

Orthostatic intolerance in hypermobile Ehlers-Danlos: Functional brain signature during lower body negative pressure

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Background / Objective

Ehlers-Danlos syndrome (EDS), a group of genetic connective tissue disorders, is often associated with orthostatic intolerance, particularly with POTS. However, the mechanisms mediating changes in cardiovascular autonomic control in these patients are not fully understood. To test the hypothesis that subcortical responses to orthostatic stress are altered, we applied functional MRI during lower body negative pressure (LBNP).

Methods

We submitted 20 individuals with hypermobile EDS and symptoms of orthostatic intolerance (15 women, 32.4 ± 8.0 years; 22.5 ± 4.2 kg/m²) and 20 matched healthy controls (12 women, 34.7 ± 10.2 years; 25.0 ± 3 kg/m²) to functional MRI scans at three LBNP levels (without pressure, -10 mmHg, -30 mmHg). We determined changes in functional connectivity by applying masked independent component analysis, followed by a dual regression using an analysis of variance and post-hoc two-sample t-tests.

Results

During LBNP, average blood pressure remained constant in both groups, whereas heart rate increased by 14 ± 10 bpm in Ehlers-Danlos and 6 ± 10 bpm in controls. Patients with EDS showed overall decreased functional connectivity between the spinal trigeminal and solitary nuclei and the left lateral hypothalamic area together with the ventromedial and supraoptic hypothalamic nuclei. Additionally, there was an interaction between groups and LBNP-level involving a functional connectivity between the inferior olivary and raphe pallidus nuclei and the left lateral and posterior hypothalamic areas. We observed another interaction effect within the hypothalamus. Finally, we observed functional connectivity differences between patients and controls in the major resting state networks.

Conclusion

We observed significant cortical and subcortical functional connectivity differences between patients with hypermobile EDS and healthy controls during an LBNP challenge. These differences comprised neuronal circuits regulating cardiovascular autonomic activity, which might contribute to orthostatic intolerance.