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BÁRBARA CRISTINA DA COSTA MONTEIRO

PREJUÍZO COGNITIVO EM PACIENTES DEPRIMIDOS COM QUEIXA DE INSÔNIA

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Dissertação de Mestrado

Dissertação de Mestrado submetida ao Corpo Docente do Programa de Pós-Graduação em Psiquiatria e Saúde Mental (PROPSAM) do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para a obtenção do Grau de Mestre em Saúde Mental.

Orientador: Sergio Eduardo de Carvalho Machado

Co-orientador: Nuno Barbosa Rocha

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Barbara Cristina da Costa Monteiro

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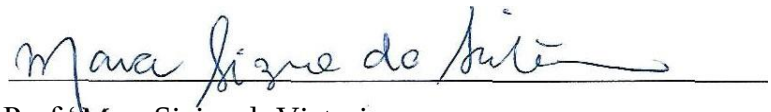

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RESUMO

A depressão é hoje um dos transtornos psiquiátricos com maior incidência sobre a população, com altas taxas de incapacitação dos indivíduos acometidos. Na grande maioria dos casos, a depressão é acompanhada por queixas em relação ao sono, principalmente aquelas relacionadas ao sono REM, o que acarreta maiores comprometimentos para o sujeito. Não raro, pacientes depressivos relatam, em algum momento, déficits cognitivos que prejudicam diretamente seu desempenho no dia a dia, levando-os, em muitos casos, ao afastamento do trabalho. Alterações no sono também estão relacionadas a déficits cognitivos acentuados e incapacitantes e, quando a alteração do sono vem acompanhada do quadro depressivo, estes déficits tendem a ser mais significativos. Nos estudos realizados, o estudo 1 mostra, através de uma meta-análise, o impacto da insônia sobre a memória de trabalho, confirmando a hipótese de comprometimento da mesma. Já no artigo 2 foi realizada uma revisão crítica sobre o papel do Brain Derived Neurotrophic Factor (BDNF) no sono e na depressão e foi possível concluir que os níveis desde fator neurotrófico está diretamente ligado ao sono e sua redução acarreta altos níveis de estresse e consequentemente maior vulnerabilidade para o desencadeamento da depressão. No artigo 3 foram publicados os resultados encontrados no estudo conduzido pela equipe, a fim de avaliar os déficits cognitivos encontrados em pacientes depressivos com queixas em relação ao sono. Ao final de nossa pesquisa encontramos correlações entre o grau de comprometimento do sono e o grau de gravidade da depressão, assim como que estes pacientes apresentam déficit na atenção, memória operacional e velocidade de processamento. Entender a relação entre depressão e déficits cognitivos é de suma importância, uma vez que o quadro afeta significativamente o indivíduo em suas capacidades laboral e psicossocial. O objetivo da tese é traçar a possível relação entre níveis de depressão, prejuízo de qualidade de sono e déficits cognitivos.

Palavras-chave: depressão, sono, funções executivas, atenção, memória operacional, velocidade de processamento, BDNF.

ABSTRACT

Depression is one of the most prevalent psychiatric disorders, with high rates of incapacitation of the individuals affected. In most of cases, depression is accompanied by complaints about sleep, especially those related to REM sleep, which causes more impairments for the subject. Often, depressed patients report, at some point, cognitive deficits that impair their daily performance leading, many cases, to withdrawal from work. Sleep is also related to marked and disabling cognitive deficits, and when sleep disturbances are accompanied by depressive symptoms, these deficits tend to be more significant. In the studies conducted, the first shows, through a meta-analysis, the impact of insomnia on working memory performance, confirming the hypothesis of impairment. In article 2 we talk about the role of Brain Derived Neurotrophic Factor (BDNF) in sleep and depression and it was possible to conclude that neurotrophic factor levels were linked to sleep and its reduction leads to high levels of stress and consequently greater vulnerability to depression. In article 3 were published the results found in the study conduct by us, which aimed to assess the cognitive deficits presented in depressed patients with sleep complaints. At the end of our research, correlations between sleep impairment and the severity of depression were found, as well deficits in attention, working memory and processing speed. Understand the relationship between depression and cognitive deficits is important once it significantly affects the individual in his psychosocial capacities. The aim of the thesis is to outline the possible relationship between levels of depression, sleep quality impairment and cognitive deficits.

Key words: depression, sleep, executive functions, attention, working memory, processing speed, BDNF.

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BNDF	Brain Derived Neurotrophic Factor.
REM	Rapid Eye Moviment.
PSQI	Índice de Qualidade de Sono de Pittsburgh.
SNC	Sistema Nervoso Central.
ICDS	Classification of Sleep Disorders
MDD	Mild Depression Disorder
ECT	Eletroconvulsive Therapy
HPA	Hypothalamic-pituitary-adrenal axis
MINI	Mini International Neuropsychiatric Interview
BDI-II	Beck Depression Inventory (BDI-II)
CBT	Cognitive Behavior Therapy
PSQI	Pittsburgh Sleep Quality Assessment
WMI	Working memory index
SPI	Speed Processing Index
BPA	Psychological Battery for Attention Evaluation (BPA)
SA	Sustained attention
DA	Divided attention (DA)
AA	Alternating attention (AA)
PET	Positron emission tomography

SUMÁRIO

1 **INTRODUÇÃO**

A depressão é um transtorno mental caracterizado por um estado de sofrimento acentuado que acarreta prejuízos físicos, emocionais e sociais (LEUBNER E HINTERBERGER, 2017). O Transtorno Depressivo Maior possui base heterogênea e estudos epidemiológicos mostram que 40% a 50% do risco para o desenvolvimento da depressão é genético (NESTLER et. Al, 2002). O transtorno afeta em torno de 10 a 30% das mulheres e 7 a 15% dos homens (YU E CHEN, 2011), e está entre os transtornos mais incapacitantes para o indivíduo (MERIKANGAS et al, 2017).

Estudos sobre a privação de sono mostram que o quadro acarreta em consequências físicas, psicológicas e comportamentais que impacta seriamente o funcionamento do indivíduo (BRUCE E ALOIA, 2006). O sono é significativo no desenvolvimento da depressão, sendo a queixa de sono não reparador comum entre pacientes depressivos (RETHORTS et. Al, 2015). Grande parte dos pacientes depressivos mostram uma ou mais alterações na neurofisiologia do sono, sendo as principais alterações observadas a diminuição do sono de ondas lentas, diminuição da latência e aumento da intensidade de sono REM (THASE, 2006).

Indivíduos afetados por problemas no sono apresentam disfunções cognitivas (SPENCER, 2013). A privação de sono geralmente está ligada a queixas de déficits cognitivos, principalmente aquelas ligadas a memória e atenção (FERNANDEZ-MENDONZA et. al, 2010). Resultados mostram que a privação de sono associada a déficits cognitivos está relacionada a mudanças metabólicas no córtex pré-frontal (BRUCE E ALOIA, 2006), fato que reforça a hipótese de que memória e atenção estão prejudicados em indivíduos com queixas em relação a quantidade e/ou qualidade de sono.

A depressão apresenta desregulação de áreas cerebrais como neocórtex pré-frontal, circuito límbico, diminuição da densidade da substância cinzenta no córtex pré-frontal orbito medial e no córtex cingulado anterior (DU et. al, 2017). Pacientes depressivos apresentam principalmente déficits de função executiva e memória, sendo alguns déficits cognitivos observados de formas diferentes nos pacientes, alguns apresentam as dificuldades exclusivamente durante o episódio depressivo, outros perpetuam os déficits durante os episódios e outros continuam com as dificuldades mesmo após a remissão do quadro depressivo (KWAK, YANG E KOO, 2016; HAMMAR E ÂRDAL, 2009).

