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Is Cognitive Dysfunction in MDD a Consequence of Sleep Abnormalities?

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Insomnia and Major Depressive Disorder (MDD) are two disorders that are commonly found comorbid, and often interact to exacerbate the severity of the other. This review explores the bidirectional relationship between sleep disruptions and MDD, and investigates the role of maladaptive cognitions underlying this relationship. A non-systematic literature review was conducted using PsychInfo, Google Scholar, and PubMed as its primary computerized databases. Cognitive dysfunction is discussed as a mechanism underlying the relationship between sleep disruptions and MDD, specifically in relation to hot and cold cognitive impairments. Circadian rhythms, melatonin, exercise, and comorbidity are each discussed as unique mechanisms that contribute to cognitive dysfunction in individuals with MDD. Future research is needed to better understand the unique relationship between sleep disruptions, MDD, and cognitions in order to improve clinicians' treatment of comorbid Insomnia and MDD.

It has been well documented that insomnia and depression have a multifaceted and bidirectional relationship. Depression has been shown to lead to sleeping difficulties, and sleeping difficulties to depression. More specifically, the relationship between Major Depressive Disorder (MDD) and insomnia can be understood in three ways as outlined by Jansson-Fröjmark, and Lindblom (2008): 1) insomnia and MDD may merely co-occur, both being caused by a common third variable; 2) the relationship between the two may be epiphenomenal (mental events are caused by physical events); or 3) the one may act as a risk factor for the other, and vice-versa.

While there have been other reviews of insomnia and MDD to date that address the underlying mechanisms of the relationship (Jansson- Fröjmark & Lindblom, 2008), to the best of our knowledge this is the first review to examine the role of maladaptive cognitions in the relationship between the two.

Depression

To satisfy the DSM-5 criteria for an episode of MDD one must have at least five symptoms in addition to depressed mood or anhedonia for a period of two consecutive weeks (American Psychiatric Association, 2013). Among all diseases, MDD is one of the most significant contributors to disability and reduced quality of life (Armitage & Arnedt, 2011). Major Depressive Disorder affects more than 300 million individuals in the world at least once in their lifetime (Armitage & Arnedt, 2011). It is extremely common and recent statistics estimate a prevalence of 7% amongst Americans (American Psychiatric Association, 2013). Taken together, the alarming prevalence and its impact on quality of life, as well as other factors including productivity underscore the impact of MDD on society at large.

It is hypothesized that MDD is composed of a complex relationship between biological, behavioral, and environmental factors. The probability of inheriting MDD is estimated to be approximately 40% (Ebmeier, Donaghey, & Steele, 2006), supporting the hypothesis of multifactorial etiology. Physiologically, many individuals diagnosed with MDD have abnormalities in the structure of their central nervous systems (CNS; Ebmeier et al., 2006). Some of these structural abnormalities include hippocampal atrophy and differences in their anterior cingulate, orbitofrontal cortex, dorsolateral cortex, striatum, and medial temporal lobes (Ebmeier et al., 2006). The environmental component of depression, as

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outlined by Hammen (2005), centers on the causal relationship between stressful life events and depressive episodes. Behaviour can also be seen as a component to depression. For example, ruminating over failures and focusing on negative stimuli. Major Depressive Disorder can be elicited by the onset of either environmental or interpersonal stressors that, in turn, act on biological or psychological predispositions (Oei, Bullbeck, & Campbell, 2006). Thus, the epidemiology of MDD involves a complex interplay between biological, environmental, and behavioural factors.

Insomnia

Insomnia is defined by the DSM-5 (American Psychiatric Association, 2013) as dissatisfaction with either quality or quantity of sleep related to either a difficulty falling or staying asleep, or the presence of early morning awakening with an inability to return to sleep. These features must be accompanied by significant distress and impairment in day-to-day functioning to qualify as insomnia (American Psychiatric Association, 2013).

