

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

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### Abstract

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.

Joint hypermobility is a common but often poorly recognised connective tissue condition.<sup>1</sup> Individuals with hypermobility are (up to 16 times) overrepresented among those with panic or anxiety disorders.<sup>2</sup> Hypermobility is also linked to stress-sensitive psychosomatic disorders including irritable bowel syndrome, fibromyalgia and chronic fatigue and is associated with hypersensitivity to nociceptive stimuli.<sup>1</sup> Additionally, individuals with hypermobility often exhibit autonomic abnormalities, typically postural tachycardia syndrome, where there is enhanced cardiovascular reactivity and a phenomenological overlap with anxiety disorders.<sup>3</sup> Thus, direct and indirect evidence links hypermobility to anxiety and stress-sensitive medical disorders. Within a programme of research motivated to detail the theoretical contribution of central autonomic control to emotion regulation and psychiatric disorders,<sup>4,5</sup> we performed a voxel-based morphometry (VBM) study of brain magnetic resonance imaging (MRI) scans in

participants with and without hypermobility, none of whom had an anxiety disorder.

## Method

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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 from 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)<sup>4</sup> were acquired using the Beighton scale, Beck Anxiety Inventory (BAI) and Porges Body Perception Questionnaire (PBPQ) respectively.<sup>6–8</sup> Regional brain volumes were quantified using VBM incorporating diffeomorphic registration (DARTEL) within SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>).<sup>9</sup> 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  $\geq 10$  contiguous voxels with significance threshold  $P < 0.001$  uncorrected. Left and right amygdala were defined *a priori* regions 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.*)<sup>10</sup> 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 8600F0; Nonin Medical, Plymouth, Minnesota, USA) and heart rate variability was analysed using the Kubios HRV tool (University of Eastern Finland, Kuopio, Finland).

## Results

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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 PBPQ 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 inter-beat interval, or high (parasympathetic) or low (predominantly sympathetic) frequency components of heart rate variability.

## Discussion

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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 correlated negatively with superior temporal volume, a region implicated in processing social and emotional signals.<sup>11</sup> 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 hyper-mobility, 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.<sup>12</sup> Anxiety itself is also linked theoretically to the abnormal generation and mapping of bodily arousal through the engagement of amygdala and insula.<sup>5</sup> 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.<sup>4,12</sup> Enhanced interoceptive sensitivity also points to a more finely tuned sensory representation of internal bodily signals within the hypermobile group. Heightened interoceptive awareness is coupled to exaggerated cardiovascular arousal responses.<sup>13</sup> Moreover, in postural tachycardia syndrome, which commonly occurs with hypermobility (and may have a common basis in collagen variants), heart rate acceleration compensates for dysfunctional vasoconstriction giving rise to physiological symptoms (e.g. palpitations and light-headedness) that are shared with panic and anxiety states.<sup>3</sup> Such deregulated responses are likely to affect neural processes supporting emotional feelings.<sup>4,5</sup>

Differences in the structural integrity of temporal and parietal cortices may underlie wider behavioural phenotypical expression of hypermobility: abnormalities in superior temporal cortex are also seen in autism.<sup>11</sup> Inferior parietal cortex can affect proprioceptive awareness and hypermobility is itself linked to dyspraxia.<sup>1</sup> Our findings suggest that processes compromising function in neuro-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.<sup>14</sup> 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.