1.1 DEPRESSÃO E SONO

A perturbação do sono é um sintoma crítico da depressão, nesta patologia há evidências de alterações na neurofisiologia do sono (WANG et al., 2015), sendo as alterações no ciclo circadiano comprovadas (COURTET E OLIÉ, 2012). Achado sugerem que há um efeito bidirecional entre sono e depressão, adolescentes com privação de sono possuem maior risco para o desenvolvimento de depressão enquanto esta se tornaria um fator de risco para a redução do sono (ROBERTS E DUONG, 2014). Uma meta análise realizada por Zhai et al. (2015) também concluiu que a diminuição no tempo de sono está associada a elevado risco para depressão. Outro estudo, com adultos de meia idade, identificou a associação entre fragmentação do sono e depressão (LUIK et al., 2015).

Na depressão, a principal perturbação do sono é a diminuição do sono REM, que já havia sido apontada em 1966 por Hartmann e Green (WANG et al., 2015). Os primeiros estudos com polissonografia, que também datam na década de 60, também mostraram alterações na arquitetura do sono em pacientes depressivos (PALAGINI et al., 2013). As persistentes alterações no sono REM observadas mesmo após a remissão do quadro depressivo é um fator de risco para a recaída (FALUSSY, BALLA E FRECSKA, 2014).

Glozier et al. (2014) mostram que o atraso no início do sono é mais frequente em pacientes depressivos, não havendo correlação com o grau de gravidade da depressão. Já Soehner, Kaplan e Harvey (2014) acharam que a ocorrência de insônia ou hipersonia no quadro depressivo está associada a episódios depressivos mais graves.

A hipótese envolvendo o papel do Brain-Derived Neurotrofic Factor (BNDF) também está no centro das discussões quando se fala em depressão. O BDNF é uma neurotrofina que possui papel principal na proteção do sistema nervoso central (MARTINOTTI et al., 2016; Leal et al., 2014), estando seus níveis reduzidos nas alterações do sono (Szabadi, 2014) e nos quadros depressivos (LIIRA, VERBEEK e RUOTSALAINEN, 2015). De acordo com uma hipótese explicativa, as perturbações do sono diminuiriam os níveis de BDNF e a perda do sono aumentaria a vulnerabilidade ao estresse, levando a uma diminuição ainda maior dos níveis de BDNF e a um fator de risco para a depressão (TORREGROSSA et al., 2006).

1.2 DEPRESSÃO E COGNIÇÃO

Os déficits cognitivos na depressão podem ser melhores avaliados utilizando na avaliação os conceitos de funções “quentes” e “frias”. As funções cognitivas “quentes” são aquelas carregadas de conteúdo emocional, enquanto as funções “frias” não possuem qualquer interferência das emoções. Essas funções impactam o quadro depressivo, assim como as

dificuldades apresentadas pelos indivíduos no que tange a cognição social e o viés de processamento emocional negativo, e poderiam representar um elemento patogenético crucial que contribui para o desenvolvimento e manutenção a longo prazo do quadro depressivo (BAUNE at al., 2018).

Geralmente os déficits cognitivos gerados pela depressão perduram mais que os próprios episódios depressivos e tendem a estar mais evidentes nas formas mais severas do transtorno (BAUNE at al., 2018). Os déficits também tendem a permanecer após a remissão dos sintomas depressivos (GREER et al., 2017).

Estudos vêm apresentando correlações entre depressão e déficits cognitivos, principalmente com funções executivas, atenção e memória (ROCK et al., 2013; McDERMOT E EBMEIER, 2009; FORTIER-BROCHU et al., 2012), além da aprendizagem verbal e visual, sendo o desempenho do indivíduo em testes cognitivos afetado também pela lentificação psicomotora gerada pelo transtorno (GREER et al., 2017). Rock et al. (2014), Mcdermot e Ebmeier (2009) observaram em seus respectivos estudos, que pacientes depressivos geralmente apresentam déficits de memória e função executivas. O estudo de Luo et al. (2013) mostraram que esses pacientes possuem déficits na memória de curto prazo, enquanto Lin et al. (2014) observaram déficits na memória viso espacial, na memória de trabalho verbal, na atenção, fluência verbal e velocidade de processamento.

Suspeita-se que a depressão impacta de forma menos evidente as demais funções cognitivas (BEBLO et. al., 2011), implicando em um comprometimento global. Resultados de estudos experimentais sobre depressão mostram a presença de um viés emocional negativo, que pode afetar os processos de punição e recompensa (ROISER E SAHAKIAN, 2013).

1.3 SONO E COGNIÇÃO

O sono é um dos processos psicofisiológicos mais importantes para a saúde mental, sendo um processo fundamental para o funcionamento cerebral, sendo sua desregulação associada com efeitos adversos no funcionamento cognitivo (BAGLIONE et al., 2016). A insônia é o transtorno do sono mais comum, com taxa de prevalência de 23-34% (TSAPANOU et al., 2015), sendo caracterizada por sintomas cognitivos, comportamentais, alterações neuroendócrinas e neuroimunológicas, além de alterações neurofisiológicas (RIEMANN et al., 2015), possuindo altas taxas de comorbidade com transtornos mentais, aumentando também o fator de risco para os mesmos (BAGLIONI et al., 2011), principalmente para depressão (BRESLAU et al., 1996). As causas para insônia são variadas, podendo o indivíduo apresentar mais de uma causa para o surgimento da mesma (HAIMOV e HANUKA, 2008).

A depressão é associada perturbações mais graves do sono, estudos com exame de polissonografia mostram alterações na profundidade do sono e alterações na pressão do sono REM. A depressão maior é o único transtorno associado a alterações nas três variações do sono REM, latência, densidade e duração (BAGLIONE et al., 2016). Uma hipótese explicativa para tais alterações, seria o fato de que na depressão, a atividade colinérgica central e sua supersensibilidade, que são responsáveis pelo sono REM, estariam excessivamente aumentadas (NISSEN et al., 2006).

O sono possui um papel essencial na consolidação de diversos tipos de memória (DEAK e STICKGOLD, 2010), estudos mostram que a memória declarativa visual está associada à quantidade total de sono REM (GODER et al., 2007). O estudo de Miyamoto et al (2016) observou que o sono NREM é essencial para a consolidação da memória perceptual, enquanto o fluxo de informação na região fronto parietal, ao longo de 4% do tempo total de sono, é importante para a consolidação da memória geral. Achados também mostram que o sono reparador melhora a atenção sustentada (ARNAL et al., 2015) e déficits atencionais gerados pela privação de sono leva a instabilidades na avaliação de comportamento e medidas psicológicas (CHUA et al., 2014).

Indivíduos insones geralmente possuem queixas em relação a concentração, memória, capacidade de decisão, além de apresentarem elevado número de erros no trabalho (FORTIER-BROCHU et al., 2012), sendo estas queixas confirmadas por estudos comparativos (VARKEVISSER E KERKHOF, 2005). Estes indivíduos também possuem níveis mais elevados de depressão, ansiedade e queixas somáticas (VARKEVISSER et al., 2007).

