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Reply to Hua Liu, HaiCun Shi and PingLei Pan: Coordinate based meta-analyses in a medium sized literature: considerations, limitations and road ahead

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Reply to Hua Liu, HaiCun Shi and PingLei Pan: Coordinate based meta-analyses in a medium sized literature: considerations, limitations and road ahead

We thank Liu and colleagues for their interest in and thoughtful comments on our neuroimaging meta-analysis on insomnia disorder (1). In their commentary, the authors highlight the conceptual and technical diversity among current neuroimaging approaches, including those that were integrated in our recent analysis. We completely concur with their summary on these differences, as indeed different modalities and analysis methods reveal different neurobiological features (2, 3). Therefore, we would like to focus on what we perceive as the critical question arising from this commentary, namely whether the findings obtained by the different methods can be combined in a useful and interpretable way by meta-analyses.

From the technical perspective, the results from any imaging modality that provides stereotaxic coordinates in a standard reference space for the peak locations of those clusters that became significant in a voxel-wise whole-brain analysis are readily includable in a coordinate-based meta-analysis (CBMA) (4). This flexibility is a key advantage of CBMA and can be attributed to the fundamental principle of assessing spatial convergence in reported locations. The admittedly sparse representation of published findings by spatial locations of the reported peaks not only avoids any influence of modality-immanent differences in signal characteristics, e.g., scaling, heteroscedastic, and smoothness. Rather, it also negates any influence of statistical choices such as thresholding procedure and significance levels. Put it simply, CBMA addresses the question, where in the brain previously reported effects for a particular topic show a higher spatial convergence than expected by a random spatial association – independently of the modality, methods and analytical choices of the original papers (5).

Such approach focusing on the spatial aspect not only acknowledges the fact that the primary objective of most neuroimaging studies is spatial inference, but also raises an important conceptual distinction between CBMA and classical effect-size meta-analyses in behavioral and clinical sciences (6). In contrast to the latter, CBMA should not be seen as the search for an absolute ground truth as it cannot establish the presence or absence of an effect at any given location due to the sparse representation and absence of effect-size measures. Rather, from the very outset, neuroimaging meta-analyses have been developed and enjoy great success as a method to consolidate a rich but heterogeneous literature by distilling spatial convergence. As rightfully pointed out by Liu and colleagues, there is an immense experimental and analytical
flexibility of neuroimaging studies. In addition, worries about p-hacking, selective reporting and publication bias towards positive findings are also well documented. This leads to a situation, where the literature may consist of many spurious, maybe even false positive effects, reflecting peculiarities of each study. CBMA then serve the critical role of consolidating the reported locations of significant effects into robust evidence by the analysis of spatial convergence (5).

Thus, indeed, CBMA has provided useful insights into the brain regions involved in various neuropsychiatric disorders (7-11). Our finding that, given the current literature, the same method has not pinpointed similar consistent findings for insomnia disorder may have several causes as discussed in the paper. In particular, the lack of findings could be attributable to, e.g., an insufficient power to find very small or noisy effects among a plethora of experimental and analytical choices resulting in spatial noise; to associations of insomnia with more subtle or distributed brain structural and functional deviations; or the presence of distinct subtypes among insomnia patients (12).

Whereas the suggested alternative approach of a qualitative review has a value if done with the aim of presenting a falsifiable model or hypothesis, such an approach has its own limitations. Even the most careful and systematic approach will be susceptible to subjective biases. Moreover, CBMA has the distinct advantage of providing an objective spatial inference, something which is hard to achieve in a qualitative review. Nevertheless, reviewing as well as CBMA is only a starting point into understanding the etiology of brain disorders. Either provides, with different aims, approaches and limitation, a consolidation of the current knowledge, but not in itself a model of pathophysiology. They may then, however, provide critical information and constraints on falsifiable models or hypothesis on why insomnia would be associated with a particular location as well as why their location differs across subjects and studies.

