the posterior memory system, especially in the posterior cingulate gyrus and precuneus [7]. Studies have shown that functional connectivity between the default mode network (DMN) and the hippocampus is reduced in SCD patients [8]. In contrast, another study found increased local and metaphase connectivity between the bilateral parahippocampal gyrus and other DMN-related regions in SCD patients, which may reflect a compensatory mechanism for the retention of memory performance in SCD individuals [9].

In addition, dynamic functional connectivity can quantify the changes of brain networks over time, which is beneficial for exploring the dynamic brain changes in neurodegenerative diseases. Recent studies have also shown that DMN-dominated dynamic functional connectivity and dynamic ALFF are significantly different from MCI in SCD patients [10]. In addition to DMN, SCD and MCI showed changes in dynamic functional connectivity variability in the salience network and executive control network compared with healthy elderly people [11]. Compared with traditional rs-fMRI, dynamic network connectivity is more accurate in differentiating SCD from healthy people [12].

Although we can see a certain number of fMRI studies on SCD, they mainly focus on the differences in brain structure and function between SCD and normal people, and more studies focus on objective cognitive decline. The relationship between psychological factors and subjective cognitive decline via cerebral fMRI data in the elderly is rarely discussed. It is necessary to carry out research to fill the gap in this field. In this study, we aimed to investigate the neural processes amid the psychological aspects of those with subclinical depression and SCD using dynamic network connectivity and to provide theoretical support for neuroimaging for improved AD prevention and therapy. We hypothesized that a number of neuronal activities in human brain had an impact on SCD and subclinical depression.

2. Materials and Methods

2.1. Participants

In this research, we included 66 SCD patients and 63 normal controls (NC) from the Department of Neurology at Xuanwu Hospital of Capital Medical University. The Medical Research Ethics Committee and the Xuanwu Hospital Review Committee both gave their approval for this research. Every subject gave their informed permission. The inclusion and exclusion criteria were the same as in our previous study [12].

2.2. Data Acquisition and Preprocessing

The criteria for data collection were similar to those previously mentioned [12]. All participants underwent a standard clinical evaluation, which included a review of their medical and family histories, a physical examination, standard blood tests, and evaluation using a battery of neuropsychological tests. It also included a review of their current medications and a physical examination.

Neuroradiologists with expertise in evaluating magnetic resonance imaging (MRI) scans looked at the scan quality and eliminated any pictures with artifacts. The DPARSFA [13] toolkit, which is based on MATLAB, was used to do the typical preprocessing on all MRI data. Anatomical and functional scans were coregistered. Slice time correction, head motion correction, linear drift removal, low-frequency filtering, spatial smoothing with a 4-mm Gaussian kernel, and spatial normalization into MNI space were all included in this preprocessing, which was primarily concerned with converting the original data format (DICOM) to a usable format.

2.3. Temporal Flexibility and Spatiotemporal Diversity

Temporal flexibility measures how often a brain area connects with regions outside of its own community across time and is a stable aspect of the dynamic patterns of time-varying connectivity [14]. A region's high temporal flexibility suggests that it mostly interacts with regions from other groups. Spatiotemporal diversity measures the consistency of a brain region's interactions with other populations' areas throughout time. High spatiotemporal diversity indicates that the distribution of these interactions across groups is equal [14, 15]. If a brain area primarily interacts with other regions in just one community, it may not exhibit great spatiotemporal diversity. Regarding the geographical distribution of time-varying connectivity, spatiotemporal diversity offers further information [14, 15]. Together, spatiotemporal diversity and temporal flexibility provide vital indicators of the dynamics of the functioning brain [14].

A functional brain template with 268 brain areas was employed [16]. Eight different functional networks were created from these brain areas. With the previously specified group static community and the temporal co-occurrence matrix, we determined the dynamic graph theoretic properties of each node—temporal flexibility and spatiotemporal variety. The specific calculation formula and procedure adhere to our earlier study [12].