2 JUSTIFICATIVA

Entender os déficits cognitivos gerados pela depressão é de extrema importância, já que o transtorno pode afetar significativamente o indivíduo em suas capacidades laboral e psicossocial (BAUNE et al., 2018). O processamento emocional negativo que ocorre na depressão, que leva a um viés atencional negativo e sensibilidade para feedbacks negativos, podem estar presentes na remissão do quadro (BAUNE et al., 2018). Além disso, um número significativo de pacientes com depressão, ao longo do transtorno, mostra alterações de sono (THASE, 2006), podendo estas serem consequências ou parte da causa da depressão. Uma vez que a depressão gera déficits cognitivos (ROCK et al., 2013), assim como o sono (SPENCER, 2013), entender como essa relação sono-depressão acontece e como pode acentuar os déficits cognitivos apresentados se torna de suma importância. Dessa forma, o presente estudo justifica-se pela compreensão do comprometimento cognitivo gerado pela depressão e o agravamento gerado ou não pelas alterações no sono, ajudando a delimitar melhores intervenções de tratamento, sejam elas medicamentosas ou não.

3 OBJETIVOS

Atualmente, as queixas de insônia têm se tornado cada vez mais comuns no mundo, e uma abundância de dados epidemiológicos apontam que este quadro é a queixa mais comum dentre os transtornos do sono no mundo industrializado (CHESSON JR et al., 2000). Estudos mostram que a insônia é um fator de risco para o transtorno depressivo e que estruturas cerebrais como núcleo talâmico, tronco cerebral, que regulam o sono, assim como os mecanismos límbicos que regulam as emoções, estão implicados na fisiopatologia dos dois transtornos, depressão e insônia (THASE, 2006). Sendo assim, esta dissertação tem como objetivo traçar o perfil cognitivo de pacientes com depressão e queixas de insônia.

4 HIPÓTESE

A hipótese do presente estudo é que pacientes com depressão possuem déficits cognitivos, apresentando também perturbações do sono, principalmente quadros de insônia, que acarretam em maiores graus de déficits cognitivos, além de piora acentuada do humor deprimido. Espera-se encontrar correlação entre os altos níveis de sintomas de depressão e queixas de sono, além de baixos níveis de cognição, principalmente no que tange funções frontais.

As hipóteses levantadas que levaram a elaboração do artigo 1, foram se a insônia gera comprometimento cognitivo, qual seria a principal função afetada, se existiam um número satisfatório de artigos sobre o tema e como estes artigos foram elaborados.

Já para a construção do artigo 2, se hipotetizou a relação entre o Brain Derived Neurotrofic Factor (BDNF), depressão e sono, se estes fatores possuem alguma relação entre si e qual seria o efeito dos níveis da neurotrofina no quadro depressivo.

Para o artigo 3 levantou-se a possível relação entre a depressão e qualidade de sono, se a depressão leva ao comprometimento da memória operacional, atenção e velocidade de processamento, a relação entre o grau de severidade da depressão e queixas relacionadas ao sono e se a baixa qualidade de sono impacta as funções cognitivas.

5 ESTUDOS REALIZADOS NA DISSERTAÇÃO

No primeiro estudo, sobre comprometimento da memória em pacientes insones é bem discutida (LEGER et al., 2001) e em nossa pesquisa inicial encontramos muitos artigos relacionando a insônia a déficits de memória operacional. Desta forma, publicamos na Revista Medical Express em 2016 (MONTEIRO et al., 2016), um estudo que avaliou 112 estudos publicados que avaliavam a relação entre insônia e memória de trabalho, onde concluímos que em muitos estudos ocorreram erros amostrais, o que dificultou a comparação entre os achados, porém é possível suspeitar de uma relação causal entre déficit de memória operacional e insônia.

No segundo artigo, levantamos a hipótese causal entre sono, depressão e o Brain-Derived Neurotrofic Factor (BDNF). Neste artigo avaliamos a relação entre sono e BDNF, depressão e BDNF e sono, depressão e BDNF. Nos nossos achados foi possível observar que em quadros depressivos e de alterações de sono os níveis de BDNF estão reduzidos e que a redução desses níveis devido ao sono é um fator de risco para o surgimento do quadro depressivo (TORREGROSSA et al., 2006).

No terceiro artigo, publicamos os achados encontrados na avaliação dos nossos pacientes. Na nossa pesquisa, pacientes depressivos passaram por uma avaliação neuropsicológica, onde foram avaliados o índice de memória operacional, fluência verbal, índice de velocidade de processamento e atenção, além do índice de qualidade de sono, através do Índice de Qualidade de Sono de Pittsburgh (PSQI) (BERTOLAZI et al., 2011). Ao final da pesquisa encontramos os pacientes avaliados apresentavam déficits em todas as funções cognitivas avaliadas, além de haver correlação entre o nível de gravidade de depressão e o nível de qualidade de sono.

ARTIGO 1

Working memory dysfunction in insomniac adults: a systematic metanalytical review

MedicalExpress

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.

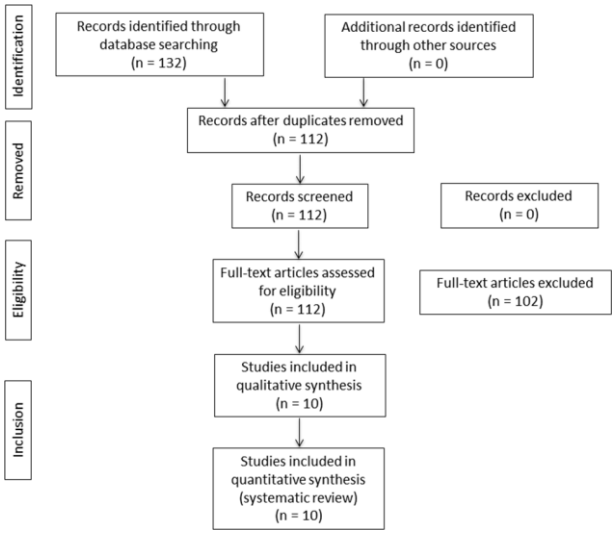

Figure 1 - Flow of information through the different phases of study selection.

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 systeminvolvedinworking 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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ARTIGO 2

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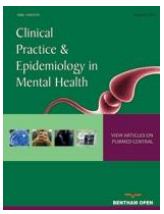

REVIEW ARTICLE

Relationship Between Brain-Derived Neurotrofic Factor (Bdnf) and Sleep on Depression: A Critical Review

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Abstract: The Brain-Derived Neurotrofic Factor (BDNF) is one of the most important neurotrophins in the brain and it is suggested influences the activity of the serotonergic, noradrenergic and dopaminergic pathways. In the last few years, it has been hypothesized that BDNF level is related with depression and sleep. Several studies show that depressive subjects present low levels of BDNF in the brain. Poor sleep quality is also related with alterations in the BDNF concentration. Some authors argue that most of the cases show that impaired sleep quality increases the stress and, consequently, the vulnerability to depressive disorders, suggesting that there is a relationship between sleep, depression and BDNF levels.

Keywords: BDNF, Sleep, Depression, Antidepressants, Sleep quality, BDNF studies.

1. INTRODUCTION

Depression is currently among the four major diseases affecting the world population and is linked to high rates of impairment and mortality [1 - 3], and can be defined as a disorder with heterogeneous biological bases with a chance of affecting 10% -30% of women and 7% -15% of men throughout their lives. Clinical and preclinical studies suggest that Brain-Derived Neurotrofic Factor (BNDF) expression could be involved in behavioral phenomena linked to depression, and that modulation of this neurotrophin would also mediate the action of antidepressants [4].

