Supplemental Information

Secondary analyses

Secondary analyses of extracted cluster data with other clinical and demographic variables were conducted within SPSS. Group contrast results remained significant or near significant when covaried for IQ, Tanner stage, depressive symptoms, general anxiety symptoms, and past months of exposure to ADHD and antidepressant medication (right vmPFC group main effect: $F_{1,41} = 3.56$, $p = 0.07$; right anterior hippocampus group X age interaction: $F_{1,40} = 11.35$, $p < 0.01$; right fusiform group main effect: $F_{1,40} = 10.89$, $p < 0.01$; left fusiform group main effect: $F_{1,41} = 8.08$, $p < 0.01$; left occipital clusters group main effect: $F_{1,40} = 5.56$, $p < 0.05$ and $F_{1,40} = 7.36$, $p < 0.05$). Within the PTSD group, the right sgACC and right anterior hippocampus volumes remained significantly inversely correlated with re-experiencing symptoms with the additional covariates above (adjusted $r = -0.81$ and -0.82 respectively, $p < 0.001$). Finally, re-analysis of the group contrast including sex as a variable of interest revealed no group X sex, or group X age X sex interactions.

Next, we conducted analyses within the PTSD group using multivariate regression to examine the relationship of each cluster to trauma exposure and PTSD variables. The model included age, sex, PTSD cluster B/C/D symptoms, PTSD duration, number of trauma types experienced, and time elapsed since the initial index trauma. Collinearity statistics were all within acceptable range (tolerance>0.1, VIF<5). Significant and trend-level findings are summarized in Table 2. With regard to trauma exposure measures, the only significant relationship was an inverse correlation between left occipital GMV and number of trauma types (std. $\beta = -0.74$). In contrast, PTSD measures showed associations with multiple clusters. PTSD duration was significantly inversely correlated with anterior vmPFC GMV (Figure S3), with a similar trend in the group X age hippocampal cluster (std. $\beta = -0.66$ and -0.54, respectively). Subgenual ACC and hippocampal GMV remained inversely correlated with re-experiencing symptoms, but also

showed relationships with other PTSD symptoms in the post-hoc regression. Here, sgACC and hippocampal GMV were both positively correlated with avoidance symptoms (std. β= 0.57 and 0.72, respectively), but showed differing associations with hyperarousal symptoms (std. β= -0.30 and 0.31, respectively). A repeat of these analyses substituting total PTSD severity for symptom cluster scores revealed no significant associations with total PTSD severity. In addition, partial correlations (controlled for age and sex) revealed no significant associations between vmPFC or hippocampal GMV and depressive or general anxiety symptoms ($p>0.25$, Figure S4). Finally, we examined potential effects of index trauma type by conducting a post-hoc GLM on the PTSD subgroups divided by index trauma type, controlling for age, sex, and number of trauma types experienced. We found no significant differences in cluster GMV among index trauma subgroups.

Discussion

Outside of our a priori regions, we found reduced GMV in visual processing areas in pediatric PTSD. Reduced gray matter volumes of the fusiform gyrus and occipital cortex have been observed in young adults with a history of childhood sexual abuse or witnessing domestic violence (Tomoda *et al*, 2009, 2012). However, other studies have suggested increased occipital cortex gray matter volume in children with a history of physical abuse (Hanson *et al*, 2010) or post-traumatic stress symptoms (Carrion *et al*, 2009). In none of these studies was fusiform/occipital cortex GMV related to symptoms of mental illness. This suggests that volume changes in visual areas may be a more general consequence of exposure to traumatic events in childhood, and may not play a causal role in the pathophysiology of pediatric PTSD. Consistent with this interpretation, our post-hoc analyses revealed an inverse correlation between occipital cortex volume and number of trauma types experienced, while there was no significant relationship with PTSD measures in any of the visual processing areas identified. Clearly,

more work will be needed to determine both the direction of volume change in visual processing areas and their functional significance following pediatric trauma and PTSD.

References

Carrion VG, Weems CF, Watson C, Eliez S, Menon V, Reiss AL (2009). Converging evidence for abnormalities of the prefrontal cortex and evaluation of midsagittal structures in pediatric posttraumatic stress disorder: an MRI study. *Psychiatry Res* **172**: 226–234.

Hanson JL, Chung MK, Avants BB, Shirtcliff EA, Gee JC, Davidson RJ, *et al* (2010). Early stress is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and behavioral risk. *J Neurosci* **30**: 7466–7472.

Tomoda A, Navalta CP, Polcari A, Sadato N, Teicher MH (2009). Childhood sexual abuse is associated with reduced gray matter volume in visual cortex of young women. *Biol Psychiatry* **66**: 642–648.