Liu and colleagues make an important suggestion in accordance to the best-practice guidelines published earlier by Muller and colleagues to include reasonable amount of homogeneous experiments (5). Put differently, they suggest to first aggregate findings within each modality and at a next level integrate the information across modalities. This would indeed represent an optimal approach, but obviously requires breaking down the available literature into smaller, more homogeneous groups of experiments. Such approach thus requires dealing with a trade-off that is inherent to any meta-analytic procedure and also well-known in CBMA. On one hand, studies included into a meta-analysis should evidently be as homogeneous as possible. On the other hand, a larger number of included studies not only increases power to detect smaller effects but also increase robustness and provide superior evidence for the generalization across
experimental and analytical procedures. Importantly, this weighting between inclusiveness and focus is fundamentally unresolvable as there is no generally optimal balance between both opposing attractors. Rather, there are guidelines establishing lower bounds for either end. For inclusiveness, the minimal number of studies needed in ALE analyses to avoid spurious effects driven by a single study is an important and clearly established lower bound (13). It also represents the reason why the analysis strategy suggested by Liu and colleagues to first conduct separate CBMA of studies with the same imaging modality was not viable in our study (1), given that there were not enough studies per modality to perform a valid neuroimaging meta-analysis over the single modalities (13).

But can we formulate a similar lower bound on focus, i.e., how diverse should we allow studies to be? Here the answer is at the same time simpler and more complex than one may intuitively think, as this floor indeed exists but is specific to each meta-analysis as it reflects the scientific question. If one wants to investigate, where in the brain task activations are most likely to occur, one would include the entire task-based literature to the extent that is technically possible (14). Likewise, combination of structural and functional studies (15-18), various tasks (19-21), or various resting-state methods (11, 22-24) has been also well-documented previously. Constructing a toy example for the opposite, i.e., very tight, approach, if the question is to find the representation of reflexive pronouns in sentences containing German action verbs, a study that uses the exact same task and material in English may already be considered too divergent. That is, the homogeneity required for a CBMA is solely dependent on the scientific question of interest. In our recent meta-analysis on insomnia disorder (1), we tried to address the question, whether there are spatially consistent abnormalities in the brains of patients relative to healthy control subjects and hence pooled the entire available literature.

As a final thought, does this exclude the emergence of convergent abnormalities in any individual modality, any particular type of analyses? Evidently it does not. Rather, it is well conceivable, that once more primary neuroimaging studies in patients with insomnia are conducted and published, subsequent meta-analyses following the same stringent methodological approach as the current but addressing a more focused question may reveal convergence within that particular part of the literature on insomnia disorder. Our meta-analysis, however, highlights the lack of spatial convergence within the hitherto existing limited neuroimaging literature. Taken together, we agree with Liu and colleagues that when more upcoming well-designed imaging studies in insomnia disorder are available, this CBMA could be revisited in the future and might then reveal consistent regional alterations. Another promising
avenue would be to use a more rich representation of the original data, e.g., by moving towards image-based meta-analysis as pioneered by ENIGMA consortium approaches. These may provide an alternative view into structural and functional regional disturbance in insomnia disorder in the future.
Conflicts of interest

The authors do not have any conflicts of interest to disclose.

Acknowledgment

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References:


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Records identified through database searching (n = 312)

Additional records identified through other sources (n = 1)

Records after duplicates removed (n = 313)

Records excluded (n = 284)
- case report (82), editorial letters (2), review or meta-analysis (42), other sleep disorders (22), functional or structural connectivity (12), irrelevant (other psychiatric or neurocognitive disorders, other medical diseases, methodological studies) (109), no control or healthy subjects (4), other language (3), children (1), animal (4), spectroscopy (3)

Records screened (n = 313)

Full-text articles assessed for eligibility (n = 29)

Full-text articles excluded, with reasons (n = 10)
- centroid coordinates (1), no reported difference between groups (3), no reported coordinates (6)

