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Neuroimaging of neuropsychological disturbances following ischaemic stroke (CONNECT): a prospective cohort study protocol

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ABSTRACT

Introduction Neuropsychiatric distubance is a common clinical manifestation in acute ischemic stroke. However, it is frequently overlooked by clinicians. This study aimed to explore the possible aetiology and pathogenesis of neuropsychiatric disturbances following ischaemic stroke (NDIS) from an anatomical and functional perspective with the help of neuroimaging methods.

Method and analysis CONNECT is a prospective cohort study of neuroimaging and its functional outcome in NDIS. We aim to enrol a minimum of 300 individuals with first-ever stroke. The neuropsychological disturbances involved in this study include depression, anxiety disorder, headache, apathy, insomnia, fatigue and cognitive impairment. Using scales that have been shown to be effective in assessing the above symptoms, the NDIS evaluation battery requires at least 2 hours at baseline. Moreover, all patients will be required to complete 2 years of follow-up, during which the NDIS will be re-evaluated at 3 months, 12 months and 24 months by telephone and 6 months by outpatient interview after the index stroke. The primary outcome of our study is the incidence of NDIS at the 6-month mark. Secondary outcomes are related to the severity of NDIS as well as functional rehabilitation of patients. Functional imaging evaluation will be performed at baseline and 6-month follow-up using specific sequences including resting-state functional MRI, diffusion tensor imaging, T1-weighted imaging, T2-weighted imaging, diffusion-weighted imaging, arterial spin labelling, quantitative susceptibility mapping and fluid-attenuated inversion recovery imaging. In addition, we collect haematological information from patients to explore potential biological and genetic markers of NDIS through histological analysis.

Ethics and dissemination The CONNECT Study was approved by the Ethics Review Committee of the First Hospital of the University of Science and Technology of China (2021-ky012) and written informed consent will be obtained from all participants. Results will be disseminated via a peer-reviewed journal.

Trial registration number ChiCTR2100043886.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The strength of this study is the use of multimodal imaging relative to other studies for neuropsychiatric disturbances following ischaemic stroke (NDIS).
⇒ Another notable strength of the study is that the longitudinal design allows for the observation of dynamic changes in the NDIS, which addresses the shortcomings of cross-sectional studies.
⇒ This study investigates various imaging indices of the NDIS and combines the results with neuropsychological scores.
⇒ This study researches ischaemic stroke, but neuropsychiatric disorders following other types of stroke need to be explored in the future.
⇒ This study is a single-centre study, which restricts external validity and generalisability.

INTRODUCTION

Ischaemic stroke is a major cause of death and disability globally. It imposes a huge burden on families and socioeconomic life.[1] Acute ischaemic strokes are often followed by various neuropsychiatric disorders, including mood disorders (depression, anxiety, apathy, mania and bipolar disorders), fatigue, cognitive decline, sleep disturbances and pain.[2] Currently, long-term follow-up of stroke survivors by multidisciplinary teams shows that neuropsychiatric disturbance is a frequent clinical symptom in acute ischaemic stroke. The prevalence of neuropsychiatric disturbances following ischaemic stroke (NDIS) may range between 6% and 90% (see table 1).[3–10] Variations in prevalence are due to the multifactorial nature, the timing of assessment and differences in assessment methods (including assessment techniques and the diagnostic cut-off value). In addition, NDIS has a significant impact on the functional outlook of stroke survivors, which increases mortality and disability.[11–16] Subsequently, the mechanisms underlying the prognostic impact of NDIS are not well understood.

MRI is a non-invasive medical imaging technique that is now widely used in patients

Table 1 Neuropsychiatric disturbances after stroke

Disorder	Prevalence	Main clinical characteristics	Adverse effects
PSD	13–57%	► Depressed mood ► Loss of energy ► Suicidal thoughts ► Guilt	Associates with higher rates of stroke recurrence, lower quality of life and higher mortality[3]
PSAD	6–90%	► Anxiety or worry ► Irritation ► Nervous tension	Increases the risk of future strokes, permanent loss of function and ultimately death[4]
PSA	12–71%	► Low motivation ► Reduced initiative ► Loss of self-activation	Prevents patients from participating in rehabilitation programmes, resulting in delayed physical and social recovery[6]
PSF	25–85%	► Self-control and emotional instabilities ► Reduced mental capacity ► Reduction in energy needed for daily activities	Associates with shorter survival times, longer hospital stays, and higher rates of disability and mortality[5]
PSH	6–44%	► Aggravation by routine physical activity ► Association with nausea ► Photophobia and phonophobia	Important cause of disability and increase in recurrence of stroke[7]
PSI	15–68%	► Difficulty initiating/maintaining sleep ► Early-morning awakening ► Daytime dysfunction	Associates with depression, disability and fatigue, as well as a significant impact on return to work 1 year after stroke[8]
PSCI	15–55%	► Memory deficits ► Higher-order visuospatial and attentional dysfunction ► Executive dysfunction	Results in reduced quality of life and increased burden on families[9]

