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Resting-state functional reorganisation in Alzheimer's disease and amnestic mild cognitive impairment: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction The incidence of Alzheimer's disease (AD) is increasing rapidly, causing a growing burden to health and economic worldwide. Several clinical trials in the past decade failed to find solutions, and there remains a lack of an effective treatment. The evidence suggests that early intervention for neurodegeneration would likely be effective in preventing cognitive decline. Cognitive decline in AD occurs continuously over a long period; however, there remains a lack of simple, rapid and accurate approach for diagnosis of amnestic mild cognitive impairment or subjective cognitive decline due to underlying Alzheimer's pathology. Resting-state functional MRI (rs-fMRI) determines the functional activities of the human brain non-invasively. The amplitude of low-frequency fluctuation (ALFF), fractional ALFF (fALFF) and regional homogeneity (ReHo) are rs-fMRI indicators with high repeatability. They have been studied as early diagnostic imaging markers for other diseases and may be promising markers also for AD.

Methods and analysis The following electronic literature databases will be searched from inception to December 2021: Medline-Ovid, Medline-PubMed, EMBase-Ovid, Cochrane Central and ClinicalTrials.gov. Two independent reviewers will select studies with eligible criteria, extract data and assess the quality of the original studies with our quality assessment tool individually. Missing data will be requested by sending emails to the corresponding authors. Brain regions will be presented for ALFF/fALFF and ReHo by performing activation likelihood estimation with the Seed-based *d* Mapping-Permutation of subject images V.6.21 software. Meta-regression will be performed to determine the potential brain regions that may strongly correlate with cognitive decline progression. Subgroup analysis, funnel plot, Egger's test and sensitivity analysis will be conducted to detect and explain potential heterogeneity.

Ethics and dissemination This study does not require formal ethical approval. The findings will be submitted to a peer-review journal.

PROSPERO registration number CRD42021229009.

Strengths and limitations of this study

► This systematic review and meta-analysis will summarise brain regions with amplitude of low-frequency fluctuation (ALFF)/fractional ALFF or regional homogeneity alterations in Alzheimer's disease (AD) and amnestic mild cognitive impairment (aMCI) patients using qualitative and quantitative analyses.
► This study will consider AD and aMCI as different stages of cognitive decline and conduct a meta-regression analysis with the pooled population to explore the brain regions closely related to the stages of cognitive decline.
► We established a modified quality assessment tool to assess the quality of the original studies for resting-state functional MRI systematic review and meta-analysis.
► We will only retrieve data from English-language databases and may overlook a few valuable original studies in other languages.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease that is causing a growing burden on health and economic.[1] AD will reportedly affect 131 million people worldwide by 2050 and will cause over US$2 trillion in economic losses by 2030.[2] However, a satisfactory therapeutic breakthrough in the field of AD is still lacking. Since the approval of memantine in 2003,[3] all clinical trials of new drugs developed for the different pathogeneses of AD have failed to improve clinical outcome.[4] The molecular targeted therapies can reduce the pathological products of AD in the human brain but it is yet uncertain if they are effective in AD.[5] The failure of such therapies has been attributed to the fact that most of the study participants were patients with moderate or severe AD. These patients exhibit pathological changes in the brain, which may be irreversible or challenging to stop the progression, and the optimal time for treatment may have already elapsed.[6,7] Thus, the early diagnosis and treatment of patients with AD may be the key to halt the disease progression. In the Alzheimer's continuum,

patients in the predementia stages may exhibit clinical symptoms difficult to identify, such as mild cognitive impairment (MCI) or subjective cognitive decline (SCD). Efficiently and accurately differentiating them from cognitively healthy individuals through clinical information and neuropsychological scales is complicated, especially for clinicians who are not experts in the AD field.[8] Therefore, there is currently a high demand for convenient and reliable markers for the diagnosis of AD.[9]