## Footnotes

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### Declaration of interest

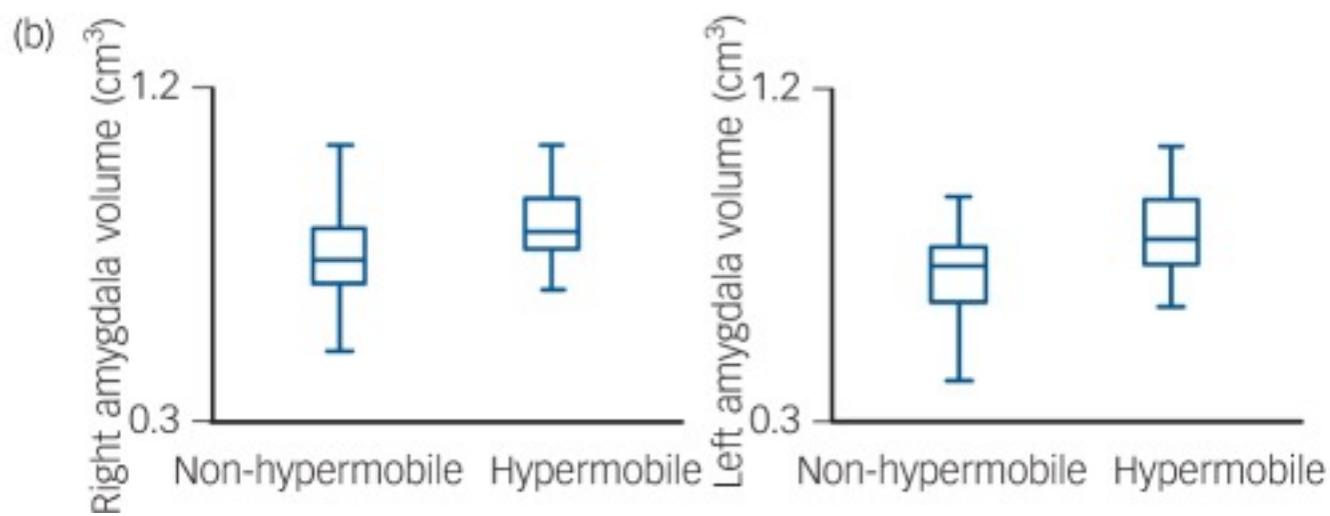
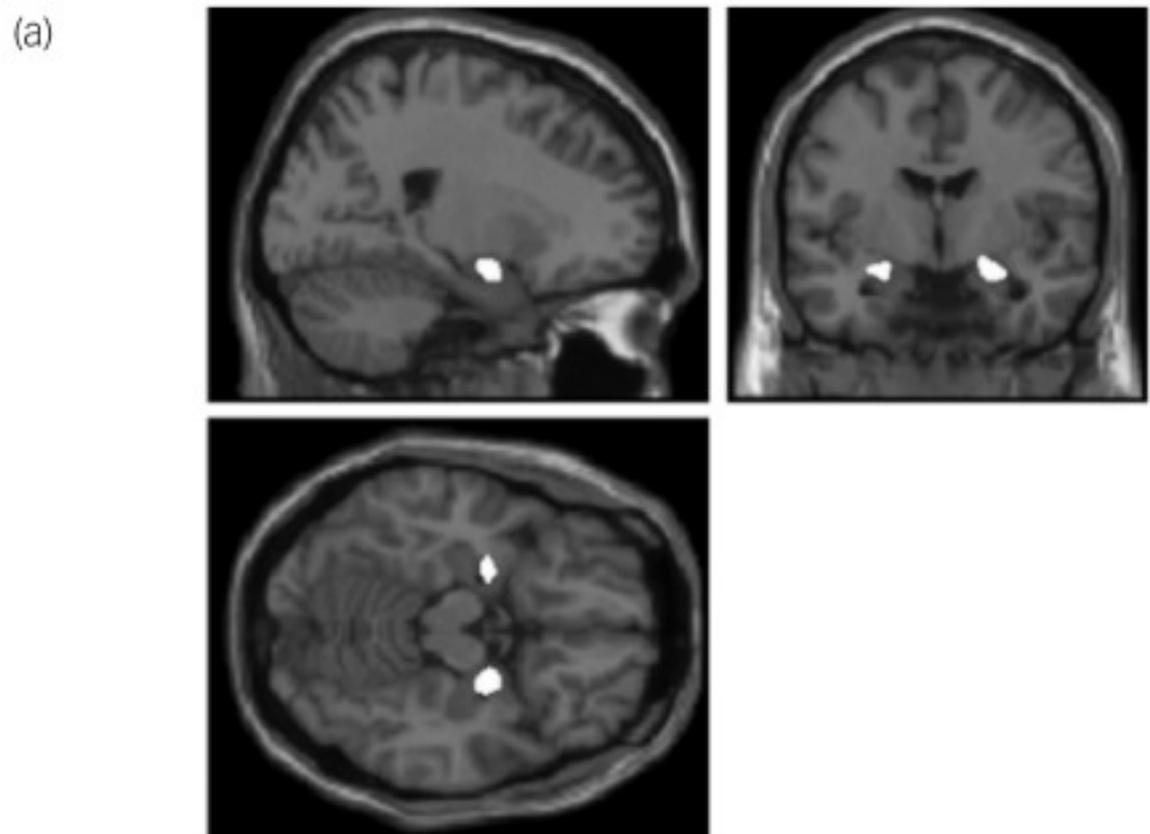
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**Figures and Tables****Fig. 1**



(a) Regions of grey-matter volume difference in hypermobile participants compared with the non-hypermobile group (white areas; threshold  $P < 0.001$  uncorrected). (b) Significant group differences in right and left amygdala volumes.