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REVIEW

Working memory dysfunction in insomniac adults: a systematic metanalytical review

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BACKGROUND: Insomnia is the most commonly occurring sleep disorder: recent reports estimate that 25-30% of adults in the general population occasional instances of experience insomnia, while 10% suffer from disturbances severe enough to meet diagnostic criteria for insomnia. Little is known about the mechanisms, causes, clinical course, and consequences of this condition. Over 30 studies have been published on the matter but only a small proportion has found differences in the working memory of individuals with vs. without insomnia.
OBJECTIVE: To summarize evidence regarding the differences in working memory performance between insomniac vs. normal adult sleepers.
METHODS: The survey was conducted using an advanced search in the ISI Web of Science and MEDLINE/PubMed with the terms "sleep", "insomnia" and "working memory" as major descriptors; these were crossed with the following keywords: "psychological tests", "neuropsychology" and "performance".
RESULTS: A total of 112 articles were identified in the search conducted in PubMed and Web of Science. After the screening, 102 articles unrelated to the proposed theme were excluded. Thus, 10 articles were analyzed by the eligibility and exclusion criteria, and included in this systematic review.
CONCLUSION: The information resulting from the analysis of the reviewed articles suggests that mild, but not definitive deficits in cognitive performance might be masked by insignificant disparities in studies comparing insomniac individuals with normal sleepers. This shortcoming can be circumvented by larger and better-characterized samples, together with optimized methodological control of factors which might otherwise result in confounding variations among participants.

KEYWORDS: Insomnia, working memory, cognitive performance.

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INTRODUCTION

Insomnia is the most common sleep disorder: recent reports estimate that 25-30% of adults in the general population experience occasional instances of insomnia, while 10% suffer from sleep disturbance severe enough to meet diagnostic criteria for insomnia.[1-3] In addition, little is known about the mechanisms, causes, clinical course, and consequences of this highly prevalent chronic condition.[4] According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5),[5] insomnia is considered as a dissatisfaction complaint relating to the quantity or quality of sleep (in the absence of psychiatric disorder, medical condition or substance use), which is present for at least three months and

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generates a functional impairment of the individual. In addition, according to the International Classification of Sleep Disorders (ICDS),[6] insomnia is characterized by frequent complaints related to difficulty falling asleep or staying asleep and/or poor sleep despite adequate conditions for sleep.

Complaints related to altered cognitive functioning are also frequent and involve memory and concentration problems, difficulty in making decisions and frequent work-related mistakes.[7-9] However, these complaints have not been unequivocally corroborated by objective performance-based measures. Over 30 studies have been published on the matter but only a small proportion has found differences between individuals with and without insomnia. For example, a recent review indicates that tests measuring working memory (e.g., Digit Span, Letter-Number Sequencing) have yielded contradictory findings. The lack of consistent evidence has led some authors to question the existence of daytime cognitive impairments in insomnia,[10] and to attribute daytime complaints to other mechanisms such as excessive attention toward expected consequences of poor sleep.[11]

Even though the findings suggest good cognitive performance by insomniac individuals, they could result from methodological errors associated with some major points, such as the use of insensitive instruments to detect cognitive deficits, heterogeneity of sample and statistical power. In fact, some studies[12-16] were performed with small samples, i.e., less than 20 individuals per group, compromising the statistical power to detect subtle differences between normal sleepers and insomniac individuals. Moreover, the individuals included in most studies seem to have not always been properly diagnosed with insomnia in terms of in terms of the severity of sleep disorders, which may have led to a measure of heterogeneity in the samples with the consequent decrease in statistical power. Another problem is the use of inappropriate instruments for the evaluation of insomnia, what may have hampered the detection of cognitive deficits. Given these limitations, it is reasonable to question whether the inconsistent findings between insomniac individuals and controls in available studies (i.e., negative findings) can be accepted as evidence of preserved cognitive functioning in individuals with insomnia. Therefore, the aim of the study is to summarize evidence regarding the differences between insomniac and normal adult sleepers on working memory performance.

METHODS

Eligibility criteria

The methodological structure of this study followed the proposals of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[17] Thus, we have adopted the PICOS (population, intervention, comparators, outcomes and study design) recommendation to determine eligibility as specified:

1. Population - young men and/or women diagnosed with insomnia according to DSM-III, IV, V or ICD-10 and not associated with neurological or psychiatric comorbidities, aged between 20 and 59 years;
2. Intervention - patients submitted to the neuropsychological assessment, associated with or without the use of medications and other assessments (i.e., polysomnography, sleep diary, Actigraph);
3. Comparators - a control group composed of healthy good sleepers without a history or any sleep disorder for comparison;
4. Results - instruments or tests that assess working memory were accepted;
5. Research design - observational studies were selected to investigate the working memory performance in insomnia.

