CROSSTALK

CrossTalk opposing view: The intermittent hypoxia attending severe obstructive sleep apnoea does not lead to alterations in brain structure and function

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Obstructive sleep apnoea (OSA) is defined by repeated nocturnal episodes of pharyngeal obstruction with resultant intermittent hypoxia (IH), reoxygenation and arousals from sleep. These events have been shown to adversely impact multiple brain regions, notably frontoparietal cortices, temporal cortex, hippocampal/parahippocampal region, cerebellum and some white matter tracts (Morrell *et al.* 2010; Jackson *et al.* 2011; Kumar *et al.* 2012). A number of animal studies by Gozal and colleagues have suggested that it is the chronic exposure to IH that leads to oxidant stress, inflammation and related structural and pharmacometabolic changes of the central nervous system (CNS) (for review see Gozal, 2009). These structural changes are further proposed to underlie the neurocognitive and neuropsychiatric deficits found in patients with OSA (e.g. Canessa *et al.* 2011). However, during the last decade a wider paradigm shift in the way the brain is viewed has occurred. This has led to reconceptualisation of many complex multisystem illnesses that display neurocognitive sequelae, such as OSA.

Today we recognise the brain as a self-organizing system with complex non-linear dynamics in which cognitive processes arise out of the dynamic interaction and oscillations between multiple regions (Jones, 2009). Accordingly, we argue here an additional, hitherto ignored, 'third-dimension' to the core symptoms of severe OSA, proposing that their relative uniqueness suggests malfunctioning of the specific large-scale brain circuitry loop.

Multiple deficits can occur in OSA, including depression, disturbances in attention, dysmetria of thought and affect, verbal memory and executive function deficits (Twigg *et al.* 2010; Jackson *et al.* 2011; Sforza & Roche, 2012). These symptoms can be conceptualised as a part of the spectrum of two other well-recognised clinical syndromes, thalamocortical dysrhythmia (Llinás *et al.* 1999) and the cerebellar cognitive affective syndrome (Schmahmann & Sherman, 1998). Llinás and colleagues (1999) suggest that the endophenotype of a number of neurological and neuropsychiatric syndromes arises when internally generated, low-frequency network oscillations disrupt the normal state-dependent flow of information between thalamus and cortex. Similarly, Schmahmann & Sherman (1998) proposed a novel clinical entity, the cerebellar cognitive affective syndrome that can arise from disruption of the cerebellar modulation of neural circuits. The neurocognitive symptoms (and indeed neuroanatomical regions of interest) frequently described in OSA patients, in our opinion, share many aspects of these two clinical entities.

Rhythmic entrainment of activity in the interconnected cortico-thalamo-cortico (Jones, 2009) and cerebellar (Ros *et al.* 2009) networks occurs during all states of consciousness and is reflected in the presence of waveforms at different frequencies in the electro- and magnetoencephalogram (EEG/MEG) (Llinás *et al.* 1999). Appositely, in a study of apnoeic patients, significant EEG slowing in rapid eye movement (REM) sleep was observed over fronto-central and parietal regions, while EEG slowing during wakefulness was observed over all cortical regions (Morisson *et al.* 1998). During the non-REM (NREM) sleep, the brainstem and basal forebrain modulatory systems impact on the thalamocortical oscillator weakens. This leads to the generation of predominantly slow oscillations, sleep spindles and other slow rhythms, most of which have been extensively investigated in the

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fields of memory and brain plasticity, and are seen as crucial to re-establishment of synaptic homeostasis (Frank, 2012; Timofeev *et al.* 2012; Vukadinovic & Rosenzweig, 2012). Predictably, in OSA, the spindles' frequency and topography are reported to be disordered, which is indicative of impairment of regulatory homeostatic mechanisms, and/or structural changes in the thalamocortical oscillator (Schönwald *et al.* 2012).

The intricate and finely tuned interplay of thalamic low-threshold calcium channel conductances probably constitutes the skeleton of most NREM sleep oscillatory activities, which then act to group other fast cortical rhythms such as beta and gamma (Crunelli *et al.* 2006). Therefore, we hypothesise that both the IH-induced changes in neuromodulatory/neurotransmitter systems (as discussed in Gozal, 2009) and the post-arousal-induced (e.g. via hyperventilation or oxidative stress) deranged excitability of thalamic neurons (Jordan *et al.* 2011; Nair *et al.* 2011) eventually combine to produce sub-acute/chronic changes in the oscillator, and the selective cortical/subcortical networks, which are probably themselves directly targeted by hypoxic injury/inflammation (Cervós-Navarro & Diemer, 1991; Gozal, 2009). Further circumstantial evidence points to the increased risk of developing OSA in epileptic patients (Benbadis & Liu, 2007). Also interestingly, patients with dual diagnosis who were non-compliant with continuous positive airway pressure (CPAP) treatment were shown to be at higher risk of seizures, prompting some to question CPAP as a possible anti-epileptic treatment (Vendrame *et al.* 2011).