Insomnia is a topic of concern for three main reasons. Firstly, obtaining insufficient sleep is correlated with decreased quality of life and daily functioning (Banks & Dinges, 2007), as well as diminished mood and affect (Bernert, Joiner, Cukrowicz, Schmidt, & Krakow, 2005). Secondly, inadequate sleep has a profound impact on factors relating to academic function, including memory (Stickgold, 2005), academic performance, and learning capacity (Curcio, Ferrara, & De, 2006). Taken together, the impact of sleep abnormalities on personal function, quality of life, and society is pronounced. Finally, the prevalence of insomnia and sleeping difficulties in adults appears to be on the rise globally (Ohayon & Paiva, 2005).

Sleep abnormalities affect a large portion of Americans. One third of Americans suffer from symptoms of insomnia, 10-15% from daytime impairments, and 6-10% meet the criteria for insomnia disorder (American Psychiatric Association, 2013). Insomnia is often found to co-occur with other mental disorders at a rate of 40-50% (American Psychiatric Association, 2013). Risk factors for insomnia include female gender, increased age, and poor mental and physical health (American Psychiatric Association, 2013). The DSM-5 (American Psychiatric Association, 2013) reports that insomnia can be associated with temperamental, environmental, genetic and physiological risk factors.

Despite its high prevalence, insomnia is undertreated and underreported by patients to their primary physician (Morin et al., 2011). In a telephone survey conducted by Morin et al. (2011), only 13% of participants with insomnia reported that they had consulted their doctor regarding their sleep abnormalities. Many individuals do not acknowledge the severity of the sleeping abnormalities, avoid seeking treatment from their physician, and instead make use of self-help strategies (Morin et al., 2011).

The vast field of sleep research cannot be covered entirely in the present review. Therefore, the present study focuses on sleep disruption and comprehensively investigates sleep disturbances by examining both objective and subjective parameters. This review focuses on the subjective component of this analysis, which includes complaints of inadequate amount, duration, and quality of sleep. These factors underlie the diagnosis of insomnia. Objective measures of sleep disruption can be obtained using polysomnography, a diagnostic tool used to measure biological changes that occur during sleep. This review does not examine parasomnias, such as night terrors and sleep-walking.

Comorbid Depression and Insomnia

Insomnia and MDD often co-occur (Staner, 2010). For instance, over 90% of individuals with MDD have comorbid insomnia or suffer from disrupted sleep (Thase, 1999). Alternatively, in a study that examined the prevalence of insomnia, 69% of insomniacs also suffered from depression (Johnson, Roth, & Breslau, 2006). Furthermore, Ford and Kamerow (1989) found that those with chronic insomnia were nearly 40 times more likely to have major depression, and over six times more likely to have an anxiety disorder compared to those without insomnia.

A bidirectional relationship between MDD and insomnia has been established where MDD and insomnia influence each other (Staner,

2010). However, they do not necessarily solely cause each other. The term comorbidity, originally introduced by Feinstein (1970) can be explained as the co-occurrence of two separate psychological disorders in the same individual. Sleep disturbances, in addition to being a symptom of and a diagnostic criterion for MDD, also increase the likelihood of developing a MDD (Breslau, Roth, Rosenthal, & Andreski, 1996; Fava, Grandi, Canestrari, & Molnar, 1990; Nierenberg et al., 1999). Insomnia is the most frequent residual symptom after treatment of MDD (Nierenberg et al., 1999). The negative impact of insomnia on mood can be a perpetuating factor for ongoing insomnia (Morin, Barlow, & Dement, 1993).

Jansson-Fröjmark and Lindblom (2008) administered a survey to 3000 participants in the general population of Sweden, with a follow up survey at the end of the year. The results of the prospective study suggest that a bidirectional relationship exists between anxiety and MDD on the one hand, and insomnia on the other. This suggests that anxiety is a significant component of the relationship between MDD and insomnia. Anxiety can be seen as the third variable involved in the relationship between insomnia and MDD (Jansson-Fröjmark & Lindblom, 2008). This can be expected due to the fact that the diagnostic criteria for MDD contains some features of anxiety (Daley, 2011).