The accurate diagnosis of AD is usually confirmed by autopsy; however, in the recent decade, with the development of laboratory tests and neuroimaging, scientists can directly detect biomarkers in vivo to identify patients with AD.[9–11] These biomarkers include detection of amyloid-β and hyperphosphorylated tau, found in the plasma, cerebrospinal fluid[6] and with positron emission tomography imaging.[12] However, interlaboratory variations lead to a lack of robustness of these biomarkers for early diagnosis. Although several other biomarkers have been proposed, repeated validation is still required to prove their reliability.[13 14] In addition, these examinations can be harmful through vascular punctures, lumbar punctures or the administration of radioactive substances. Conversely, MRI can non-invasively visualise structural and functional changes in the brain. The current diagnostic criteria are mainly based on the structural MRI reports of atrophy of the whole brain, medial temporal lobe or hippocampus, and other brain alterations.[12] However, functional MRI (fMRI) may reflect the brain's functional state through the changes in cerebral blood-oxygen signal, detect brain abnormalities before detectable structural changes, and indicate risk of cognitive decline.

Resting-state fMRI (rs-fMRI) is a non-invasive, harmless and efficient imaging detection method with high spatial resolution, showing the functional status of the central nervous system. Since 1995, rs-fMRI has been increasingly used in scientific research.[15] Several indicators of rs-fMRI have been used to reflect functional activity, including functional connectivity,[16] the amplitude of low-frequency fluctuation (ALFF),[17] fractional ALFF (fALFF)[18] and regional homogeneity (ReHo).[19] Among the commonly used indicators, ALFF/fALFF and ReHo are reported to have relatively higher test-retest reliability than other biomarkers,[20] and the calculation process does not require prior assumptions of the specific brain regions to be studied. ALFF is considered to represent spontaneous brain activity, and fALFF is derived from an improved algorithm of ALFF.[21] ReHo assesses the synchronisation among one voxel and its neighbours (eg, 26 voxels) and is considered to represent the homogeneity of a given cluster.[21] These indicators were also proven to correlate with disease progression in other diseases through general linear models or machine learning approaches and are considered potential diagnostic markers.[22–24] However, fMRI is still used as an additional resource in conjunction with other tests. We speculate that ALFF/fALFF and ReHo may be promising imaging markers for the early diagnosis of AD.

Previous studies in the field of AD or amnestic MCI (aMCI) have reported several brain regions with increased or decreased ALFF/fALFF or ReHo.[25 26] However, a few studies have examined patients with SCD.[27] Uniform diagnostic criteria for SCD was not established for decades, resulting in the heterogeneity of subjects in different studies.[27] This lack of clarity may be due to the concept of SCD was introduced in recent years,[28] its definition and clinical significance has not been fully clarified. Additionally, SCD is a naturally heterogeneous state and a construct that is greatly affected by psychosocial factors including cultural background.[29 30] Thus, this systematic review and meta-analysis will exclude SCD-related studies from pooled estimations if there are not enough original studies with high quality and consistent diagnostic criteria. A previous meta-analysis summarised 12 original studies and reported that eight brain regions showed altered ALFFs in aMCI patients compared with healthy controls.[25] Another meta-analysis included ten original studies of aMCI patients and reported 11 brain regions with altered ReHos in these patients compared with healthy controls.[26] The above reviews were published several years ago, and their findings might change with recent original studies.

Objective

We will conduct this systematic review and meta-analysis to summarise previous rs-fMRI studies comparing patients with AD or aMCI to adults with normal cognition and determine the group differences in ALFF/fALFF or ReHo. SCD studies will also be included, if available. Furthermore, we will also identify the brain regions associated with the severity of the disease or cognitive decline by using meta-regression. Brain regions with increased or decreased ALFF/fALFF or ReHo will be determined through a meta-analysis, and reported for potential incorporation in clinical practice and the establishment of diagnostic criteria.