Studies included in qualitative synthesis (n = 19)

Studies included in quantitative synthesis (meta-analysis) (n = 19)

### Table S1. Description of diagnostic criteria, measurements, duration and type of insomnia in the included studies.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Diagnostic criteria</th>
<th>Inclusion/ exclusion criteria of subjects</th>
<th>Duration of insomnia per year (mean ±SD)</th>
<th>PSQI Scores (mean ±SD)</th>
<th>ISI Scores (mean ±SD)</th>
<th>PSG Variables (mean ±SD)</th>
<th>Type of insomnia</th>
</tr>
</thead>
</table>
| Son et al, 2017 (35) | DSM-5 & PSG | **Inclusion:**  
Age between 18 – 60 years; right handed; history of illness lasting at least 1 year; a total score ≥ 8 on the Korean version of PSQI; not having taken any psychiatric medications or hypnotics or cognitive behavioral therapy in the last 2 weeks.  
**Exclusion:**  
Present or previous major sleep disorder other than insomnia disorder; shift worker or traveler experiencing frequent jet lag; current or past diagnosis of other comorbid psychiatric disorders; evidence of either depression or anxiety; history or presence of significant neurological or medical illnesses; BMI ≥ 30; contraindications for MRI; pregnancy; lactation; or plans to become pregnant during the study; structural brain abnormalities based on MRI. | 4.9 ± 5.7 | 12.2 ± 3.5 | 17.9 ± 5.3 | N/A | Patients with insomnia |
| Kim et al, 2017 (38) | ICSD-2 & PSG | **Exclusion:**  
A current or past history of serious medical or neurological illness; axis I psychiatric disorders other than PI on DSM-IV; sleep disorders other than PI (based on CSD-2 criteria); short-term insomnia (duration < 6 months); shift worker; borderline or antisocial personality disorder; pregnancy; contraindication for MRI. | N/A | 13.4 ± 4.0 | 15.9 ± 9.0 | TST: 323.4 ± 61.6 (min)  
SL: 16.6 ± 14.3 (min)  
SE: 80.3 ± 9.5%  
WASO: 64.9 ± 44.4(min) | Psychophysiological insomnia |
| Huang et al, 2017 | DSM-5 | **Inclusion:**  
Age of 25–65 years; a duration | 10.68 ± 8.27 | 13.15 ± 2.43 | N/A | N/A | Chronic primary insomnia |
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou et al, 2017</td>
<td>DSM-IV</td>
<td><strong>Inclusion:</strong> duration of insomnia ≥1 year; without medical treatment; age 25–65 years; and right-handed.</td>
<td>Clinical evidence of any moderate-to-severe sleep disorder other than insomnia; abnormal sleep–wake rhythms; medical illnesses; other neurological or psychiatric diseases; illicit drug or alcohol abuse or current intake of psychoactive medications; structural lesion in MRI; and MRI contraindications.</td>
<td>Mean not reported (Reports From each subject are available) 10.98 ± 8.85 13.29 ± 2.54 N/A N/A chronic primary insomnia</td>
</tr>
<tr>
<td>Ran et al, 2017</td>
<td>DSM-IV &amp; PSG</td>
<td><strong>Inclusion:</strong> adult patients; absence of moderate or severe class anxiety in the last month; no role of substance or medication abuse in insomnia; no other sleep-related diseases; no additional mental disorders; central nervous system diseases; head trauma or psychiatric disorders; neither pregnant nor breast-feeding.</td>
<td>Medical illnesses or any neurological or psychiatric diseases; alcohol or illicit drug abuse or current intake of psychoactive medications; contraindications for MRI.</td>
<td>Mean not reported                                                13.33 ± 3.02 N/A Mean not reported chronic primary insomnia</td>
</tr>
<tr>
<td>Kay et al, 2016</td>
<td>DSM-IV &amp; PSG</td>
<td><strong>Exclusion:</strong> age younger than 18 y or older than 60 y; self-reported left handedness; self-reported sleep disorders other than insomnia; apnea-hypopnea index ≥ 15; periodic limb movements with awakening ≥ 20/h; caffeine &gt; 400 mg per day on average; inability to abstain from tobacco and alcohol during the study; inability to abstain from drugs known to affect sleep for at least 2 w before participation</td>
<td>Medical illnesses; other neurological or psychiatric diseases; alcohol or illicit drug abuse or current intake of psychoactive medications; structural lesion in MRI; and MRI contraindications.</td>
<td>N/A                                                                12 ± 3 N/A primary insomnia</td>
</tr>
</tbody>
</table>
and 4 w for fluoxetine; positive pregnancy test; and presence of a significant current medical or psychiatric condition; DSM-IV Axis I Disorders.