Not only do individuals with depression exhibit abnormalities regarding duration of sleep, they also display poor quality of sleep, which is related to reduced paradoxical sleep latency, and disturbance of sleep architecture (Holsboer-Trachsler, & Seifritz, 2000). Chronic insomnia is related to increased risk of relapse and recurrence of mood disorders, and an elevated risk of suicide (Holsboer-Trachsler, & Seifritz, 2000).

The Clinical Implications of Comorbid Insomnia and MDD

Major Depressive Disorder and sleep disturbance impact physiological pathways related to the onset of cardiovascular disease (CVD) and diabetes, including inflammation, abnormal hypothalamic-pituitary-adrenal (HPA) functioning, and increased autonomic output (Joynt, Whellan, & O'Connor, 2003; Mullington,

Haack, Toth, Serrador, & Meier-Ewert, 2009). The bidirectional relationship and common comorbidity found between insomnia and MDD pose important clinical implications.

Firstly, insomnia is associated with various detrimental clinical outcomes. For example, Okun et al. (2011) reported that variability in sleep timing and shift work has been correlated with inflammation, which increases one's risk of hypertension, obesity, type-2 diabetes, metabolic syndrome and morbidity. Recent evidence reports various detrimental effects of chronic sleep restriction, such as enhanced risk for depression, type-2 diabetes, obesity and cardiovascular diseases (Porkka-Heiskanen, Zitting, & Wigren, 2013). Second, chronic depression has vast adverse consequences such as increased psychiatric comorbidity, physical health problems, suicidal behaviors, and increased health service use (Satyanarayana, Enns, Cox, & Sareen, 2009).

Together these two psychological disorders have a two-fold impact on the health outcomes of individuals. Specifically, Mezick, Hall, and Mathews (2011) note that comorbid depression and insomnia have been associated with increased BMI and obesity. Obesity increases ones susceptibility for developing cardiovascular disease and type-2 diabetes (Joynt et al., 2003). Thus, it is pertinent that action is taken to prevent and treat comorbid insomnia and MDD.

Method

A non-systematic literature review was conducted using the following computerized databases: PubMed, PsychInfo and Google Scholar. English language articles with the following search terms: sleep, depression, major depressive disorder (MDD), insomnia, mechanisms, bidirectional, relationship, exercise, obesity, inflammation, hot cognition, cold cognition, cognition, sleep deprivation, cognitive dysfunction, melatonin, circadian rhythms, and hypothalamus were considered for review. Articles were independently examined by investigators for relevance. If an article was believed to be suitable based on an evaluation of the title and abstract, a full-text review was completed. Reference lists of chosen articles were considered for supplementary relevant

articles. To be included in the review, studies had to measure parameters relevant to sleep and/or MDD, and depressive symptomatology. Articles were not excluded based of the number of research participants included in their studies.

Results

Mechanisms Underlying Comorbid MDD and Insomnia

The remainder of the review will focus on the mechanisms that contribute to cognitive dysfunction in MDD and thus mediate the bidirectional relationship between insomnia and MDD. The major mechanisms impacting this relationship include comorbidity, cognitions, the brain, melatonin, circadian rhythms, and exercise.

Cognitive dysfunction. An understanding of cognitions and how they affect depression and insomnia is considered to be fundamental in explaining their bidirectional relationship. Three main forms of cognitive dysfunction exist: cold cognition, hot cognition, and social cognition. Cold and hot cognitive deficits are commonly found in patients with MDD. Cold cognitive impairments include deficits in executive functioning, short-term memory and attention (Murrough, Iacoviello, Neumeister, Charney, & Iosifescu, 2011). Hot cognition refers to a cognitive bias, which impairs thought/information processing due to focusing on negative stimuli (Murrough et al., 2011). Roiser and Sahakian (2013) explain that whereas cold cognitions are thoughts that are emotion-independent, hot cognitions are thoughts that are emotion-laden. Lastly, impairments with regards to social cognition are displayed in the form of an inability to read or appropriately process social cues (Sasson, Nowlin, & Pinkham, 2013).

