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Original article

Emotion processing in joint hypermobility: A potential link to the neural bases of anxiety and related somatic symptoms in collagen anomalies

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ABSTRACT

Background: Joint hypermobility syndrome (JHS) has repeatedly been associated with anxiety and anxiety disorders, fibromyalgia, irritable bowel syndrome and temporomandibular joint disorder. However, the neural underpinnings of these associations still remain unclear. This study explored brain responses to facial visual stimuli with emotional cues using fMRI techniques in general population with different ranges of hypermobility.
Methods: Fifty-one non-clinical volunteers (33 women) completed state and trait anxiety questionnaire measures, were assessed with a clinical examination for hypermobility (Beighton system) and performed an emotional face processing paradigm during functional neuroimaging.
Results: Trait anxiety scores did significantly correlate with both state anxiety and hypermobility scores. BOLD signals of the hippocampus did positively correlate with hypermobility scores for the crying faces versus neutral faces contrast in ROI analyses. No results were found for any of the other studied ROIs. Additionally, hypermobility scores were also associated with other key affective processing areas (i.e. the middle and anterior cingulate gyrus, fusiform gyrus, parahippocampal region, orbitofrontal cortex and cerebellum) in the whole brain analysis.
Conclusions: Hypermobility scores are associated with trait anxiety and higher brain responses to emotional faces in emotion processing brain areas (including hippocampus) described to be linked to anxiety and somatic symptoms. These findings increase our understanding of emotion processing in people bearing this heritable variant of collagen and the mechanisms through which vulnerability to anxiety and somatic symptoms arises in this population.

1. Introduction

Joint hypermobility syndrome (JHS) is an inherit connective tissue condition that represents a qualitative variation in the structural protein collagen. The estimated prevalence of JHS in the general (Western European) population ranges between 10–15% [4,24] and it is more frequent in women (3:1). Although JHS is a common and disturbing disorder, it remains poorly recognised.

Our research group found an overrepresentation of JHS among people with anxiety but especially among the so-called endogenous anxiety disorders (i.e.: panic, agoraphobic and social phobia) [5,8]. Also, individuals with JHS often present stress-sensitive illnesses such as irritable bowel syndrome, fibromyalgia,

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temporomandibular joint disorder and chronic fatigue syndrome [16] as well as autonomic abnormalities [28]. Likewise, JHS is also overrepresented among the general population with a high range of trait anxiety [9] and it has recently been described as a risk factor for developing anxiety disorders in a longitudinal study [10].

The mechanisms underlying the association between JHS and anxiety-related disorders are still unclear. However, a structural neuroimaging study of healthy non-anxious individuals have shown that people with features of hypermobility manifest larger amygdala volume bilaterally compared to participants without any hypermobility [11]. Furthermore, recent findings revealed interoceptive sensitivity mediated the relationship between state anxiety and hypermobility in a non-clinical sample. Also in this last study the hypermobile participants, when compared to the non-hypermobile, displayed heightened neural reactivity to sad and angry scenes within brain regions implicated in anxious feeling states; notably insular cortex [21].

The aim of the present study was to characterize how hypermobility scores are associated with brain activity in response to facial stimuli with emotional cues. Facial expressions are a classical way to probe automatic emotional responses [6]. We hypothesize that hypermobility measures will be positively correlated with higher anxiety measures and with a higher BOLD signal in key affective processing regions that could underlie anxiety and somatic symptoms (i.e.: amygdala, hippocampus, insular cortex, and anterior cingulate cortex) [1,7,18,27,30] in response to stimuli with higher emotional contents.

2. Method

2.1. Participants

Sixty-eight right handed non-clinical volunteers (thirty-nine women) were recruited for the study. All participants were evaluated through a medical and psychiatric history as well as assessed by two structured clinical diagnostic interviews [13,25]. None of the participants had taken psychotropic medication in the previous 12 months or had any pathology that could interfere in the hypermobility assessment. Four participants were excluded for neurological or psychiatric reasons. Thirteen more subjects were omitted from the analysis due to movement artefacts in the MR images. The final sample consisted of fifty-one participants free from any Axis I disorder, psychotropic medication or any other pathology that could interfere in the fMRI paradigm brain response and/or in the hypermobility assessment. All volunteers were given a complete description of the fMRI and clinical examination before written informed consent was obtained, and all of them voluntarily agreed to take part in the study. Parc de Salut Mar Barcelona clinical research ethical committee approval was obtained.

