BMJ Open

MRI-based comparative study of different mild cognitive impairment subtypes: protocol for an observational case–control study

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ABSTRACT

Introduction: Amnestic mild cognitive impairment (aMCI) and vascular mild cognitive impairment (VaMCI) comprise the 2 main types of mild cognitive impairment (MCI). The first condition generally progresses to Alzheimer's disease, whereas the second is likely to develop into vascular dementia (VD). The brain structure and function of patients with MCI differ from those of normal elderly individuals. However, whether brain structures or functions differ between these 2 MCI subtypes has not been studied. This study is designed to analyse neuroimages of brain in patients with VaMCI and aMCI using multimodality MRI (structural MRI (sMRI), functional MRI and diffusion tensor imaging (DTI)).

Methods and analysis: In this study, 80 participants diagnosed with aMCI, 80 participants diagnosed with VaMCI, and 80 age-matched, gender-matched and education-matched normal controls (NCs) will be recruited to the Hongqi Hospital of Mudanjiang Medical University, Heilongjiang, China. All participants will undergo neuroimaging and neuropsychological evaluations. The primary outcome measures will be (1) microstructural alterations revealed by multimodal MRIs, including sMRI, resting-state functional MRI and DTI; and (2) a neuropsychological evaluation, including the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Auditory Verbal Learning Test (AVLT), Memory and Executive Screening (MES), trail making test, Stroop colour naming condition and Clinical Dementia Rating (CDR) scale, to evaluate global cognition, memory function, attention, visuospatial skills, processing speed, executive function and emotion, respectively.

Trial registration number: NCT02706210; Pre-results.

Strengths and limitations of this study

- Comparison of different subtypes of mild cognitive impairment.
- Use of a combination of multimodal imaging systems.
- Lack of clinicopathological diagnosis.

individuals. Dementia resulting from Alzheimer's disease (AD) has received much public attention. Dementia has many causes in addition to AD. Vascular dementia (VD) is also one of the main types of dementia. Mild cognitive impairment (MCI) constitutes an intermediate stage between normal ageing and dementia.[1] A widely shared view is that future treatment strategies should focus on the treatment of MCI.

The rate of conversion of the amnestic MCI (aMCI) subtype to AD is 10–15% annually. Research has focused on the predementia stage of AD, which is likely to be the clinical transition stage of AD.[2 3] In addition vascular MCI (VaMCI) represents the early stage of VD.[4 5] The pathogenesis of these two diseases differs. aMCI is a neurodegenerative disease caused by endogenous neuronal factors, including τ and amyloid pathology,[6] whereas VaMCI is caused by vascular diseases such as infarcts or profuse white matter (WM) disease.[4 7] One study has demonstrated that the structure of the hippocampus is different in patients with aMCI and VaMCI.[8] However, differences in other parts of the brain have not been detected. Both VaMCI and aMCI are associated with deficits in multiple cognitive domains, but they result in mainly the same symptoms of memory deficits.[9 10] Using neuropsychological tests, a previous study indicated that the mode of memory defects in patients with aMCI and VaMCI differs.[10] A considerable body of literature has concluded that patients with VaMCI generally exhibit

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INTRODUCTION

Owing to the prolongation of the life span, the incidence of chronic diseases has increased. Dementia is a progressive brain disease and is one of the main chronic non-communicable diseases associated with disability and mortality among elderly

greater impairment of semantic memory, executive/attentional functioning, and visual–spatial and perceptual skills, whereas the clinical condition of AD is characterised by deficits in episodic memory.[4 11 12] Patients with these conditions may exhibit different performances on specific neuropsychological tests. However, few studies have examined the relationship between these two types of MCI regarding brain structure and cognitive behaviour. Determining the conditions that will result in different types of dementia in patients with cognitive impairment may be helpful for understanding the mechanisms of the two forms of MCI.