BDNF is the main neurotrophin in the human brain [5], playing a critical role in the development and protection of the central nervous system as well as synapse regulation, learning and memory [6, 7]. BDNF widely contributes to neuroplasticity in the human brain, namely axonal and dendritic growth and remodeling, neuronal differentiation, synaptic growth and transmission, neurotransmitters modulation and long-term potentiation [8 - 10]. One of the main functions of BDNF is to promote the development and stability of neuronal connections, with the hippocampus being an important site for its action [11]. It's known that BDNF is required for the proper development and survival of GABAergic neurons, cholinergic and serotonergic antidepressants [2, 4].

The relationship among BDNF, sleep and depression has been speculated. A low neurotrophic activity is associated with a reduced number of cells in the prefrontal cortex, amygdala, and decreased hippocampal size, indicating that

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BDNF may play an important role in the development of depression [12]. Some authors speculate that BDNF has a potential role in the pathology and treatment of numerous psychiatric disorders [2]. Studies showed low BDNF levels in un-medicated depressed individuals, but without association with disorder severity [13]. BDNF gene is an important candidate in the discovery of the action mechanisms of antidepressants, since BDNF plays an important role in the functioning of the serotoninergic system [14]. The relationship between antidepressants and BDNF in rats has shown that the administration of different types of antidepressants increases the levels of BDNF production in the hippocampus [14], but this effect can been see only with nonpeptidic agonists [15]. Antidepressants that decrease BDNF levels can be effective in treatment of depression, however can alter sleep pattern [16], which may increase $GABA_A$Rs on the membrane of excitatory cortical neurons, while increase of slow wave sleep can return to baseline levels [17], while adenosine A_1 receptors (A_1R) plays a decisive role for antidepressant effects on sleep deprivation [18].

The relationship between depression and sleep disturbance is well delimited, but while typical depression is usually accompanied by insomnia, atypical depression is usually related to symptoms of hypersomnia [19]. It has been speculating the relationship between BDNF, sleep and depression. There is evidence that BDNF levels influence sleep patterns in individuals with depression [12]. Some authors postulate that increasing BDNF levels may improve the sleep quality of depressed subjects, and in these cases the BDNF levels make a difference in the results found in treatment. The impact of increasing BDNF on sleep will be discussed later. Thus, the purpose of this article is to trace the relationship between BDNF and insomnia in depression and what the possible result of the interaction of these factors [19]. With respect to the neurobiology of depression, many authors consider that one of the main triggers of the disorder is stress. Thus, the BDNF hypothesis in depression, postulates that stress reduces the concentration of BDNF in structures of the limbic system, responsible for the emotions [17]. Therefore, the comprehension about this possible relationship could support better decision making for treatments, for example, choosing the more appropriate antidepressant to be used for a certain patient. Although few studies appointing to a relationship among BDNF levels, depression and sleep, this issue is still unclear.

1. BDNF AND SLEEP

Sleep can be defined as "...a recurring, reversible neuro-behavioral state of relative perceptual disengagement from and unresponsiveness to the environment. Sleep is typically accompanied (in humans) by postural recumbence, behavioral quiescence, and closed eyes...". The sleep-wake cycle involves neurophysiological states like wakefulness, slow wave sleep and rapid eye movement sleep [17]. The relationship between duration, efficiency, and timing are crucial to understand sleep, and alterations in this factor may lead to sleep disorders [19, 20].

Sleep disturbances have been characterized in terms of abnormalities in alertness/sleepiness, continuity or efficiency, duration and timing. According with International Classification of Sleep Disorders the most common sleep disorders are: Dyssomnias, Parasomnias, Sleep Disorders Associated with Mental, Neurologic, or Other Medical Disorders and Proposed Sleep Disorders [21]. Insomnia and hypersomnia are the most frequent sleep disorders in population [22, 23]. The management of these two sleep disturbances includes several therapeutically approaches, such as pharmacological treatments [24 - 26].

Sleep impairment may lead to severe physical and mental problems, as sleep deprivation is usually followed by enhanced vulnerability to stress which can decrease BDNF production. It's known that serum BDNF levels are associated to sleep, even in patients who do not have sleep problems [27, 28]. In a study with 126 patients with MDD, was found that increased BDFN levels has been associated with N-REM sleep improvement and enhanced slow wave activity, but on the other hand, reported no relationship between BDFN and insomnia improvement. It was found that the reduction of BDFN levels is associated with improvement in hypersomnia [16].

Giese and cols investigated if stress levels influence the association between sleep and BDNF levels, and found that the sleep quality interfere directly in the relation of stress with BDNF levels [16]. In another study they investigated BDNF serum levels in 26 patients with insomnia and compared the results with a control group and found that insomniacs present decreased serum BDNF levels, when compared to control group [28]. Other study examined 44 insomniacs and found that sleep problems are related to impaired BDNF synthesis and that improvement in sleep patterns leads to enhance quality of life [28] (Table **1**).

Table 1. Results on the relationship between BDNF and sleep.

Authors	Aim	Sample	Methods	Instruments	Results
Rethorst *et al*. [19]	Examine biomarkers associated with changes in hypersomnia and insomnia.	126 Individuals with MDD.	Individuals were randomly assigned to two groups of aerobic exercise.	Inventory of Depressive Symptomatology (IDS-C). Blood Analysis.	Reduction of BDNF levels associated with decreased hypersomnia.
Giese *et al*. [31]	Investigate the serum BDNF level in adults with insomnia and compare them to a control group.	19 Individuals with RLS/PLM 7 patients with RLS 24 controls	BDNF levels were collected and correlated with the scores reported in the Insomnia Severity Index.	Insomnia Severity Index. Blood Analisys.	Insomniacs exhibit a significantly lower serum BDNF level than controls.
Rusch *et al*. [32]	Determine the relationship between increased sleep quality and improvement of depressive symptoms.	44 Individuals with insônia.	Subjects underwent a clinical evaluation and blood samples were taken from all participants. Participants were classified into two groups: sleep improved (n = 28) and sleep declined (n = 16). Participants underwent 4-8 sessions of CBT for insomnia (CBT-I).	Health-Related Quality of Life (HRQOL) Pittsburgh Sleep Quality Index (PSQI) Blood Analisys	The promotion of sleep quality is an effective way to improve depression and quality of life.
Giese *et al*. [30]	Investigate whether the level of stress influences the association of sleep and BDNF levels.	7 Individuals without insomnia and with RLS/PLM 24 controls 11 Individuals with subclinical insomnia and with RLS/PLM 8 Individuals with insomnia and with RLS.	Patients underwent clinical evaluation where the data were correlated.	Insomnia Severity Index (ISI) Perceived Stress Scale (PSS)	Sleep is a mediator in the relationship stress and BDNF. Sleep disturbance may explain how some people cope well with stress and other people get sick.

Note: MDD = Major Depressive Disorder; RLS = restless legs syndrome; PLM = periodic limb movement.

1. BDNF AND DEPRESSION

Research has evidenced the link of BDNF as a molecular factor involved in the pathophysiology of mental disorders. Low levels of this factor are directly linked to major depressive disorder [29]. Studies have shown that infusion of BDNF into the brains of animals produces an antidepressant effect [30, 21]. In addition to this action, BDNF promotes the functioning and expansion of serotonergic neurons in the brains of adult rats [11]. The administration of BDNF produces an antidepressant effect in two animal models of depression. According to the study, infusion of BDNF near the PAG and raphe nucleus allows the factor to have access to a greater number of serotonergic cells. According with the authors, experiments in the infusion of BDNF into rat brain show an increase in activity in the serotonergic, noradrenergic and dopaminergic pathways of numerous brain areas such as cortex, hippocampus, striatum and nucleus accumbens [29]. To reinforce this point of view, some studies show that at the time of necropsy, a greater expression of BDNF in the hippocampus of individuals treated with antidepressants when compared to untreated depressants [32,33,34].

