

Title: Cognitive and mood dysfunction in adult obstructive sleep apnoea (OSA): Implications for psychological research and practice.

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Abstract

Adult Obstructive Sleep Apnoea (OSA) is characterised by repeated, upper airway collapse resulting in sleep fragmentation and oxygen desaturation. Consequences of OSA include excessive daytime sleepiness, un-refreshing sleep, fatigue, increased risk of depression, reduced quality of life, and cognitive deficits. This article delineates the cognitive- and mood-related difficulties faced by individuals with OSA, discusses the theoretical accounts of nocturnal harm and daytime cognitive and mood dysfunction, and suggests practical tools to assess and treat psychological consequences of OSA.

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Prevalence and description of OSA

Adult Obstructive Sleep Apnoea (OSA) is a frequent and often under-diagnosed (Simpson et al., 2012) condition, characterised by repeated, upper airway (pharyngeal) collapse resulting in sleep fragmentation and oxygen desaturation (Butkov & Lee-Chiong, 2007). OSA commonly manifests in snoring, nocturnal gasping, and choking (Kryger, 2010).

The umbrella term 'OSA' includes individuals with and without daytime symptoms, individuals who have been diagnosed and those undiagnosed, and excludes individuals with predominantly Central Sleep Apnoea (CSA), Mixed Sleep Apnoea (MSA), or simple snoring. CSA is characterised by a lack of physiological drive to breathe, not an obstruction of the airway, as in OSA. While CSA also results in hypoxia and sleep fragmentation, it is associated with a number of other diseases associated with neurological problems, including kidney and heart failure (Bradley & Floras, 2003) which could, in turn, uniquely influence the disease-related cognitive profile. MSA exhibits features of both OSA and CSA, which may further complicate the cognitive profile. Simple snoring does not usually result in the same degree of hypoxia and sleep fragmentation as seen in OSA and would be expected to have much milder psychological consequences than OSA (Tworger, Lee, Schernhammer, & Grodstein, 2006). Thus this review focuses on the cognitive and emotional aspects of OSA.

The estimated prevalence of OSA in the general population is 9% of middle-aged women and 27% of middle-aged men (Young, Palta, & Dempsey, 1993; Young, Peppard, & Gottlieb, 2002). However, the clinical prevalence (i.e. OSA with daytime

symptoms of sleepiness) is between 1-5%, leaving a large proportion of people with OSA undiagnosed and, importantly, untreated (Butkov & Lee-Chiong, 2007).

Untreated OSA is associated with increased healthcare utilization, occupational injuries, and motor-vehicle accidents (Al-Ghanim, Comondore, Fleetham, Marra, & Aya, 2008). A comprehensive study evaluating the financial cost of sleep disorders in Australia estimated that the total economic burden of sleep disorders in 2004 was \$US7.5 billion (Hillman, Murphy, Antic, & Pezzulo, 2006). In the United States, in the year 2000, sleep apnoea was implicated in more than 800,000 motor-vehicle collisions, costing more than \$15.9 billion, and claiming more than 14,000 lives (Sassani et al., 2004). Potentially, these figures could be more than halved if sleep apnoea were appropriately treated (Sassani et al., 2004).

OSA is most commonly, and effectively, treated with adherent use of Continuous Positive Airway Pressure (CPAP). The CPAP device applies air pressure via the nose and/or mouth to prevent the pharyngeal airway from narrowing or collapsing (Sullivan, Berthon-Jones, Issa, & Eves, 1981). Whilst treatment of OSA with CPAP improves quality of life and reduces accident rates, cognitive and mood dysfunction do not always remit entirely (Hubukawa et al., 2005; Kylstra, Aaronson, Hofman, & Schmand, 2013). Furthermore, between 46-83% of people with OSA use their device for less than 4 per night (Weaver & Grunstein, 2008). Such low usage may also result in inadequate treatment of OSA-related cognitive impairment and mood difficulties.

The impact of OSA on cognition and mood

Adequate, undisturbed sleep is critical for brain health effective and daytime functioning (Poe, Walsh, & Bjorness, 2010). The repeated episodes of upper airway collapse and oxygen desaturation experienced by individuals with OSA reduce

oxygenation of cerebral tissues (Kryger, 2010) and disturb normal sleep architecture. Such night-time effects have been shown to result in daytime cognitive dysfunction by comparison with matched, non-OSA controls (Alchanatis et al., 2005; Alchanatis et al., 2008), as well as mood disturbances (Chen, Keller, Kang, Hsieh, & Lin, 2013).