PSA, post-stroke apathy; PSAD, post-stroke anxiety disorder; PSCI, post-stroke cognitive impairment; PSD, post-stroke depression; PSF, post-stroke fatigue; PSH, post-stroke headache; PSI, post-stroke insomnia.

who had a stroke. MRI includes various structural and functional sequences. Structural sequences can aid in diagnosing the type of stroke, show the level of vascular stenosis and cerebral perfusion, and quantify the stroke lesion and other voxel-based quantitative analyses. Functional sequences include resting-state functional MRI (rsfMRI), diffusion tensor imaging (DTI) and their derivatives. Among these methods, rsfMRI is now one of the most widely used to explore functional localisation and examine the physiological properties of different brain structures.[17 18] Currently, DTI is the primary imaging technique used to examine white matter fibre integrity. DTI uses a standard MRI sequence and magnetic field gradients to quantify water diffusion, specifically fractional anisotropy, which reflects white matter tract microstructural integrity.[19] In addition, the T1-weighted image can be used to calculate intracranial volume, white matter/grey matter density and cortical thickness. The patient's infarct volume size and infarction site will be determined using diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR). Several studies have shown a link between the infarction site and the development of NDIS.[20–22] Although there have been many studies on NDIS, the neuroanatomical mechanisms of NDIS are unclear. In addition, many studies are small-sample, cross-sectional studies and only use single-modality imaging, making the results less reliable.[23–26] There is evidence that structural and functional brain changes in chronic ischaemic stroke may be associated with neuropsychiatric disorders.[27 28] Therefore, it is imperative to establish a longitudinal cohort with multimodal imaging data. This approach will enable us to track the temporal evolution of brain changes, thereby providing a more comprehensive and reliable understanding of the neuropathological mechanisms underlying NDIS.

Moreover, recent researches have demonstrated the association between neuroimaging substrates, genetics and metabolism. It shows that genetic variations can influence the risk and progression of neuropsychiatric disorders by altering neuroimaging phenotypes. In terms of metabolism, it has been found that metabolic processes covary with neuroimaging phenotypes. These changes in metabolism can affect neurochemical systems and pathways in the brain, potentially influencing behaviour, personality and the risk of psychiatric disorders.[29 30] Considering the complexity of NDIS pathogenesis, the heterogeneity of individual patients exhibiting NDIS may not be only due to different mechanisms of cerebrovascular injury. Therefore, it is necessary to take into account the genetic background and individual metabolic differences of patients with NDIS.

In general, to date, the breadth and depth of studies employing structural MRI and functional MRI to investigate the neurophysiological mechanisms of NDIS are limited. Therefore, we intend to establish a cohort study on neuroimaging of neuropsychological disturbances

following ischaemic stroke (CONNECT). The purpose of this study is to investigate the possible aetiology and pathogenesis of NDIS from an anatomical and functional perspective. This comprehensive approach is intended to enable more accurate treatment and better long-term functional prognosis for stroke survivors.

METHODS/DESIGN

Study design and objectives

CONNECT is a prospective cohort study examining the neuroimaging characteristics of patients with NDIS. The primary objective of this study is to investigate the relationship between neuroimaging characteristics and NDIS in order to identify potential neurophysiological and anatomical mechanisms.

The primary outcome of CONNECT is the incidence of NDIS at the 6-month mark. The secondary outcomes include:

1. The incidence of NDIS at all other follow-up times.
2. The severity of NDIS at all follow-up times.
3. The recovery status of patients at all follow-up times.

Study population

The patients will be consecutively recruited from the Stroke Center and Department of Neurology, the First Affiliated Hospital of University of Science and Technology of China. Patients diagnosed with acute ischaemic stroke within 14 days of onset are considered eligible for participation. We plan to include 300 stroke cases or more. Two-year follow-ups are planned for all patients. The inclusion and exclusion criteria for this study are as follows:

Inclusion criteria

1. Diagnosis of first-ever acute ischaemic stroke.
2. Age ≥18 years.
3. Onset of stroke within 2 weeks.
4. Written informed consent.

Exclusion criteria

1. Pre-stroke modified Rankin Rating Scale (mRS) score >1.
2. Currently suffering from severe systemic or life-threatening diseases, as well as chronic physical illnesses that affect fatigue or other mood-related conditions and are currently under treatment (eg, cancer, chronic heart disease, chronic kidney failure, Parkinson's disease).
3. Severe neurological-related or psychiatric-related illnesses that could interfere with the study outcomes (schizoaffective disorder, multiple sclerosis, traumatic brain injury, epilepsy, cerebral oedema, depression, apathy, fatigue, anxiety, insomnia, headache, cognitive impairment, etc).
4. Severe dementia or impaired consciousness, which makes participation in complete neuropsychological testing impossible.
5. A history of drug dependence such as long-term alcohol and drug use.
6. Pregnant and lactating women.
7. Claustrophobia, pacemakers and other metal foreign bodies in the body.