METHODS AND ANALYSIS
Study guidelines and registration

This systematic review and meta-analysis will include studies reporting ALFF/fALFF or ReHo in AD or aMCI patients compared with cognitively healthy controls. Thus, the Quality of Reporting of Meta-Analyses guidelines is not applicable for this study.[31] The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were updated from the Quality of Reporting of Meta-analyses (QUOROM) statement and apply to all types of systematic reviews.[32] Meta-analysis of Observational Studies in Epidemiology (MOOSE) has also been established for meta-analysis of observational studies.[33] Therefore, a systematic review and meta-analysis will be conducted and presented following the PRISMA statement,[32] MOOSE guidelines[33] and Cochrane Handbook.[34] This protocol follows the PRISMA protocols statement.[35]

Table 1	Search strategy for Medline-PubMed
Search	**Query**
#1	(alzheimer*[Title/Abstract]) OR (alzheimer disease[MeSH Terms])
#2	(dementia[MeSH Terms]) OR (dement*(Title/Abstract))
#3	(((((MCI[Title/Abstract]) OR ("mild cognitive impairment"[Title/Abstract])) OR ("amnestic mild cognitive impairment"[Title/Abstract])) OR (aMCI[Title/Abstract])) OR (SCD[Title/Abstract])) OR ("subjective cognitive decline"[Title/Abstract])
#4	(cognit*[Title/Abstract]) OR (memor*[Title/Abstract])
#5	((impair*[Title/Abstract]) OR (decline[Title/Abstract])) OR (reduc*[Title/Abstract])
#6	#4 and #5
#7	((((((("functional magnetic resonance imaging"[Title/Abstract] OR ("magnetic resonance imaging"[Title/Abstract])) OR ("resting-state functional magnetic resonance imaging"[Title/Abstract])) OR ("resting state functional magnetic resonance imaging"[Title/Abstract])) OR (fMRI[Title/Abstract])) OR ("functional MRI"[Title/Abstract])) OR (MRI[Title/Abstract])) OR ("rs-fMRI"[Title/Abstract])
#8	((((("amplitude of low frequency fluctuation*"[Title/Abstract]) OR ("fractional amplitude of low frequency fluctuation*"[Title/Abstract])) OR ("regional homogeneit*"[Title/Abstract])) OR (ReHo*[Title/Abstract])) OR (ALFF*[Title/Abstract])) OR (fALFF*[Title/Abstract])
#9	#1 or #2 or #3 or #6
#10	#7 and #8 and #9

Search strategy

We will search the following electronic databases from inception to December 2021 for published literature: Medline-Ovid, Medline-PubMed, EMBase-Ovid and Cochrane Central. We will also search the Clinical-Trials registration platform for missing, unpublished, or ongoing studies. Two independent reviewers (DL and TL) will also examine the reference lists of each article that qualifies for the full-text screening step and of each review article in this field. After data extraction, we will send emails to the corresponding authors of the included studies for additional information to avoid potentially missing data. The search strategy for Medline-PubMed is presented in table 1, and the full search strategy is presented in online supplemental file 1.

Eligibility criteria

Studies will be included in the systematic review and meta-analysis according to the following criteria:

▶ Patients: The patients enrolled in the original studies have been diagnosed with mild, moderate or severe AD or aMCI according to clearly reported diagnostic criteria. We will not limit the exact diagnostic criteria in the original studies, although there are some of the most commonly used criteria for AD[9 12] or aMCI.[36 37] The exact scores for cognitive assessments are preferably reported; however, a specific format is not required. We will not restrict data collection on the age, sex, or race of participants in the original studies; however, it will be reported in detail. Moreover, studies focused on AD or aMCI with other complications, such as postdementia depression, are eligible if there are clear descriptions in the literature.

▶ Controls: The control group will include cognitively healthy subjects with comparable demographic characteristics to the AD or aMCI group in the original studies.

▶ Outcomes: Only rs-fMRI studies will be included. The original studies should report the results from whole-brain analysis, rather than analyses of specific brain networks or regions. Brain regions with increased or decreased ALFF/fALFF or ReHo will be included in the pooled estimation through activation likelihood estimation (ALE) analysis. The outcomes will preferably be reported with the peak coordinates, cluster size, and statistics of each brain region. Additionally, only the studies which mentioned the use of multiple comparison correction will be included in the meta-analysis to avoid significant false-positive results induced by the authors,[15] while all results reported in these studies will be put into pooled estimation to avoid missing important data.

