The ageing brain in sleep apnoea: paradoxical resilience, survival of the fittest, or simply comparing apples and oranges?

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The elevated prevalence of obstructive sleep apnoea (OSA) and its association with a long and ever expanding list of end-organ morbidities has prompted substantial interest in identifying mechanistic pathways underlying such deleterious consequences, and their potential reversibility with treatment. Over the last several decades, we have witnessed substantial increases in the granularity of the morbid phenotype of OSA, and such observations have prompted us to rethink some of the stricter early concepts. Among them, rather than viewing OSA as a single disease model that is applicable to all patients, we have formulated the conceptual framework of distinct phenotypes of OSA that may be driven by different mechanisms, link to different clinical manifestations, and display divergent responses to therapy [1–6]. In this contextual setting, the aspirational goals of the field are to first and foremost identify those OSA patients likely to benefit from treatment and administer the correct intervention, *i.e.* precision medicine [7, 8].

The initial awareness to the importance of excessive daytime sleepiness (EDS) in the therapeutic response [9] spurred subsequent exploration of additional factors influencing clinical aspects of OSA and associated morbidities. Among these, ageing has emerged as an important modifier of OSA disease cardiovascular outcomes [10, 11], whereby the odds of significant associations between OSA and end-organ morbidity appear to decline with advancing age beyond 55 years of age [12–15]. Thus, it would seem that a "survival effect" may be operational among a selected group of OSA patients, and becomes particularly discernible after a specific age threshold has been crossed. However, to what extent ageing-related survival is protective across all morbidities of OSA is unclear.

One of the important, yet vastly heterogeneous adverse manifestations of OSA is the increased risk for neurocognitive deficits [16]. It has become apparent that at any level of OSA severity, there will be patients manifesting cognitive morbidity and those who are apparently unaffected. Initial studies in animal models and humans posited that both developing and ageing brains would be uniquely susceptible to the intermittent hypoxia and sleep perturbations that characterise OSA, and manifest as neuronal cell losses

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within neural regions underlying cognitive functions [14, 17–20]. Furthermore, it would be reasonable to anticipate that such OSA-associated cognitive deficits and the rate of their progression would be further exacerbated by the concurrent presence of risk factors such as a known propensity for Alzheimer disease [21]. Under these circumstances, several studies have provided rather robust evidence appearing to support the assumption that OSA accelerates the ageing processes [22], and as such that their co-existence would therefore augment the risk for adverse outcomes, including cognition and central nervous system (CNS) integrity [22–24]. However, not all of the studies have yielded similar conclusions. Indeed, Celle *et al.* [25] report in this issue of the *European Respiratory Journal* that when they evaluated a rather extensive cohort of asymptomatic and otherwise healthy elderly subjects, magnetic resonance imaging (MRI) studies did not reveal changes in local brain volumes or in cortical thickness that were significantly associated with polysomnographic measures traditionally used to evaluated OSA severity. Furthermore, there were no significant differences among the overall rather restricted subgroups for those subjects who had OSA and were treated *versus* those with OSA who were not treated or healthy controls. The authors attributed their findings to several potential factors, namely the more sophisticated image analysis approach consisting of voxel-based morphometry, the recruitment approach based on a healthy ageing general population without *a priori* evidence of OSA, and the fact that all subjects were essentially asymptomatic and in their vast majority did not manifest any evidence of EDS. Regarding the latter, EDS was evaluated subjectively by Celle *et al*. [25] using the Epworth sleepiness scale rather than objectively, a factor that has previously been considered as disabling the ability to detect those patients with OSA who are more susceptible to develop systemic inflammation, a major determinant of cognitive dysfunction [26–28].

So what do we deduce from so much contradictory evidence? First, that the frequency of cognitive deficits and their underlying brain imaging correlates in a general community-based overall healthy population in whom occasional participants have OSA is likely to be substantially reduced when compared to a clinical symptomatic referral population in whom the presence of both subjective and ultimately objective EDS, along with many other end-organ morbidity related manifestations, will likely result in a much higher proportion of cognitively affected individuals, and consequently a much higher probability of finding structural correlates in brain MRI scans. Of note, one of the potential consequences involved in a healthy asymptomatic cohort selection may include the possibility of such cohort being underpowered to detect the small subset of individuals in whom OSA will translate into positive MRI findings. Second, we need to consider that there is likely a larger subset of aged individuals who are more likely to be protected from OSA-induced damage, if indeed the magnitude of oxidative stress and the changes in a large array of other brain properties elicited by OSA are not as prominently recruited when compared to younger patients [29, 30]. Third, and perhaps more importantly, that the presence of other risk factors increasing the propensity for cognitive deficits in the context of OSA is probably a critical determinant of the clinical phenotype and of the underlying CNS pathology among aged patients. Finally, that similar to many other confounders, age is clearly one important factor that needs to be incorporated into the prediction models of risk, cost and benefit in the context of decisions on therapeutic interventions for OSA. However, we will still need to figure out whether biological or chronological age is the correct temporal factor in the decision-making algorithm. Notwithstanding, as we continue to expand the number of phenotypic groups in OSA, and define increasingly better the unique differentiators between one OSA phenotype and the next, it is very likely that future selection of optimal interventional strategies will need to be predicated on combinatorial clinical and biomarker approaches [7, 31, 32], and that among the latter, surrogate reporters of senescence will certainly assume a major role. Till then, and in the words of Mark Twain "Age is an issue of mind over matter. If you don't mind, it doesn't matter."

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