Sources

The studies were retrieved from a MEDLINE/PubMed and ISI Web of Knowledge. Experts on the subject of the present study were also contacted to send articles. To find additional articles, all tables were examined for evidence of previous systematic reviews and found references to observational studies as necessary. In addition, we analyzed the references of all selected articles. Searches were closed on October 20th of 2015.

Search

The search was conducted in all databases using the following terms: "sleep", "insomnia" and "working memory" as major descriptors; they were crossed with the following keywords: "psychological tests", "neuropsychology" and "performance".

Selection of studies

The selection of studies was performed by two independent researchers that, in case of disagreement, sought a consensus on the selection. The evaluation consisted of a selection of studies by analysis of the title, followed by analysis of the summary and then the full text. With persistent disagreement between these two researchers, a third one was requested to complete the process. Relevant articles were obtained and assessed for inclusion and exclusion, according to the criteria described below.

Data collection

The following data were extracted from the articles: sample size, participant characteristics, types of tasks, tests/instruments used, working memory measu-

rements and main significant results. In addition, other information about the methods and outcomes were collected. These procedures were performed by two independent investigators, who reached a consensus in case of disagreement.

Exclusion Criteria

We excluded articles that (1) provided no effective results, (2) generated questions but no answers, (3) included samples composed of elderly, children and adolescents, or (4) included individuals who did not have detailed statistical procedure applicable.

Risk of bias in studies

For assessing the risk of bias, each included article was analyzed according to the following factors: (a) the presence of eligibility criteria for participants in the sample, (b) results of all moments from the analysis for more than 85% of the sample, (c) presence of a control group, and (d) presentation of intergroup variability of the results.

RESULTS

Based on the defined criteria, 132 articles were found in the search conducted in PubMed and Web of Science; 20 duplicates were excluded. After screening, 102 articles were excluded, which were not related to the proposed theme. Therefore, ten articles were analyzed by eligibility criteria, according to "PRISMA", and by exclusion criteria as shown in Figure 1. All of them met the criteria for this review and were included in this study. The data presented in these studies are summarized in Table 1.

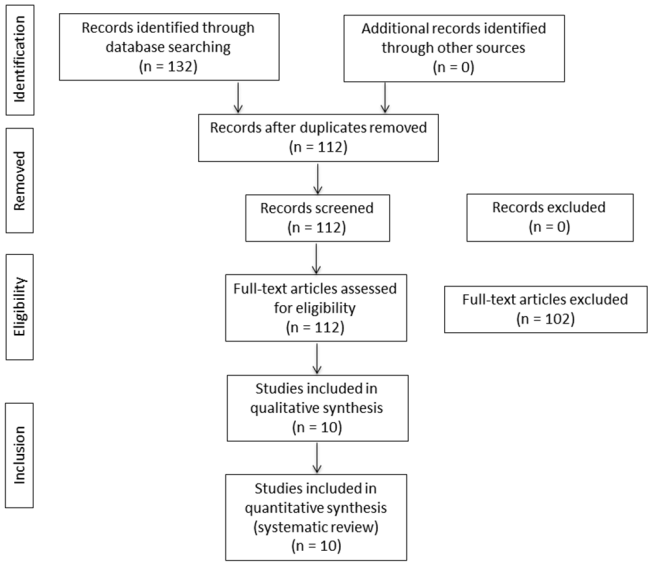

Figure 1 - Flow of information through the different phases of study selection.

None of the studies indicated if psychologists administered the neuropsychological tests. The diagnosis for insomnia was conducted according to DSM-IV, International Classification of Sleep Disorders and Technion Sleep Questionnaire. No study reported the severity of insomnia

For assessment of insomnia, the following instruments were used: "Wechsler Test of Adult Reading (WTAR)", "Auditory psychomotor vigilance task (PVT)", "PVT-TT, Switching Attention Task (SAT)", "N-Back task (N-BACK)", "Performance Evaluation and Effort Scale (PEES)", "Karolinska Sleepiness Scale (KSS)", "Visual Analogue Scale-Alertness (VASA)", "Stroop Color and Word Test (SCWT)", "Digit Span Subtest of the WAIS-III", "Brief Test Attention (BTA)", "Letter-number Sequencing subtest of the WAIS-III", "Sustained Attention (SA)", "Digit Symbol Substitution Test (DSST)", "Trail Making Test (TMT)", "Controlled Oral Word Association Test (COWAT)", "Hopkins verbal learning test (HVLT)", "Paced Auditory Serial Addition Task (PASAT)", "Tower Test from the D-KEFS", "Verbal Fluency", "Continuous Performance Test-II (CPT-II)", "California Verbal Learning Task (CVLT-II)" and "Easy letter memory task".