Hippocampus is a brain region designated as one of the BDNF foci, and studies aiming to assess the level of neurotrophin in depressed patients generally turn their attention to this site. Clinical and preclinical studies point to a loss of the total volume of neurons in the Hippocampus of adults with depression. In the pathophysiological basis of the disease we have the question of neuronal plasticity and it is now well established that BDNF plays an important role in neuronal plasticity and maintenance [33].

Animal studies show that the use of agomelatine, an antidepressant drug, for the treatment of depressive disorders leads to an increase in BDNF expression in the prefrontal cortex and in the hippocampus [5]. This fact reinforces the hypothesis of the BDNF x depression relationship, since the use of antidepressant would improve the expression of the neurotrophic factor. Non-drug treatments for depression, such as Electroconvulsive Therapy (ECT), also generate an increase in BDNF expression in the brain, which further underscores the linkage of BDNF levels with depressive disorders [35].

Increased levels of BDNF protein in the brain are consistent with the efficacy of MAO inhibitors and electroconvulsive therapy and may be a predictor of the antidepressant action of interventions that are more effective in the treatment of major depression. All the evidence pointing to the fact that treatment for depression shows an improvement in BDNF expression, it is still unclear how discontinuation of antidepressant medication would affect these levels [35]. Thus, BDNF levels are apparently positively regulated in humans through antidepressant treatments [2, 36] (Table **2**).

Table 2. Results on the relationship between BDNF and depression.

Authors	Aim	Sample	Methods	Instruments	Results
Shimizu *et al.* [10]	Determine how BDNF levels are related to treated and untreated depressive conditions and how these levels differ between individuals with MDD and controls.	16 individuals with MDD without antidepressant treatment. 17 individuals with MDD on antidepressant therapy. 50 controls.	Patients were assessed using the Hamilton Scale for depression (HAM-D). BDNF levels were accessed through the ELISA method.	Hamilton Depression Rating Scale (HAM-D)	Low levels of BDNF were found in untreated depressive patients when compared to the treatment group and the control group.
Siuciak *et al.* [34]	Determine how the administration of BDNF can produce an antidepressant effect in two animal models of depression.	Male rats treated in the laboratory.	Infusion of BDNF into the animals' brains for a week.	-	An antidepressant effect was observed after administration of BDNF in the two animal models of depression tested in the study. The increase could be mediated by increased activity in monoaminergic systems.
Martinotti *et al.* [5]	Investigate the effects of Agomelatine on serum BDNF levels in a sample of depressed patients.	27 individuals with MDD.	Serum levels of BDNF were achieved by the ELISA method at the beginning of treatment after two weeks and after 8 weeks of treatment.	Hamilton Depression Rating Scale (HAM-D). Snaith-Hamilton Pleasure Scale.	Patients showed an increase in BDNF levels after two weeks of treatment with Agomelatine.

Note: MDD = Major Depressive Disorder.

1. HYPOTHETICAL RELATIONSHIP BETWEEN BDNF AND SLEEP ON DEPRESSION

In most of cases, Major Depressive Disorder is accompanied by complaints about sleep quality. Sleep disturbance is one of the main residual symptoms after treatment with antidepressants and the main risk factor for relapse in major depression who are in remission [18] Some biomarkers present in the development of depression and response to treatment are linked to sleep quality [16].

Studies that observe the relationship of the effect of agomelatine with BDNF levels show that the effect that the drug generates on the circadian rhythm would be a consequence of the increase of BDNF levels, since the neurotrophin expression is regulated by the light-dark cycle, both in rats, and in humans [5].

There is a hypothesis that not all antidepressants generate an improvement in the serum BDNF level, like bupropion [16], and the improvement of this neurotrophin does not coincide with an improvement in the clinical symptoms of depression. According to some results found, changes in BDNF concentration are followed by a reduction in insomnia and its consequences, rather than the improvement of depressive symptoms [28].

Low levels of BDNF in depressive patients are also linked to relationship between stress and depression. Sleep disturbances decrease BDNF levels and the loss of sleep results in high vulnerability to stress and consequently leads to decrease in BDNF levels [15]. Stress is a potent risk factor for depression and is associated with decreased BDNF concentration in animal models. This hypothesis is since stress activates the Hypothalamic-pituitary-adrenal (HPA) axis leading to increased cortisol secretion and elevated cortisol concentrations could suppress the production of BDNF [16]. Stress reduces the expression of BDNF in the hippocampus and this reduction can be prevented by treatment with antidepressant drugs [3, 37].

If we look at all the exposed characteristics, it's possible to observe that there is a chain of events that links sleep to depression. The loss of sleep quality (not necessarily a sleep disorders) leads to a high stress that suppresses BDNF secretion and consequently leads to great vulnerability to depressive conditions. One study showed that sleep is a

mediator in the relationship between stress and BDNF, and that sleep disturbance would be a delimiter between people who deal well with stress and those who get sick [27]. In this sense, it is not possible to state that there is a causal pattern about sleep deprivation, BDNF and depression, but carefully examining all the studies in the field we can hypothesize it.

1. FUTURE PERSPECTIVES AND FINAL CONSIDERATIONS

Depression is nowadays the most common psychiatric disorder and is associated with high levels of disability [38]. Thereby, as sleep impairment is the main residual symptom of depression and a major risk factor for relapse, treatments that increase BDNF levels and consequently improve sleep quality will not only allow to improve depressive symptoms but also decrease relapse rates. Increasing the levels of this neurotrophin seems to improve the quality of sleep, allowing reducing vulnerability to stress and to create a protective factor to depression [16]. Furthermore, increasing our knowledge to deeply understand the role of BDNF in depression will allow developing more effective pharmacological agents to treat this disorder.

Further studies are necessary to clearly understand how BDNF levels influence and are influenced by depression and sleep deprivation. Moreover, alternative treatments that increase BDNF levels may also help to address the needs of non-depressive patients who also experience sleep impairment [39]. Finally, researchers should also make efforts to define the relationship between BDNF and sleep, as improving the quality of sleep may be a crucial step to improve patient's quality of life [40, 41].

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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Artigo 3

Cognitive status in depressive patients with insomnia complaints: a pilot study

Cognitive status in depressive patients with insomnia complaints: a pilot study

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Abstract

Background: Depression is a very common psychiatric disorder that usually leads to cognitive impairment. Sleep complaints are common in depressed patients and also leads to cognitive deficits, and the association of these two complaints can lead to more severe complaints of cognitive functions. **Objective:** Identify cognitive deficits presented by depressed patients and if these deficits are more severe if patient present sleep complaints. **Methods:** Patients underwent a neuropsychological assessment where were evaluated attention, memory and processing speed. To identify severity of depression, were applied BDI II, while PSQI were used to access sleep complaints. **Results:** A total of 18 patients with major depressive disorder were evaluated and were classified as bad sleepers. We found that these patients have deficits in working memory, processing speed and attention in all three forms evaluated. There's no significative correlation between sleep complaints and depression severity level. **Conclusion:** Results found in this research corroborate the hypothesis of cognitive impairment in depressive patients with sleep complaints.