In addition, age-matched, sex-matched and education-matched normal individuals from the same time period are included. These subjects will be examined in the same way as patients with NDIS. Subjects with brain lesions like cerebral infarction, haemorrhage, brain tumour, etc will be further excluded.

The scales used for NDIS evaluation

In this study, we mainly focus on patients with seven symptoms of depression, apathy, fatigue, anxiety, insomnia, headache and cognitive impairment. The Hamilton Depression Scale-24[31] and the Chinese version of the Self-Rating Depression Scale[32] are used to assess post-stroke depression. The Hamilton Anxiety Scale-14[33] and the Chinese version of the Self-Rating Anxiety Scale[32] are used to assess post-stroke anxiety disorder. The Chinese Version of Apathy Evaluation Scale[34] and the Lille Apathy Rating Scale[35] are used to assess post-stroke apathy. Fatigue Severity Scale[36] and the Multidimensional Fatigue Inventory-20[37] are used to assess the severity of post-stroke fatigue. The Insomnia Severity Index is used to assess the degree of post-stroke insomnia.[38] Meanwhile, the Visual Analogue Scale[39] and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)[40] and its derivative scale SLANSS[41] are used to assess post-stroke headache. In addition, the Mini-Mental State Examination,[42] Montreal Cognitive Assessment[43] and Telephone Interview for Cognitive Status Questionnaire[44] are used as screening tools for global cognitive function. The above scales have shown good reliability and validity in the Chinese population.[42 45–49] Higher scores indicate more severe symptoms, except for the cognitive assessment scales, where lower scores indicate more severe symptoms (specific scoring is shown in table 2).

PROCEDURES

Patients will be formally entered into the study after informed consent and written approval. We plan to complete 2 years of follow-up after the patient has been enrolled. Baseline assessments will be performed during hospitalisation via face-to-face review. Based on previous prospective studies on NDIS,[50–52] the telephone follow-up visits will be conducted at 3 months, 12 months and 24 months, respectively. Outpatient follow-up visit will be conducted at 6 months. Telephone follow-up primarily assesses patients with neuropsychiatric measurements. During outpatient follow-up, patients will receive the same examinations as in the baseline protocol. A summary of baseline and follow-up assessments is shown in table 3, whereas the entire flow of the study is shown in figure 1.

Assessments: baseline

During admission, a face-to-face interview will be conducted to collect baseline patient information and

Table 2 Specific information about the scales

Neuropsychiatric disturbances	Scales	Scale items	Range of scores	Symptom classification
Depression	HAMD-24	24	0–72	<8: without depressive symptoms 8–20: possible depressive symptoms 21–35: definitely depressive symptoms >35: major depression
	SDS	20	0–100	53–62: mild depression 63–72: moderate depression >72: major depression
Anxiety	HAMA-14	14	0–56	<7: without anxiety symptoms 7–13: possible anxiety symptoms 14–20: definitely anxiety symptoms 21–28: significant anxiety symptoms ≥29: major anxiety symptoms
	SAS	20	0–100	50–59: mild anxiety 60–69: moderate anxiety 70–79: major anxiety
Apathy	AES	18	0–72	<37: without apathy symptoms ≥37: definitely apathy symptoms
	LARS	33	−36 to 36	The higher the score, the more severe the symptoms
Fatigue	FSS	9	0–63	<36: without fatigue symptoms ≥36: definitely fatigue symptoms
	MFI-20	20	20–100	The higher the score, the more severe the symptoms
Insomnia	ISI	7	0–28	0–7: without insomnia symptoms 8–14: subclinical insomnia 15–21: moderate insomnia 22–28: major insomnia
Headache	VAS	1	0–10	0: without headache symptoms 1–3: mild headache 4–6: moderate headache 7–10: major headache
	LANSS	7	0–24	<12: unlikely to have headache ≥12: possible headache
	SLANSS	7	0–24	<12: unlikely to have headache ≥12: possible headache
Cognitive impairment	MMSE	30	0–30	Illiterate <17 as dementia Elementary school <17 as dementia Middle school and above <17 as dementia
	MoCA	11	0–30	<26: possible dementia 27–30: without cognitive impairment (add 1 point to score for years of education less than or equal to 12 years)
	TICS	22	0–51	The higher the score, the more normal the cognitive function

AES, Apathy Evaluation Scale; FSS, Fatigue Severity Scale; HAMA-14, Hamilton Anxiety Scale-14; HAMD-24, Hamilton Depression Scale-24; ISI, Insomnia Severity Index; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; LARS, Lille Apathy Rating Scale; MFI-20, Multidimensional Fatigue Inventory-20; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; SLANSS, S-Leeds Assessment of Neuropathic Symptoms and Signs; TICS, Telephone Interview for Cognitive Status; VAS, Visual Analogue Scale.