With regard to the type of study, all the articles were observational studies, with healthy good sleepers as the control. For the main outcomes, results are unclear (see Table 1); this will be explained in the discussion.

DISCUSSION

Our objective was to summarize evidence regarding the impact of insomnia on the performance of working memory. Collectively, results suggest that insomniac patients present worse performance in tasks requesting working memory; however, further studies are necessary. Therefore, our discussion is divided into subtopics in order to better explore the impact of insomnia on working memory.

Instruments used in the studies selected

One factor that often contributes to inconsistent findings is the large number of measurements of cognitive performance, often used without a plausible justification.[18] Tasks that have different levels of complexity, with different processing demands, are commonly applied, and then, used for comparison between studies.[18] The selected studies used different tests, and only four tests were used in common among these ten studies. The N-back task was used in three studies,[19-21] the Digit Span in two studies,[15,16,22] the Digit Symbol in two studies[12,15] and the Trail Making Test in two studies.[12,22]

Table 1 - Studies that investigated the influence of insomnia on working memory performance

Reference	Sample, years	Objective	Outcomes
19	N = 96 (18-65 y)	Identify neurobehavioral consequences of insomnia.	Alternating attention and working memory were significantly worse in insomniacs patients. In the control group performed worse sustained attention is associated with subjective sleepiness.
15	N = 49 (26-63 y)	Evaluating the neuropsychological impairments and daily complaints of patients with insomnia.	Insomnia patients showed no overall deficits on neuropsychological tests. Sleep was significantly associated with the field of motor speed.
20	N = 50 (25-50 y)	Examining neural correlates of working memory in patients with primary insomnia	There is an abnormal neural function in patients with insomnia resulting in decreased performance of brain regions and an inability to modulate neurally that is irrelevant during a working memory task.
16	N = 41 (29-56 y)	Investigate cognitive impairments in insomniac patients and compare profile differences between insomniac patients with cognitive complaints and patients with insomnia without complaints in relation to cognitive performance.	Insomnia patients have clinically significant deficits. Patients with higher cognitive complaints showed a worse performance in neuropsychological tests. All observed deficits were significantly associated with difficulty continuation of sleep, whether subjectively or objectively measured and regardless of the sleep pattern.
21	N = 59 (40-58 y)	Investigate the daytime cognitive performance of patients with chronic insomnia	The authors found no significant differences between the two groups on the memory test. In the N-Back task insomniac patients showed a worse performance when compared to the control group.
12	N = 20 (18-50 y)	To investigate daytime cognitive performance in chronic insomnia	Insomniac patients showed a worse performance in selected tests when compared to the control group.
22	N = 60 (62.5 ± 5.8 y) Healthy	Determine the impact of insomnia and chronic use of benzodiazepines on cognition and psychomotor performance in older adults.	Sleepless participants in use or not of benzodiazepines, have a poorer performance of working memory when compared to healthy individuals.
13	N = 26 (20-28 y)	To investigate the relationship between mnemonic performance, task difficulty and the internal activation level in a group of insomniac patients, comparing them to a control group.	The authors found no significant differences between the two groups on the memory test. In N-Back task the insomniac patients showed a worse performance when compared to the control group.
14	N = 24 (31-54 y)	To investigate the association of insomnia with possible cognitive deficits and their effects on the circadian rhythm	Insomniacs showed greater impairment of working memory.
40	N = 99	To investigate the association between chronic insomnia and cognitive changes in the elderly.	Insomniacs had a poorer performance on memory tasks when compared to healthy subjects.

Cognitive impairment in patients with insomnia

Over the years, researchers interested in the area of sleep and cognition have been aiming at developing cognitive impairment profiles in patients with insomnia with daytime complaints performance.[23] Several studies pointed out that insomniac subjects commonly present cognitive deficits or no deficit at all.[24-26] Nevertheless, these studies suffered from a limitation, namely small and heterogeneous samples, which is a limiting factor to detect small differences between individuals with insomniac individuals and healthy sleepers. In line with recent reports that insomnia preferentially interrupts the performance of complex but not of easy tasks,[27,28] we have detected deficits in working memory. A functional prefrontal cortex is the biological requisite for the normal performance of these complex tasks.[29,30] It may be noted that similar cognitive processes are also disturbed as a consequence of experimental induction of partial chronic sleep deprivation[31] or of shallow sleep,[32] the presence of which has been reported in, at least, some clinical insomniac cases, thereby suggesting their potential association with cognitive function.