According to previous publications, both aMCI and VaMCI are types of a 'disconnection syndrome'.[13 14] By applying structural MRI (sMRI), resting-state functional MRI (fMRI) and diffusion tensor imaging (DTI) technology, we can comprehensively analyse brain structure and function in patients with aMCI and VaMCI directly and non-invasively. Previous studies have detected atrophy of brain volume and abnormal functional connectivity (FC) in patients with MCI,[8 15–18] along with brain structure impairment in VD that is not consistent with AD, especially in the corpus callosum.[19 20] However, whether these structures differ in various types of MCI has not been determined. Moreover, the changes in brain structure and function are not completely similar.[21–23] In contrast to using a single technique, the brain structure and function can be analysed in an omnidirectional and multiangular manner using multimodal MRI. The use of multimodal MRI could also consolidate our understanding of how functional networks interact with their structural substrates.

This project seeks to reveal neural circuits involved in the development of network connections and changes that occur in the context of diseases involving cognitive impairment. We seek to further understand the pathogenesis of cognitive impairment and discover the relationship between brain structure, function and cognitive behaviour.

METHODS
Participants
A total of 240 right-handed participants (80 patients with aMCI, 80 patients with VaMCI, and 80 normal age-matched, sex-matched and education-matched controls) will be recruited from the Neurology Department of Hongqi Hospital of Mudanjiang Medical University, Heilongjiang, China. All participants will undergo a baseline evaluation, including complete sociodemographic and clinical data collection. Patient histories will be collected from informants, typically from their spouses or children. Two experienced neurologists will perform the diagnosis of the participants.

Inclusion criteria
Criteria for aMCI
The diagnosis of aMCI will be based on the recent international consensus criteria as follows:[1 24] (1) subjective cognitive symptoms reported by the informant; (2) objective cognitive impairments that do not meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for dementia; (3) normal or near-normal performance of general cognitive functioning and no or minimum impairments in daily life activities; (4) abnormal memory function documented by an extensive neuropsychological evaluation, normal general cognitive function and a Clinical Dementia Rating (CDR) scale score=0.5;[25] and (5) neuropsychological testing including a Hachinski ischaemic score (HIS) ≤4 and Montreal Cognitive Assessment score (MoCA, Beijing Version).[26]

Criteria for VaMCI
The diagnosis of VaMCI will be based on the Diagnostic Criteria for Vascular Cognitive Disorders (VCD)[4 5] and DSM-V criteria; and vascular aetiology as follows: cognitive impairment due to subcortical small vessel disease[27] defined as moderate WM changes (at least one region score <2 according to the Wahlund rating scale) or multiple lacunar infarcts (<2) on brain imaging that may or may not be suggested by minor neurological signs. Neuropsychological tests for aMCI, MoCA scoring and HIS determination (HIS≥7) will also be performed.

Exclusion criteria
Participants with the following conditions will be excluded: (1) psychiatric disease (eg, depression, Hamilton Depression Rating Scale (HAMD) >20, Center for Epidemiologic Studies Depression Scale >21), systemic disease or other neurological disorders; (2) visual or auditory abnormalities, severe aphasia, or palsy that renders clinical assessments infeasible; (3) any medical or psychological conditions that might affect cognitive functioning, including tranquilisers, antianxiolytics, hypnotics, nootropics and cholinomimetic agents; (4) inability to undergo brain MRI, such as claustrophobia; (5) insufficient Mandarin language abilities to complete the assessment; and (6) marked head motion according to MRI.

The exclusion criteria for VaMCI will also include the following: signs of large vascular disease, such as cortical or corticosubcortical or non-lacunar territorial infarcts and watershed infarcts or haemorrhages.

Neuropsychological evaluations
All participants will receive a battery of neuropsychological tests to assess general mental status and other cognitive domains. These tests will include the CDR scale,[1 25] Mini-Mental State Examination (MMSE),[28] MoCA,[26] Auditory Verbal Learning Test (AVLT),[29] Memory and Executive Screening (MES),[30] trail making test (TMT),[31] Stroop colour naming condition,[32] CDR and HAMD.[33] These tests will be used to evaluate global cognition, memory function, attention, visuospatial skills, processing speed, executive function and emotion, respectively.