Table 3 Schedule of assessments

Assessment	Baseline	Follow-up			
		3 months	6 months	12 months	24 months
Demographics					
Age	X				
Sex	X				
Marital status	X		X		
Working status	X		X		
Race	X				
Right-handed	X				
Years of education	X				
Length and weight, BMI	X		X		
Blood pressure	X		X		
Alcohol consumption	X		X		
Smoking status	X		X		
Neurological function score					
NIHSS	X				
mRS	X	X	X	X	X
Disease history					
Hypertension	X				
Diabetes mellitus	X				
Atrial fibrillation	X				
Dyslipidaemia	X				
Coronary artery disease	X				
Treatment history					
Surgical history	X				
Medication history*	X	X	X	X	X
Fasting laboratory investigations					
Blood glucose	X				
Haematology routine†	X				
Blood biochemistry‡	X				
Thyroid functions§	X				
Inflammatory indicators¶	X				
Scale assessment					
Mini-Mental State Examination	X		X		
Montreal Cognitive Assessment	X		X		
Telephone Interview for Cognitive Status	X	X	X	X	X
Hamilton Depression Scale	X	X	X	X	X
Self-Rating Depression Scale	X		X		
Hamilton Anxiety Scale	X	X	X	X	X
Self-Rating Anxiety Scale	X		X		
Fatigue Severity Scale	X	X	X	X	X
Multidimensional Fatigue Inventory-20	X		X		
Apathy Evaluation Scale	X	X	X	X	X
Lille Apathy Rating Scale	X		X		
Insomnia Severity Index	X	X	X	X	X
Visual Analogue Scale	X		X		

Continued

Table 3 Continued

Assessment	Baseline	Follow-up			
		3 months	6 months	12 months	24 months
Leeds Assessment of Neuropathic Symptoms and Signs	X		X		
S-Leeds Assessment of Neuropathic Symptoms and Signs	X	X	X	X	X
Lubben Social Network Scale	X		X		
Stroke-Specific Quality of Life Scale	X		X		
Fugl-Meyer Assessment Scale	X		X		

Empty cells indicate no assessment.
*Types, dosages and frequency of use of thrombolytic drugs, hypoglycaemic drugs, antihypertensive drugs and other drugs that can affect neuropsychiatric disorders.
†Red cell count, white cell count, blood platelet, granulocyte, eosinophilic granulocyte, basophilic granulocyte, lymphocyte and monocyte.
‡Total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, very low-density lipoprotein, glutamic oxaloacetic transaminase, alanine aminotransferase, total bilirubin, direct bilirubin, indirect bilirubin, uric acid, urea nitrogen and creatinine.
§Free triiodothyronine, free tetraiodothyronine, thyroid-stimulating hormone, thyroglobulin antibody and thyroid peroxidase antibody.
¶C reactive protein and high-sensitivity C reactive protein.
BMI, body mass index; mRS, modified Rankin Rating Scale; NIHSS, National Institutes of Health Stroke Scale.

confirm the authenticity of information to families. Patients are treated in accordance with a specialised acute ischaemic stroke protocol, which includes those recommended in local and international guidelines.[53]

Demographic information

Standardised, structured questionnaires will be used to obtain information on demographics. Demographics include age, sex, body mass index, marital status, race, working status and left or right-handedness. The education level can be classified into five levels: elementary, middle school, high school, college and above. The years of education are also counted. In addition, the Lubben Social Network Scale will be used to assess social interaction status in order to better understand the level of social support for each patient. Each item has a score ranging

