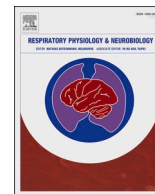




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Letter to the editor

**COVID-19 and its psychological consequences: Beware of the respiratory subtype of panic disorder**

Dear Editor,

The psychological toll of the current SARS-CoV-2 pandemic has now been widely acknowledged (Javelot et Weiner, 2020). Increased risk of post-traumatic stress disorder and obsessive-compulsive disorder has been reported in a number of studies (Javelot et Weiner, 2020). To date, however, very few studies have considered whether the current pandemic could predispose to the onset or the aggravation of panic attacks (PA) or panic disorder (PD), although the ‘panic’ word has been abundantly linked to the SARS-CoV-2 pandemic in the press (Javelot et Weiner, 2020). This is surprising given the predominance of respiratory symptoms in both COVID-19 and PD, on the one hand, and the generalized fear of contamination and fear of suffocation heightened by the pandemic, on the other hand.

There are several similarities between PA and normal fear reactions, both in terms of psychopathological features and neurobiological hypotheses. For example, in PA a vast number of respiratory symptoms (along with other cognitive and physiological symptoms) can be found, which are usually associated with normal fear responses triggered by a real threat (Freire et al., 2010). It has been observed in clinical trials and in PD challenge test studies that PA does not activate the hypothalamic-pituitary-adrenal axis, while this is the case in normal fear reactions (Freire et al., 2010). Nevertheless, a vast amount of data supports the connection between PD, normal fear reactions, and the respiratory system (Freire et al., 2010). For instance, a number of studies have found subclinical respiratory abnormalities in patients with PD, and, conversely, patients with respiratory disorders or intense fear reactions are more prone to develop PD. The not-so-long history of PD diagnosis in the medical literature has highlighted the importance of respiratory symptoms in PA whether they were associated with PD or not. Excessive fear reactions may present as PA, with respiratory symptoms as the main complaint (Zugliani et al., 2015).

When respiratory symptoms are predominant, i.e., the respiratory subtype, hyperventilation is associated with fear of suffocation – i.e., fear response conditioning to interoceptive respiratory sensations – which leads to hypervigilance to these interoceptive signals (Javelot et Weiner, 2020). Among the predisposing factors of the respiratory subtype of panic disorder, increased sensitivity to CO₂, family history of panic disorder, and history of traumatic suffocation events have been reported more often compared to “non-respiratory” panic disorder subtypes (Zugliani et al., 2015; Bouwer et Stein, 1997).

Among the data supporting the role of respiratory abnormalities as a core symptom of PA in patients with PD, heightened CO₂ sensitivity deserves special attention (Zugliani et al., 2015). A number of studies have shown that serotonergic neurons in the nucleus of the dorsal and ventrolateral periaqueductal grey matter modulate the behavioral and cardiorespiratory response to panicogenic agents such as sodium lactate and CO₂ (Javelot et Weiner, 2020). An abnormally sensitive fear network has been reported in patients with PD, including the hippocampus, the medial prefrontal cortex, the amygdala and its projections into the brainstem (Freire et Nardi, 2012). In the respiratory forms of PD in particular, key structures are found in the brainstem including the periaqueductal grey matter, which acts as a central suffocation alarm system, and the parabrachial nucleus, which is connected to the fear network by the amygdala and controls the respiratory rate (Javelot et Weiner, 2020).

Respiratory symptoms are identified by the general population as a core COVID-19 symptom. Dyspnea, even in its mildest forms, can induce a fear of suffocation and the anticipation of a worsening of symptoms, including acute respiratory distress syndrome (ARDS) and its most feared outcomes, i. e., hospitalization in intensive care units, intubation, and death (Javelot et Weiner, 2020). This, in turn, might heighten fear response, false alarms and exacerbate vigilance towards respiratory symptoms both in affected and unaffected individuals.

Given the relationship between “normal” fear responses and respiratory abnormalities in PA and PD, there is psychopathological and neurobiological evidence that the current COVID-19 pandemic might lead to an increase of cases of PA and PD, especially the respiratory subtype. For instance, patients affected by COVID-19 and who struggled with dyspnea and fear of suffocation might be particularly at risk for PD. Moreover, in those who were not affected by the virus, hypervigilance towards respiratory symptoms and fear of suffocation might also be involved in the onset or the aggravation of PD. This is even more likely to occur in patients with a history of anxiety disorder, with an anxious temperament and/or a preexisting respiratory-related disorder, such as hyperventilation syndrome.

Conflicts of competing interests

None.

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References

- Bouwer, C., Stein, D.J., 1997. Association of panic disorder with a history of traumatic suffocation. *Am. J. Psychiatry* 154, 1566–1570. <https://doi.org/10.1176/ajp.154.11.1566>.
- Freire, R.C., Nardi, A.E., 2012. Panic disorder and the respiratory system: clinical subtype and challenge tests. *Braz J Psychiatry*. 34 (Suppl 1), S32–S41. <https://doi.org/10.1590/s1516-44462012000500004>.
- Freire, R.C., Perna, G., Nardi, A.E., 2010. Panic disorder respiratory subtype: psychopathology, laboratory challenge tests, and response to treatment. *Harv. Rev. Psychiatry* 18, 220–229. <https://doi.org/10.3109/10673229.2010.493744>.
- Javelot, H., Weiner, L., 2020. Panique et pandémie : revue de la littérature sur les liens entre le trouble panique et l'épidémie à SARS-CoV-2. *Encephale* 46 (3S), S93–S98. <https://doi.org/10.1016/j.encep.2020.05.010>.
- Zugliani, M.M., Freire, R.C., Perna, G., Crippa, J.A., Nardi, A.E., 2015. Laboratory, clinical and therapeutic features of respiratory panic disorder subtype. *CNS Neurol. Disord. Drug Targets* 14, 627–635. <https://doi.org/10.2174/1871527314666150430163142>.

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