**Altered gray matter volume and structural co-variance in adolescents with social anxiety disorder: evidence for a delayed and unsynchronized development of the fronto-limbic system**

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**Supplementary Materials**

**1. Ruling out the effects of TIV by including it as a covariate in the statistical analysis**

In the VBM analysis, both the affine and non-linear parts were modulated during the spatial normalization and the estimated TIV was included in the statistical model that examined group differences. All other procedures were kept the same as the original method in the manuscript.

As shown in Table S1, as the p-values were slightly different (as expected), the significance level was set at FWE-corrected *p* < 0.05 (one-tailed testing) and the regions showing significant group difference were consistent between the two TIV-correction methods in our study.

**Table S1** The significant clusters in voxel-based morphometry analysis by including TIV as a covariate between SAD and HC.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Cluster index | Anatomical labela | Hemisphere | Cluster size | Effect size (95% confidence interval )b | Peak coordinates (X Y Z) | Peak *p*-value (FWE corrected) |
| 1 | superior OFC | R | 328 | 0.75 (0.26, 1.24) | (16, 28, -27) | 0.016 |
| 2 | middle/superior OFC | L | 187 | 0.61 (0.13, 1.09) | (-27, 62, -10) | 0.040 |
| 3 | middle/inferior OFC | L | 170 | 0.74 (0.26, 1.23) | (-46, 45, -9) | 0.043 |
| 4 | insula | L | 288 | 0.70 (0.21, 1.18) | (-39, -12, 9) | 0.028 |

a The anatomical labels of clusters were based on the AAL parcellation. OFC, orbitofrontal cortex; R, right; L, left.

b The effect size (measured by Cohen’s d) and its confidence interval were calculated using the mean gray matter volume within the clusters.

**2. Ruling out the influence of symptom severity on structural co-variance analysis**

After controlling the SCARED total scores, for the HC group, there were still widespread significant co-variance between the left and right amygdala (*r* = 0.84, FDR corrected *p* < 0.001), between the left amygdala and left insula (*r* = 0.48, FDR corrected *p* = 0.013), between the left amygdala and right superior OFC (*r* = 0.43, FDR corrected *p* = 0.026), between the right amygdala and left insula (*r* = 0.53, FDR corrected *p* = 0.0058), between the left insula and right superior OFC (*r* = 0.60, FDR corrected *p* = 0.0015), and between the left insula and left middle/superior OFC (*r* = 0.41, FDR corrected *p* = 0.034). For the SAD group, there were significant co-variance between the bilateral amygdala (*r* = 0.82, FDR corrected *p* < 0.001), and between the left insula and right superior OFC (*r* = 0.52, FDR corrected *p* = 0.021).

For the group difference, there was a significant positive correlation between the left middle/superior OFC and left insula in HC (*r* = 0.41，FDR corrected *p* = 0.034), which was attenuated in adolescents with SAD (*r* = -0.18，FDR corrected *p* = 0.61). The group difference was marginally significant (Z = 2.38, FDR corrected *p* = 0.069, uncorrected *p* = 0.017). No group differences were identified in other structural co-variances.

After controlling the SASC total scores, for the HC group, there were still widespread significant co-variance between the left and right amygdala (*r* = 0.83, FDR corrected *p* < 0.001), between the left amygdala and left insula (*r* = 0.48, FDR corrected *p* = 0.013), between the left amygdala and right superior OFC (*r* = 0.42, FDR corrected *p* = 0.035), between the right amygdala and left insula (*r* = 0.53, FDR corrected *p* = 0.0062), between the left insula and right superior OFC (*r* = 0.59, FDR corrected *p* = 0.0020), and between the left insula and left middle/superior OFC (*r* = 0.41, FDR corrected *p* = 0.035). For the SAD group, there were significant co-variance between the bilateral amygdala (*r* = 0.83, FDR corrected *p* < 0.001), and between the left insula and right superior OFC (*r* = 0.49, FDR corrected *p* = 0.044).

For the group difference, there was a significant positive correlation between the left middle/superior OFC and left insula in HC (*r* = 0.41，FDR corrected *p* = 0.035), which was attenuated in adolescents with SAD (*r* = -0.22，FDR corrected *p* = 0.45). The group difference was marginally significant (Z = 2.53, FDR corrected *p* = 0.046). No group differences were identified in other structural co-variances.

In general, the group difference in structural co-variance reported in the manuscript remained after controlling the effects of symptoms severity.