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Letter to the Editor **Open Access**

Do the ADHD subtypes exist on a physiological continuum? A reply to Reiersen and Todorov (2013)

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To the Editor:

Reiersen and Todorov (1) published their findings exploring the relationship between the various subtypes of attention-deficit/hyperactivity disorder (ADHD) and related psychopathologies in a large population-based sample of adolescents and children. The authors reported that subjects who presented with symptoms from both the inattentive subtype and the hyperactive subtype experienced a greater severity of co-occurring psychopathology. This led the authors to conclude that, although the continued clinical use of ADHD subtypes may be appropriate, these distinct diagnostic subtypes may be resulting in a failure to identify an important subgroup of ADHD patients—those who experience symptoms from both subtypes—and thus potentially leading to more severe psychopathological outcomes. The authors advised that upcoming editions of the *Diagnostic and Statistical Manual of Mental Disorders* be revised to include a diagnostic category of ADHD "not elsewhere classified."

In support of this idea, another recent meta-analysis qualified the role of hyperactivity in patients with ADHD (2) and indicated that hyperactivity may not be a ubiquitous feature of ADHD. Rather, its manifestation may be particularly dependent on environmental factors, including cognitive functioning demands. Prolonged cognitive load has been associated with sympathetic hyperactivity in healthy humans (3). Given that medication-naïve patients with ADHD experience parasympathetic overarousal (4), it may be that excessive motor activity is associated with sympathetic mechanisms that are affected by changing cognitive demands (5).

Other recent findings have corroborated an association between air pollution and childhood behavior problems (6). It has subsequently been suggested that chronic environmental exposure to the widespread and underestimated air pollutant nitrous oxide (N_2O) may be the primary etiologic factor in neurodevelopmental disorders like ADHD (7-9). Subanesthetic and subanalgesic N_2O exposures in humans have been characterized by impairments in attention and working memory (10,11) as well as by the induction of a parasympathetic dominant state (8), thereby suggesting that a compensatory hyperkinetic state may reverse these physiological effects (3,5).

When considering the role of hyperactivity in ADHD for the facilitation of sympathetic resuscitation, it may be important to consider the spontaneously hypertensive rat, which is a validated model of ADHD (12) before the onset of hypertension (i.e., sympathetic overflow) (13). It may therefore be reasonable to speculate that a hyperactive state precedes (in spontaneously hypertensive rats) and possibly potentiates (in humans) sympathetic resuscitation. This would imply that the various ADHD subtypes may not be exclusive conditions; rather, the subtypes may exist on a continuum in a significant contingent of patients with ADHD, as Reiersen and Todorov have found (1). Therefore, chronic environmental N_2O exposure may lead to attention deficits and a parasympathetic dominance, whereas a hyperkinetic phenotype may be a compensatory mechanism of sympathetic and cognitive resuscitation. However, a recent meta-analysis contradicts the notion of autonomic dysregulation and parasympathetic dominance in patients with ADHD (14). Therefore, the

relationship between the ADHD subtypes and chronic environmental N_2O exposure warrants further clarification to understand whether the subtypes exist on a physiological continuum in response to environmental exposure to N_2O.

Conflict of Interest
The author declares no conflict of interest.

Disclosure
Similar manuscripts related to this hypothesis may be under review, in press or published elsewhere, although the specific content contained in this manuscript is original and not in review or previously published. Relevant prior works are cited.

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