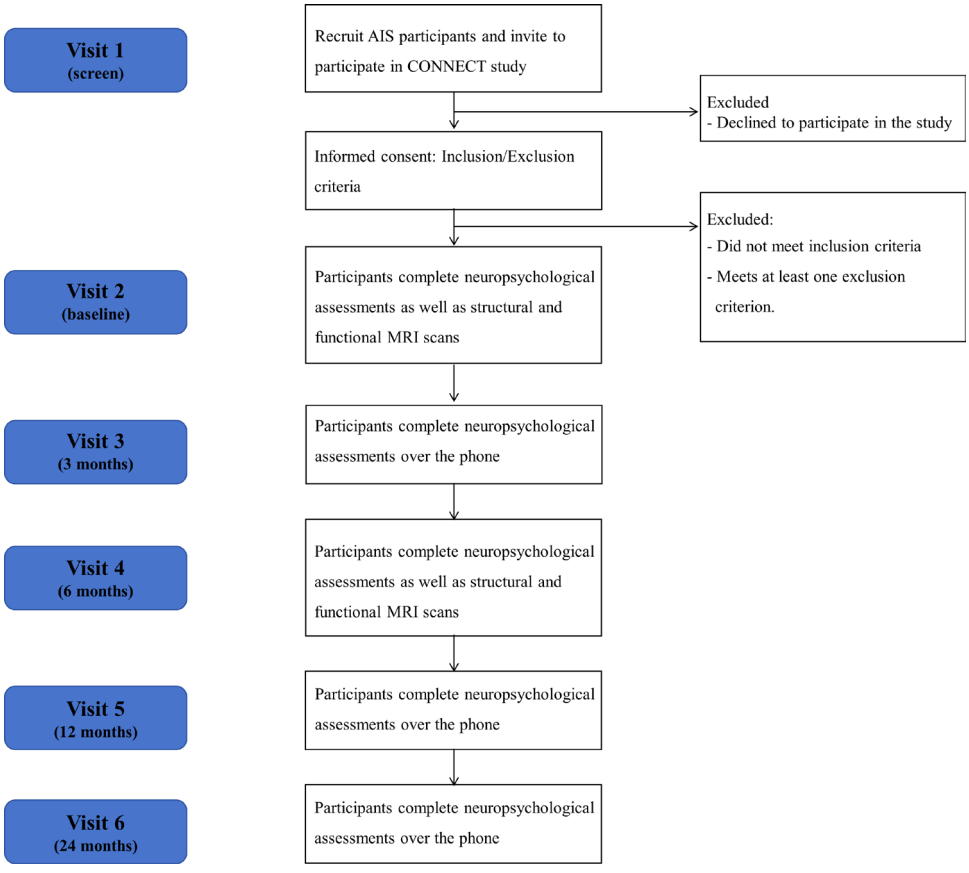

Figure 1 The entire flow chart of the CONNECT Study. AIS, acute ischaemic stroke.

from 0 to 5. The higher the score, the better the social network.[54]

Disease history and risk factors

Existing and potential stroke risk factors will be determined by a standardised, structured questionnaire using the American Heart Association classification.[55] Identified risk factors include dyslipidaemia, diabetes, hypertension, smoking, drinking and atrial fibrillation. Potential risk factors include medication history and coronary artery disease.

Treatment history

The patient's medication history and surgical history will be recorded and the authenticity of information will be confirmed by families.

Neurological function score

The National Institutes of Health Stroke Scale is used to assess stroke severity at admission.[56] The mRS is used to assess the patient's neurological status and functional outcome before admission, on admission and at discharge.[57] In addition, we use Stroke-Specific Quality of Life Scale[58] and Fugl-Meyer Assessment Scale[59] to assess the patient's quality of life and exercise capacity.

Haematological indices

Haematological information will be collected by professionals, including haematology routine, blood biochemistry, thyroid functions, blood glucose, blood lipids and inflammatory parameters such as C reactive protein. The blood samples are obtained in the second morning after admission under fasting conditions and are collected by an experienced nurse. Blood samples are sent to the central laboratory and the results are recorded by the electronic case system. In addition, 10 mL of blood will be saved and centrifuged, to keep serum and plasma in −80° refrigerator for proteomics and genomics testing.

Assessments: follow-up

Patients will be contacted for follow-up at 3, 6, 12 and 24 months after discharge. Telephone follow-ups will be completed at 3, 12 and 24 months, while the 6-month follow-up will be conducted in the outpatient department through a face-to-face interview. To ensure the reliability and validity of the telephone follow-up scales, neuropsychiatric scales commonly used in such follow-ups will be used.[50 60–63] Standard flow charts are used to assess each symptom of NDIS. The entire telephone follow-up takes no more than half an hour (specific scales are shown in table 1, general flow of telephone follow-ups is shown in figure 2 and details are included in online supplemental figures 1–7). In addition, the mRS is used to assess the functional outcome of patients who had a stroke. During outpatient follow-up, patients will be examined in the same way as in the baseline protocol. If participants are unable or unwilling to complete assessment at any stage of follow-up, the reasons would be recorded.

Incident events

A standardised structured questionnaire will be administered to determine the occurrence of new cerebrovascular events and other causes of death during the follow-up period, where new cerebrovascular events include transient ischaemic attack, cerebral infarction, cerebral haemorrhage and other cerebrovascular-related events; other causes of death include cardiovascular events, cancer and other unexplained diseases. Whenever an event is suspected, additional information will be collected regarding the diagnosis, treating physician and exact date of initiation of treatment. If necessary, the treating physician will be contacted for further information. All suspicious events will be evaluated and adjudicated by a medical professional trained in the specific area.