Two-sample t-test was used to compare the difference between NC and SCD by temporal flexibility and

spatiotemporal diversity. Pearson correlation analysis was used to measure the correlation between two parameters [17].

2.4. Mediation Analyses

The PROCESS v4.1 toolbox [18] was used to investigate the mediation effect. The bias-corrected percentile bootstrap CI technique was used to do parameter verification. The algorithm's basic idea is to sample N samples first at random and again for N times, after which the estimated value E of the mediation effect is determined using the N samples. The estimated values of these M mediation effects are taken as the point estimate value of the mediation effect after the aforementioned stages have been performed M times (5000 times in this article). The 2.5 percentile and 97.5 percentile of sequence C were used to determine the 95% confidence interval of the mediation effect after the M estimated values were sorted to produce sequence C.

3. Results

3.1. Demographic Characteristics

Demographic details are summarized in Table 1.

Table 1. *Group characteristics and subject demographics.*

	SCD N = 66	NC N = 63	t or $\chi 2$	p
Age (year)	65.8±5.17	64.3±5.56	1.6399	0.7734
Gender (female / male)	41 / 25	32 / 31	$\chi 2$= 1.684	0.1944
Years of education	11.7±2.93	11.9±3.33	-0.2656	0.7244
BMI	24.4±2.61	25.2±2.80	-1.7593	0.6682
MES	88.53±7.17	89.68±7.26	-0.9070	0.9882
HAMD	5.74±4.29	2.24±2.39	-5.6948	<0.0000
CFs	5.32±2.37	5.46±2.34	0.3423	0.7327
SCD-9	5.30±1.82	3.10±2.19	-6.2313	<0.0001
MMSE	28.7±1.22	28.7±1.29	0.0556	0.3860

MES: Memory and executive function screening instrument
HAMD: Hamilton depression scale
CFs: Close friends
SCD-9: Subjective cognitive decline questionnaire of 9-item
MMSE: Mini–mental state examination

3.2. Results of Temporal Flexibility and Spatiotemporal Diversity

A total of 116 temporal flexibility brain regions and 56 spatiotemporal diversity brain regions showed significant differences ($p < 0.05 / 268 = 0.00019$). They are: (1) temporal flexibility: No. 1, 2, 13, 14, 15, 16, 17, 19, 22, 27, 29, 30, 32, 33, 35, 36, 37, 39, 40, 42, 43, 44, 45, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 63, 66, 67, 68, 69, 70, 71, 72, 73, 74, 77, 78, 79, 80, 81, 82, 83, 85, 89, 90, 93, 99, 101, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 115, 117, 118, 119, 123, 125, 127, 130, 131, 132, 133, 134, 136, 144, 147, 148, 149, 150, 153, 154, 155, 157, 158, 159, 160, 161, 163, 167, 171, 172, 186, 198, 224, 232, 234, 250, 251, 252, 254, 257, 261, 262, 263, 265, 268; (2) spatiotemporal diversity: No. 5, 47, 62, 74, 93, 99, 102, 103, 104, 106, 107, 108, 109, 110, 111, 112, 115, 117, 118, 119, 120, 123, 126, 127, 133, 134, 143, 145, 147, 148, 149, 150, 152, 154, 155, 156, 157, 158, 159, 160, 161, 163, 164, 166, 170, 171, 172, 198, 206, 222, 235, 246, 250, 257, 262, 268. Thirty-nine brain regions were repeated. They are: No. 47, 62, 74, 93, 99, 106, 107, 108, 109, 110, 111, 112, 115, 117, 118, 119, 123, 127, 133, 134, 147, 148, 149, 150, 154, 155, 157, 158, 159, 160, 161, 163, 171, 172, 198, 250, 257, 262, 268.

Pearson correlation was used to calculate the correlation between the temporal flexibility and spatiotemporal diversity value of repetitive brain regions and scale parameters (HAMD and SCD-9), with age, gender and years of education as covariates for partial correlation. Only patients with SCD showed a correlation between temporal flexibility value of No. 74 brain region and both HAMD and SCD-9. Figure 1A shows the location of No. 74 brain region with Peak MNI coordinate (21, 12, -27; ParaHippocampal_R in AAL template) and center of gravity MNI coordinate (20, 17, -20; Frontal_Inf_Orb_R in AAL template).