▶ Study design: Observational studies with or without further follow-up measurements will be included. Controlled clinical trials that reported the differences between patients and controls at baseline will also be included if they meet the above criteria.

Study selection

Two independent reviewers (DL and TL) will screen the titles and abstracts of the articles found in each electronic database after removing duplications with EndNote V.X9 software. The studies that are inconsistent with our eligibility criteria will be excluded by the each reviewer individually. Then, the reviewers will examine the full text of the articles and further exclude those that do not meet our criteria. The reasons for each exclusion in this step will be recorded individually. An independent reviewer (XL) will solve any disagreement between the two reviewers, which will be recorded with detailed explanation. The
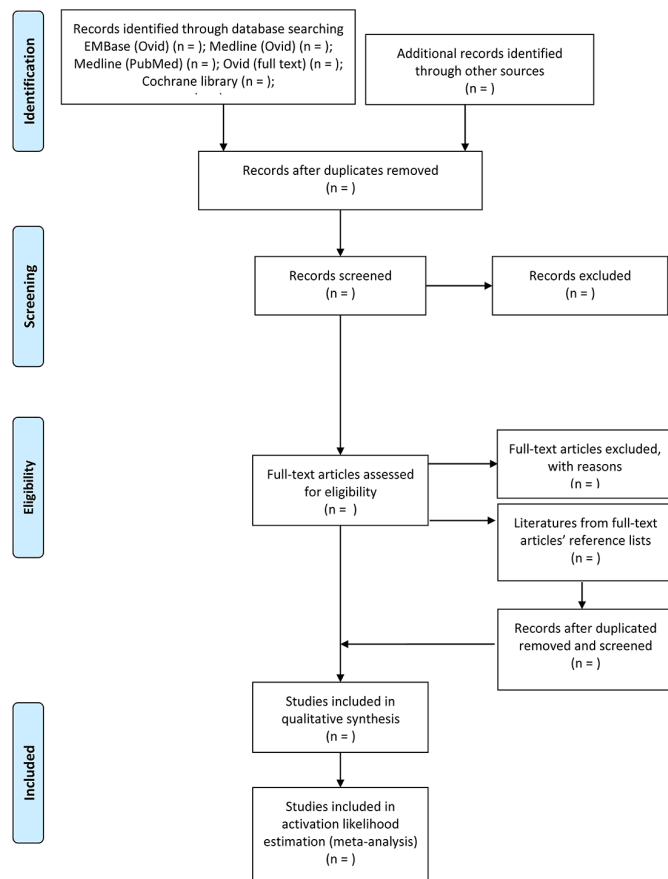
Figure 1 The PRISMA flow diagram of this systematic review and meta-analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

complete process of the study selection will be presented in a PRISMA flow diagram (figure 1).

Data extraction

The same reviewers (DL and TL) will extract demographic information, the study design, data analysis and outcomes individually using Microsoft Excel. The complete information and data extraction lists are presented in table 2. Demographic information includes age, sex, nationality, race, apolipoprotein E genotype (*APOE*), years since first

symptom or initial diagnosis, education level and cognitive assessment scores. Information about the disease stage will be extracted directly from the original articles and determined through their clinical dementia rating scores (0.5 for aMCI, 1 for mild AD, 2 for moderate AD and 3 for severe AD).[38] Information about the study design and data analysis will include the field strength and exact machine model of the MRI scanner, the statistical method of multiple comparison correction, the software and packages used, the frequency range for ALFF/fALFF, the number of neighbouring voxels for ReHo, and the parameter of full width at half maximum smooth kernel of each original study. The results include the anatomical labels, peak coordinates, and cluster size of each reported brain region from the original studies, and the cognitive assessment outcomes, such as the Mini-Mental State Examination scores. Continuous variables will be recorded as means±SD, and discrete variables will be recorded in percentages. Values reported as median with range or IQR will be converted into mean±SD with validated algorithms.[39 40] The recorded data will be verified by comparing the reports of the two reviewers. In case of studies without multiple comparison correction or with missing data, we will also contact the corresponding authors as necessary.

