An Emotional Roller Coaster Ride: Amygdala Functional Connectivity and Emotion Regulation

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Emotion Regulation and the Amygdala

Emotion Regulation (ER)

- ER is the ability to appropriately and effectively deal with feelings and emotions
- There are two main types of ER studied:[10]
  - Reappraisal – effortful reinterpretation of a situation to decrease negative feelings (typically more successful)
  - Suppression – focusing elsewhere or ignoring feelings to decrease negative affect

Resting-State Functional Connectivity (rs-fcMRI)

- Investigates the relationship between low frequency oscillations in brain activity in disparate brain regions while a subject is at rest (not performing a task)
- Regions whose activity patterns are highly correlated/anti-correlated at rest are said to display "functional connectivity" and can be thought of as "networks" of regions that are often involved in similar processes.
- Using a rs-fcMRI approach allows us to ask questions about how networks of regions are related and whether the strength of these relationships are associated with various cognitive processes including emotion regulation (ER).

Past ER studies in healthy adults: Are individual differences in (ER) ability related to decreased in connectivity between regions of the brain involved in emotion processing and control?

- A network of brain regions including frontal control and limbic regions are involved in ER.[10]
- Control regions in the prefrontal cortex (PFC) are thought to modulate activity of regions involved in emotionality, such as the amygdala (AMY).
- The timing of and relationship between activity in the AMY and regions of the PFC may vary depending on the success of ER and type of regulation strategy employed.[11, 12, 13]

Childhood MDD and ineffective ER: Are children with or at risk for Major Depressive Disorder (MDD) characterized by changes in Amygdala (AMY) resting state functional connectivity (rs-fcMRI)?

- Dysfunctional emotion regulation (ER), the ability to effectively and appropriately control thoughts, feelings and mood, is a key characteristic of MDD.[e.g. 1,2,3]
- Adult MDD: reduced cortico-limbic functional connectivity thought to indicate decreased top-down control of emotion.[4,5,6,7]

Examine children with/without MDD and with/without maternal MDD history (4 groups)

ER Hypotheses: children with reduced ER ability will show:

1) **reduced connectivity between AMY and PFC regions** thought to be important for ER
2) potentially **reduced connectivity between AMY and other limbic regions** involved in the expression of emotional experience or the retrieval of emotional information

MDD Hypotheses: children with MDD and those at risk for MDD will show similar changes as children with reduced ER ability.

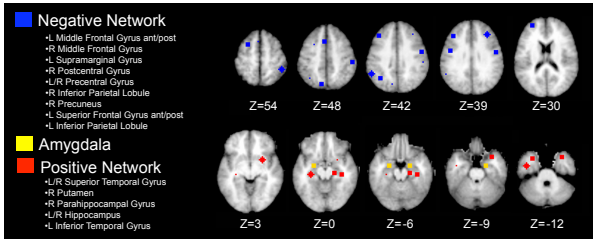
Participants and Diagnosis

- Fifty children (four groups) ages 7-11 years completed resting state functional connectivity scans on a 3T Tim TRIO at WUSM (1-2 per participant, 164 frames, 6.8 minutes)
  1) PH-MDD (N=13) personal history of MDD; if child ever displayed clinical levels if MDD using the Preschool-Age Psychiatric Assessment (PAPA).
  2) HR-MDD (N=11) a maternal history of affective disorders; if the mother reported ever being diagnosed with MDD or bipolar disorder (BP).
  3) PHR-MDD (N=13) both maternal and personal history.
  4) CON (N=14) without either a personal or maternal history.
- Children were recruited as part of an ongoing preschool MDD study and had completed 3 in person diagnostic sessions over 4-6 years prior to scan.
- Groups did not differ based upon ethnicity or gender but did differ in age and maternal education such that the age of the CON group was significantly younger than the PHR-MDD group and the education level of the PH-MDD group was significantly less than the CON and PHR-MDD groups.
- Participants were not excluded based on medication or co-morbidity status.