Cold cognitive impairments. Roiser and Sahakian (2013) explain MDD as a cognitive disorder, which impairs one's ability to concentrate. Similarly, the diagnostic criteria for major depressive episodes in the diagnosis of MDD include "cold" cognitive impairments (Roiser & Sahakian, 2013) such as concentration, and problem solving (Murrough et al., 2011).

A review by Murrough et al. (2011) notes the various cold cognitive impairments that have been documented in individuals with MDD. Specifically, Murrough et al. (2011) concluded that deficits on several attention related tasks are often observed in the acute phase of MDD. Specifically, cold cognitive impairments are displayed in effortful attention, which include processing speed and selective attention. Memory is also notably affected in MDD, cold cognitive impairments in the domain of memory in MDD include: verbal delayed memory, visuo-spatial memory, verbal working memory and long-term memory, and working memory. Specific cognitive deficits may be present in only a proportion of depressed individuals (Murrough et al., 2011). Executive functioning has also been reported to be disrupted in individuals with MDD. Deficits have been shown on tests measuring inhibition, problem solving and planning, mental flexibility, verbal fluency decision-making. Mental flexibility appears to be among the most significant cognitive impairment documented in patients with MDD. Evidence has shown that individuals with MDD experience persistent cognitive deficits, particularly in sustained attention, verbal learning and memory, and executive functions, even after significant improvement of depressive symptoms (Murrough et al., 2011).

Hot cognitive impairments. In individuals suffering from MDD, the pattern of overdramatizing one's failures and ruminating about them can raise physiological arousal levels, create anxiety associated with sleep, foster feelings of hopelessness, and disrupt sleep, which perpetuates a deteriorating cycle of insomnia and MDD (Carney, Edinger, Manber, Garson, & Segal, 2007). Cognitive biases include negative information processing where an individual focuses on failures.

The phrase "catastrophic response to perceived failure" (p. 600) was coined by Beats, Sahakian, and Levy (1996) using the Cambridge Neuropsychological Test Automated Battery (CANTAB) in relation to the pattern of cognitions exhibited by individuals with depression. Similarly, individuals with insomnia have been reported to catastrophize more about the consequences of not sleeping, in comparison to individuals with no sleeping difficulties (Harvey, & Greenal, 2003). Negative automatic

cognitions, behavioral dysregulation, and dysfunctional schemas are fundamental components in the maintenance of MDD, insomnia, and comorbid MDD and insomnia (Carney et al., 2007). Specifically, insomnia is manifested by faulty beliefs and expectations in relation to sleep, as well as perceptual and attention biases (Espie, 2002).

Roiser and Sahakian (2013) suggest that poor achievement on neuropsychological tests in people diagnosed with depression might partly result from their hot (emotion-charged) cognitions. Moreover, emotionally neutral cognitive tasks, particularly tasks that involve feedback on performance, can become emotionally charged when completed by individuals with MDD. These individuals develop emotionally laden, catastrophic interpretations that undermine their present and future performance on these neuropsychological tests.

Hot and cold cognition. Hot and cold cognition is associated with multiple brain structures, and intricate interactions between neural circuitry. The dorsolateral prefrontal cortex, the dorsal anterior cingulate cortex, hippocampus, and limbic system are all heavily involved in hot and cold cognitive processing (Roiser & Sahakian, 2013). The hippocampus, an area of the brain that has been linked to learning and memory, is increasingly activated during cold cognitions (Roiser & Sahakian, 2013). Conversely, the areas associated with the limbic system, the emotion center of the brain, are increasingly activated during hot cognitions, compared to cold cognitions (Roiser & Sahakian, 2013). Additionally, neurotransmitters thought to be implicated in emotions such as serotonin, norepinephrine and dopamine may impact cold cognitions by alternating actions in cortical and subcortical regions of the brain (Roiser & Sahakian, 2013).

