Article

ADHD Prevalence: Altitude or Sunlight? Better Understanding the Interrelations of Dopamine and the Circadian System

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In this issue, Huber and colleagues (2015) report on the negative association between altitude and regional variation of ADHD in children. They reported lower rates of ADHD in areas with higher altitude (explained variance is 38%). Their rationale for investigating this link was based on data suggesting that hypobaric hypoxia is associated with increased dopamine (DA) levels, which would theoretically be preventive of ADHD, in which lower levels of DA are typically found. The main studies cited by the authors for this association demonstrated an 80% increase in DA levels at 10% oxygen (fraction of inspired oxygen [FiO_2]) levels (Orset et al., 2005), an oxygen pressure corresponding to an altitude of 4 to 5 km (Peacock, 1998), and an increased DA level at simulated heights of 7.6 km (Ray et al., 2011). The mean altitudes, in states with the highest altitude in the United States, are far below these altitudes (U.S. states with highest mean altitude: Colorado, 2.1 km; Wyoming, 2.0 km; Utah, 1.8 km). Even though the cited studies of extreme altitudes would not support the hypothetical explanation of the correlation of altitudes of these states with their reported rates of ADHD, the authors do cite a study by Brenner, Cheng, Clark, and Camargo (2011) that suggests individuals may experience behavioral effects (increased suicide rates) at altitudes as low as 2,000 feet.

In their discussion, Huber et al. (2015) cited an alternative hypothesis based on our study (Arns, van der Heijden, Arnold, & Kenemans, 2013), which documented an association between solar intensity (SI) and geographical variations in ADHD prevalence rates (PREV). Based on the same data that Huber et al. (2015) used, we demonstrated that geographical areas with high SI have lower prevalence of ADHD (Arns et al., 2013). In our analyses, we also suspected a possible role for altitude as reported by Huber and colleagues (2015), which we actually tested and reported on in our study. When we added altitude as a covariate to our original analysis of SI and PREV, the SI results remained significant for 2007 ($p = .007$) and at trend level for 2003 ($p = .076$). However, running the same analysis for altitude and adding SI as a covariate resulted in non-significant associations ($p > .4$; Arns et al., 2013). We also reported that in a non-U.S. adult ADHD sample from Fayyad and colleagues (2007), the association of ADHD prevalence with altitude was not significant (even before adjustment of SI), but the association with SI was significant. This suggests that the association between altitude and ADHD prevalence reported by Huber et al. (2015) may be due to a confound with SI, which is known to increase with altitude, as radiation at higher altitudes traverses a shorter path length through the atmosphere and thus undergoes less scattering and absorption, also called the altitude effect (Blumthaler, Ambach, & Ellinger, 1997). Therefore, although an interesting observation, the inverse association of altitude with PREV seems to be driven by differences in SI (i.e., the altitude effect) and not by altitude per se.

In addition to the original results we reported using the Centers for Disease Control and Prevention (CDC) 2003 and 2007 ADHD prevalence data, our finding also replicated in the CDC data from 2011 (see Figure 1A),[1] as well as in data from Hoffmann and colleagues, *except* for Nordic areas such as Scandinavia and the United Kingdom/Scotland (Arns, van der Heijden, Arnold, Swanson, & Kenemans, 2013). Initially, we had hypothesized a sigmoidal dose-response effect (see Figure 1A) where intense sunlight above 5 kWh/m^2/day had a threshold protective effect for developing ADHD. However, we re-analyzed data from Hoffmann et al. (2014), which suggested this association may be better explained by a quadratic dose-response effect, where specific geographic areas ("Nordic" countries such as Scandinavia, the United Kingdom, and Iceland) with