Brain MRI protocol

For each participant, conventional brain T1-weighted image (T1WI) and T2-weighted image (T2WI) data will be obtained to exclude serious brain diseases. For inpatients, the data will be collected at Hongqi Hospital of Mudanjiang Medical University. For outpatients, the T1WI and T2WI data may be acquired from other hospitals. The imaging data used for analysis will be acquired using a 3.0 T Trio Siemens scanner (Magnetom Tim Trio; Siemens Medical Solutions, Erlangen, Germany) at Hongqi Hospital of Mudanjiang Medical University.

Structural MRI

High-resolution anatomical images will be acquired using a three-dimensional magnetisation-prepared rapid gradient echo T1-weighted sequence with the following parameters: repetition time (TR)=1900ms, echo time (TE)=2.2 ms, inversion time (TI)=900 ms, flip angle (FA)=9°, number of slices=176, slice thickness=1 mm, voxel size=1×1×1 mm^3 and matrix=256×256. Brain MRIs will be inspected by an experienced neuroradiologist to determine the presence of gross abnormalities.

Functional MRI

An echo-planar imaging (EPI) sequence with the following parameters will be used: TR=2000 ms, TE=40 ms, FA=90°, number of slices=28, slice thickness=4 mm, gap=1 mm, voxel size=4×4×4 mm^3 and matrix=64×64. Participants will be asked to lie quietly in the scanner with their eyes closed during data acquisition. Each scan will last for 478 s.

Diffusion tensor imaging

An EPI sequence will be used in 32 independent, non-collinear directions with a b-value of 1000 s/mm^2, and one additional image with no diffusion weighting (b=0) will be acquired (TR=11 000 ms, TE=98 ms, FA=90°, field of view=256 mm×256 mm, imaging matrix=128×128, number of slices=60 and slice thickness=2 mm). Three acquisitions will be averaged to increase the signal-to-noise ratio.

MRI data analysis

sMRI data analysis

Both the cortical reconstruction and morphological feature extraction will be conducted using FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/) with a standard cortical automatic handling protocol. First, a grey matter (GM) template will be created, and the GM will be normalised to the template. The data will be registered to a standard anatomical template,[34] and the resulting aligned T1 data set will be segmented and converted to a Montreal Neurological Institute (MNI) space atlas MNI152 1 mm brain template using the DARTEL toolbox[35] and corrected for bias-field inhomogeneity. Subsequently, the images will be skull-stripped using a watershed algorithm[36] then segmented into subcortical WM and deep GM volumetric structures.[37 38] The initial

tessellation will be conducted for anatomical topological defects. Finally, a variety of morphological features at each vertex on the pial surface will be computed. The parameters will include the entire GM volume, cortical thickness and surface area.

fMRI data analysis

Image preprocessing will be performed using SPM V.8 (http://www.fil.ion.ucl.ac.uk/spm/) and the Data Processing Assistant for resting-state fMRI.[39] Preprocessing procedures will be performed, including removal of the first 10 volumes, slice timing and head motion correction. All fMRI data will satisfy the criteria of spatial movement in any direction <3 mm or 3°, and the participants will exhibit no significant group differences in the head motion parameters (ie, three translation and three rotation parameters). To spatially normalise the fMRI data, the T1 data used in sMRI will be normalised to the mean functional data, segmented and transformed into MNI152 space using the DARTEL toolbox,[35 40] and a group template will be generated. Next, the motion corrected functional volumes will be specifically normalised to the group template using the transfer parameter estimated by DARTEL segmentation and resampled to 3 mm isotropic voxels. Furthermore, the functional images will be spatially smoothed with a 4 mm Gaussian kernel. Linear detrend and temporal bandpass filtering (0.01–0.08 Hz) will be performed to reduce the effects of low-frequency drift and high-frequency physiological noise. Finally, several nuisance signals will be regressed from the data, including the six motion parameters and the global, WM, and cerebrospinal fluid signals. FC analysis will be performed using DPARSF software (http://www.restfmri.net/forum/DPARSF).