Age-related changes in susceptibility to alterations in brain structure and function resulting from IH

In children with OSA, diminished learning capabilities, increased hyperactivity and incidence of attention deficit disorders have been shown (Gozal, 2009). More recently, an increased propensity for accelerated cognitive decline was implied from data in older people with OSA (Ayalon *et al.* 2010; Sforza & Roche, 2012). Unique periods of susceptibility during the life span, along with genetic, environmental and lifestyle conditions, appear to determine the severity of IH effects on the CNS (Haddad & Yu, 2009; Sforza & Roche, 2012; Kim *et al.* 2012). Some of these effects at both ends of the age spectrum possibly also reflect the direct and epigenetic impact of IH during the heterochronus neurodevelopmental myelination process, which in humans, unlike that in other primates, spans several decades and probably contributes to later-life cognitive gains (Bartzokis, 2011; Rosenzweig *et al.* 2012).

Animal models of OSA

The central role for IH leading to alterations in brain structure is strongly contended by animal models of OSA (for review see Gozal, 2009). However, the results of clinical studies in adults with OSA are less convincing (Morrell & Glasser, 2011; Sforza & Roche, 2012). It is of note that in animal studies both IH and sleep fragmentation (episodic arousal from sleep) have been shown to independently affect similar CNS regions (Nair *et al.* 2011; Sforza & Roche, 2012) possibly, at least in part, via a nicotinamide adenine dinucleotide phosphate oxidase-dependent pathway (Nair *et al.* 2011). Moreover, studies of the effects of sleep deprivation on cognition in the general population suggest comparable impairments to those seen in OSA (Killgore, 2010; Jackson *et al.* 2011). Sleep deprivation studies also imply that the highest impact is on cognitive systems that rely on emotional data (Killgore, 2010). The pathophysiology behind this effect might be indicated in reports showing that manipulation of noradrenaline levels during sleep alters olfactory-based and hippocampal-amygdalar-based learning (Frank, 2012). Given our previous argument, it is of note that the main forebrain source of this neuromodulator is the locus coeruleus and that its activity is shown to be timelocked to the upstate of cortical slow oscillations of NREM sleep (Eschenko *et al.* 2012).

Conclusion

We have argued that the progressive interplay of both sides of the Janus-faced OSA pathophysiology (i.e. IH and sleep fragmentation) aids structural and pharmacometabolic changes in the thalamocortical oscillator that can eventually translate into decreased cortico-thalamo-cerebellar interaction and a variable clinical presentation on the cerebellar cognitive affective syndrome and thalamocortical dysrhythmia spectrum. The ensuing cortical diaschisis probably underlies some of the cardinal neurocognitive morbidities recorded in susceptible OSA patients. It is hoped that by conceptualizing the alterations in brain structure and function attending severe OSA into one, albeit large, malfunctioning brain-loop (rather than IH *vs.* sleep fragmentation) we may offer a focused theoretical tool for clinically targeted research of treatment pathways, and future therapeutical interventions.

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References

Ayalon L, Ancoli-Israel S & Drummond SP (2010). Obstructive sleep apnea and age: a double insult to brain function? *Am J Respir Crit Care Med* **182**, 413–419.

Bartzokis G (2011). Neuroglialpharmacology: white matter pathophysiologies and psychiatric treatments. *Front Biosci* **16**, 2695–2733.

Benbadis SR & Liu L (2007). CPAP: a treatment for epilepsy? *Neurology* **69**, 1814–1815.

Canessa N, Castronovo V, Cappa SF, Aloia MS, Marelli S, Falini A, Alemanno F & Ferini-Strambi L (2011). Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. *Am J Respir Crit Care Med* **183**, 1419–1426.

Cervós-Navarro J & Diemer NH (1991). Selective vulnerability in brain hypoxia. *Crit Rev Neurobiol* **6**, 149–182.

Crunelli V, Cope DW & Hughes SW (2006). Thalamic T-type Ca^{2+} channels and NREM sleep. *Cell Calcium* **40**, 175–190.

Eschenko O, Magri C, Panzeri S & Sara SJ (2012). Noradrenergic neurons of the locus coeruleus are phase locked to cortical up-down states during sleep. *Cereb Cortex* **22**, 426–435.

Frank MG (2012). Erasing synapses in sleep: is it time to be SHY? *Neural Plast* **2012**, Article ID 264378.

Gozal D (2009). Effects of intermittent hypoxia on neurological function. In *Brain Hypoxia and Ischemia*, 1st edn, ed. Haddad GG & Yu SP, pp. 187–212. Humana Press, NY, USA.