Individuals with MDD display both negative bottom-up (inductive) and negative top-down (deductive) cognitive processing biases (Roiser & Sahakian, 2013). The negative bottom-up bias is a result of interrupted monoamine transmission, which result in maladaptive self-perpetuating negative cognitive structures that maintain depressive symptoms in individuals with MDD (Roiser & Sahakian,

2013).

Individuals with MDD display consistent impairments on cold (emotionally independent) neuropsychological tests at the time of remission, which implies that these impairments are not caused by the disorder (Roiser & Sahakian, 2013). Rather, they are a result of the maladaptive negative thinking style that led to the depression (Roiser & Sahakian, 2013). The finding that medication can decrease the negative emotional and reward biases exhibited by depressed patients, highlight that both bottom-up and top-down processing play a role in perpetuating depressive "hot" thinking and that they are not completely independent of one another (Roiser & Sahakian, 2013).

Considering that faulty cognitions are a fundamental component of depression and insomnia, cognitive behavioral therapy (CBT) is one of the treatments of choice (Morin et al., 2009). It may be pertinent to combat this cognitive disorder with a cognitive therapy that deals with the underlying faulty cognitions. Therefore, further research concerning CBT will have noteworthy implications for treatment of insomnia and depression (Morin et al., 2009). It may also be of significance psycho-pharmacologically to look closely at the clinical implications of the drugs chosen to combat MDD. Specifically, drugs that negatively impact sleep should be avoided for the treatment of MDD due to the cyclical nature of the two disorders.

Social cognitions. Social cognitive impairments are exhibited as an inability to read social cues appropriately, as well as interact appropriately with others (Sasson, Nowlin, & Pinkham, 2013). An example of such cognitive impairments can be seen in Autism (Sasson, Nowlin, & Pinkham, 2013). Deficits in social cognitions do not appear to be a marker of MDD, nor commonly present in individuals with MDD.

Rationale for cognitive dysfunction. Cognitive dysfunction is significant for three reasons: it is common, it impairs functioning, and it impacts treatment. Cognitive dysfunction, in both hot and cold cognitive processing, is extremely common in both MDD and insomnia (Park, An, Jang, & Chung, 2012; Roiser & Sahakian, 2013). Cognitive impairment can

impact the functioning of an individual by inhibiting his or her performance on neuropsychological tests and his or her ability to process thoughts without a negative and emotion laden cognitive bias (Snyder, 2013). Cognitive impairments in individuals with MDD have a large impact on the treatment for the individual (Snyder, 2013). Thus, it may be hypothesized that clinicians must be cautious when prescribing medications that impair cognitive functioning, sleep, or mood to patients with MDD or insomnia. As a result of the bidirectional relationship between MDD and insomnia, it can be understood that a drug that impairs sleep should not be prescribed to a patient with MDD because impairment in one area may lead to impairment in the other.

The Causes of Cognitive Dysfunction in MDD: Mechanisms

Sleep Abnormalities

One may experience fatigue as a result of sleep abnormalities. Fatigue may impair cognitive functioning by reducing one's arousal, which may contribute to the development of depressive symptoms. Thus, physiology can affect cognition. For example, metabolic syndrome, a group of conditions that together increase ones likelihood of developing heart disease, diabetes or a stroke, has been shown to contribute to cognitive impairment in elderly individuals, but mainly in individuals with high levels of inflammation in the blood vessels (Yaffe et al., 2004). Additionally, studies in the elderly report that raised levels of some inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) have been associated with cognitive impairment (Trollor & Agars, 2010).