Cognitive dysfunction

OSA is associated with disturbances in attention (Findley et al., 1986), memory (Bedard, Montplaisir, Richer, Rouleau, & Malo, 1991), and executive dysfunction (Bedard et al., 1991; Beebe & Gozal, 2002; Salorio, White, Piccirillo, Duntley, & Uhles, 2002). The broad domain of attention and vigilance shows widespread slowing of processing speed and reductions in accuracy (Beebe, Groesz, Wells, Nichols, & McGee, 2003; Bucks et al., 2012; Fulda & Schulz, 2003). Within memory, dysfunction has been reported in both episodic visual and verbal memory (Aloia, Arnedt, Davis, Riggs, & Byrd, 2004; Bucks et al., 2012; Wallace & Bucks, 2012). Executive dysfunction is affected globally, with impairments reported in shifting, updating, inhibition, fluid reasoning and generativity (Olaithe & Bucks, 2013). Even visual-spatial/constructional abilities are affected (Bucks et al., 2012). Some aspects of cognition appear spared, however, including language abilities (Beebe et al., 2003; Bucks et al., 2012), visual immediate recall and visual-spatial learning (Wallace & Bucks, 2012), and psychomotor functions (Bucks et al., 2012).

Mood dysfunction

Prevalence studies indicate that individuals with OSA have higher rates of depression and depressive symptomatology (7% to 63%) than the general adult population (9% to 10%) (Saunamäki & Jehkonen, 2007; Sharafkhaneh, Giray, Richardson, Young, & Hirshkowitz, 2005). The relationship between OSA and depression is yet to be clarified, in part, due to the high comorbidity between OSA,

depression and other disorders such as diabetes, and the difficulty in defining the primary disorder (depression or OSA) due to symptom overlap.

Proposed mechanisms of harm

Beebe and Gozal (Beebe, 2005; Beebe & Gozal, 2002) have proposed a conceptual framework based around critical roles for sleep fragmentation and blood gas abnormalities in the development of cognitive and mood dysfunction in OSA. In their model, sleep is viewed as a necessary restorative activity, regulating processes including reinforcing foundations for learning and memory (Poe et al., 2010) and modulating neuroendocrine demands (Everson, 1995). Disruption of these processes due to sleep fragmentation, blood gas abnormalities (i.e. hypoxia: reduced oxygen, and hypercapnia: increased carbon dioxide) due to periodic obstructed breathing, and neurochemical changes (including alterations to the serotonergic system; Bilyukov et al., 2005) lead to an inability of the body to return to a balanced state, damaging the nervous system. This damage results in a dysfunctional cognitive profile, mood disturbances and other daytime difficulties. These concepts are expanded upon below.

INSERT FIGURE 1 HERE

Evidence for a pivotal role of sleep fragmentation comes from the similarities of cognitive deficits and mood instability seen in individuals with OSA and individuals subjected to experimental sleep deprivation (Alhola & Polo-Kantola, 2007; Durmer & Dinges, 2005; Gujar, Yoo, Hu, & Walker, 2011; Verstraeten, Cluydts, Pevemagie, & Hoffman, 2004). Specifically, individuals deprived of sleep due to chronic sleep fragmentation show widespread cognitive deficits, with particular impairment in attention and executive function (Alhola & Polo-Kantola, 2007; Durmer & Dinges, 2005; Verstraeten et al., 2004), and emotional reactivity (Gujar et al., 2011): a pattern of deficits also seen in OSA.

There is also evidence that sleep fragmentation and blood gas abnormalities underlie lasting impairments by virtue of the irreparable neural damage they cause (Beebe & Gozal, 2002; Beebe et al., 2003). OSA is associated with grey matter loss in frontal (associated with executive function) and temporo-parieto-occipital cortices (broadly associated with attention and visuospatial processing), the thalamus (largely involved in relaying information, and regulating sleep-wake cycles), the hippocampal region (critical for memory) (Yahoui et al., 2009), and the amygdala (responsible for emotion regulation) (Kheirandish-Gozal, Yoder, Kulkarni, Gozal, & Decety, 2013). It is possible that these long-term changes in brain structure result from sleep fragmentation and hypoxia (Canessa et al., 2011; Macey et al., 2002) and that these lead to the cognitive and emotional difficulties seen in OSA (Bartlett et al., 2004; Chiang, 2006; Gale & Hopkins, 2004; Harper, Kumar, Ogren, & Macey, 2013; Hopkins, Kesner, & Goldstein, 1995; Naismith, Winter, Gotsopoulos, Hickie, & Cistulli, 2011).