It was recently reported that insomnia and short sleep duration could have an adverse effect on tasks tapping the executive control of attention, whereas people with longer sleep duration did not suffer from such symptom.[33] Interestingly, several studies also unveiled performance abnormalities in insomniac patient undiagnosed by

polysomnography,[22] who presented sometimes, with even more pronounced impairment than those successfully diagnosed by polysomnography.[34] This indicates that mechanisms other than poor sleep may also contribute to the cognitive decline in individuals with insomnia. For instance, fatigue, anxiety and negative mood that are well-recognized in insomnia have been reported to induce cognitive impairments in association with dysfunction of the prefrontal cortex.[35-39]

The working memory impairment in insomniac patients was observed in the studies by Shekleton et al.,[19] Varkevisser et al.,[14] Vignola et al.,[22] and Haimov et al.[40] This impairment seems to happen regardless of whether insomnia is being treated with medication or not. For example, the study of Cellini et al.[13] shows that insomniacs have a worse performance in tests involving work memory. The study by Drummond et al.[20] points out that insomniac patients show less activation of the frontoparietal system involved in working memory. In these patients, brain areas typically involved in tasks involving working memory would not be engaged in the operation; no activation was observed for any other brain area to compensate for non activation of this system.

Magnitude of impact of insomnia in working memory

Although it is already well established that insomniac patients have daytime losses that interfere directly and significantly with their social, emotional and occupational life, not all insomniac patients will present this pattern of deficit.

Subclinical aggravation of depression and anxiety symptoms were often coincidentally observed in insomniac individuals. Likewise, subclinical cognitive impairments might also be observed from this systematic review showing differences in performance. The discoveries mentioned above may as well be explained by individual variability in cognitive impairments. Parenthetically, and based on the evidence from epidemiological studies on the distribution of daytime symptoms, different patients may not be necessarily subject to identical consequences. For example, sleep deprivation has been shown to induce cognitive vulnerability with trait-like individual differences.[41] Similarly, fatigue resulting from sleep loss may also have differential effects on insomniac individuals.[42] From this perspective, it seems reasonable to speculate that the contribution of sleep loss, fatigue and other psychological factors to cognitive impairments, as well as to the severity itself, may differ among insomniac patients. To complicate matter, a dose-dependent detrimental effect on cognitive function was observed following prolongation of sleep-restriction duration.[31] It is noteworthy that with the access to a night of normal sleep, individuals could get a complete recovery from the aforementioned impairments by sleep restriction.[32] Because insomniac individuals demonstrated considerable variations in night-to-night sleep,[43] it is possible that the quality of sleep just prior to the test, or more generally, the duration of poor sleep before the test, may affect the cognitive performance. Finally, cognitive impairments in insomniac patients may vary from one to another, owing to idiosyncratic vulnerability to sleep loss, fatigue, mood, and so forth. Moreover, for any individual, cognitive impairments may also differ at varied time points; this is probably determined by the quality and duration of his/her recent sleep.

The clinical significance of cognitive impairments in insomnia

In accordance with impaired working memory, individuals with insomnia have subjectively reported their memory problems.[7,8] Of note, there may be discrepancies between objective and subjective measurements on such cognitive impairments, which may result from exaggeration or overestimation of daytime deficits by the insomniac patients themselves.[15] Nonetheless, such differences are nonspecific to insomniac individuals, given that these symptoms have been documented not only in a variety of disorders, including mild cognitive impairment,[44] schizophrenia,[45] and multiple sclerosis,[46] but also in healthy people.[47] Although the impairments could be influenced by multiple factors, such as fatigue and mood, in some studies,[48,49] subjective performance (as compared to objective performance) has the potential advantage of predicting structural brain damage or cognitive decline. However, whether actual day-to-day functioning can be better predicted by objective or self-reported cognitive deficits remains the object of controvery.[50,51] Objective cognitive deficits observed in some studies have been in compliance with daytime activities typically reported to be impaired in insomniac individuals.[12-14,16,19,21,22,40] Given the importance of working memory in conducting complex tasks,[51] even subtle impairment of these functions may cause an increased frequency of non-motor vehicle accidents (e.g., falls, work-related, etc.), or a decreased work productivity related to insomnia.[7,52,53]

Limitations

There are several factors to be considered in the selected studies, with regard to age, educational levels and who administrated the tests. No study indicated who administered the neuropsychological tests. Only six articles matched participants for age,[12-14,16,20,21] in contrast to the other four articles.[15,19,22,40] None of the studies indicated the level of education of the participants, even though it is a well known fact that these variables influence cognitive performance.[26] For instance, four studies selected participants over 60 years, which lead us to question whether the cognitive deficits found are not arising from old age cognitive loss.[15,19,22,40] Some studies report on an insufficient sample, with few individuals analyzed so that it questionable whether one can confirm the presence of a deficit.