Tomoda A, Polcari A, Anderson CM, Teicher MH (2012). Reduced visual cortex gray matter volume and thickness in young adults who witnessed domestic violence during childhood. *PLoS ONE* **7**: e52528.

Supplemental Figures

Figure S1. Reduced gray matter volume in bilateral fusiform gyrus in pediatric PTSD compared to healthy youth. The right panels show scatterplots of extracted cluster data. Findings are covaried for age and sex. n=27 per group.

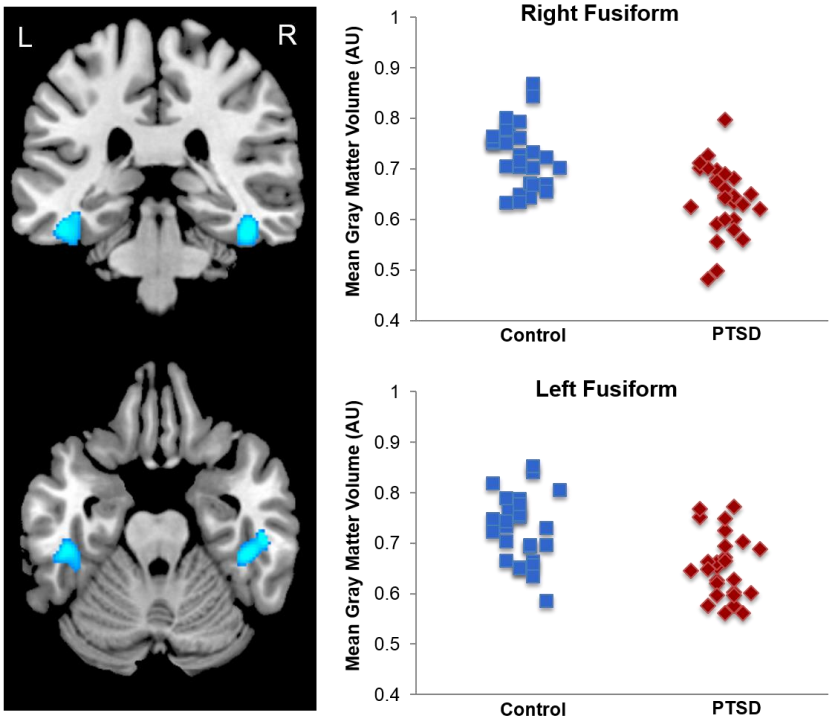


Figure S2. Altered gray matter volume (GMV) in left occipital cortex in pediatric PTSD compared to healthy youth. (a) Youth with PTSD have reduced GMV in the left occipital cortex compared to healthy youth, covaried for age and sex. Highlighted here is the 379 voxel cluster located at -46, -82, -12. (b) A trend for a group X age interaction in the left occipital cortex was observed in pediatric PTSD compared to healthy youth. The interaction, covaried for sex, revealed that age negatively predicted occipital GMV in healthy youth, but not in youth with PTSD (adjusted r = -0.80 and 0.04, respectively). However, this finding did not survive cluster thresholding at the whole brain level (peak Z = 4.33, k = 198, xyz = -32, -87, -9). Scatterplots of extracted cluster data are shown in the right panels. n=27 per group.