Haddad GG & Yu SP (eds) (2009). *Brain Hypoxia and Ischemia*. Humana Press, NY, USA.

Jackson ML, Howard ME & Barnes M (2011). Cognition and daytime functioning in sleep-related breathing disorders. *Prog Brain Res* **190**, 53–68.

Jones EG (2009). Synchrony in the interconnected circuitry of the thalamus and cerebral cortex. *Ann N Y Acad Sci* **1157**, 10–23.

Jordan AS, Eckert DJ, Wellman A, Trinder JA, Malhotra A & White DP (2011). Termination of respiratory events with and without cortical arousal in obstructive sleep apnea. *Am J Respir Crit Care Med* **184**, 1183–1191.

Killgore WD (2010). Effects of sleep deprivation on cognition. *Prog Brain Res* **185**, 105–129.

Kim J, Bhattacharjee R, Khalyfa A, Kheirandish-Gozal L, Capdevila OS, Wang Y & Gozal D (2012). DNA methylation in inflammatory genes among children with obstructive sleep apnea. *Am J Respir Crit Care Med* **185**, 330–338.

Kumar R, Chavez AS, Macey PM, Woo MA, Yan-Go FL & Harper RM (2012). Altered global and regional brain mean diffusivity in patients with obstructive sleep apnea. *J Neurosci Res* **90**, 2043–2052.

Llinás RR, Ribary U, Jeanmonod D, Kronberg E & Mitra PP (1999). Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci U S A* **96**, 15222–15227.

Morisson F, Lavigne G, Petit D, Nielsen T, Malo J & Montplaisir J (1998). Spectral analysis of wakefulness and REM sleep EEG in patients with sleep apnoea syndrome. *Eur Respir J* **11**, 1135–1140.

Morrell MJ & Glasser M (2011). The brain in sleep-disordered breathing: a vote for the chicken? *Am J Respir Crit Care Med* **183**, 1292–1294.

Morrell MJ, Jackson ML, Twigg GL, Ghiassi R, McRobbie DW, Quest RA, Pardoe H, Pell GS, Abbott DF, Rochford PD, Jackson GD, Pierce RJ, O'Donoghue FJ & Corfield DR (2010). Changes in brain morphology in patients with obstructive sleep apnoea. *Thorax* **65**, 908–914.

Nair D, Zhang SX, Ramesh V, Hakim F, Kaushal N, Wang Y & Gozal D (2011). Sleep fragmentation induces cognitive deficits via nicotinamide adenine dinucleotide phosphate oxidase-dependent pathways in mouse. *Am J Respir Crit Care Med* **184**, 1305–1312.

Ros H, Sachdev RN, Yu Y, Sestan N & McCormick DA (2009). Neocortical networks entrain neuronal circuits in cerebellar cortex. *J Neurosci* **29**, 10309–10320.

Rosenzweig I, Vukadinovic Z, Turner AJ & Catani M (2012). Neuroconnectivity and valproic acid: The myelin hypothesis. *Neurosci Biobehav Rev* **36**, 1848–1856.

Schmahmann JD & Sherman JC (1998). The cerebellar cognitive affective syndrome. *Brain* **121**, 561–579.

Schönwald SV, Carvalho DZ, de Santa Helena EL, Lemke N & Gerhardt GJL (2012). Topography-specific spindle frequency changes in obstructive sleep apnea. *BMC Neurosci* **13**, 89.

Sforza E & Roche F (2012). Sleep apnea syndrome and cognition. *Front Neurol* **3**, 1–7.

Timofeev I, Bazhenov M, Seigneur J & Sejnowski T (2012). Neuronal synchronization and thalamocortical rhythms in sleep, wake and epilepsy. In *Jasper's Basic Mechanisms of the Epilepsies*, 4th edn, ed. Noebels JL, Avoli M, Rogawski MA, Olsen RW & Delgado-Escueta AV. National Center for Biotechnology Information, Bethesda, MD, USA.

Twigg GL, Papaioannou I, Jackson M, Ghiassi R, Shaikh Z, Jaye J, Graham KS, Simonds AK & Morrell MJ (2010). Obstructive sleep apnea syndrome is associated with deficits in verbal but not visual memory. *Am J Respir Crit Care Med* **182**, 98–103.

Vendrame M, Auerbach S, Loddenkemper T, Kothare S & Montouris G (2011). Effect of continuous positive airway pressure treatment on seizure control in patients with obstructive sleep apnea and epilepsy. *Epilepsia* **52**, e168–171.

Vukadinovic Z & Rosenzweig I (2012). Abnormalities in thalamic neurophysiology in schizophrenia: could psychosis be a result of potassium channel dysfunction? *Neurosci Biobehav Rev* **36**, 960–968.

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