2.2. Measures

Participants were screened and evaluated through a medical and psychiatric history as well as assessed by the MINI structured diagnostic interview [25] and the Structured clinical interview for Axis I (SCID-I) [13]. The fifty-one non-clinical participants of the final sample completed the Spielberg state-trait anxiety inventory (STAI) [29], conducted a functional imaging task and were assessed with the Beighton exploration for hypermobility [3]. The Beighton clinical exploration of hypermobility requires a physical examination that was conducted by a trained and experienced clinician (according to the basis of the clinical rheumatologists' standards, kappa inter-examiners reliability ranged from 0, 8 to 1). The Beighton scoring system consists of five items (describing nine movements), that explores the joint mobility range of 5 body areas: wrists/thumb, knees, spine/hips, paired elbows and fifth meta-carpo-phalangeals. The highest score is nine and an accepted cut-off point is 4/5 (man/women).

2.3. Functional imaging task

Participants were trained on the emotional face task before the fMRI session. During the acquisition the volunteers participated in an event-related paradigm of emotional facial stimuli in which two groups of images were presented: 14 images of crying faces and 14 images of neutral faces. Images were derived from the Gur et al. series and supplemented with similar valence-matched images [17]. The stimuli were displayed for 1500 ms, followed by an interstimulus interval of between 750 to 1300 ms, with mean trial duration of 2500 ms. Pictures presentation was completely randomized for each participant. Participants performed an incidental task: they were instructed to press a button with their right hand when an adult face was presented and with their left hand when they saw an infant.

2.4. Image acquisition parameters

Images were acquired in a Philips Achieva 3T scanner. T1-weighted images were obtained using a FSPGR sequence (TR: 8.2 ms, TE: 3.7ms, FA: 8°, matrix size: 256 × 256 × 180, voxel size: 0.94 × 0.94 × 1.00 mm, gap: 0 mm). An EPI-T2* sequence allowed obtaining the functional volumes, each comprising 30 three mm-thick slices (TR 3000 ms, TE: 35 ms, FA: 90°, in-plane voxel size 1.80 × 1.80 mm, Slice thickness 3.0 mm, gap = 1.0 mm, matrix size: 128 × 128, 30 slices).

2.5. Image processing

Images were pre-processed within SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB 7.14 (Mathworks Inc. Sherborn, M.A.). The first three volumes of each session were discarded to remove non steady-state effects. Head motion correction was carried out by means of spatial interpolation, employing parameters derived from a six-parameter rigid body transformation with a least squares algorithm. Functional images were realigned to the first volume, normalized to the MNI EPI template, and smoothed with a12 mm FWHM kernel using SPM8.

2.6. Statistical analysis

At the first level of analysis, voxel-wise changes in Blood-oxygen-level dependence (BOLD) response across conditions were assessed for each subject and analysed according to the general linear model. The regressors of interest were convolved with the canonical hemodynamic response function implemented in SPM and optimal parameter estimates were computed using a least squares function. A linear contrast crying face > neutral face (corresponding to an increased BOLD response for the crying faces as compared to neutral faces) was applied to estimate the effect sizes for each participant and generate the associated statistical parametric map. Second level analyses were implemented for the main studied variable (i.e.: hypermobility scores) and the established crying face > neutral face contrast. We checked for the dependence of the contrast values on the hypermobility scale values. This was done using SPM, by introducing the hypermobility scale as a covariate in a one-sample t-test of the entire sample. We then evaluated the effect of this covariate by converting the beta coefficient to a *t*-score (*P*-value threshold was set at 0.05, FWE-corrected). We studied hypermobility as a continuous variable because we wanted to explore the whole spectrum of joint