In the NC group, no significant correlation was observed in No. 74–SCD-9 ($r = 0.0379$, $p = 0.7737$, Figure 1B) and HAMD–SCD-9 ($r = -0.0131$, $p = 0.9211$, Figure 1D), whereas No.74–HAMD showed significant correlation ($r = 0.2862$, $p = 0.0267$, Figure 1C). In the SCD group, all of the three parameters exhibited significant correlation: No. 74–SCD-9 ($r = 0.2620$, $p = 0.0380$, Figure 1B), No. 74–HAMD ($r = 0.3047$, $p = 0.0152$, Figure 1C) and HAMD–SCD-9 ($r = 0.3605$, $p = 0.0037$, Figure 1D).

In the slope test, a significant difference existed between NC and SCD in HAMD–SCD-9 ($Z = -2.49$, $p = 0.0128$, Figure 1D), whereas no significant difference existed between NC and SCD in No. 74–SCD-9 ($Z = -1.01$, $p = 0.3125$, Figure 1B) and No. 74–HAMD ($Z = -0.04$, $p = 0.9681$, Figure 1C).

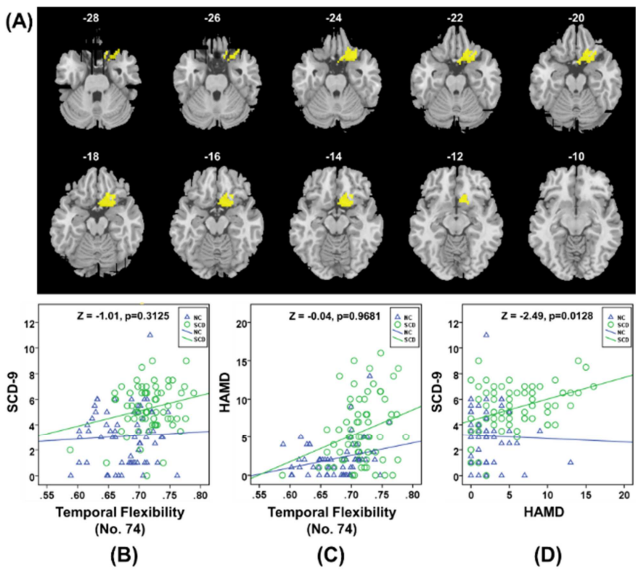

Figure 1. *(A) the location of No. 74 brain region in Shen's 268 brain template [19] with Peak MNI coordinate (21, 12, -27; ParaHippocampal_R in AAL template) and center of gravity MNI coordinate (20, 17, -20; Frontal_Inf_Orb_R in AAL template); (B) no significant difference existed between NC and SCD in No. 74–SCD-9 and (C) No. 74–HAMD; (D) a significant difference existed between NC and SCD in HAMD–SCD-9.*

3.3. Results of Mediation Analyses

The aforementioned statistical study revealed a pairwise correlation between the temporal flexibility value of the No. 74 brain area, HAMD, and SCD-9 in the SCD group. So, using age, gender, and years of schooling as covariates, we ran a mediation study. The substantial (and complete) mediated association was maintained (Figures 2A). Table 2 provides the indirect impact and 95% confidence interval of the mediation effect for each of the six models. If the confidence interval contains 0, there is no mediation connection; if it does not, there is a substantial (and complete) mediation relationship.