Key-words: neuropsychological assessment; working memory; attention; processing speed; depression; sleep complaints.

Introduction

Depression is a very common psychiatric disorder, [1] with lifetime recurrence by ≥40–75% [3,4,5]. Although remitted depressed patients have been studied for many years [6], the understanding of mechanisms responsible for recurrence remain unclear due to most studies examine depression during the acute phase [7]. Within the mechanisms and symptoms underlying depression, one of them deserves to be highlighted, i.e. insomnia, which consists in complaints about the quantity or quality of sleep [8], for at least three months and leads to daytime dysfunctions [9].

During depression, patients shows deregulation in the prefrontal cortex and limbic circuits [4]. These patients present deficits mainly in executive functions, memory and attention, that usually persist after the remission of symptoms [10]. Insomnia affects around 25-30% of adults presenting altered cognitive functioning, mainly memory, attention and executive functions, being sleep complaints common in depressed patients and few studies were conducted examining the relationship between cognitive impairment and poor sleep quality [5]. Few years ago, the role of sleep in cognitive processes began to attract attention of scientists.

Despite the large number of studies on neurocognitive functions in mood disorders, there are few studies that have proposed depressed patients present mnemonic, attentional and executive deficits, rather than a trait of this population [11]. In addition, mechanisms that underlie the variability across cognitive tasks demands still unclear [12, 13]. Due to the lack of concrete data about the association of cognitive impairment in depressed patients with insomnia complaints, this study aimed to examine if there is relationship among sleep quality and cognitive functions in depressed patients.

Methods

Sample

Sample was composed of 24 individuals (8M and 16 F). They were evaluated by senior researchers using diagnostic and neuropsychological instruments. Mini International Neuropsychiatric Interview (MINI), the Beck Depression Inventory (BDI-II) and the Pittsburgh Sleep Quality Assessment (PSQI) for all subjects with the objective of excluding any possibility of inclusion of patients with other diseases as a complaint than depression. Inclusion criteria are: both genders, aged between 18 and 59 years, diagnosis of depression complaining of insomnia according to the DSM-5 criteria, having a minimum level of education of a full high school degree and being in use of antidepressant and doing cognitive behavioral therapy (CBT). The exclusion criteria are: being on more than one antidepressant using psychostimulants such as methylphenidate or lisdexamphetamine, pregnant or

breastfeeding women, severe psychiatric disorders such as psychotic signs and symptoms, obsessive-compulsive disorder, hypomanic/manic episodes, severe personality disorder, neurological disorders, mental retardation, epilepsy, alcohol abuse and other drugs.

Experimental Procedures

All the patients were submitted to the clinical, psychological and neuropsychological tests in a single moment, immediately after the diagnosis confirmation. All assessments were conducted at the Laboratory of Panic and Respiration and took around 2 hours.

Instruments

For clinical, psychological and neuropsychological assessment, we used the following instruments: PSQI, BDI-II, WMI, SPI and BPA.

To evaluate depression symptoms participants filled the Beck Depression Inventory II (BDI II), a scale extensively used worldwide, that is validation for Brazilian population showed temporal stability and was internally consistent and valid for predicting the presence of depressive symptoms[16]. We considered able to participate the study those individuals who presented a score ≥14. BDI II is a self-rating instrument with 21 questions that assesses different groups of symptoms by asking the patient to respond each question weighting it in a scale from 0 to 3, basing his answer in the symptom severity. The total score is reached by summing all the 21 questions, and is classified: 0-13 minimal depression, 14-19 mild depression, 20-28 moderate depression and 29-63 severe depression [1].

To verify sleep quality and complaints we used Pittsburgh Sleep Quality Assessment (PSQI). The scale was validated for Brazilian population and showed that is a valid instrument for the assessment of sleep quality, equivalent to its original version and can be used for clinical management or research[17]. The scale consists of 19 (nineteen) self-administered questions and 5 (five) questions answered by their roommates. The latter are used only for clinical information. The 19 (nineteen) questions are grouped into 7 (seven) components, with weights distributed on a scale of 0 to 3. The PSQI components, standardize versions of areas routinely assessed in clinical interviews of patients with complaints about sleep are the subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorders, use of sleeping pills, and daytime dysfunction. The scores of these components are then summed to produce a global score, ranging from 0 to 21, where the higher the score, the worse the quality of sleep. The objective is to evaluate the quality of sleep during a period of one month, classifying

patients as "good sleepers" or "bad sleepers". A global PSQI score > 5 indicates that the individual is experiencing major difficulties in at least 2 components, or moderate difficulties in more than 3 components [14]. Patients also filled the consent term to participate in the study.

With respect to the neuropsychological measures, we used the working memory index (WMI), Speed Processing Index (SPI) and the Psychological Battery for Attention Evaluation (BPA). WMI assesses the capacity to memorize new information, to keep it in short-term, maintain focus and to manipulate that information [15]. To evaluate this index the following subscales were used: arithmetic, digit span and letter-number sequencing. The Arithmetic subscale contains 20 questions about arithmetic problems that the participant must solve mentally in a determined period of time, the digit span subscale contains 7 items in direct order and 7 in indirect order that have to be exactly repeated and the letter-number sequencing subscale is a serie of numbers and letters presented in oral form that has to be repeated putting first the numbers in ascending order and after the letters in alphabetic order [16]

SPI assesses abilities to focus attention on distinct stimuli, to discriminate them, and to sustain the focus of attention over a period of time, being a measure of the speed of processing information [15]. To evaluate SPI the following subtests are applied: code and symbol search. Code subscale consists on a series of numbers associated to one symbol where the individual has, in two minutes, associated predetermined numbers with the correspondent symbol. In the symbol search subscale, there are a model group of symbols and a search group, where the person has to point if there is a presence of one model in the search group [16].

BPA aims to conduct an assessment of the general attention capacity, as well as an evaluation of individualized types of attention, which are sustained attention (SA), divided attention (DA) and alternating attention (AA). It is made up of three tests, each of them aiming to evaluate one of the proposed attentional types. In turn, the analysis of the three tests together provides the measure of attention. The tests were constructed from several stimuli that served to compose the three answer sheets (SA, DA and AA), and now they were target stimuli, or distracting stimuli. The distribution of the stimuli follows the same amount in each instrument, containing 400 stimuli distributed in 20 lines with 20 stimuli each. Of total, 120 are target stimuli (maximum score possible) and 280 distractors. The final result of each test is obtained considering the target stimuli that the person scored, subtracted from the errors and omissions it has committed. Of that the total points. In the case of general capacity of attention, the result is obtained by the sum of the total points of each of the (SA + DA + AA), the maximum possible being 360 points. As regards the time of application, in the case of the SA is 2 minutes; for DA, 4 minutes;

and for the AA, 2 minutes and 30 seconds. The order of application must be followed strictly, beginning with the SA, followed by DA, and finally AA. The application can be individual and collective [17].

Statistical Analysis

A homoscedasticity and normality analysis of the data will be performed by the Levene and Shapiro-Wilk tests, respectively. Assuming the assumptions of the parametric analysis, we used the Person's parametric correlation test for the variables BDI-II, PSQI, WMI, SPI and BPA. In both analyzes the level of significance will be adjusted at $p < 0.05$. For Person's correlation we used the classification of proposed by Mukaka [18].