To perform the whole-brain resting-state FC (rsFC) analysis, Pearson's correlations between the time courses of all pairs of voxels will be computed, resulting in a whole-brain connectivity matrix for each participant. This procedure will be limited within a GM mask, which is typically generated by a specific thresholding (previous cut-off=0.2) of the mean map of all GM maps involving all participants without cerebella. These individual correlation matrices will then be transformed as a z-score matrix using Fisher's r-to-z transformation to improve normality. Then, the FC strength (FCS) will be computed as the sum of the connections between a given voxel and all other GM voxels. This computation will be conservatively restricted to connections with a correlation coefficient, which could eliminate the weak correlations possibly arising from noise.

DTI data analysis

DTI data processing will be performed using software from FMRIB Software Library (FSL, http://http://www.fmrib.ox.ac.uk/fsl)[41]. Initially, eddy current corrections will be performed to correct gradient-coil distortions and small head motions using affine registration to a reference image (b0 volume). The brain voxels of DTI data

will be extracted using the Brain Extraction Tool (BET). The maps of diffusion tensor parameters, including fractional anisotropy (FA), axial diffusivity (DA), radial diffusivity (DR) and mean diffusivity (MD), will be calculated using the DTI-FIT tool, which fits a diffusion tensor model to diffusion-weighted images for each voxel. Voxel-wise statistical analysis of the FA, DA, DR and MD data will be performed for regional differences using tract-based spatial statistics (TBSS), which is a whole-brain voxel-wise analysis method. Then, FSL non-linear image registration algorithm will be used. FA maps of all participants will be aligned into a $1 \times 1 \times 1$ mm^3 standard MNI 152 space. The target template will be the FMRIB58_FA (http://www.fmrib.ox.ac.uk/fsl/data/FMRIB58_FA). Then, a mean FA image will be created by averaging the aligned FA maps. The mean FA image will be thinned to build a mean FA skeleton representing the centre of all tracts common to all participants in the study. Each participant's aligned FA data will be projected onto the FA skeleton to obtain their FA skeletons and deformation matrixes. Using the deformation matrixes, skeletonised DA, DR and MD maps will be created by the tbss_non_FA tool. The skeletonised FA, DA, DR and MD map images will be subsequently subjected to statistical analysis.

Statistical analysis

Repeated measures analysis of variance (ANOVA) will be performed to compare the global differences across the three groups, with follow-up post hoc analyses performed as needed to explain the main effects and interactions.

Multivariate analysis of covariance (ANCOVA) will be conducted with the MCI type as the independent variable, each brain volume as a dependent variable, and age and gender as covariates to analyse differences in brain volume by different types of MCI. In addition, Pearson correlations (two-tailed) will be used to investigate correlations between neuropsychological test scores and the GM volume, cortical thickness and surface area.

A general linear model with multivariate ANOVA and post hoc Bonferroni correction will be performed to compare the FA, MD, DA and DR of each tract among the groups. SPSS (V.20; SPSS, Cary, North Carolina, USA) will be used for this statistical analysis.

A one-way ANCOVA will also be performed to determine the main effect of groups on FCS using age and gender as covariates followed by two-sample t-tests for post hoc analyses. The two-sample t-tests post hoc analyses will be conducted within regions exhibiting significant group effects. All the cluster sizes will be determined by Monte Carlo simulations[42] using the REST AlphaSim utility.[43]