Circadian Rhythms

Abnormalities in circadian rhythms are exhibited in phases of mood disorders (Chung et al., 2012). Specifically, MDD has been associated with circadian phase delay (Chung et al., 2012). The circadian rhythms have a significant effect on sleep habits. Morningness and eveningness are endogenous and heritable individual preferences that specify when an individual is most alert (i.e. either during the day

or night) (Amorim, Lecrubier, Weiller, Hergueta, & Sheehan, 1998). Individual preferences to morningness or eveningness are also related to the phase of circadian rhythms (Duffy, Rimmer, & Czeisler, 2001), as well as an individual's body temperature, cardiovascular stress levels, and rhythms related to performance, eating, and exercise (Baehr, Revelle, & Eastman, 2000; Horne, & Ostberg, 1976; Nebel et al., 1996). Morningness and eveningness are related to circadian gene polymorphisms (Katzenberg et al, 1998; Mishima et al., 2005), which play a role in the development of mood disorders (Benedetti et al., 2008; Desan et al., 2000; Royball et al., 2007). Specifically, individuals with MDD tend to be substantially more evening-type in comparison to controls (Drennan, Klauber, Kripke, & Goyette, 1991).

The sleep wake cycle is composed of circadian and homeostatic activities (Borbely, 1982; Daan, Beersma, & Borbely, 1984). Additionally, changes in circadian rhythmicity due to clock gene variations, genes associated with the regulation of timing, play a role in the development of circadian rhythm sleep disorders (CRSD) (Ebisawa, 2007). For example, Delayed Sleep Phase Syndrome (DSPS), a condition where falling asleep and waking up are chronically delayed can be attributed to clock gene variations (Ebisawa, 2007). Human circadian activity is influenced by gene variations (Ebisawa, 2007). The phosphorylation state of clock proteins are affected by several different CRSD variations (Ebisawa, 2007). Changes in clock genes can lead to an altered sleep-wake cycle in relation to the environmental light-dark cycle (Ebisawa, 2007). This mismatch in cycles can be detrimental to the quality of sleep that an individual receives.

The preceding evidence supports the belief that disruptions to circadian rhythms are implicated in both insomnia and MDD. This may explain why insomnia and MDD are often found together. Specifically, disruption to circadian rhythms contribute to cognitive dysfunction in MDD.

Melatonin

Another mechanism that contributes to cognitive dysfunction in MDD is the hormone

melatonin. One prominent hypothesis regarding the cause of MDD claims that depression due to a deficiency in monoamines, specifically the neurotransmitter serotonin (5-HT; Lanfumey, Mongeau, & Hamon, 2013). In the pineal gland, 5-HT is converted into melatonin, a neurohormone responsible for regulating circadian rhythms in the body's biological clock, which are often dysregulated in individuals with MDD (Lanfumey et al., 2013). Melatonin is regulated by the SCN and secreted by the pineal gland at night (Lanfumey, Mongeau, & Hamon, 2013). The secretion starts upon reduced light in the evening and stops in the morning light, providing the brain with information of the duration of the light period (Shaw, 1977; Shanahan, Zeitzer, & Czeisler, 1997). Melatonin is a natural hormone that is also involved in bodily processes responsible for sleeping (Lanfumey et al., 2013). Melatonin acts on specific high affinity G-protein coupled receptors, which modulate circadian rhythms, seasonal responses, and various retinal, cardiovascular and immunological functions (Sugden, Davidson, Hough, & Teh, 2004). Patients with unipolar or bipolar depression show overall low melatonin levels (Lam et al., 1990) and abnormalities in the onset, offset, and duration of melatonin secretion in comparison to individuals without MDD (Nurnberger et al., 2000; Srinivasan et al., 2006). The administration of melatonin has shown to enhance short-term memory permanently (Argyriou, Prast, & Philippu, 1998). Changes in the rhythm and amplitude of melatonin secretion may play a role in the disruption of both sleep and mood (Lanfumey et al., 2013).

One treatment for depression is the intake of agomelatine, a melatoninergic receptor agonist, which has been shown to reduce depressive symptoms by resynchronizing circadian rhythms (Cardinali, Srinivasan, Brzezinski, & Brown, 2012; Lanfumey et al., 2013). This is important because the effect that agomelatine produces on serotonin and melatonin are synergistic. Melatonin is not only relevant to depression but also insomnia, as a review conducted by Cardinali et al. (2012) reported that elderly individuals with insomnia display irregularities in melatonin in comparison to a control group (Brzezinski, 1997; Haimov et al.,1994; Zee &

Manthena, 2007).