<table>
<thead>
<tr>
<th>Study</th>
<th>Overview</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>N/A</th>
<th>12.72 ± 3.97</th>
<th>N/A</th>
<th>N/A</th>
<th>primary insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al, 2016 (34)</td>
<td>DSM-IV &amp; Chinese Classification of mental disorder (CCMD-3)</td>
<td><strong>Inclusion:</strong> PSQI &gt; 7 and HAMD &lt; 14; not have onfounding mental or physical conditions; be aged between 18 and 55; not be currently prescribed anti-anxiety; anti depression or sleeping medications (within 2 weeks directly prior to participation); right handed.</td>
<td>N/A</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Li et al, 2016 (42)</td>
<td>-DSM-IV</td>
<td><strong>Inclusion:</strong> insomnia lasting ≥ 1 months; no other sleep disorders or other psychiatric disorders; insomnia dose not due to the effects of medications/substance abuse; such as caffeine or nicotine or alcohol; right-handed; no serious organic disease; no foreign implants in the body; age 25–60 years; no abnormal signal; and head motion 1.5 mm or 1.5° during MRI.</td>
<td>46.04 ± 29.63 (Month)</td>
<td>12.51 ± 3.25</td>
<td>19.69 ± 3.28</td>
<td></td>
<td></td>
<td>primary insomnia</td>
</tr>
<tr>
<td>Dai et al, 2016 (43)</td>
<td>ICSD-2, DSM-IV &amp; PSG</td>
<td><strong>Inclusion:</strong> duration of insomnia &gt; 2 months; PSQI &gt; 5; sleep diary for &gt; 2 weeks duration; and right-handedness. <strong>Exclusion:</strong> inborn or other acquired diseases; present or past psychiatric or central nervous system disorders; substance dependency or substance abuse (including heroin; nicotine; or alcohol addiction for good sleepers; any history of swing shift; shift work; sleep complaints or other sleep disorder; or circadian rhythm sleep disorder confirmed by PSG.</td>
<td>5.44 ± 5.23</td>
<td>15.17 ± 2.16</td>
<td>18.43 ± 2.96</td>
<td></td>
<td></td>
<td>chronic primary insomnia</td>
</tr>
<tr>
<td>Wang et al, 2015 (45)</td>
<td>DSM-IV</td>
<td><strong>Inclusion:</strong> at least one month with insomnia; had no other sleep disorders; right-handed; younger than 60 y. <strong>Exclusion:</strong></td>
<td>12.4 ± 3.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>primary insomnia</td>
</tr>
</tbody>
</table>
abnormal signal; insomnia was caused by serious organic disease or severe mental disease secondary to depression or generalized anxiety; pregnant; nursing; or menstruating.