Critically, however, there has been a consistent failure to find evidence of a dose-response relationship between the severity of sleep apnoea (i.e. of sleep fragmentation or hypoxia) and the severity either of cognitive dysfunction (Aloia, Arnedt, Davis, et al., 2004; Olaithe & Bucks, 2013; Wallace & Bucks, 2012) or of lowered mood (Asquari, Mohammadi, Kamrava, Tavakoli, & Farhadi, 2012). Detailing the relationship between nocturnal symptoms and daytime cognitive and mood dysfunction is crucial, for it will outline who is most at risk, and direct future treatment. For example, should sleep fragmentation prove to be the primary mechanism of harm, it will be crucial to resolve sleep disruption to prevent cognitive or mood difficulties.

While nocturnal indices of hypoxia have not been related to depression or anxiety (Daabis & Gharraf, 2012), it is well established that individuals with chronic diseases are at higher risk of depression, and individuals who experience depression perform worse on cognitive tasks (Airaksinen, Larsson, Lundberg, & Forsell, 2004; Barnes, Schneider, Boyle, Bienias, & Bennett, 2006; Foley, Ancoli-Israel, Britz, & Walsh, 2004). Those with OSA may suffer cognitive problems due to chronic nocturnal symptomatology (sleep fragmentation and blood gas abnormalities), and depression. Likewise, OSA-induced depression may produce cognitive disturbance (Ravnskilde et al., 2002).

Implications for psychologists

Despite no clear evidence of a relationship between the *severity* of OSA, as indexed by hypoxia and sleep fragmentation, and the *severity* of cognitive or mood dysfunction, what is clear is that OSA is associated with cognitive and mood problems. This has implications for the training and practice of psychologists from all disciplines (health, clinical, neuropsychology, educational and occupational).

Identifying sleep-related difficulties in clinical practice

There is a need for greater awareness of OSA and earlier detection. The cognitive and social implications of OSA are substantial (Al-Ghanim et al., 2008; Hillman et al., 2006), and to some degree irreversible (Bedard, Montplaisir, Malo, Richer, & Rouleau, 1993). Hence, developing systems for early detection is necessary. Due to the high co-morbidity between depression (Schroder & O'Hara, 2005), cognitive disturbance (Beebe, 2005) and OSA, psychology practitioners are likely to meet a significant number of individuals with OSA. Practicing psychologists should be encouraged to consider the potential role of sleep disturbance in their assessment, asking about sleep quality and habits.

Unfortunately, sleep, and sleep problems, are often ‘silent’ problems as they occur at night. Many people, and present-day society, place little value on sleep (Rajaratnam & Arendt, 2001) and underreport sleep issues (Blunden et al., 2004). Where individuals do complain of sleep problems, these complaints are often non-specific. In our clinical experience, clients describe ‘sleep disturbance’, ‘sleepiness’ or symptoms of insomnia. Approximately, 24 to 56% of patients with OSA have insomnia (Beneto et al. 2009). As such, we have tailored the ‘implications for psychologists’ section to the complaints clinicians will hear by client report, and provided measures to ‘tease’ out breathing disorders.

Mahowald (2002; cited in Isler, et al., 2005) recommends the use of three key questions to assess for these sorts of symptoms: 1. How is your sleep at night?, 2. Are you too sleepy during the day?, and 3. Does anything unusual happen during your sleep? In this way, psychologists can quickly flag if the individual is having sleep problems, and if those sleep problems suggest apnoea. Should any sleep issues be evident, further questions can elicit more detail about the problems. Useful resources include Isler et al. (2005), who provide a list of questions (see page 132) to further detail a client’s sleep issues (See also Mahowald (2002) and Butkov & Lee-Chiong (2007)).

If such symptoms are reported then, there are a number of paper-and-pencil measures that can be used to assess if these may be due to OSA. For example, the Berlin Questionnaire is a 5-minute, self-report measure that identifies the risk of OSA (Netzer, Stoohs, Netzer, Clark, & Strohl, 1999).

A number of presenting characteristics indicate increased risk of OSA. Firstly, psychologists should be aware that the major risk factors for OSA are older age, overweight and obesity, and being male (Young et al., 1993; Young et al., 2002).

Secondly, individuals who report snoring, frequent nocturnal awakenings with a feeling of dread or gasping for air, feeling un-refreshed upon awakening, or falling asleep or feeling tired during the day are at greater risk of OSA (Netzer et al., 1999).