Quality assessment

To our knowledge, there is no standard checklist or tool for the quality assessment of fMRI studies. Thus, we have developed a quality assessment tool for this study, as shown in table 3, based on a previous meta-analysis.[26 41] The two independent reviewers (DL and TL) will examine the full texts for any potential bias according to our quality assessment tool and grade each original study. The total quality assessment score will be reported in the main text, and a detailed quality assessment table will be provided in our systematic review and meta-analysis.

Qualitative and quantitative synthesis
Qualitative data synthesis

First, we will create a summary table to present the characteristics of the selected studies, including the

Table 2	Data and information extraction list
Item	**Content**
Publication information	Authors, publish year, email of the corresponding author, country.
Demographic data	Age, sex, human race, right-handed or not, *APOE* genotype, sample size, education level, diagnostic criteria, years since first symptom or first diagnosis, disease stage, cognitive assessment scores.
Data acquisition	The field strength and the exact machine model of the MRI scanner, slice numbers and thickness of each sequence, time points and total scanning time of functional MRI.
Outcome data	Coordinate space, anatomical label, peak coordinate, cluster size, t-value or other statistics.
Data processing	Software used, number of time points to be discarded, resampling parameters, full-width at half-maximum smooth kernel size, variables to be regressed out, the frequency range for ALFF/fALFF and the number of neighbouring voxels for ReHo, method to control false positive rate.

ALFF, amplitude of low frequency fluctuation; *APOE*, apolipoprotein E; fALFF, fractional ALFF; ReHo, regional homogeneity.

Table 3 Quality assessment tool of original fMRI studies

Category 1: sample characteristics (10)

1	Participants were enrolled with clearly described standardised diagnostic criteria (2).
2	Comprehensive demographic data with comparable baseline between groups (1).
3	Inclusion and exclusion criteria are reasonable, taking into account the possible affecting factors (2).
4	Cognitive outcomes were reported in detail (3).
5	Sample size >10 in each group (2).

Category 2: methodology and reporting (10)

6	The machine model and field strength of the MRI scanner is reported (1).
7	A clear description of the study procedure and quality control, includes the methods to ensure that the subjects are in a 'resting state' (2).
8	At least 5 minutes of resting state acquisition (2).
9	The report of scanning parameters is comprehensive and reasonable, and the quality control method of image scanning is reported (1).
10	Detailed description of software and toolkits used (1).
11	Results were applied and reported in original literature, including peak coordinate and cluster size of each brain region (1).
12	Multiple comparison corrections were applied and reported in the original literature (1).
13	Conclusions were consistent with the results obtained and the limitations were discussed (1).

MRI, Magnetic resonance imaging.

information to be extracted, such as the publication year, demographic characteristics of participants, study design, analysis parameters, and outcome indicators, as shown in table 2. Then, we will provide a general summary of the study outcomes.

Quantitative data synthesis

We will conduct a quantitative analysis of each outcome. First, all brain coordinates will be converted to their corresponding Montreal Neurological Institute (MNI) space. Then, we will perform an ALE meta-analysis for ALFF/fALFF and ReHo. The pooled estimations will reveal consistent brain regions with significant functional alterations reported from different studies using the Seed-based d Mapping-Permutation of subject images (SDM-PSI) V.6.21 software (www.sdmproject.com).[42] The SDM-PSI algorithm is updated using the ALE algorithm. Compared with the software using the ALE algorithm, SDM-PSI can retain positive and negative activation results and avoid bias due to overlapping activation positions in the brain. The peak coordinates in the MNI space and their effect sizes (eg, t-values) extracted from original studies will be registered as centres in the 3D Gaussian

probability distribution to recreate standard MNI brain maps for each study.[43 44] Subsequently, the brain maps will be used to generate pooled estimations for each outcome separately. The sample size, sex, age and other demographic information of each group will also be used to achieve a linear mixed model analysis to control the effect of potential confounding factors. We will perform correlation analyses or partial correlation analyses to exclude variables with strong collinearity. Finally, a principal component analysis will be performed to extract several principal components as necessary; the principal components will be used as variables. The above analyses will be performed with R V.4.0.3. We will also employ a familywise error correction to control the false-positive rate.

