Disrupted intra- and extra- amygdaloid effective connectivity in presence of early life stress

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Introduction: In relation to the findings based on influence of stress on the amygdala, chronic stress has been suggested to play a key role in the cause of several anxiety disorders [1,2]. Specifically, presence of early life stress (ELS) has been reported to cause an increase in amygdala reactivity that is not observed in the absence of ELS in both healthy controls (HC) and major depressive disorder (MDD) [3,4]. Although the amygdaloid complex is regarded as a singular structure present in both hemispheres of the human brain, it is actually comprised of thirteen heterogeneous nuclei and cortical regions [5].The most clearly defined nuclei of amygdala based on their functionality are the central (CeA; fear expression), lateral and basal (BLA; consolidation of fear learning) and superficial (SF; a relay system for learning based autonomic and output) nuclei. Despite observing a change in the modulation of the amygdala reactivity due to the presence or absence of ELS history, it is not very clear which nuclei are the cause for these differences and whether the intra- and extra- amygdaloid connectivities are altered. We aim to answer these questions using a combination of high resolution imaging and effective connectivity analysis.

Methods: Twenty one healthy controls with no history of Axis I disorders based on evaluation with the Structured Clinical Interview for DSM-IV (SCID) were administered the Childhood Trauma Questionnaire-Short Form (CTQ-SF) and scanned using functional magnetic resonance imaging (fMRI) during a pavlovian conditioning paradigm investigating the predictability of stress (with conditions conditioned stimulus (CS+), CS+ followed by unconditioned stimulus (UCS), UCS). Groups were created based on CTQ-SF scores indicating presence/absence of ELS. After standard preprocessing and activation analysis, both mean time series and the beta weights were extracted from eighteen activated regions of interest (ROIs) including amygdala subregional nuclei (left/right CeA, left/right BLA and left/right SF) based on probabilistic anatomical maps [6]. The underlying neuronal response for these ROI times series were extracted by hemodynamic blind deconvolution [7] and input into a dynamic multivariate autoregressive model (dMVAR) [8, 9, 10] to obtain the connectivity matrices, which were then populated into different samples (for CS+; CS+UCS; UCS) separately for the two participant groups (ELS and non-ELS participants). A two tailed t-test was performed to identify paths that were significantly ($p<0.05$) different from zero for the UCS condition for both the groups (ELS and non-ELS participants). The connectivity between all ROIs were plotted using the brainnet viewer toolbox [11].

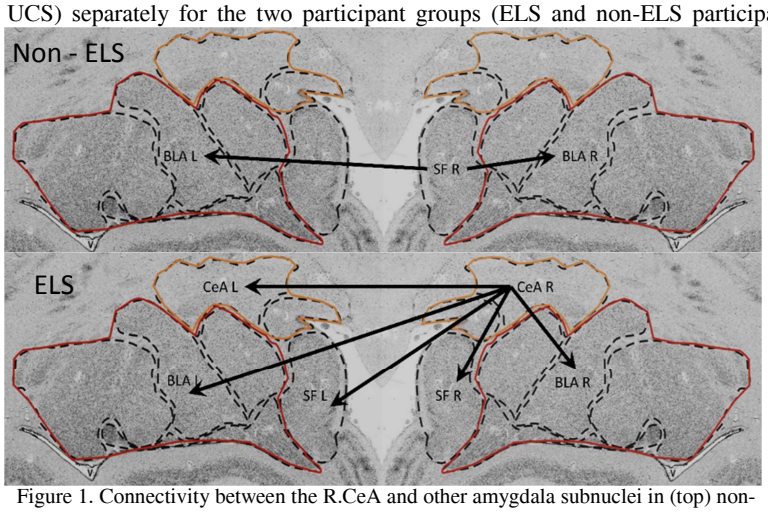

Figure 1. Connectivity between the R.CeA and other amygdala subnuclei in (top) non-ELS participants (bottom) participants with ELS

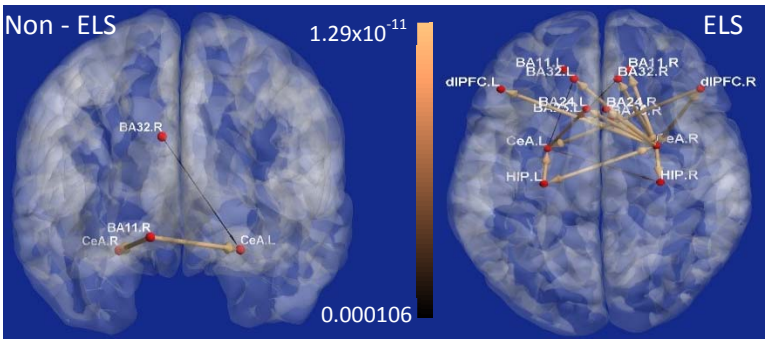

Figure 2. Connectivity between the CeA and other extra amygdaloid regions in (top) non-ELS participants (bottom) participants with ELS

Results: A repeated measures ANOVA was performed with the group (presence/absence of ELS) as between subjects factor and the trial type (CS+; CS+UCS; UCS) being the repeated measure. A significant (left; $p=.009$ and right; $p=0.01$) trend was found only for the main effect for response to the UCS for trial type, while the main effect of group and the group x trial interaction was non-significant ($p>0.05$). Figures 1 & 2 show the results of directional connectivity within the amygdala as well as between amygdala nuclei and other ROIs outside amygdala, respectively. A differential connectivity pattern between the groups (non-ELS and ELS participants) was observed. Specifically, a pattern of increased connectivity originating from right CeA was observed for both intra- and extra amygdaloid regions for ELS-exposed healthy controls. However this type of connectivity was not observed in participants with no history of ELS.

Discussion: In this study we demonstrate how early life stress affects the neural circuits involving amygdala sub-regional nuclei in healthy humans with no history of psychiatric disorder. The findings in our study can be summarized as follows 1) A history of ELS appeared to be associated with a robust intra- and extra-amygdaloid connectivity. There was increased connectivity originating from the CeA and also increased connectivity from all amygdala sub-regional nuclei. 2) Participants without a history of ELS did not show enhanced intra- or extra amygdala connectivity. This demonstrates the utility of directional connectivity models for gaining a mechanistic understanding of neural circuits underlying fear learning and expression in subjects with and without a history of ELS. This might have important implications for mental disorders characterized by malfunctioning fear circuits.

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