Exercise

Exercise also underlies the complex relationship between depression and insomnia and mediates cognitive dysfunction in MDD. Exercise has been shown to increase total sleep time and create shifts in circadian rhythms (Cheek, Shaver, & Lentz, 2004). The benefits of exercise on mood have also been well established (Leppamaki, Haukka, Lonnqvist, & Partonen, 2004). A study conducted by Daley (2011) explores Exercise Based Cognitive Therapy (EBCT), which proved efficacious in the treatment of comorbid insomnia and MDD. What sets this treatment apart from previous modalities is that it combines traditional Cognitive Behavioral Therapy (CBT) with exercise. For instance, patients were prescribed one-hour biweekly sessions of physical activity for a total of six weeks in addition to focused problem solving therapies (Daley, 2011).

The physical activity component of ECBT is efficacious for two main reasons. Firstly, it increases potential beta-endorphin release and corticotropin releasing hormone (CRH), which correlates with heightened positive mood (Antunes et al., 2005; Harte, Eifert, & Smith, 1995). The other reason for its efficacy pertains to the optimization of one's homeostatic drive for sleeping (Youngstedt, 2005). This is due to increased body temperature and tissue damage as a result of the stressors associated with cardiovascular exercise (Oktadalen et al., 2001; Youngstedt, 2005).

Exercise also influences one's psychological well-being by facilitating improvements with regards to self-efficacy and self-esteem, while diminishing concerns related to one's problems (Craft, 2005). This may be beneficial because one may be less likely to derive hot cognitive catastrophic interpretations for cold cognitive performance tasks. These benefits are directly applicable to individuals diagnosed with depression and insomnia. Excess glucocorticoids have been implicated as a cause of cognitive impairment in patients with MDD (Leproult, Copinschi, Buxton, & Van, 1997; Vgontzas et al., 1998). Results from psychobiological studies suggest that insomnia elevates cortisol secretion (Leproult et al., 1997; Vgontzas et al., 1998) a

hormone associated with stress in which elevated levels are also seen in depression. Furthermore, the elevated cortisol levels related to stress and depression are immediately reduced and the benefits prolonged as a result of exercise (Stathopoulou et al., 2006; Zheng et al., 2006). This increase in cortisol secretion may be responsible for increased risk of MDD in individuals diagnosed with insomnia (Riemann & Voderholzer, 2003). Exercise was found to reduce cortisol levels associated with stress and depression and resulted in lasting cortical changes demonstrating reversal of biochemical basis for depression (Stathopoulou et al., 2006; Zheng et al., 2006). Thus, exercise can be seen as an efficacious component for the treatment of comorbid insomnia and MDD, as well as cognitive impairments in individuals with MDD.

Comorbidity as a Mechanism

Comorbidity of MDD with other psychological disorders can lead to cognitive dysfunction. For example, an individual suffering from both MDD and substance abuse may have cognitive impairments due to the effects of alcohol or drug abuse (Hunt, Baker, Michie, & Kavanagh, 2009). Cognitive impairments in individuals with comorbid MDD and substance abuse may include memory loss and other cold cognitive impairments, and may result in future disruption of sleep (Hunt et al., 2009).

Human and Animal Sleep Restriction Studies

A review by McCoy and Strecker (2011) note that studies in rats suggests that vigilance and attention are compromised by sleep deprivation (Christie, McKenna, Connolly, McCarley, & Strecker, 2008). There have been a number of studies to date that have explored the impact of sleep deprivation on human participants. More specifically, sleep deprivation appears to lead to significant cognitive impairments. For example, studies in women have shown reduced attention, memory, arithmetic ability (addition of numbers and abstraction), and decreased speed in the inhibition of a dominant response on the Stroop task, after three nights of sleep restriction (Stenuit & Kerkhofs, 2008). Casement, Broussard, Mullington and Press (2006)