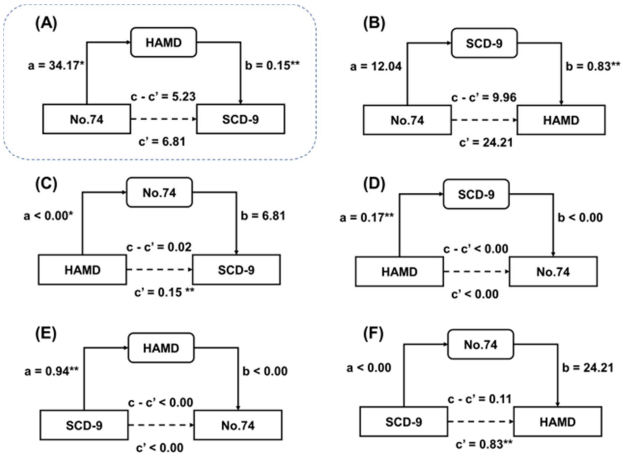

Figure 2. *Results of mediation analysis between temporal flexibility value of No. 74 brain region, HAMD and SCD-9. (A) showed a substantial (and complete) mediated relationship while no mediated relationship exists in (B), (C), (D), (E) and (F) models.*

Table 2. *The indirect effect value and 95% confidence interval of the mediation effect of the six models.*

Mediation relation	Indirect effect (X on Y)	BootLLCI (95%)	BootULCI (95%)
No.74→HAMD→SCD-9	5.23	0.3145	11.3170
No.74→SCD-9→HAMD	9.96	-1.9612	23.2633
HAMD→No.74→SCD-9	0.02	-0.0125	0.0605
HAMD→SCD-9→No.74	<0.00	-0.0004	0.0016
SCD-9→HAMD→No.74	<0.00	-0.0001	0.0041
SCD-9→No.74→HAMD	0.11	-0.0291	0.3399

4. Discussion

In this study, HAMD and SCD-9 scores showed a significant difference between SCD group and NC group. Through dynamic network connectivity via fMRI data of two groups of participants, we calculated two very important brain network parameters: temporal flexibility and spatiotemporal diversity. Shen's 268 brain template was used. No. 74 brain region was selected by t-test and correlation analysis. In the NC group, no significant correlation was observed in temporal flexibility value of No. 74–SCD-9 (Figure 1B) and HAMD–SCD-9 (Figure 1D), whereas No. 74–HAMD showed a significant correlation (Figure 1C). In the SCD group, all of the three parameters exhibited significant correlation: No. 74–SCD-9 (Figure 1B), No. 74–HAMD (Figure 1C), and HAMD–SCD-9 (Figure 1D). Mediation analysis obtained the mediation model of No. 74 brain region, subclinical depression, and subjective cognitive decline. The fundamental observations are discussed below.

4.1. Visual System Plays an Important Role in Subclinical Depression

There was a significant correlation between temporal flexibility and HAMD in the No. 74 brain region in both NC and SCD groups, and the correlation was stronger in the SCD group (Figure 1C). In Shen's 268 template, brain area No. 74 is classified as visual association regions. The physiology and neural processes of the visual system have been extensively studied and are well known [20]. In recent years, systematic reviews and longitudinal cohort studies have shown that visual impairment increases the incidence of depression in the elderly [21, 22]. Studies have found that older adults with visual impairment show more limitations than their peers in participating in activities, have less social interaction, feel lonelier, and are at risk of developing depressive symptoms [23]. Visual impairment seriously affects the quality of life of the elderly. A large number of studies have found that visual impairment is correlated with depression, but the direction of this correlation is unclear [23]. Some studies have suggested that treating depression with drugs and psychotherapy in the elderly community improves their perceptual function, and some researchers believe that depressive symptoms can explain nearly half of the decline in visual-related subjective quality of life [24]. This suggests that depressive symptoms and visual impairment are mutually affected; that is, visual impairment leads to severe depressive symptoms, and the severity of depressive symptoms in turn aggravates patients' own experience of visual impairment, leading to the subjective deterioration of quality of life caused by visual impairment.