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Details</th>
<th>Data (Mean ± SD)</th>
<th>Exclusion Details</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dai et al, 2014 (41)</td>
<td><strong>Inclusion:</strong> Insomnia lasting &gt;5 months; a PSQI score &gt;7; had a sleep diary for at least 2 weeks' duration; right-handed; no history of inborn or other acquired diseases; no addictions; and no other sleep disorders; or circadian rhythm sleep disorder; no foreign implants in the body; and moderate body shape and weight.</td>
<td>6.0 ± 5.2</td>
<td><strong>Exclusion:</strong> current shift work; any history of psychiatry and sleep disorders; and medical conditions.</td>
<td>chronic primary insomnia</td>
</tr>
<tr>
<td>Baglioni et al, 2014 (33)</td>
<td><strong>Inclusion:</strong> be right-handed; free of any psychoactive medication for at least 2 w prior to and during the study participation; refrained from alcohol; caffeine; and daytime naps during the recording days.</td>
<td>N/A</td>
<td><strong>Exclusion:</strong> current shift work; any history of psychiatry and sleep disorders; and medical conditions.</td>
<td>Insomnia disorder</td>
</tr>
<tr>
<td>Chen et al, 2014 (46)</td>
<td><strong>Exclusion:</strong> any past or present DSM-IV Axis I disorder; any past or present sleep disorder except insomnia; current use of prescription psychotropic or hypnotic medication; BMI &gt; 30; and MRI contraindication.</td>
<td>N/A</td>
<td></td>
<td>insomnia</td>
</tr>
<tr>
<td>Stoffer et al, 2014 (36)</td>
<td><strong>Inclusion:</strong> abstinence from hypnotic medication for at least 2 months; normal cognitive functioning and absence of any comorbid disorder; other sleep disorders.</td>
<td>N/A</td>
<td></td>
<td>primary insomnia</td>
</tr>
<tr>
<td>Joo et al, 2014 (29)</td>
<td><strong>Exclusion:</strong> controls with an average nightly sleep time of less than 7 h over the recent 2 w based on sleep diaries; obstructive sleep apnea; moderate to severe periodic</td>
<td>8.4 ± 9.1</td>
<td></td>
<td>chronic primary insomnia</td>
</tr>
<tr>
<td>Study</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>WASO: 59.2 ± 38.7(min)</td>
<td></td>
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<tr>
<td>Joo et al, 2013 (30)</td>
<td><strong>Inclusion:</strong> age of 40-70 y; conformity to the definition of PI by ICSD-2; and a duration of insomnia ≥ 1 y.</td>
<td><strong>Exclusion:</strong> total sleep time &lt; 7 h on history only for normal sleepers; obstructive sleep apnea syndrome; moderate to severe periodic limb movement; abnormal sleep wake rhythms; medical illnesses; other neurological or psychiatric diseases; alcohol or illicit drug abuse or current intake of psychoactive medications; a structural lesion on brain MRI.</td>
<td>primary primary insomnia</td>
<td></td>
</tr>
<tr>
<td>Altena et al, 2010 (26)</td>
<td><strong>Inclusion:</strong> Neurological; psychiatric; or metabolic diseases possibly accounting for their sleep complaints.</td>
<td>N/A</td>
<td>primary insomnia</td>
<td></td>
</tr>
<tr>
<td>Altena et al, 2008 (37)</td>
<td><strong>Exclusion:</strong> somatic disorder that might affect sleep and use of sedative medication; other sleep disorders.</td>
<td>N/A</td>
<td>chronic insomnia</td>
<td></td>
</tr>
<tr>
<td>Nofzinger et al, 2004 (32)</td>
<td><strong>Inclusion:</strong> duration of ≥1 month; the sleep disturbance causes clinically significant distress or impairment; insomnia does not occur exclusively during the course of a mental disorder; and insomnia is not due to another medical or sleep disorder or effects of medications/ substance abuse. <strong>Exclusion:</strong> using any medications that might affect sleep or regional cerebral metabolism excessive use of caffeine (&gt;300 mg or</td>
<td>N/A</td>
<td>primary insomnia</td>
<td></td>
</tr>
</tbody>
</table>
three cups of coffee per day); major depressive disorder or other mental disorder on the basis of a Structured Clinical Interview for DSM-IV.