Neuropsychological assessment

To determine the presence of depression, anxiety, apathy, fatigue, headaches and sleep disturbances, scales

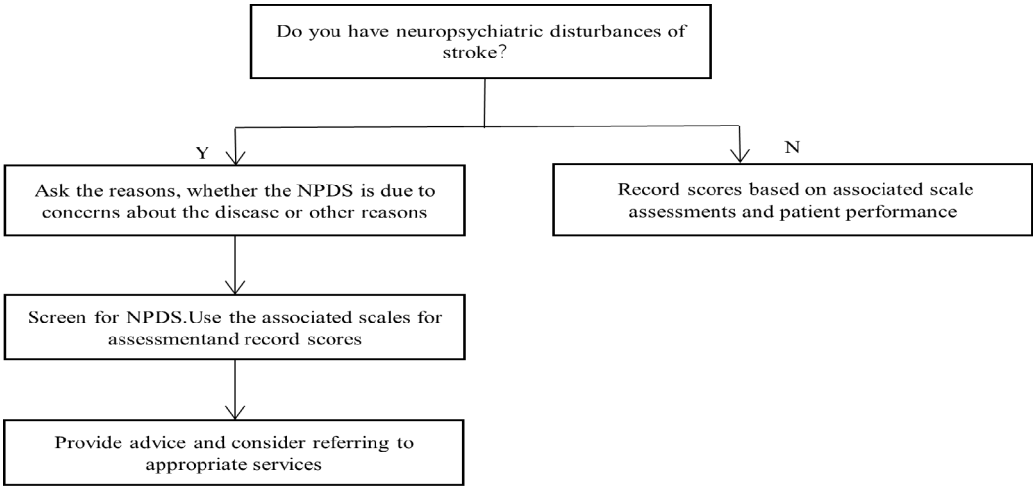

Figure 2 If it is a 3-month telephone follow-up, the patients will be informed to come to hospital for outpatient follow-up at 6 months. NPDS, neuropsychiatric disturbances of stroke.

with good reliability and validity during the telephone follow-up will be used. Patients will be specifically asked to reflect on the presence of these symptoms in the past 2 weeks. In addition, mRS will be used to assess the functional outcome at each follow-up time point.

The above procedures are completed by two experienced neurologists. If opinions are in conflict, a higher-level physician will be asked for final judgement.

MRI protocol

Imaging acquisition

All enrolled patients will undergo conventional MRI, rsfMRI, DTI, quantitative susceptibility mapping (QSM) and arterial spin labelling (ASL) scans after enrolment. Patients undergo identical MRI scans at baseline and 6-month follow-up after stroke onset. A 3.0 T GE750W MRI system (General Electric, USA) with a standard cranial 24-channel coil is used. Subjects are asked to lie flat in the scanner with their eyes closed, to remain quiet and to refrain from any movement or intentional thought, if possible, but not to fall asleep, and to make sure they are not asleep during the scan by asking them after the scan. The specific parameters of each study sequence are described in table 4. The scan is in the order of rsfMRI, DTI, QSM, ASL and finally conventional MRI sequences. The complete scanning protocol takes approximately 40 min. All imaging data are evaluated by two independent specialised neuroimaging radiologists (blinded to clinical data), and disagreements are resolved by a third-party appraisal.

Preprocessing

Two experienced neurologists use a semiautomatic method in the ITK-SNAP software (itksnap.org) to segment the lesion mask in high-resolution FLAIR images. Special attention is given to distinguish lesion from cerebrospinal fluid (CSF), and haemorrhage from surrounding vasogenic oedema. A neurologist reviews all segmentation a second time, paying special attention to the borders of the lesions and degree of white matter disease. The patient's clinical data are not known to the neurologists. Lesions are summed to display the number of patients with structural damage for each voxel.

The rsfMRIs are preprocessed in the Matlab V.2013b.[64] First, co-registration to structural T1 (bbregister), realignment (mcflirt, FMRIB software library (FSL) V.5.0.9), normalisation to Montreal Neurological Institute standard space (ANTs V.2.2.0) and resampling to 3 mm isometric voxels will be performed. For patients who had a stroke with lesions interrupting automatic registration or realignment, values within lesioned voxels are filled with normal atlas values before segmentation, and then masked immediately after. The realignment is performed using a non-linear volume alignment or surface-based registration.[65 66] After preprocessing, the CONN toolbox (V.18.a; https://www.nitrc.org/projects/conn/) smoothed functional data with a 6 mm kernel and flagged functional outliers for each participant if head