High scores on the Berlin, coupled with identification of the risk factors above, should lead to a recommendation to visit a GP or sleep physician who can assess if further investigation is warranted.

Aside from directly addressing sleep disturbances, a recommendation that a client has their sleep assessed may also assist in treatment of co-existing psychological disorders. There is a growing body of evidence to suggest that individuals with co-morbid OSA and depression experience some improvements in depression symptoms with OSA treatment (Harris et al., 2009). Collaboration and communication between health professionals will be crucial for managing individuals with comorbid sleep and psychological disturbances, as well as those who require specific treatment for sleep disorders.

By making these accessible adjustments to their assessment practice, practitioners can then be well-informed points of contact for individuals with sleep disturbances, referring as appropriate for further assessment.

Even those who specialise in working with children will meet clients for whom undiagnosed OSA may be a key feature of their behavioural, cognitive or learning difficulties (Astill, VanDerHeijden, VanIJzendoorn, & VanSomeren, 2012; Blunden, Lushington, & Kennedy, 2001). Given the complexity of the assessment and treatment of OSA in children, this article has focussed on adults. However, the disorder is also common in children, albeit with different aetiology (Cheng, Dai, Wu, & Chen, 2012). However, two robust features of the psychological presentation of OSA in children are worth mentioning, as these make consideration of sleep

important for all child clients: these are hyperactivity and behavioural disinhibition.

The reader interested in learning more about the diagnosis and management of OSA in children, and the daytime sequelae could start with Mindell and Owens (2010).

Assessing cognitive dysfunction

In some instances, a full neuropsychological evaluation may be required. For example when the client demonstrates, or is distressed by, cognitive dysfunction. Figure 1 outlines key areas of cognition particularly sensitive to the harmful effects of OSA that neuropsychologists may wish to test in finer detail. Decary, Rouleu, and Montplaisir (2000) propose a preliminary neuropsychological test battery that a psychologist may adapt to suit the individual client. Given that OSA affects executive function, complex and divided attention, delayed long-term verbal and visual memory, and visual-spatial constructional abilities, these will be domains of cognition on which an assessor can focus (Bucks et al., 2012; Olaithe & Bucks, 2013; Wallace & Bucks, 2012). In any cognitive assessment, it is critical to assess cognitive reserve.

There is a growing body of literature showing that pre-morbid cognitive functioning alters the neurocognitive expression of sleep apnoea (Tsai, 2010). Cognitive reserve is the concept that a high level of pre-morbid cognitive ability acts to 'buffer' the effect of neurocognitive trauma (Stern et al., 2005). Such 'reserve' has been noted in individuals with OSA. Alchanatis et al. (2005) reported that high-intelligence participants with OSA had the same attention and alertness patterns as high-intelligence participants without OSA. However, normal-intelligence participants with OSA experienced a decline in attention and alertness performance compared to normal-intelligence controls. These authors theorised that high-intelligence protected participants from the negative impact of OSA on cognition. Cognitive reserve has been shown to be protective in other chronic disorders,

including Alzheimer's disease (Querbes et al., 2009). With the exception of the above study, no other published studies have considered cognitive reserve when exploring the effects of OSA on cognition.

Cognitive reserve is usually estimated and indexed by education or occupational attainment, participation in leisure activities, irregular word reading skills, or a combination of the above. Educational and occupational attainment can be limited in certain circumstances and not reflect an individual's intellectual capacity, hence a variety of tests assessing irregular word reading have been designed, e.g. for the US (Wechsler Test of Adult Reading, Holdnack, 2001), and the UK (National Adult Reading Test- Revised, Nelson & Willison, 1991). The number of errors is used to estimate IQ using a regression equation that accounts for other factors including age and occupation. Fewer errors are associated with higher premorbid IQ. Irregular word reading ability has been shown both to correlate highly with full scale IQ (Nelson & Willison, 1991) and to be resistant to decline due to neurodegeneration (McGurn et al., 2004).

Assessing mood

The assessment of depression in OSA is complicated by the overlap of symptoms, including insomnia, decreased libido, fatigue, and poor concentration (Kaplan, 1992). Due to this overlap, it can be unclear whether individuals have depression (as a comorbid psychiatric disorder) or are experiencing depressive symptoms due to OSA itself.