Other relevant factors include (1) the distinct methods for assessing these criteria, considering possible discussions about comparability of results among different studies; and (2) the generalizability to subjects with primary or prolonged insomnia. Nevertheless, our major concern was the application of performance tests, which were originally developed and validated to assess the cognitive deficits in neurological disorders and brain injuries, rather than insomnia. Moreover, these tests may fail to distinguish differences of cognitive functions among insomniac patients, owing to their insensitivity to insomnia.

FINAL CONSIDERATIONS AND CLINICAL IMPLICATIONS

The discoveries reported in our current research suggest that mild, but not definitive deficits in cognitive performance might be masked by insignificant disparities in studies comparing insomniac individuals with normal sleepers. Further investigations determining these underrepresented roles are undoubtedly required before drawing definite conclusions concerning the specific nature and extent of cognitive impairments relating insomnia.

Determination of the clinical significance of cognitive deficits by means of normative data or by examining their relation to actual everyday function warrants further investigation. Moreover, strategies such as ecological momentary assessment, qualitative analysis or daytime monitoring with diaries may be advantageous in terms of their ability to help enhance the comprehension on how performance in experimental cognitive tests could be associated with the actual day-to-day function. To provide an entry point for the elucidation of the detailed mechanisms, more studies are wanted to estimate the correlates of diurnal impairments, which should extend beyond the sleep continuity variables, comprising sleep quality and other daytime insomniac symptoms including fatigue, arousal, anxiety and negative mood. Because daytime deficits have been the object of speculation as important determinants relating to seeking treatment, it is important to introduce measurements assessing cognitive function into intervention studies to determine the clinical significance of treatment outcomes. Identification of definite cognitive deficits in chronic insomnia is also informative to clinical practice. A complete inquiry on cognitive functioning together with other diurnal insomniac symptoms (e.g. irritability, fatigue, excessive worry) is indispensable.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Monteiro B, Candida M, Monteiro S, Paes F and Machado S developed the project, discussed the data, wrote the first draft of the article, and reviewed its final form; Yuan TF, Li A, Sun X, Rocha NBF, Campos C, Nardi AE, discussed the data and reviewed the final form of the article.

DISFUNÇÃO DA MEMÓRIA DE TRABALHO EM ADULTOS INSONES: UMA REVISÃO SISTEMÁTICA

INTRODUÇÃO: A insônia é o distúrbio do sono mais comum: relatórios recentes estimam que 25-30% dos adultos sofrem episódios de insônia, enquanto 10% sofrem de distúrbio do sono suficientemente grave para cumprir os critérios de diagnóstico para insônia. Além disso, pouco se sabe sobre os mecanismos, causas, evolução clínica, e consequências desta doença crónica altamente prevalente. Mais de 30 estudos foram publicados sobre o assunto, mas apenas uma pequena proporção encontrou diferenças entre os indivíduos com e sem insônia, por exemplo, na memória de trabalho.

OBJETIVO: Examinar as evidências sobre as diferenças entre adultos insones e normais no desempenho da memória de trabalho.

MÉTODOS: A pesquisa foi realizada usando uma pesquisa avançada no ISI Web of Science e MEDLINE/PubMed com os termos "sleep", "insônia" e "memória de trabalho" como os principais descritores, que foram cruzados com as seguintes palavras-chave: "testes psicológicos", "neuropsicologia" e "performance".

RESULTADOS: Um total de 132 artigos foram identificados na pesquisa realizada no PubMed e Web of Science; 20 duplicações foram excluídas. Após a triagem, 102 artigos foram excluídos, que não estavam relacionadas com o tema proposto. Assim, 10 artigos foram selecionados por critérios de elegibilidade e de exclusão, e incluídos na revisão sistemática.

CONCLUSÃO: As descobertas relatadas em nosso estudo sugerem que os deficits leves mas não permanentes de desempenho cognitivo podem ser mascarados por disparidades insignificantes em estudos que comparam indivíduos com insônia com pessoas com sono normal. Tal deficiência pode ser contornada pela análise de amostras maiores e mais bem caracterizadas, em conjunto com o controle metodológico otimizado de fatores que potencialmente podem incorrer em variações entre os participantes.

PALAVRAS-CHAVE: Insônia, memória de trabalho, desempenho cognitivo.

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