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LETTER TO THE EDITOR

Notes on establishing fear conditioning as causal in the postural orthostatic tachycardia syndrome

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We read, with great interest, the recent study by Norcliffe-Kaufmann and colleagues[1] exploring the possibility of fear conditioning underlying the postural orthostatic tachycardia syndrome (POTS). However, we feel the study falls short to fully justify its claims with regards to the aetiology of the syndrome.

The authors demonstrate convincingly that POTS patients respond to verticalization with tachycardia, increased catecholaminergic secretion, hyperventilation and lower middle cerebral arterial velocities compared to controls. In addition, two-thirds of the maximum heart rate variance upon verticalization can be associated with hypocapnia and somatic vigilance in a multivariate analysis, which demonstrates clustering of several of these features. As the authors rightfully point out in the 'Discussion' section of the paper, the data cannot resolve how each of these features relates to the symptomatology of these patients: are these features underlying POTS, or secondary to it?

In addition, they demonstrate that compared to controls, a statistically significant tachycardia occurs in POTS patients upon mere announcement of verticalization, indicative of fear conditioning. The authors rely on this finding to propose that POTS is a functional neurological disorder, since tachycardia is already induced by the notion of imminent verticalization rather than the positional change itself.

We think this observation must be placed in its proper context. First, the magnitude of the anticipatory change in heart rate (~8 beats/min in patients, Fig. 1A and B in Norcliffe-Kaufmann *et al.*[1]) is minor compared to the change upon actual verticalization (36 beats/min in patients, 11 beats/min in controls); this means that the response upon actual verticalization cannot directly be equated to the 'cortical' response alone. Second, these patients had a median illness duration of 49 months, indicating their profound acquaintance with the effects of verticalization. One wonders whether announcing a Dix-Hallpike test to patients with long-standing benign paroxysmal positional vertigo (BBPV) would induce a similar anticipatory tachycardia (and perhaps other features of sympathetic hyperactivity) compared to non-BPPV controls, despite BPPV at its core not being considered a functional neurological disorder. In summary, anticipatory fear and signs of sympathetic hyperactivity can be expected to arise as secondary phenomena in any patient well-acquainted with an affliction triggered by a stimulus, either when exposed or merely threatened by this particular stimulus. In fact, the patients with POTS may have been subjected to the tilt-table procedure as part of the diagnostic workup before their participation in the study, allowing fear for this procedure as well, presumably in contrast to the healthy controls.

In order to establish detrimental fear conditioning as an underlying causative factor in POTS, the modification of this putative cause should be associated with a change in the disease symptomatology. The authors suggest the clinical use of cognitive behavioural therapy: if proven to be effective, this would reinforce their hypothesis that anticipatory fear underlies POTS at least to a certain extent. However, these data are not yet available. Alternatively, repeating the tilt-table test with benzodiazepines may help separate the cognitive ('cortical') contribution to POTS from the contribution of e.g. the physiological baroreflex response.

A further analysis of one particular part of the already acquired data may also help to dissect the relation between the anticipatory fear and POTS. The spread of disease duration (49 ± 51 months) may allow the authors to analyse whether there is a correlation between disease duration and the occurrence (or magnitude) of the anticipatory response. Indeed, if one postulates that POTS requires this feature for its existence, no correlation is expected since it should be present from the clinical debut onwards; if, however, patients with a longer disease duration have grown more fearful of verticalization as a secondary phenomenon, this correlation may be manifest in the data.

In short, we believe that these findings, though interesting and novel, are insufficient to solidly establish POTS as a functional neurological disorder (or, perhaps even more appropriate, a stimulus-specific anxiety disorder). Nevertheless, we greatly encourage others in this field to further develop these provoking ideas, since they may ultimately help clinicians to offer the best treatment for POTS patients.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Competing interests

The authors report no competing interests.

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Reference

1. Norcliffe-Kaufmann L, Palma JA, Martinez J, Camargo C, Kaufmann H. Fear conditioning as a pathogenic mechanism in the postural tachycardia syndrome. *Brain*. 2022;145: 3763-3769.