To overcome this issue, some studies have removed items from validated measures that overlap with OSA, such as items that relate to sleep quality and quantity (Peppard, Szklo-Coxe, Hla, & Young, 2006). Peppard et al. (2006) removed two items ("I have trouble sleeping through the night" and "I get tired for no reason")

from the Zung Self-Report Depression scale in order to reduce confounding OSA symptoms with depression symptoms. However, removing items may reduce the validity and reliability of a measure. It may be preferable to utilise measures that are less affected by symptom overlap such as the Geriatric Depression Scale (GDS; (Sheikh & Yesavage, 1986)) or the Hospital Anxiety Depression Scale-D (HADS-D; Zigmund & Snaith, 1983) (Nanthakumar, Bucks, & Skinner, under review). Further research into how best to identify the attributable symptoms of depression in individuals with OSA is needed, given the implications for diagnosis and treatment.

Psychological interventions in OSA

In the same way that psychological treatment for insomnia has proven to be effective (Harvey, 2008; Harvey, Ree, Sharpley, Stinson, & Clark, 2007; Murtagh & Greenwood, 1995; Smith et al., 2002), psychologists are also well positioned to advise on ways to improve CPAP treatment adherence, especially given the low reported CPAP adherence rates (Weaver & Grunstein, 2008). It is essential that CPAP treatment is optimised as such treatment has been shown to improve quality of life, reduce motor vehicle accidents, improve cognition (Weaver & Grunstein, 2008), and reduce the risk of work place accidents, work absenteeism, and presenteeism (Swanson et al., 2011).

Psychological factors play a role in CPAP acceptance, and psychological-based treatments assist with CPAP uptake (Olsen, Smith, Oei, & Douglas, 2012).

Motivational interviewing has been successfully used in individuals with OSA to increase CPAP uptake (Aloia, Arnedt, Riggs, Hecht, & Borrelli, 2004; Aloia et al., 2001). Olsen et al. (2012) have produced a brief, manualised and effective motivational intervention (Motivational Interview Nurse Therapy; MINT). MINT

therapy includes three sessions of motivational interviewing which has been shown, in a Randomised Controlled Trial, to increase adherence by nearly 50% more hours.

Furthermore, there is preliminary evidence that CBT assists with CPAP uptake. In a randomised control trial Richards, Bartlett, Wong, Malouff, and Grunstein (2007), administered two one-hour CBT intervention sessions, aimed at improving self-efficacy and expectancy. CPAP 'uptake' was increased in individuals who undertook the intervention over a one-month follow-up. Clearly, there is a need for longitudinal follow-up, given that CPAP usage declines over time (Weaver, 2002).

It is likely that the low adherence to CPAP is due, in part, to illness-beliefs. Individuals who attribute their OSA to a psychological stressor are less likely to adopt a physiological treatment, such as CPAP (Olsen, Smith, Oei, & Douglas, 2008; Skinner et al., 2013). Psychologists can assess and address the impact that such beliefs may have on treatment adherence. The Illness Perception Questionnaire-Revised (Moss-Morris et al., 2002) is a brief self-administered questionnaire that assesses illness beliefs, and has demonstrated utility with an OSA population (Skinner et al., 2013). Else, the Dysfunctional Beliefs About Sleep scale (DBAS) was specifically developed to assess dysfunctional sleep beliefs in individuals with insomnia (Morin, 1993), and has been successfully used in individuals with OSA (Yang, Liao, Lin, Chou, & Wang, 2011).

There are many tools available should a psychologist decide to assist in CPAP uptake and track a client's sleep quality and CPAP use. Tools such as the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) can be used to assess and track a client's sleep quality during treatment. The PSQI is a simple, 10-minute questionnaire developed to assess subjective sleep quality across a range of domains. The PSQI has been successfully used to assess sleep quality in many research studies of OSA, and

demonstrates good internal consistency and test-re-test reliability, in populations with sleep disorders (Buysse et al., 1989; Suleiman & Yates, 2011). Furthermore, many CPAP devices record hours of total use and average use per night, and have a viewing screen. Psychologists wishing to track objective use data to assess CBT for CPAP uptake can find simple instructions online for many devices, or enlist the client as collaborator to track objective CPAP hours.

Furthermore, individuals with little social support demonstrate lower rates of adherence (Stepnowsky, Marler, Palau, & Brooks, 2006). Providing social support or assisting the client to rebuild their social support may also assist with treatment compliance (Richards et al., 2007). There are a number of associations that provide social meetings, and informational support to individuals with OSA and other sleep disorders (For Australian readers see ‘Sleep Disorders Australia’: www.sleepoz.org.au/, for American readers see web.stanford.edu/~dement/sleeplinks.html#sdsg), and other associations that provide many online self-help documents and support groups (See ‘Sleep Health Foundation’: www.sleepoz.org.au/ and www.sleepapnea.org/support.html has A.W.A.K.E.).