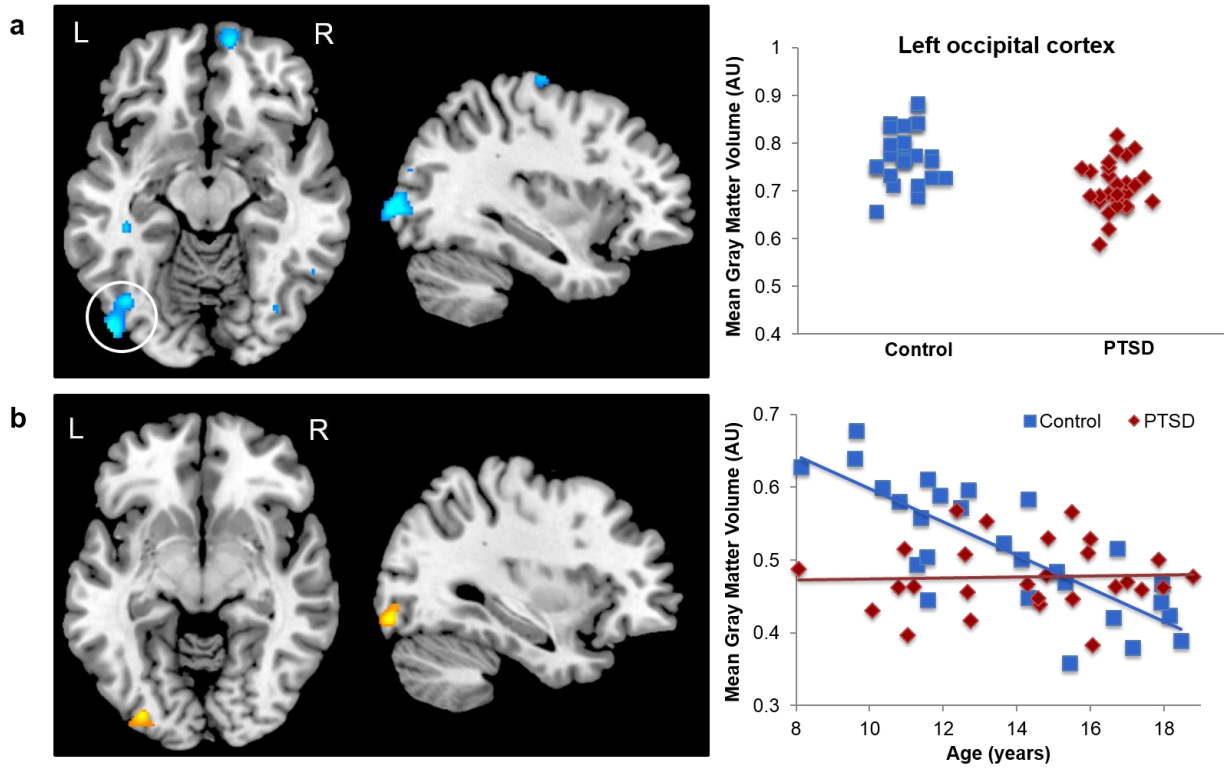


Figure S3. Anterior vmPFC gray matter volume (GMV) is inversely correlated with illness duration in pediatric PTSD. The left panel shows the right anterior vmPFC cluster derived from the group contrast as in Figure 1. The scatterplot on the right panel shows extracted cluster data in relation to PTSD duration. Findings are covaried for age and sex. vmPFC = ventromedial prefrontal cortex. n=27.