Results

Initially, we had 24 patients, however, during the experiment, 6 patients drop out, because they presented psychiatric disorders that make it impossible to participate, like OCD. Thus 18 remained in the study. Table 1 presents the characterization of our sample. All patients were classified as bad sleepers according to PSQI (mean= 13.9±3.1; n= 18) and as moderate depression (mean= 29.1±3.3). In addition, patients showed medium inferior levels of WMI (89.7±18.1), and of SPI (87.3±18.3), and medium levels of CA (87.8±19), AA (90.8±17.6), and DA (90.4±15.4).

Table 1 - Sample characterization (n=18).

Features	n	mean±DS	%
Age (years)	18	34±9	-
Education (years)	18	14±1.9	-
Gender (F/M)	18	-	2M (11%)/16 F (89%)

Regarding the classification of correlations, we found 1 high positive and 10 moderate negative correlations. The first correlation was positive, between BDI-II and PSQI ($r= 0.48$; $p= 0.025$; figure 1). The others correlations were all negative. There were 5 significant differences between BDI-II and WMI scores ($r = -0.41$; $p \leq 0.05$; figure 2), between BDI-II and SPI scores ($r = -0.46$; $p \leq 0.03$; figure 3), between BDI-II and SA scores ($r = -0.41$; $p \leq 0.05$; Figure 4A), between BDI-II and DA scores ($r = -0.42$; $p \leq 0.05$; Figure 4B), between BDI-II and AA scores ($r = -0.42$; $p \leq 0.05$; Figure 4C).

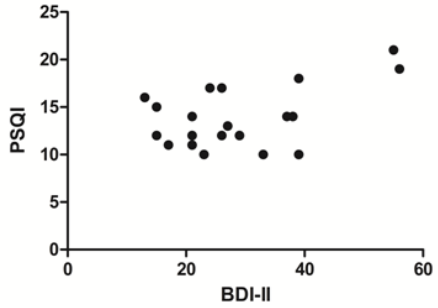

Figure 1. Correlation between BDI-II and PSQI.

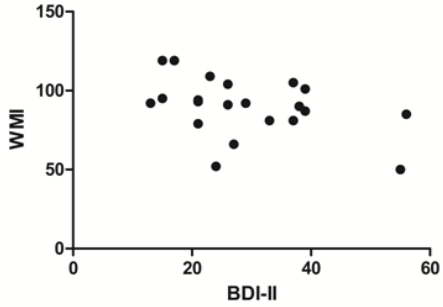

Figure 2. Correlation between BDI-II and WMI.

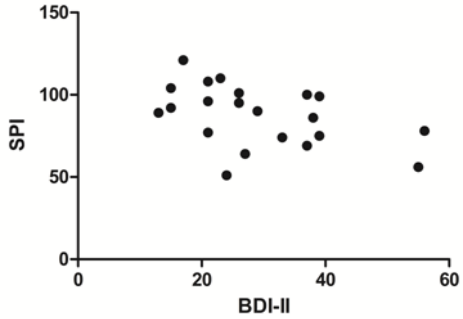

Figure 3. Correlation between BDI-II and SPI.

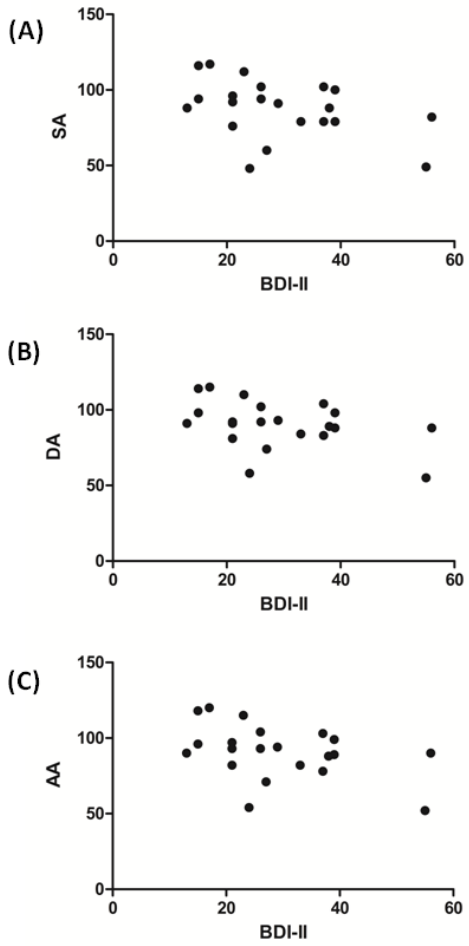

Figure 4. Correlation among BDI-II and attention subtypes. A) SA; B) DA; C) AA.

In addition, there were 5 more significant differences between PSQI and WMI scores ($r = -0.57$; $p \leq 0.007$; Figure 5), between PSQI and SPI scores ($r = -0.57$; $p \leq 0.006$; Figure 6), between PSQI and CA scores ($r = -0.58$; $p \leq 0.006$; Figure 7A), between PSQI and DA scores ($r = -0.57$; $p \leq 0.006$; Figure 7B), between PSQI and AA scores ($r = -0.57$; $p \leq 0.007$; Figure 7C).

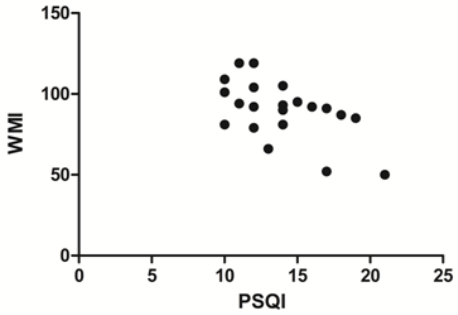

Figure 5. Correlation between PSQI and WMI.

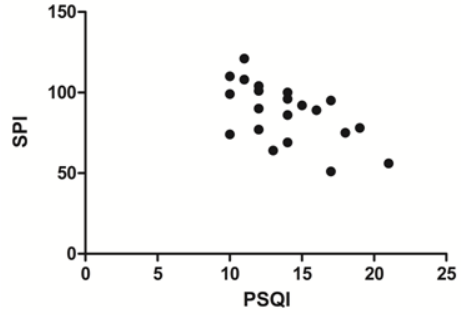

Figure 6. Correlation between PSQI and SPI.

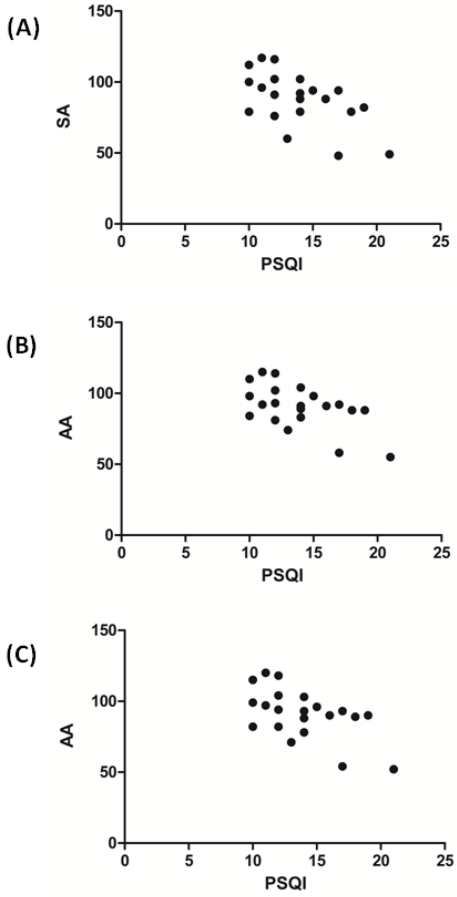

Figure 7. Correlation among PSQI and attention subtypes. A) SA; B) DA; C) AA.