Table 4 Specific MRI parameters

Imaging parameters*	Image sequence
	3D T1-BRAVO
MRI system	3.0 T GE750W MRI system (General Electric, USA)
Standard cranial channel coil	24
TR	8.5 ms
TE	3.2 ms
FOV	256×256 mm
Matrix	256×256
Thickness	1 mm
Gap	0 mm
FA	12°
	rsfMRI
MRI system	3.0 T GE750W MRI system
Standard cranial channel coil	24
Echo sequence	Planar echo sequence (GRE-EPI)
TR	2000 ms
TE	30 ms
FOV	240×240 mm
Matrix	64×64
Thickness	4 mm
FA	90°
Number of layers	36
Time phases	240
Scan time	8 min
	DTI
MRI system	3.0 T GE750W MRI system
Standard cranial channel coil	24
Echo sequence	Planar echo sequence (GRE-EPI)
TR	Auto
TE	Minimum
FOV	224×224 mm
Matrix	112×112
Thickness	3.5 mm
FA	90°
Gap	0.7 mm
Voxels	2×2×3.5 mm^3
Diffusion-sensitive gradient directions	64
Diffusion sensitivity factor	1000 s/mm^2
Ungradient diffusion-weighted imaging	b=1
Consecutive levels per gradient direction	19
	QSM
MRI system	3.0 T GE750W MRI system
Standard cranial channel coil	24

Continued

Table 4 Continued

Imaging parameters*	Image sequence
Echo sequence	Planar echo sequence (GRE-EPI)
TR	31 ms
TE	1.9 ms
FOV	256×256 mm
Matrix	256×256
Thickness	1 mm
FA	12°
	ASL
MRI system	3.0 T GE750W MRI system
Standard cranial channel coil	24
Echo sequence	Planar echo sequence (GRE-EPI)
FOV	240×240 mm
Thickness	4 mm
TR	4852 ms
TE	10.7 ms

*The imaging parameters used allow complete coverage of the whole brain of the subjects.
†
ASL, arterial spin labelling; 3D, three-dimensional; DTI, diffusion tensor imaging; FA, flip angle; FOV, field of view; gap, layer spacing; GRE-EPI, gradient-echo echo planar imaging; QSM, quantitative susceptibility mapping; rsfMRI, resting-state functional MRI; TE, echo time; thickness, layer thickness; TR, repetition time.

motion exceeded 0.5 mm and global signal threshold was Z=3. In later steps, the CONN toolbox treated individual resting-state scans as a continuous session. Next, linear detrending, outlier censoring, motion regression with six subject-specific motion parameters and their first-order derivatives, and aCompCor to remove six principal components of noise based on white matter and CSF mask were performed simultaneously. Finally, a 0.01–0.1 Hz bandpass filter focused on low-frequency fluctuations.

DTI data are preprocessed using the FSL (http://www.fmrib.ox.ac.uk/fsl). The preprocessing process is divided into the following steps: (1) transformation of DICOM data format to NIfTI data format; (2) eddy current correction; (3) gradient direction correction; (4) getting the brain mask based on the b0 image; (5) tensor calculation. The dtifit function in FSL is used to calculate the tensor.

ASL imaging data are preprocessed using the Statistical Parametric Mapping (SPM) V.8 software. The preprocessing is divided into the following steps: (1) normalisation; (2) spatial smoothing; (3) quality check of preprocessed data. After the data are preprocessed, the rsfMRI data are combined for subsequent analysis.

QSM images are generated using a morphology-enabled dipole inversion method. This method inverts an estimated local magnetic field to generate a magnetic susceptibility distribution that is structurally consistent with an anatomical prior. The anatomical prior is derived from the magnitude image obtained during the same imaging. The local magnetic field is calculated from a field map derived from MR-phase images, and then a projection onto dipole fields method is used to remove the background field induced by susceptibility sources outside the brain parenchyma.

In addition, structural MRI can be used to perform morphological analysis and volume calculations. Before structural MRI for voxel-based analysis, the imaging data are preprocessed in the Voxel-Based Morphometry 8 (VBM-8) toolbox[67] in SPM V.12 (http:/ /www.fil.ion.ucl.ac.uk/spm/). First, all images for artefacts are checked and repositioned so that the origin of the images is set at the pre-combination point. Subsequently, the T1-weighted images are segmented into grey matter, white matter and CSF to obtain the total volume of grey matter used to estimate the true volume of tissue in each native space. Then, the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) method is used for optimal alignment of individual segments. During non-linear normalisation, the segments are modulated by Jacobi volume[68] to correct for volume changes. The modulated segments are further normalised to the Montreal Neurological Institute space and smoothed using an 8 mm full-width half-maximum Gaussian kernel. The generated smoothed, modulated, non-linear, distorted, segmented grey matter images allow comparison of the absolute number of tissues and are used for subsequent group comparisons. After the data are preprocessed, the grey matter/white matter volume and density can be obtained by VBM analysis and combined DWI and FLAIR to depict the infarct lesion and calculate the infarct volume.