AMY Network Definition

- Used a whole-brain seed-based resting state functional connectivity (rsfcMRI) analysis in an independent sample of 24 healthy adults to identify networks showing two types of connectivity with the AMY
  - positive (e.g., limbic regions), referred to as "positive" network
  - negative (e.g., dorsal frontal/parietal regions), referred to as "negative" network
- Time series for all voxels within either a left or right AMY ROI correlated with all other voxels in the brain
  - Converted individual correlation maps to Fisher Z maps
  - Computed a voxelwise one-sample t test thresholded at a whole brain false positive rate of .05

Amygdala Networks



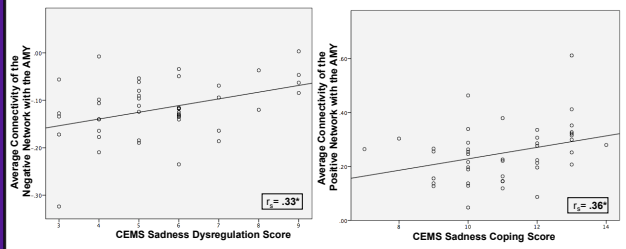
rs-fcMRI Processing and ROIs for Connectivity Analyses

The centroid coordinates for ROIs identified as showing positive and negative connectivity with the AMY in the analyses described above were used to create 12mm spherical ROIs for use with our child sample. Pre-processed timeseries data from these ROIs were extracted on an individual basis, data was high-pass filtered (0.009 Hz), nuisance signals were regressed out (motion parameters and ventricle, deep white matter, whole brain and task signals).

Individual Differences and Connectivity

Individual Difference Measure: The Children's Sadness Management Scale (CSMS)

- Administered at time of scan
- 3 scales measuring a sadness management: dysregulation, inhibition and coping

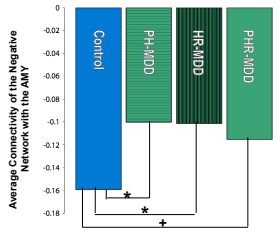


- **Across all participants, greater sadness dysregulation was associated with reduced connectivity of the AMY with the "negative" network**
- **Across all participants, better sadness coping was associated with increased connectivity between the AMY and the positive network**

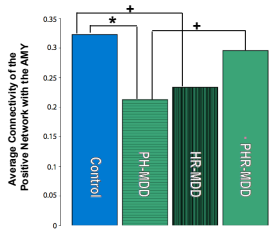
rs-fcMRI Network Analysis

- Conducted a repeated measures ANOVA for each network
  - Within subject factors: region (NEG network ROIs or POS network ROIs) and hemisphere (right/ left AMY)
  - Between subject factors: maternal affective disorder history and child MDD history.
- **Only the interaction of personal and maternal MDD history was significant (F(1,48) = 7.349. p<0.01) and (F(1,48) = 4.805, p=0.033) for POS and NEG networks respectively.**
- Interaction remained significant when controlling for gender, race, age, internalizing and externalizing co-morbidity, medication status, and maternal education.

NEGATIVE NETWORK CONNECTIVITY



POSITIVE NETWORK CONNECTIVITY



+ p<0.1 * p<0.05 ** p<0.01

AMY to NEG network connectivity is reduced in the PH-MDD and HR-MDD groups compared to controls
(PHR-MDD group displays the same trend)

AMY to POS network connectivity is reduced in the PH-MDD group compared to controls
(HR-MDD group displays the same trend)

CONCLUSIONS

- **Across all groups, greater sadness dysregulation was associated with reduced connectivity of the AMY with the "negative" network**
- **Across all groups, better sadness coping was associated with increased connectivity between the AMY and the positive network**
- **Connectivity between the AMY and the negative network was reduced compared to controls in children with either a personal or maternal MDD history or both.**
- **Connectivity between the AMY and the positive network as reduced in children with a personal history of MDD compared to controls (children with a maternal MDD history display the same trend).**
- **Results suggest a relationship between altered AMY connectivity and maternal affective disorder history independent of the child's MDD history.**
- **Results are consistent with hypothesis that preschool onset depression involves impairments in the neural systems associated with emotion regulation, as is seen in adult depression**
- **Future research is needed to determine whether these differences are predictive of later MDD symptom severity/duration and development.**

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Acknowledgements: This work was supported by the National Institutes of Mental Health (R01 MH090786-01, 5R01-MH064769) **Correspondence: krluking@wustl.edu**