Brain structure and joint hypermobility: relevance to the expression of psychiatric symptoms

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Summary
Joint hypermobility is overrepresented among people with anxiety and can be associated with abnormal autonomic reactivity. We tested for associations between regional cerebral grey matter and hypermobility in 72 healthy volunteers using voxel-based morphometry of structural brain scans. Strikingly, bilateral amygdala volume distinguished those with from those without hypermobility. The hypermobility group scored higher for interoceptive sensitivity yet were not significantly more anxious. Our findings specifically link hypermobility to the structural integrity of a brain centre implicated in normal and abnormal emotions and physiological responses. Our observations endorse hypermobility as a multisystem phenotype and suggest potential mechanisms mediating clinical vulnerability to neuropsychiatric symptoms.

Declaration of interest
None.

Method
High-resolution (0.9 mm isometric voxels) structural brain MRI scans (192 sagittal slices, repetition time 11.4 ms, echo time 4.4 ms, inversion time 300 ms) were acquired using a Siemens Avanto 1.5 T scanner (Siemens, Erlangen, Germany) from 72 volunteers, free of clinical anxiety. The participants' characteristics are shown in online Table DS1. Objective measures of hypermobility, anxiety and interoceptive sensitivity (subjective awareness of internal bodily physiological responses) were acquired using the Beighton scale, Beck Anxiety Inventory (BAI) and Porges Body Perception Questionnaire (PBPOQ) respectively. Regional brain volumes were quantified using VBM incorporating diffeomorphic registration (DARTEL) within SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Voxel-wise comparisons of spatially normalised grey-matter volume maps of the hypermobile and non-hypermobile groups were performed within a general linear model treating age, gender, handedness and whole brain volume as potentially confounding covariates. Main effects of group, and within-group correlations with hypermobility score, are reported for all brain clusters of interest using 8 mm spheres centred on coordinates (27, −1, −19) and (−24, −2, −19), based on reported associations between amygdala and anxiety (see e.g. Hayano et al.). We report these results using a stringent family-wise error (FWE) volume-corrected threshold of $P < 0.05$. Resting supine heart rate was recorded for 5 min prior to scanning using a pulse oximeter (Nonin 8600Fo; Nonin Medical, Plymouth, Minnesota, USA) and heart rate variability was analysed using the Kubios HRV tool (University of Eastern Finland, Kuopio, Finland).

Results
Thirty-six participants scored 1 or more on the Beighton scale (the hypermobile group). There was no significant group difference in age, gender or handedness. Bilateral amygdala volume was significantly greater in the hypermobile group than in the non-hypermobile group, meeting both uncorrected ($P < 0.001$) and small-volume corrected FWE thresholds (right amygdala $P = 0.014$; left amygdala $P = 0.021$) (Fig. 1, online Table DS2). Cohen's $d$ effect sizes were large for the amygdala bilaterally (left 0.80, right 0.85). Other group volumetric differences are reported in online Table DS2 and included regions within anterior cingulate and parietal cortices.

Within the hypermobile group, degree of hypermobility correlated positively with the volume of left lateral occipital cortex and negatively with right superior temporal cortex and bilateral inferior parietal cortices (online Fig. DS1, Table DS2). Interestingly, this group scored significantly higher for interoceptive sensitivity (mean PBPOQ scores: non-hypermobile 88.4, s.d. = 31.0; hypermobile 104.3, s.d. = 32.2; $t_{(1,70)} = 2.13$, $P = 0.018$) and showed a trend towards higher anxiety (non-hypermobile 6.47, s.d. = 7.0; hypermobile 9.31, s.d. = 9.7; $t_{(1,70)} = 1.42$, $P = 0.08$). The relationship between hypermobility and interoceptive sensitivity persisted after controlling for anxiety differences ($P = 0.041$). There was no significant group difference in resting heart rate, standard deviation of interbeat interval, or high (parasympathetic) or low (predominantly sympathetic) frequency components of heart rate variability.

Discussion
We observed structural differences in key emotion-processing brain regions. Notably, the effect size of this amygdala volume difference was comparable to, or greater than, observations from volumetric studies of clinical psychiatric populations. The hypermobile group also displayed decreased volume within other regions implicated in emotional arousal and attention (anterior cingulate, parietal lobe). Moreover, the degree of hypermobility was associated with...
correlated negatively with superior temporal volume, a region implicated in processing social and emotional signals. Differences in brain structure were not due to overt psychopathology (the hypermobile group only trended toward higher anxiety scores) or basal physiology (no difference was observed in cardiovascular measures at rest).

Our data implicate the amygdala as a likely neural substrate mediating previously reported clinical associations between hypermobility, anxiety and psychosomatic conditions. Speculatively, potential mechanisms include heightened susceptibility of individuals with hypermobility to (threat of) pain and/or a perturbation of autonomic control. Differences in amygdala activity occur in pain disorders including fibromyalgia, irritable bowel syndrome and chronic regional pain syndrome. Anxiety itself is also linked theoretically to the abnormal generation and mapping of bodily arousal through the engagement of amygdala and insula. It is also noteworthy that the hypermobility group showed structural differences within anterior cingulate cortex, a central driver of autonomic arousal and a region implicated in the cognitive control of pain and negative emotions. Enhanced interoceptive sensitivity also points to a more finely tuned sensory integration and may have a common basis in collagen variants), heart rate tachycardia syndrome, which commonly occurs with hypermobility and exaggerated cardiovascular arousal responses. Moreover, in postural perturbation of autonomic control. Differences in amygdala show structural differences within anterior cingulate cortex, a central driver of autonomic arousal and a region implicated in the cognitive control of pain and negative emotions. Enhanced interoceptive sensitivity also points to a more finely tuned sensory integration and may have a common basis

findings suggest that processes compromising function in developmental conditions may occur in individuals with hypermobility, putatively enhancing vulnerability to stress and anxiety.

Limitations to our study include the use of a non-clinical sample; interestingly, neuroimaging studies of clinical anxiety groups rarely report enlarged amygdala, suggesting that hypermobility is a distinct phenotype or that amygdala enlargement might be protective in our non-clinical group. Additionally, we used an inclusive definition of hypermobility, although the categorisation of this condition remains debatable. To conclude, we present the first neuroimaging study of hypermobility that also examines autonomic and interoceptive indices. The observed differences in the structural integrity of specific emotional brain regions provide a starting point for future research into constitutional vulnerabilities to common psychiatric symptoms that have the potential to inform more individually tailored therapeutic approaches.