Statistics

For demographic and clinical data, all variables will initially be analysed descriptively; categorical variables will be analysed using frequency tables, and continuous variables will be analysed using sample statistics such as mean, median, SD, minimum and maximum values, etc. The P-P plot, Q-Q plot or Kolmogorov-Smirnov test and Shapiro-Wilk test are used to determine if the variables have a normal distribution. Continuous variables satisfying the normal distribution are analysed using analysis of variance (ANOVA), whereas those not satisfying the normal distribution are analysed using Kruskal-Wallis test or Wilcoxon rank-sum test. Pearson's X^2 test and Fisher's exact test are applied to categorical variables. Multifactorial logistic regressions are employed to investigate the independent risk factors for NDIS. Multiple linear regressions are employed to investigate the relationship between biological indicators and clinical scale scores. Data are analysed using Stata V.14.1, R software V.4.2.1 or SPSS Statistics V.27.0 software. The ANOVA and post-hoc two-sample t-test will be applied for preprocessed imaging

data. Covariables include the demographic and clinical data variables with significant differences. Moreover, the relationship between imaging data and neuropsychological scores is further analysed to investigate the underlying neurobiological mechanisms of NDIS.

DISCUSSION

In recent decades, neuroimaging has provided a fascinating non-invasive window into the human brain. With the advancement of MRI technology, it is now possible to examine all aspects of the human brain non-invasively with unprecedented accuracy. Structural, functional and diffusion MRIs provide localised spatial information about the brain's structure and function, as well as detailed functional and structural connectivity maps. These methods have given hope to researchers studying the human brain, one of the most complex systems in the universe. Nevertheless, little is known about the neurophysiological mechanisms of NDIS.

In 2009, the National Institute of Mental Health proposed the Research Domain Criteria (RDoC) framework, which assumes that mental illness research should be multidimensionally categorised based on genetic, ethological and neurobiological discoveries.[69] A growing body of research inspired by RDoC in recent years suggested that there might be some shared mechanisms between some mental illnesses, and the transdiagnostic approach that cuts across traditional disease boundaries provides a useful means for understanding these conditions.[70] For example, Kanellopoulos *et al* classified depression into three dimensions using factor analysis and found that only the apathy dimension was associated with executive cognitive function impairment. This research demonstrates the significance of multidimensional research in the NDIS.[71] Future research should adopt a multidimensional and cross-diagnostic approach to NDIS study in order to gain a deeper understanding of the neurobiological mechanisms underlying NDIS after stroke. In addition, the fact that a stroke can cause damage in virtually any region of the brain makes it advantageous to investigate the effects of local changes on the functional organisation of the brain. Furthermore, the development of human brain connectomics has enabled a broader method for investigating changes in brain networks using localised injury. For example, the lesion network maps are used to explain the diaschisis and lesion–behaviour mapping is used to explore the association between multiple behavioural variables and loss lesions.[72 73] As a result, the utilisation of stroke as a natural model of focal lesions will aid in the investigation of the pathophysiological mechanisms of NDIS. Moreover, it is possible to integrate genetics and neuroimaging to explore the link between bioinformatics, neuroimaging information and psychiatric disorders. This approach, in recent years, has shown greater potential. For example, a study has examined different genetically heterogeneous features of late depression by combining multidimensional perspectives.[74] Hence, by collecting haematological data, the aim of this study is to explore the disease heterogeneity associated with genetic characteristics of NDIS.

This study uses multimodal imaging relative to other studies for NDIS. In addition, the longitudinal design of this study allows for the observation of dynamic changes in the NDIS, which addresses the shortcomings of cross-sectional studies. However, this study researches ischaemic stroke. Other types of neuropsychiatric disorders in stroke need to be explored in the future. In addition, this study is a single-centre study; thus, multisite studies of NDIS are needed later.

In summary, this study is aimed to investigate the possible aetiology of NDIS by combining neuropsychiatric scores and haematological indices with imaging performance, as well as to explore the impact of neuroimaging on the functional prognosis of patients in order to find effective treatment options for NDIS. Through this study, we believe CONNECT may help people realise that NDIS is not only an acute-phase manifestation, but may also be long term, which will raise the awareness level of patients, families and medical personnel. It will allow them to quickly identify NDIS for early identification, diagnosis and treatment, improving prognoses of patients who had a stroke and reducing the economic burden on families and society.

Ethics and dissemination

The CONNECT Study has received ethical approval from the Ethics Review Committee of the First Hospital of the University of Science and Technology of China (2021-ky012) and written informed consent will be obtained from all participants. All methods will be performed in accordance with the Declaration of Helsinki. Results will be disseminated via a peer-reviewed journal.

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