Common and dissociable contributions of alexithymia and autism to domain-specific interoceptive dysregulations – a dimensional neuroimaging approach

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Supplementary Methods and Materials for Review

Subjects

252 healthy, right-handed Chinese students participated in the experiment after providing written informed consent. Four subjects were excluded due to excessive head motion during fMRI acquisition (>3 mm or 3 degrees). Data from6 subjects were lost due to technical failure. Consequently, data from n = 242 subjects was included in the final analyses (122 males; mean age, 21.60 ± 2.35 years). All subjects were free from current or a history of physical, neurological, or psychiatric disorders. Subjects were excluded in case they reported regular or current use of nicotine, alcohol, illicit drugs and medication. The study procedures were approved by the local ethics committee at the University of Electronic Science and Technology of China (UESTC) and in accordance with the revision of the Declaration of Helsinki.

fMRI paradigm and Stimuli

The pain empathy networks were assessed using a modified version of validated pain empathy paradigm. The block-design fMRI paradigm incorporated previously validated visual stimuli including pictures displaying painful everyday scenes from a first-person perspective (physical pain) and painful facial expressions (affective pain) as well as corresponding non-painful control stimuli for both stimuli types [1, 2]. All physical pain stimuli showed a person's hand or foot in painful everyday situations from a first-person perspective (e.g. cutting a hand with a knife, the matched non-painful control stimulus shows cutting vegetables with a knife) [2]. The affective stimuli consisted of painful and neutral expressions from 16 Chinese subjects (8 males). In previous studies, both painful stimuli sets have been rated as more painful and increased activity in the pain empathy networks relative to the control stimuli [1, 2, 3].

For the present study, a total of 64 pictures were included (16 per experimental condition: physical pain/affective pain/physical control/affective control). The block design incorporated 16 blocks (4 blocks per condition) with 4 stimuli per block from the same category (each presented for 3s), and the blocks were interspersed by a jittered inter-block interval of 10s (8-12s). Total duration of the paradigm was 436s acquired in a single fMRI run. In order to minimize interference by cognitive processing, subjects were instructed to passively view the stimuli during scanning.

Alexithymia and autism scales and quality assessment

To determine common and distinct contributions of alexithymia and autism to the neural pain

empathic responses, levels of trait autism and alexithymia were assessed using validated Chinese versions of the Autism Spectrum Quotient (ASQ) [4] and Toronto Alexithymia Score (TAS) [5]. Cronbach's α scores in the present sample were 0.744 for ASQ and 0.817 for TAS. Assessing the normal distribution of the scales revealed that ASQ scores in the present sample were non-normal distributed (Shapiro-Wilk test, $p < 0.05$), to this end associations with neural indices were determined using non-parametric approaches [6]. ASQ and TAS scores were positively associated in the present sample ($r$ho = 0.408, $p < 0.001$), therefore the variance inflation factor (VIF) was assessed to test for problematic collinearity [6, 7]. VIF in present study was 1.21, arguing against problematic collinearity [8, 9].

Image Acquisition

MRI data were collected using a 3.0 Tesla GE MR750 system (General Electric Medical System, Milwaukee, WI, USA). A total of 218 functional volumes of T2*-weighted echo planar images were obtained for each subject using the following acquisition parameters: repetition time, 2000ms; echo time, 30 ms; slices, 39; slice-thickness, 3.4mm; gap, 0.6mm; field of view, 240 × 240 mm^2; matrix size, 64 ×64; flip angle, 90°.High-resolution whole-brain volume T1-weighted images were additionally acquired to improve normalization of the functional images (spoiled gradient echo pulse sequence with oblique acquisition, acquisition parameters: repetition time, 6 ms; echo time, minimum; flip angle, 9°; field of view =256 × 256 mm; acquisition matrix, 256 × 256; thickness, 1 mm; 156 slices).OptoActive MRI headphones (http://www.optoacoustics.com/) were used to reduce acoustic noise exposure for the participants MRI acquisition.

MRI data analysis – preprocessing and whole-brain analyses

fMRI data processing

fMRI data were analyzed using SPM12 software (Wellcome Trust Center of Neuroimaging, University College London, London, United Kingdom). The first ten volumes were discarded to (1) achieve magnet-steady images and (2) allow active noise cancelling by the headphones. The remaining functional images were realigned to correct for head motion, co-registered with the T1-weighted structural images and normalized using the segmentation parameters from the structural images to Montreal Neurological Institute (MNI) standard space. Normalized images were written out at $3mm^3$ voxel size and spatially smoothed using a Gaussian kernel with full-width at half-maximum (FWHM) of 8mm.

On the first level, the four experimental conditions, 'physical pain', 'affective pain', 'physical control' and 'affective control' were modeled using a box-car function subsequently convolved with the standard hemodynamic response function (HRF). The six head-motion parameters were included in the design matrix to further control for movement-related artifacts. Specific contrast images between painful and non-painful conditions were created for each subject (physical pain>physical control, affective pain>affective control). To examine associations with distinct brain networks engaged in physical and affective pain [10, 11, 12], the interaction contrast [(physical pain>physical control) > (affective pain>affective control)] was considered as main contrast of interest.

Given that the ASQ scores in the present sample were non-normal distributed (Shapiro-Wilk test, $p < 0.05$), non-parametric tests were employed using the Statistical nonParametric Mapping toolbox (SnPM13, http://warwick.ac.uk/snpm) based on 10,000 random permutations to implement separate regression analysis for ASQ, TAS and their interaction [6]. For the three regression models, one of the values was entered as predictor whereas the other two terms were entered as additional regressors of no interest. Results were thresholded at $p < 0.05$ FWE-corrected on the cluster level. In line with recent recommendations for the control of false-positives in cluster-based correction methods [13], an initial cluster-forming threshold of $p < 0.001$ (uncorrected) was employed. Analyses were restricted to voxels with a high probability to represent gray matter (SPM gray.nii> 0.3).

Further analysis: extraction of parameter estimates and moderation

To further disentangle and visualize associations between the predictors and empathy related neural activity, parameter estimates were extracted from significant clusters using MarsBaR. The differences of associations between (physical pain>physical control) contrast and (affective pain>affective control) contrast were computed using percentile bootstrap [14] based on 10,000 times bootstrap, which is used to compare dependent correlation coefficients. To further disentangle the alexithymia × autism interaction, a moderation analysis was conducted using the SPSS 22 PROCESS macro. Using the Johnson-Neyman approach [15], the moderation variable was cut into three levels to visualize the interaction: high group (1 standard deviation above the mean scores), middle group (mean scores), and low group (1 SD below the mean scores).

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