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Letter to the Editor
Exposure to nitrous oxide and intrusive memory formation in psychological trauma

Das *et al.* (2016) conducted a study to assess the effect of nitrous oxide (N_2O) on intrusions following a traumatic event. The researchers invited 50 adult participants to watch two graphic movie scenes, followed by a 30-min exposure of either 50% gas mixture of N_2O in oxygen or medical air. Participants kept a daily record of intrusive memories for a week following the traumatic exposure. The authors noted that the incidence of intrusions decreased by as much as 50% the day after viewing in the N_2O group. However, in participants experiencing dissociation following the traumatic event, N_2O exposure produced an increased intrusion frequency. These results led the authors to conclude that N_2O may speed the decline in intrusive memory frequency following a traumatic event, presumably through its inhibitory action on central glutamatergic signaling. Though, the reverse may be true in dissociated individuals, and this finding was underemphasized by the authors, as indicated by the study's title, and the subsequent media reports commenting on the study. This concern is underscored by previous paradoxical findings on the link between subanalgesic N_2O exposure and human memory.

Ramsay *et al.* (1992) reported that subjects breathing N_2O required a greater number of acquisition trials to reach a learning criterion (i.e., number–noun pairs). Though N_2O exposure during acquisition of material decreased accessibility of the information, the ability to recall the material 2 weeks later improved compared with placebo. Importantly, correlational analyses suggested that this enhanced N_2O-mediated delayed recall did not appear to be dependent on the increased number of trials during acquisition in the N_2O-exposed group. Taken together, these findings suggest that N_2O exposure during acquisition or in already dissociated individuals may affect enhanced delayed recall.

In addition to the links between N_2O exposure and memory, we have proposed through repeated epidemiological investigations and review that exposure to trace levels of environmental emissions of N_2O, which, in addition to its clinical usefulness, also acts as a pervasive agricultural and combustion air pollutant, may precipitate neurodevelopmental impairment in vulnerable populations. Our epidemiological investigations to date have associated the use of nitrogen fertilizers in agriculture – as the most concentrated source of environmental N_2O emissions – with hospitalization for attention-deficit hyperactivity disorder (ADHD), representing a severely impaired phenotype (Fluegge, 2016*a*; Fluegge & Fluegge, 2017). Our review of this novel hypothesis discussed the known physiological mechanisms of low-dose N_2O exposure from both *in vitro* and *in vivo* models, including disruption of the cholinergic system (Suzuki *et al.* 2003), endogenous release of dynorphin, and activation of the kappa opioid receptor (KOR) (Branda *et al.* 2000) as well as activation, at subanalgesic levels, of the corticotropin-releasing factor and brainstem noradrenergic nuclei (Zhang *et al.* 1999; Sawamura *et al.* 2003). Moreover, we cited preclinical animal studies and clinical evidence in human subjects demonstrating significant cognitive impairment and alterations in neurotransmission from trace levels of exposure to N_2O (Fluegge, 2016*a*). Additionally, chronic recreational N_2O may lead to psychiatric symptoms, including dissociation (van Amsterdam *et al.* 2015). These specific physiological targets may directly affect attention-related neural networking as well as neural correlates of trauma-related psychopathology (Fluegge, 2016*b*).

Pietrzak *et al.* (2014) conducted a novel brain-imaging study wherein they have linked the brain KOR to a constellation of symptoms among trauma victims. The authors administered a radioactive tracer to the KOR to all participants and compared the PET brain scans of healthy volunteers *v.* those clinically diagnosed with severe trauma-related psychopathology, including PTSD. Results indicated a negative correlation between KOR availability in the amygdala–anterior cingulate cortex–ventral striatal neural circuit and symptoms of loss (i.e., dysphoria), indicating that dynorphinergic excess may desensitize brain KOR, contributing to more intense dysphoric symptoms among prior trauma victims. Animal studies show that pharmacological KOR blockade administered before extinction sessions – and not before or after the conditioning – did not led to a decrease in freezing behavior in extinction sessions (Bilkei-Gorzo *et al.* 2012), confirming that excess dynorphinergic-mediated KOR desensitization or blockade may contribute to trauma-related psychopathology.

Chronic, intermittent exposure (i.e., 6 h/day, 5 days a week for 2 weeks) to trace levels of N_2O pollution

(i.e., as low as 50 ppm, 0.005%) decreased dopamine levels in the corpus striatum of CD-1 mice ($p < 0.05$) (Abdul-Kareem *et al.* 1991). The depression in dopamine levels may be associated with compensatory increases in striatal dynorphinergic activity (Steiner & Gerfen, 1998), given the role that dynorphin opioid peptides play in N_2O-mediated antinociception especially at low doses before higher order anesthetic mechanisms are induced (Branda *et al.* 2000). Collectively, these studies support the hypothesis that exposure to N_2O may affect memory formation in a time and exposure-dependent manner. Importantly, though, the extent of direct modulation of opioidergic signaling (i.e., KOR desensitization) after the traumatic event due to trace environmental N_2O-mediated dynorphinergic reactivity may not only enhance delayed recall among prior trauma victims, but also facilitate co-morbid psychiatric conditions, like ADHD (Spencer *et al.* 2016; Fluegge, 2016b), as our prior epidemiological investigations have discussed.

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Declaration of Interest

The author reports no conflict of interest relevant to this article to disclose.

Ethical Approval

This paper does not contain any studies with human participants or animals performed by the author.

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