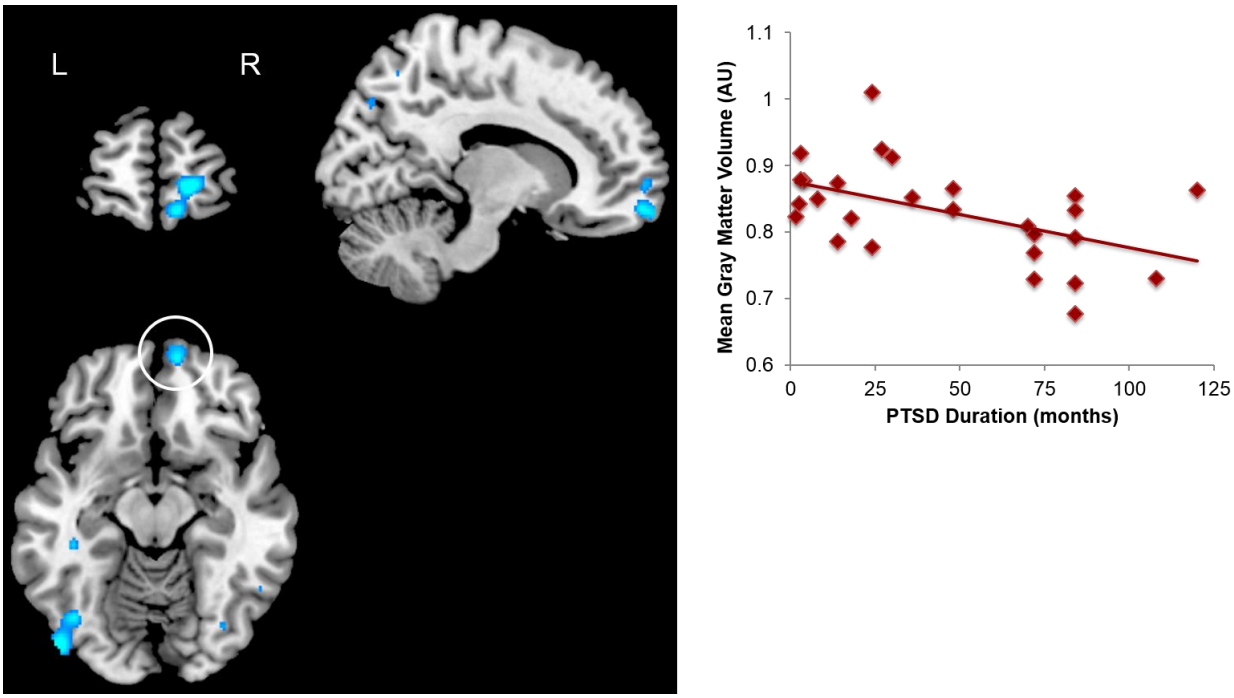
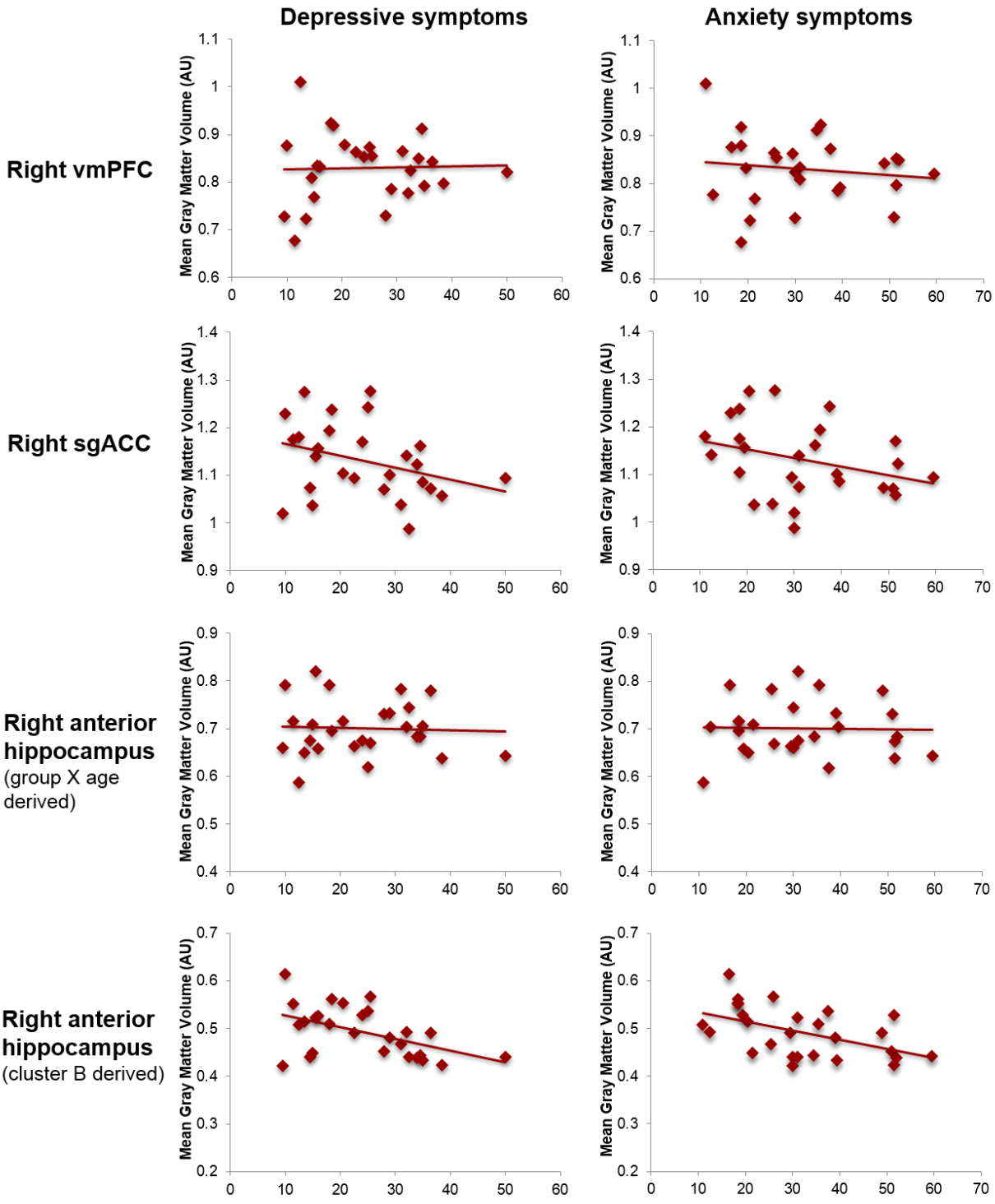


Figure S4. Gray matter volume (GMV) of vmPFC and hippocampal clusters are not associated with depressive or general anxiety symptoms within the PTSD group. The scatterplots show extracted cluster data in relation to depressive symptoms (left column) and general anxiety symptoms (right column). There were no significant correlations between vmPFC or hippocampal GMV and depressive or anxiety symptoms (all $p>0.25$). Data are covaried for age and sex. vmPFC = ventromedial prefrontal cortex, sgACC = subgenual anterior cingulate cortex. n=27.

(Figure on page below)


Depressive symptoms
Anxiety symptoms
Right vmPFC
Right sgACC
Right anterior hippocampus (group X age derived)
Right anterior hippocampus (cluster B derived)
Mean Gray Matter Volume (AU)