Training psychologists

The impact of OSA, and sleep disturbance more broadly, on psychological and cognitive health are not routinely taught in postgraduate psychology programs. For example, the Australian Psychological Society (APA) does not list sleep disorders as a necessary facet of psychology teaching programs, and most neuropsychological and clinical training text books do not include information on sleep disorders (Waters & Bucks, 2011). A lack of sleep education is not unique to Australia, being an issue for many international postgraduate psychology and medical courses (Meltzer, Phillips,

& Mindell, 2009). Furthermore, psychologists would benefit from greater sleep education due to the high comorbidity between sleep and psychological disorders, and the placement of many psychologists on multidisciplinary medical teams (Meltzer et al., 2009).

Conclusions

Although the mechanisms by which OSA impacts on cognition and mood are not well understood, it is clear that individuals with OSA experience cognitive dysfunction and lowered mood. Psychology practitioners are well placed to assist individuals in identifying sleep disturbance and seeking appropriate help. However, in order for this to occur, training institutes need to include the cognitive impact of sleep disturbance, and particularly OSA, in their curricula.

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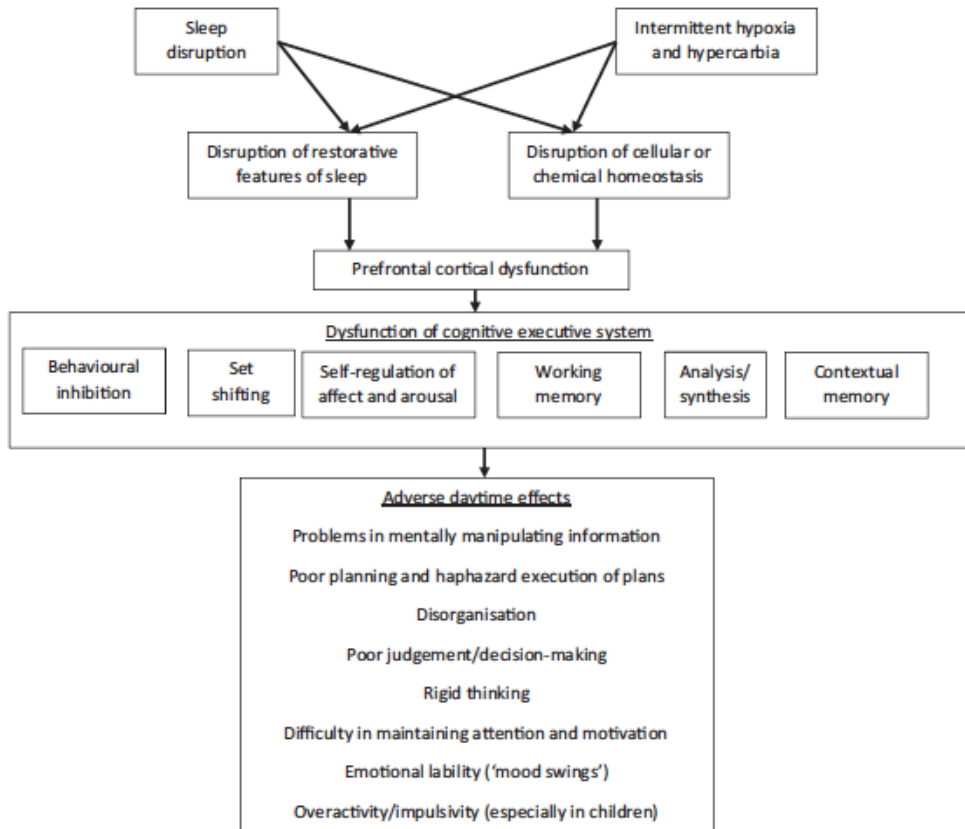


Figure 1. Model of mechanisms of harm in OSA. See Bucks, Olaithe, and Eastwood (2013) for a full review of articles supporting damage to these cognitive domains. From "Obstructive Sleep Apnea and the Prefrontal Cortex: Towards a Comprehensive Model Linking Nocturnal Upper Airway Obstruction to Daytime Cognitive and Behavioral Deficits," by D. W. Beebe and D. Gozal, 2002, *Journal of Sleep Research*, 11, p. 3. Copyright 2002 by John Wiley and Sons. Reprinted with permission.