INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Abnormalities of intrinsic brain activity in chronic primary insomnia: a protocol for systematic review and meta-analysis of resting-state functional imaging

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Review question / Objective: **Studies of abnormal regional homogeneity (ReHo) in insomnia have reported inconsistent results. The objective of this protocol is to conducted a meta-analysis using the Seed-based d Mapping software package to identify the most consistent and replicable findings.**
Eligibility criteria: **Studies that satisfied the following conditions were included in the meta-analysis: (1) patients had been diagnosed with PI; (2) ReHo comparison of patients with PI versus healthy controls was conducted; (3) three-dimensional coordinates (Talairach or Montreal Neurological Institute [MNI]) were reported for the whole-brain ReHo analysis; (4) significant results were reported using thresholds for significance corrected for multiple comparisons or uncorrected with spatial extent thresholds; (5) the study was published in a peer-reviewed English language journal.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 May 2021 and was last updated on 29 May 2021 (registration number INPLASY202150103).

INTRODUCTION

Review question / Objective: **Studies of abnormal regional homogeneity (ReHo) in insomnia have reported inconsistent results. The objective of this protocol is to conducted a meta-analysis using the Seed-based d Mapping software package to identify the most consistent and replicable findings.**

Condition being studied: **Clinical and psychometric studies have demonstrated that primary insomnia is related to inhibited**

and repressive personality traits of patients. Electro-physiological studies in insomnia mainly include three aspects:electroencephalogram (EEG) monitoring, cerebral metabolism measurement and cerebral blood flow measurement. EEG studies have found that, compared to healthy controls, patients with PI show increased activity in the cerebral cortex during non-rapid eye movement (NREM) stage 2 sleep. Using positron emission tomography (PET), Nofzinger et al. assessed regional brain glucose metabolism in PI patients and healthy controls. They found that the relative glucose metabolism of PI patients showed smaller declines from sleep to wakefulness in regions associated with cognition and emotion, including the anterior cingulate cortex, hippocampus, amygdala, and insular and prefrontal cortices, as well as in wake-promoting regions, including the thalamus, hypothalamus and ascending reticular activating systems. Cano et al. used a rat model to investigate the brain circuitry responsible for stress in patients with insomnia. They found co-activation of the cerebral cortex, arousal and autonomic systems, limbic system and the sleeppromoting regions in stressed rats. As a neurologic disease, studies on multiple psychological and electrophysiological levels have provided information on insomnia; however, the neurobiological mechanisms underlying PI are not clear.

METHODS

Participant or population: Adults with primary insomnia (as diagnosed by a clinician, or using any recognized diagnostic criteria) will be included.

Intervention: NA.

Comparator: Normal people.

Study designs to be included: Published randomized controlled trials.

Eligibility criteria: Studies that satisfied the following conditions were included in the meta-analysis: (1) patients had been diagnosed with PI; (2) ReHo comparison of patients with PI versus healthy controls was conducted; (3) three-dimensional coordinates (Talairach or Montreal Neurological Institute [MNI]) were reported for the whole-brain ReHo analysis; (4) significant results were reported using thresholds for significance corrected for multiple comparisons or uncorrected with spatial extent thresholds; (5) the study was published in a peer-reviewed English language journal.

Information sources: We searched the randomized controlled trials in PubMed, Embase, and Web of Science databases.

Main outcome(s): ReHo differences between patients with PI and healthy controls was conducted using the SDM software package (version 4.31 for Windows) in a standard process (www.sdmproject.com).

Quality assessment / Risk of bias analysis: A heterogeneity analysis was conducted used a random effects model with Q statistics to explore unexplained between study variability in the results. Heterogeneous brain regions were obtained using the default SDM kernel size and thresholds (FWHM=20 mm, p=0.005, uncorrected for FDR, peak height Z=1, cluster extent=10 voxels) . In addition, Egger's test was performed using the Stata/SE 12.0 software for Windows to assess possible publication bias by extracting the values from statistically significant relevant peaks between patients with PD and healthy controls. A p-value less than 0.05 was considered significant.

Strategy of data synthesis: Voxel-wise meta-analysis: A meta-analysis of ReHo differences between patients with PD and healthy controls was conducted using the SDM software package (version 4.31 for Windows) in a standard process (www.sdmproject.com). The SDM approach has been thoroughly described elsewhere. In brief, we first extracted peak coordinates and effect sizes (e.g., t-values) of differences in ReHo between patients with PD and healthy controls from each

dataset. A standard MNI map of the ReHo differences was then separately recreated for each dataset using an anisotropic Gaussian kernel. The mean map was finally generated by voxel-wise calculation of the random-effects mean of the dataset maps, weighted by the sample size, intra-dataset variability, and between-dataset heterogeneity. To optimally balance false positives and negatives, we used the default SDM kernel size and thresholds (full width at half maximum [FWHM]=20 mm, p=0.005, uncorrected for FDR, peak height Z=1, cluster extent=10 voxels). It should be noted that this FWHM kernel is intended to assign indicators of proximity to reported coordinates but not to smooth any image that is different in nature. If necessary, a subgroup meta-analysis was further conducted.

Subgroup analysis: NA.

Sensitivity analysis: Jackknife sensitivity analysis:Following preprocessing of the data, a whole-brain voxel-based jackknife sensitivity analysis was performed to test the robustness of the findings by iteratively repeating the same analysis, excluding one dataset each time.

Country(ies) involved: China.

Keywords: primary insomnia, fMRI, ReHo.

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