The two-sample t-tests will be performed on the rsFC maps for each seed using age and gender as covariates. The significance level will be set at p<0.05 with a cluster size of 1350 mm^3, corresponding to a corrected p<0.05. The analysis mask will be generated by selecting the voxels that may have a significant positive rsFC in any of the two MCI groups. To investigate the relationship
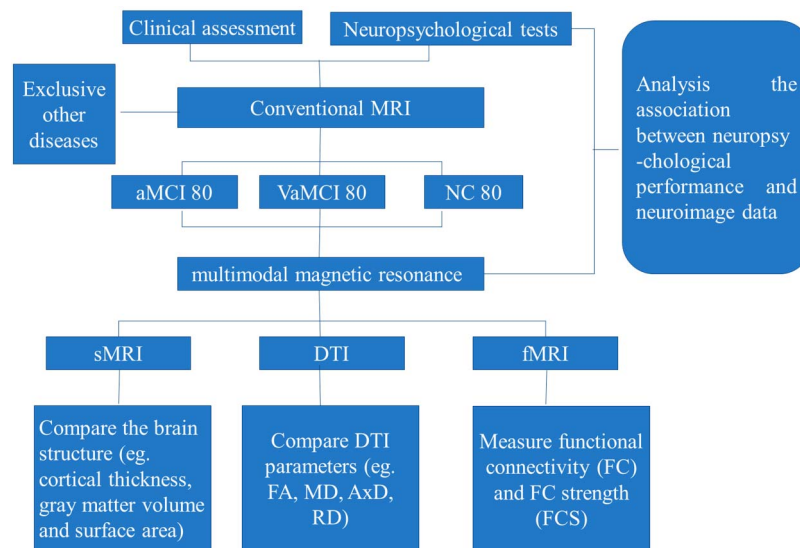
Figure 1 Flow chart of the current prospective diagnostic trial. Eighty participants diagnosed with aMCI, 80 participants diagnosed with VaMCI, and 80 age-matched, gender-matched and education-matched NCs will be subjected to full neuropsychological tests, including the MMSE, MoCA, AVLT, MES, TMT, Stroop colour naming condition, CDR scale and neuroimaging tests, including sMRI, DTI and fMRI. aMCI, amnestic mild cognitive impairment; AVLT, Auditory Verbal Learning Test; CDR, Clinical Dementia Rating; FA, fractional anisotropy; axial diffusivity (AxD); DR, radial diffusivity; DTI, diffusion tensor imaging; fMRI, functional MRI; MD, mean diffusivity; MES, Memory and Executive Screening; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NC, normal control; sMRI, structural MRI; TMT, trail making test; VaMCI, vascular mild cognitive impairment.

among brain function, structure and cognitive behaviour, a general linear model analysis (dependent variable for function: FCS; for structure: FA, MD, DA and DR; independent variables: clinical variables, including MMSE, MoCA, AVLT-immediate recall, AVLT-delayed recall, AVLT-delayed recognition, MES and TMT scores) will be conducted separately.

Association between neuroimaging and neuropsychological performance

We will analyse the interaction between the parameters acquired by multimodal magnetic resonance and cognition measures.

A scheme of the current prospective trial is described in figure 1.

Ethics and dissemination

The study will be conducted in accordance with the approved guidelines. Written informed consent will be obtained from all participants, and the participants will be able to withdraw from the study at any time.

DISCUSSION

In previous studies, researchers have typically focused on the differences between patients and normal elderly individuals, and little attention has been given to the differences between similar diseases. In the late stage of dementia, the WM microstructure in the corpus callosum, especially in the forceps minor, exhibits differences in patients with VD and AD.[19] However, the differences that occur in the early stages of dementia are uncertain. Although the mode of memory defects in patients with aMCI and VaMCI is different,[10] comparisons of the relationship between these abnormal cognitive behaviours and brain structure and function are lacking. Thus, use of multimodal magnetic resonance to observe neuroimages in the two subtypes of MCI is relevant.

Some limitations of this study should be noted. First, this trial is only an observational study without follow-up; whether these patients will convert to AD or VD in the future is uncertain. Therefore, we plan to conduct follow-up to track the dynamic evolution of these patients. Second, our facility is a primary hospital. We do not have a positron emission tomography scanner to increase the precision of diagnosis. However, the diagnosis of the two groups will strictly follow the criteria for the diseases to allow the diagnosis to be as precise as possible. We plan to collect blood and cerebrospinal fluid in future studies.

The purpose for this study is to identify differences in neuroimaging results between patients with aMCI and VaMCI and to explore the possible mechanisms of cognitive disorders in the two diseases. Moreover, we seek to provide scientific evidence for the diagnosis of different subtypes of MCI.

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