4.2. Subclinical Depression Increases the Risk of SCD

This study found a positive relationship between subclinical depressive symptoms and the subjective cognitive decline score SCD-9 in SCD patients but not in normal controls (Figure 1D). Multiple studies have also shown that depressive symptoms are closely related to subjective memory function, and the more severe the degree of depression, the worse the memory satisfaction and subjective memory ability [25]. This also indicates that depressive symptoms have a greater impact on the overall subjective cognitive decline evaluation score of patients with subjective cognitive decline, which supports the clinical view that depression is a risk factor for the occurrence of cognitive impairment [26]. Elderly patients with depressive symptoms often show delayed thinking, low mood, decreased physical activity, decreased speech activity, and so on. This psychological distress will lead to the decline of their overall cognitive level of self-evaluation. And compared with other general cognitive abilities, memory declines with age, faster executive function, depressed mood and verbal memory,

attention, executive function, visual space, and other fields related [27]. The field of cognitive decline connects to affect people's daily lives, the old year out, such as cooking, financial, medical, etc. As a result, such elderly people's social participation is gradually reduced, their connection with the surrounding environment is also gradually weakened, and the evaluation of their daily executive memory ability is decreased. Therefore, while improving the cognition of patients, attention should be paid to the emotional state of such patients, encouraging them to actively seek to adapt to their own activities and actively participate in them, avoiding self-enclosed bad lifestyles, reducing the occurrence of depression, so as to reduce the occurrence of subjective cognitive decline.

4.3. Relationship Between ORBinf.R / PHG.R and SCD: the Mediating Role of Subclinical Depression

The temporal flexibility value of right Inferior frontal gyrus, orbital part (ORBinf.R) and right parahippocampal gyrus (PHG.R) showed significant correlation with SCD-9 in SCD group (Figure 1B) while the mediation model suggests subclinical depression score (HAMD) play a mediating role between temporal flexibility value of No. 74 region and SCD-9 score. This suggests that it is likely the symptoms of preclinical depression that trigger subjective cognitive decline. The reward or emotional value of basic reinforcers, including taste, touch, texture, and facial expression, is represented by the orbitofrontal cortex. It gains the ability to link other stimuli to these in order to create representations of the predicted reward value for visual, aural, and abstract inputs, including monetary reward value. As a result, the orbitofrontal cortex, which symbolizes the value of rewards associated with action objectives, is crucial to emotion [28]. We draw the conclusion that the orbitofrontal cortex's function has changed in the SCD group. In the encoding and retrieval of memories, the parahippocampal gyrus is crucial. Although participants with subjective cognitive impairment did not exhibit objective cognitive decline, the parahippocampal gyrus underwent alterations. SCD is thought of as a state of increased risk for Alzheimer's disease despite the absence of objective cognitive impairment because those who have it are more likely to display Alzheimer's disease biomarker evidence and, when monitored longitudinally, they are more likely to eventually develop the disease than those who don't have any concerns about their subjective cognition [1, 29]. However, it is still unknown what neurological processes connect SCD with an increased risk of Alzheimer's disease. Self-awareness of memory alteration and mood dysregulation may be the first overt signs of Alzheimer's disease-related neural network disruption in the absence of objective memory impairment. The relationship between depressive symptoms and objective memory capacity may be mediated by SCD because self-perception of memory deterioration may represent greater effort in using encoding and retrieval processes to make up for modest memory malfunction.

5. Limitations and Conclusions

This study has some limitations. First, the number of participants was small, and a longitudinal study was lacking to make the conclusions more convincing. Second, the criterion for the existence of mediation relationship in mediation analysis is that the confidence interval does not include 0. Although we have reached a conclusion, the confidence intervals of some mediation models seem to be very close to 0, which is probably caused by the insufficient sample size. Third, there are many brain regions obtained by binocular t-test, which indicates that the difference between SCD and NC is very complex. The No. 74 brain region we finally selected is only a statistical conclusion, which may need to be verified by physiological experiments.

In conclusion, this study established a relationship between subjective cognitive decline and preclinical depression through two important characteristic parameters of dynamic network connectivity: temporal flexibility and spatiotemporal diversity. The results show that visual system plays an important role in subclinical depression, and subclinical depression increases the risk of SCD.

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