We will further analyse the results with subgroup analyses to detect potential heterogeneity and explain its possible reasons. The data from different disease stages (AD or aMCI), with or without complications, and MRI scanners with different field strengths (1.5T or 3.0T) will be analysed separately. After the subgroup analyses, we will perform a sensitivity analysis by excluding studies one by one to determine whether the pooled estimations are stable or not. In this step, significant changes may indicate significant heterogeneity among the studies. Significant heterogeneity will be reported on occurrence. We will apply funnel plots to detect potential reporting biases, when no less than ten original studies are pooled in a meta-analysis.[45] We will attempt to identify possible reasons and interpret existing publication biases. We will perform a meta-regression to identify potential factors that may contribute to the stage-specific changes in different brain regions, we will perform a meta-regression. In this step, we will put all included studies into pooled estimation. The following variables will be analysed: age, sex, cognitive assessment score and *APOE* genotype. We will perform a meta-regression using the SDM-PSI software V.6.21. We will contact the corresponding authors via email To retrieve missing data; if these values are unavailable, we will remove the related regression factors or the original study.

Patient and public involvement
As this is a protocol for a systematic review and meta-analysis, we will obtain data from published literature or the corresponding authors. Thus, patients or the public will not be involved.

ETHICS AND DISSEMINATION
This study does not require any formal ethical approval. The findings will be submitted for publication in a peer-reviewed journal.

DISCUSSION
This systematic review will comprehensively summarise and analyse the results of previous fMRI studies

investigating AD or aMCI using ALFF/fALFF or ReHo. We will present whole-brain ALFF/fALFF and ReHo analyses and report significant differences between patients with AD or aMCI and cognitively healthy controls.

A previous meta-analysis summarised 12 original studies and reported that 4 brain regions exhibited decreased ALFFs, while another four showed increased ALFFs in aMCI patients compared with healthy controls.[25] The authors also reported that a greater decrease in ALFFs in the cuneus/precuneus cortex may be associated with the severity of cognitive impairment.[25] Another meta-analysis included 10 original studies of patients with aMCI and focused on ReHo.[26] The authors found that the ReHo of 11 brain regions from four brain networks differed between aMCI patients and healthy controls. The above meta-analyses were conducted several years ago, and their results varied. However, these studies included AD and aMCI only, and we will also include studies on SCD, if possible. Furthermore, our meta-analysis may provide different estimations by including recent studies in this field.

To our knowledge, only one previous meta-analysis investigated the functional characteristics of AD and aMCI patients compared with healthy controls through both ALFF/fALFF and ReHo.[46] Their findings revealed that patients with aMCI and AD exhibited consistently impaired functional characteristics, and the alterations in the brain regions were relatively consistent. Although this study was published 6 years ago, the findings support our idea of combining studies of AD and aMCI patients, including SCD studies if possible, and attempting to determine the brain regions that have altered ALFF/fALFF or ReHo with strong correlations with cognitive decline measured by neuropsychological scales through a meta-regression.

It is generally known that there are various limitations of fMRI including it being expensive and need of specific expert interpretation so that it can used by non-experts to applying in various clinical scenarios. However, previous studies have reported a large amount of data in this field, making it feasible for scientists to establish diagnostic tools for clinician use through data mining or machine learning. Similarly, our findings may highlight utility of fMRI as an adjunctive tool in early diagnosis of AD and predicting cognitive decline in addition to other diagnostic tools.

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