conducted a study of prolonged sleep restriction in healthy adults, which measured working memory scanning speed over a nine-day period. The control group which received eight hours of sleep per night showed improvements in working memory scanning speed, in comparison to the experimental group who did not exhibit any significant differences after 4 hours of sleep a night (Casement et al., 2006). Kim et al. (2001) conducted a 24-hour sleep restriction study on normal adult males which found that cognitive functions such as motor, rhythm, receptive and expressive speech, memory and complex verbal arithmetic function were decreased after sleep loss, all of which are associated with right anterior hemisphere or subcortical areas. Therefore, evidence appears to support the notion that sleep loss leads to cognitive impairments.

Limitations

A limitation of the present review is that it is not a systematic review, nor a formal meta-analysis, due to methodological heterogeneity. Furthermore, using only three search engines may have limited the collection of articles under review.

Conclusion

This review has provided an overview of the literature on the relationship between insomnia and MDD and cognition, two psychological disorders that often co-occur (are comorbid). This review is unique as it looks at the role of maladaptive cognitions in the relationship between insomnia and MDD. Both hot and cold cognitive impairments have been implicated in insomnia and MDD (Roiser & Sahakian, 2013). Cognitive dysfunction in insomnia and MDD have been explained focusing on the following moderating variables: circadian rhythms, melatonin, and exercise. Cold cognitive impairments include deficits in attention, memory, and executive function (Roiser & Sahakian, 2013). Cognitions that by nature are cold become hot when depressed individuals catastrophize and ruminate about their failures, which in turn leads to further depression and difficulties sleeping (Roiser & Sahakian, 2013). Deficits in social cognition include the inability to read social cues appropriately (Sasson et al.,

2013). Disruption of circadian rhythms and low levels of melatonin have been reported in individuals with both insomnia and MDD (Cardinali et al., 2012; Chung et al., 2012). Specifically, exercise has shown to improve symptoms of both insomnia and depression, largely due to the release of endorphins, increasing ones homeostatic drive for sleep, and fostering greater self-esteem and self-efficacy (Craft, 2005; Stathopoulou et al., 2006; Zheng et al., 2006). The aforementioned mechanisms all interact to create a multifaceted and complex relationship between insomnia, cognition, and MDD. Thus, it can be understood that sleeping difficulties lead to cognitive impairment (Stickgold, 2005), which predisposes one to developing MDD and a perpetuating cycle of comorbid insomnia and MDD.

Future Directions

Given the prevalence of individuals who suffer from MDD, insomnia and comorbid insomnia and MDD, future research is needed to explore this bidirectional relationship and the impact of cognition. As a result of the established bidirectional relationship between insomnia and MDD future research should explore the implications of certain medication in comorbid patients. Specifically, clinicians should not prescribe medication that has a deleterious effect on sleep, mood, or cognition to individuals with comorbid insomnia and MDD. Future research would benefit from further analysis into the long-term effects of taking synthetic forms of melatonin in children. Longitudinal data does not exist at the present date to support the safety of melatonin use in children and how it affects their development. Furthermore, future research should examine the efficacy of exercise programs implemented for children exhibiting sleeping difficulties in preventing future MDD, or depressive episodes.

Seasonal affective disorder (SAD) is treated often with photo-therapy, which is exposure to bright light to reset circadian rhythms. It may be fruitful in future research to explore whether photo-therapy would be an effective treatment option for individuals who have comorbid MDD and insomnia. It can be hypothesized that it would reset one's circadian rhythm, help to reinitiate normal sleeping habits, and reduce depressive symptoms.

Future research would benefit from answering the following questions; Do sleep problems mediate cognitive dysfunction in individuals diagnosed with MDD? Is the comorbid presentation of MDD and insomnia associated with increased severity of depression, longer course, and/or increase resistance to treatment? Does comorbid insomnia and MDD present a different type and more severe form of depression? Should a clinician treat this combination differently than MDD on its own?

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