Discussion

Our study aimed to examine if there is relationship among sleep quality and cognitive functions in depressed patients. We found several correlations, 10 moderate and negative and 1 high and positive. In most cases, depression is accompanied by sleep complaints, which are the main residual symptoms together with cognitive complaints [19]. Depressed patients take longer to initiate sleep, have shortens period of REM sleep and is subject to hyperactive brain regions during sleep [20]. A review with 205 articles showed that studies indicate a remarkable

relationship between sleep and depression [21] and in addition, a comparative study suggest that insomniacs have a higher risk for developing depression when compared to non-insomniacs [22].

According to some studies [23,24] depressed patients commonly present cognitive impairments, mainly in relation to executive functions and memory [10]. For example, a number of studies showed a relationship between depression and deficits in visual spatial and verbal working memory, attention and processing speed [25] and short-term memory [26]. Other interesting and recent study demonstrated that patients with recurrent depression showed higher memory and executive functions deficits when compared to those with only one depressive episode [27].

Sleep deprivation also leads to cognitive deficits [28], mainly in memory and attention [29]. It is known that sleep plays an important role in consolidation of different types of memory and contributes to inferential thinking [30]. A study showed that declarative visual memory is associated with total sleep time and amount of REM sleep [31]. Another study showed that NREM sleep is essential for consolidation of perceptual memory, while general memory consolidation is dependent of causal fronto-parietal information flow during 4% of total sleep time [32]. Some studies show that sleep improve sustained attention [33], while alteration in sleep patterns is responsible for 30% of variance in attentional results [34]. Deficits in attention after sleep deprivation is also associated with instability in behavioral and psychological measurements [35].

The main objective of this study was investigated if there is some relationship between sleep quality, cognitive functions and depression. Our results corroborate the hypothesis of cognitive impairment in depression with sleep complaints. Individuals with these complaints, generally, present deficits in memory, decision making and concentration [36] and processing speed [25] showing higher levels of depression [37]. We found that these patients present deficits in working memory, speed processing and attention (i.e., sustained, divided and alternated) evaluated, like suggested by Talarowska et al [38]. Generally depressed patients with sleep complaints show greater impairment in these functions.

Cognitive deficits found in our patients can be generated by the deregulation in pre-frontal cortex found in depression and sleep deprivation. Depressed patients present deregulation of prefrontal neocortex, limbic circuit, decreasing gray matter density in the prefrontal cortex medial orbital and anterior cingulate cortex [4]. Sleep deprivation is also associated with metabolic changes in the prefrontal cortex [39]. These neurochemical dysfunctions generated by these two disorders can explain cognitive complaints, but what still unclear is why cognitive impairment perpetuates after pharmacological and psychological treatment, once that the neurochemical issue would be resolved. A study that used positron emission tomography (PET) to measure regional cerebral

blood flow (rCBF) in 33 patients with depression showed that in these patients with cognitive complaints were seen rCBF abnormalities consisting in decrease in the left anterior medial prefrontal cortex and increase in the cerebellar vermis [40]. A study using rats corroborate with Dolan et al. [40], showing that glutamate levels in the hippocampus are involved in both sleep and memory regulation [41]. Cognitive impairment plays an important role in maintenance of depression, once it leads to several commitments, such as difficulty in problem resolution and decision making, what could lead to negative feelings about yourself and others [42].

We also found that there is significant correlation between depression and sleep quality, thus the level of depression is associated with higher rates of poor sleep quality. The association between depression and sleep is bidirectional, therefore depression can lead to sleep complaints, and the stress caused by alterations in sleep can trigger depression, and one interferes in the severity of other [43]. Brain structures such as thalamic nucleus, brainstem and limbic mechanisms are implicated in the pathophysiology of depression and insomnia, which is the most common sleep disorder in this population [44].

Conclusion

Our findings corroborate the hypothesis of cognitive impairment in depressive patients with sleep complaints. Deficits in working memory, attention and processing speed were found in the individuals that underwent neuropsychological assessment, also finding that there is correlation between the level of depression and the severity of sleep complain. More studies about cognition, sleep and depression are necessary, since there is need to explore other cognitive functions beyond memory and executive functions.

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6 CONSIDERAÇÕES FINAIS

Dentre os sintomas observados na depressão, as alterações de sono são as mais evidentes e fonte de grandes queixas por parte dos pacientes (CHUNG et al., 2015). Geralmente pacientes depressivos apresentam pelo menos uma alteração na neurofisiologia do sono (THASE, 2006). Quadros depressivos estão ligados a déficits cognitivos (KWAK, YANG e KOO, 2016), assim como alterações no sono (SPENCER, 2013), sendo os principais déficits encontrados aqueles que abrangem memória, funções executivas (McDERMOT e EBMEIER, 2009; FORTIER-BROCHU et al, 2012) e atenção (ARNAL et al, 2015).

A relação entre sono e depressão é bidirecional e no estudo que conduzimos, publicado no artigo 3, encontramos correlação entre o grau de comprometimento da qualidade de sono e o grau de gravidade da depressão, onde foi possível observar que aqueles que apresentam queixas em relação a qualidade de sono, possuem maiores graus de gravidade em relação a depressão, fato também apontado por Soehner, Kaplan e Harvey (2014).

No artigo 2 foi abordado a possível relação do nível de BDNF com alterações encontradas na depressão e sono. O BDNF é uma neurotrofina essencial para o SNC, estando seus níveis reduzidos na depressão e em quadros de alteração de sono (SZABADI, 2014; LIIRA, VERBEEK e RUOTSALAINEN, 2015). Em toda pesquisa realizada para a elaboração do artigo, foi identificado que níveis reduzidos de BDNF acarretam em riscos elevados para a manifestação do estresse, sendo este um fator de vulnerabilidade para o surgimento de quadros depressivos (TORREGROSSA et al., 2006).

A hipótese sobre déficits cognitivos em quadros depressivos com alterações de sono é corroborada pelos achados dos artigos 1 e 3. No primeiro artigo, foi realizada uma meta-análise para avaliar a hipótese de comprometimento de memória de trabalho na depressão (SPENCER, 2013; FERNANDEZ-MENDONZA et. al, 2010; BRUCE e ALOIA, 2006), sendo esta confirmada pelos resultados encontrados em nosso estudo, publicados no artigo 3.

Segundo Du et al. (2017), pacientes depressivos apresentam alterações nas funções do córtex pré-frontal, assim como pacientes com alterações no sono (BRUCE e ALOIA, 2006), o que acarreta déficits das funções executivas, memória e atenção (KWAK, YANG e KOO, 2016). A hipótese levantada pelos autores corrobora nossos achados, que sugerem a presença de déficits em funções frontais.

Esta tese se mostra importante para estudos na área devido ao fato de que, apesar de termos consideráveis estudos na área alterações neuropsicológicas em quadros psiquiátricos, a maior parte se concentra na avaliação da memória, não investigando as demais funções cognitivas (BEHZADFAR, FIROOZABADI e BADIE, 2016). Devido a este fato observado,

optamos por, em nossa pesquisa, ir além da avaliação da memória e findamos por encontrar alterações da atenção e velocidade de processamento da informação, além do índice de memória operacional, como apontado no artigo 3.

Novos estudos na área são recomendados, a fim de avaliar as demais funções cognitivas e suas possíveis relações causais com os transtornos de humor, principalmente depressão.

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8 APÊNDICE I – OUTRAS PRODUÇÕES RELEVANTES

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