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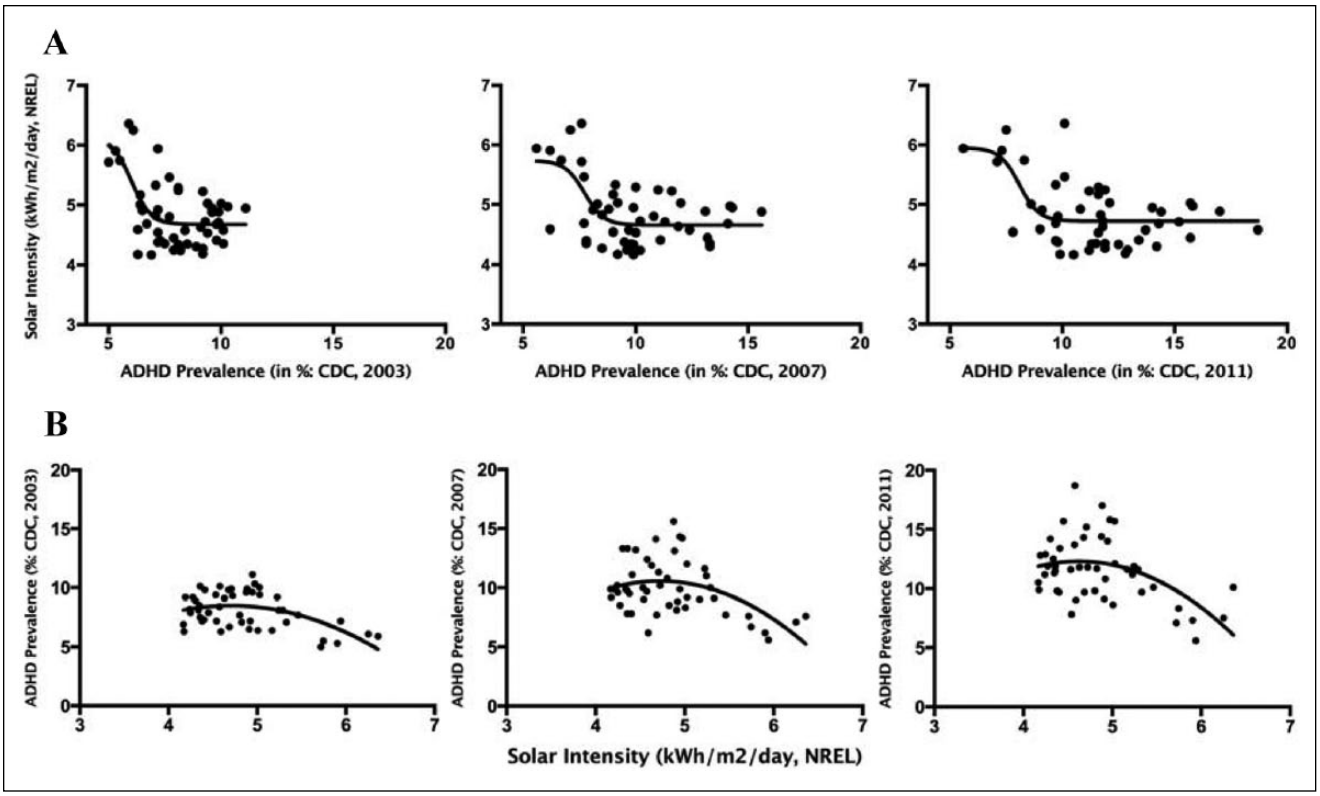

Figure 1. The original sigmoidal dose-response effect between SI and ADHD PREV as reported in our original article for the United States (2003, 2007; Arns, van der Heijden, Arnold, & Kenemans, 2013) updated with the new 2011 CDC data (A), and the revised quadratic dose-response effect (B) based on the Hoffmann et al. correspondence (Arns et al., 2013).
Note. All quadratic models explain significantly more of the variance than a linear trend (all $p < .05$), and explained variance for 2003, 2007, and 2011 are 27%, 23%, and 25%, respectively; SI = solar intensity; PREV = prevalence rates; NREL = National Renewable Energy Laboratory.

very low sunlight intensity are also characterized by low rates of ADHD.

Huber et al. (2015) suggested a potential biological mechanism for their hypobaric hypoxia effect of altitude (increased DA). We have also proposed a potential biological mechanism for our effect of SI based on DA. The DA receptor D4 (DRD4), which has a polymorphism associated with ADHD, is highly expressed in the retina and is involved in photo transduction (Kim et al., 2010). Interestingly, in rodents, DRD4 expression is circadian and under photoneural control, and DRD4 mRNA level in the pineal gland varies >100-fold from day to night compared with other brain areas (Kim et al., 2010). Since the pineal hormone melatonin feeds back to the circadian system through melatonin receptors in the suprachiasmatic nucleus, this suggests a potential interaction between the DRD4 receptor and the circadian system. We explained the negative SI-ADHD association to be mediated by neutralization of phase advancing of delayed circadian rhythms induced by environmental influences (evening exposure of blue "short wave length" light sources such as LED lights, PCs, and iPADs); these result in reduced sleep-duration and associated problems with attention, executive function, and externalizing behavior (for a review, see Arns, Feddema, & Kenemans, 2014; Arns & Kenemans, 2014). Bright sunlight during the day may preventively over-ride these effects of artificial blue light and result in lower PREV.

A meta-analysis in 690.747 children confirmed that children today sleep 1 hr 15 min less as compared to 100 years ago; however, when looking at geographical areas separately, they noted that " . . . positive rates of change [i.e., increases of sleep time] were found for Scandinavia, the UK and Australia, while negative rates of change [decreases of sleep time] were found for Asia, Canada, the USA and Europe . . . " (Matricciani, Olds, & Petkov, 2012). In 2010, Nikolaidis and Gray (2010) performed a meta-analysis on the DRD4 7R gene and ADHD-risk, and they found that indeed the 7R allele was associated with ADHD in Caucasians (odds ratio [OR] = 1.64), but there was significant heterogeneity, which was caused by two studies, one from Ireland and one from Norway (there was even a trend for the DRD4 7R allele being protective in these studies!). Excluding these two studies increased the odds ratios for Caucasians from OR = 1.64 to OR = 1.84, suggesting that the DRD4 7R–ADHD association is different for these

same Nordic regions. In addition, it has been found that rates of seasonal affective disorder (SAD) in Canada were lower for people of Icelandic descent (Axelsson, Stefánsson, Magnússon, Sigvaldason, & Karlsson, 2002). Taken together, these findings suggest that indigenous populations of Nordic areas are somehow "genetically protected" from the disruptive effects of blue light in the presence of low sunlight levels, most likely as they evolved against low levels of sunlight. Alternatively, the protection may come from the longer average sleep time or from a diet high in ocean fish and omega-3 fatty acids.

From the genetic point of view, variation in the DA receptor types D4 (DRD4) and D2 (DRD2) could be interesting and important. The DRD4 has functional variation due to polymorphism in a coding region: The number of repeats (R) of a 48 base pair variable number of tandem repeat (VNTR) sequence in Exon 3 produces variants in the receptor that differ in potency for inhibiting cAMP, with reduced potency for the variant coded by the 7R allele compared with the most common 4R allele. The 7R allele has been implicated as a risk gene in ADHD, and this is grounded in analysis of data from sequencing that revealed nucleotide patterns indicating positive selection (see Grady, Moyzis, & Swanson, 2005). The DRD2 has short (D_{2s}) and long (D_{2l}) isoforms that are primarily presynaptic and postsynaptic receptors, and their ratio is associated with the rs2283265 single nucleotide polymorphism (SNP). Recent studies demonstrated that the D2 and D4 receptors form heteromers (combinations) and that heteromerization depends on these genetic variants. The DRD4 7R receptor variant has reduced ability to form heteromers with the DRD2 D_{2l} receptor variant, and this dysfunctional heteromerization would further impair dopaminergic control of corticostriatal glutamatergic neurotransmission, which may underlie functional deficits in ADHD (González et al., 2011). Based on this hypothesis of allelic variation in DRD4-DRD2 heteromerization, an interaction of the DRD4 and DRD2 genes was predicted and confirmed in humans by Mota et al. (2013) for association with comorbid substance use in ADHD samples.

As mentioned above, DRD4 expression is circadian and under photoneural control, and a high expression of DRD4 in the pineal gland as compared with other brain areas has been reported (Kim et al., 2010). As the pineal hormone melatonin feeds back to the circadian system through melatonin receptors in the suprachiasmatic nucleus, this suggests there could be a potential interaction between these DRD4 genetic variants and the circadian system. The DRD4 7R allele also has a characteristic geographical distribution, with progressively higher prevalence in aboriginal ethnic groups in North America and South America associated with "the migratory distance out of Africa" (Chen, Burton, Greenberger, & Dmitrieva, 1999; Matthews & Butler, 2011), and a low prevalence in Asian ethnic groups, in which the DRD4 2R allele may be elevated and have functional characteristics similar to the DRD4 7R allele (Leung et al., 2005). Given the circadian expression of the DRD4 receptor, it would be interesting to investigate the interaction between SI and the DRD4 alleles in more detail. We expect that relative to the prevalence of the DRD4 7R allele, in geographical areas with high SI (e.g., Brazil, Spain), high SI could compensate for reduced potency of the 7R receptor variant by the effects on the circadian system and thus result in lower ADHD PREV.

In conclusion, although an interesting finding, the association between altitude and ADHD prevalence seems to be mediated by SI and not by altitude per se. Future studies should investigate details of the different DA genes and receptors and their interaction with SI and the biological clock. Additional interesting possibilities include the interaction of nutrients with SI and genes (e.g., effects of sunlight on available diet, such as fresh vegetables), fish consumption and the genome of Nordic populations, contribution of humidity (which may be confounded with SI), and influence of different climate-induced flora and fauna, including gut microbiome, interacting with genome.

Declaration of Conflicting Interests

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Note

1. Sourced from http://www.cdc.gov/ncbddd/adhd/prevalence.html

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