Published in final edited form as:

J Child Adolesc Subst Abuse. 2014 May 1; 23(3): 200–204. doi:10.1080/1067828X.2014.889515.

Amygdala Activation and Emotional Processing in Adolescents at Risk for Substance Use Disorders

Dawn L. Thatcher^a, Stefan Pajtek^a, Ralph Tarter^{a,b}, Elizabeth C. Long^a, and Duncan B. Clark^a

^aDepartment of Psychiatry, University of Pittsburgh, 3811 O'Hara St., Oxford Bldg. Suite 800, Pittsburgh, PA 15213

^bCenter for Education and Drug Abuse Research, School of Pharmacy, University of Pittsburgh, 711 Salk Hall, Pittsburgh, PA 15261

Abstract

Studies are needed that examine neurobiological characteristics in high risk individuals prior to substance use disorder (SUD) development. In this pilot study, 4 adolescent subjects at high risk (having at least 1 parent with a SUD) for SUD were compared with 4 adolescent reference subjects on a corticolimbic reactivity paradigm, where they were presented with affect-laden faces or geometric shapes. FMRI was used to measure cortical activation in response to these stimuli. High risk subjects, compared to low risk, exhibited greater left amygdala activation ($t=3.60$, $df=6$, $p=0.01$), suggesting they may exhibit hyper-responsivity of the amygdala in response to emotional stimuli.

Psychological dysregulation has been shown to distinguish children and adolescents at high versus low risk for early involvement with alcohol and other drugs. Psychological dysregulation, including decreased executive cognitive functioning, emotional regulation and behavioral control has been shown to predict substance use disorders (SUD) in adolescence and young adulthood (Clark et al., 2005; Clark, Thatcher, & Tapert, 2008; Tarter et al., 2003; Vanyukov et al., 2009). Indicators of emotional, behavioral, and cognitive regulation have been developed and have been found to differ between groups at high and low risk for SUD. Psychological dysregulation has hypothesized neural substrates in frontal-subcortical circuitry. In this study, we investigated a possible neurobiological endophenotype for emotional dysregulation, reactivity of the amygdala in response to affect-laden faces.

Emotional regulation in particular has been shown to be influenced by the maturation of the limbic system, especially the amygdala (Salzman & Fusi, 2010). Experimental evidence from both non-human and human studies has revealed that the amygdala has an important role in the generation and regulation of emotionally motivated behavior (Hariri & Holmes, 2006; Hariri et al., 2009). Frontal-subcortical circuitry is actively developing during adolescence, the developmental period representing the greatest risk for initiation and

escalation of problematic alcohol and drug use (Clark et al, 2008; Sowell et al, 2002), and has been successfully studied using fMRI protocols (Costafreda et al., 2007).

In an fMRI task developed by Hariri and colleagues (Hariri et al., 2002), an emotional reaction is reliably provoked when the subject matches pictures of people with fearful and angry facial expressions. The task has been shown to activate frontal-subcortical circuitry. Amygdala responsiveness to emotional stimuli may be regulated by prefrontal cortex activity, a response conceptualized here as representing the neurobiological substrate of psychological regulation (Clark et al, 2008).

Studies that investigate the link between the affective component of psychological dysregulation and altered corticolimbic neurocircuitry in adolescents who have not engaged in significant SUD use are needed in order to fully characterize risk for problematic substance involvement. This study compared adolescents at high risk for SUD with low risk adolescents on amygdala reactivity during a corticolimbic reactivity task as well as self-report indices of emotional dysregulation. We hypothesized that high risk adolescents would exhibit greater amygdala reactivity in response to affect-laden faces relative to low risk adolescents. We hypothesized that amygdala reactivity would be significantly correlated with behavioral measures of emotional regulation.

Method

Study Participants

Participants were eight adolescents, ages 12–19, participating in an ongoing longitudinal study of risk factors for SUD (Tarter & Vanyukov, 2001). Four adolescents had at least one parent with a documented history of SUD disorder, and were therefore considered to be at high risk for SUD disorder. The other four adolescents had no parental history of SUD disorder, and were considered to be at low risk for SUD disorder. There were three females in each group. Subject ages in years were as follows: High risk group: 14.0, 14.9, 18.0, 18.3. Low risk group: 12.5, 13.9, 17.9, 19.1. All subjects were right-handed. Exclusion criteria for both groups included inability to communicate in English, mental retardation or other significant developmental disorders, and a history of significant brain injury resulting in likely concussion.

Study Procedures

This study was conducted with the approval of and in accordance with the University of Pittsburgh Institutional Review Board, which oversees all research studies involving human subjects. Written assent from the adolescent and consent from a biological or adoptive parent was obtained prior to any study procedures. Adolescents 18 years of age or older provided their own written informed consent.

Study measures

Transmissible Liability Index—(TLI: Vanyukov et al., 2009). The TLI was derived from item response theory as a dimensional index of liability for SUD that is independent from any symptoms of the disorder. The TLI was demonstrated to have acceptable

psychometric characteristics. Results of a twin study suggested a high level of heritability of this index (85%).

Dysregulation Inventory—(DI: Mezzich et al., 2001). The DI was constructed as a coherent index of psychological dysregulation. The scale is comprised of Affect, Behavior, and Cognitive subscales. The Affect subscale was investigated for the purposes of this study.

Threat-related corticolimbic reactivity paradigm—This task, developed by Hariri and colleagues (Hariri et al., 2009), is designed to engage the amygdala and ventromedial prefrontal cortex, key brain systems that participate in generating and regulating emotion-related physiology and behavior. This task also reliably engages an extended visuospatial object processing network, which includes the occipital, inferotemporal, parietal and frontal cortices. In this paradigm, blocks of a perceptual face processing task presenting affect-laden faces were interleaved with blocks of a sensorimotor control task. We chose not to use neutral faces as primary control stimuli because they can be subjectively experienced as affectively-laden or ambiguous and thus engage the amygdala (Schwartz et al., 2003; Wright et al., 2003).

During the face blocks, subjects viewed a trio of faces and selected one of two faces (bottom) that was identical to a target face (top). The order of face and shape matching blocks was counterbalanced across subjects within each group (i.e., HR and LR). Each of these blocks consisted of six images, three of each sex (and target affect), presented sequentially for 4 seconds. All face stimuli were derived from a standard set of pictures of facial affect (Eckman & Friesen, 1976).

During the sensorimotor control blocks, subjects view a trio of geometric shapes (circles, vertical and horizontal ellipses) and select one of the two shapes (bottom) that match a target shape (top). Each control block consists of six different images presented sequentially for 4 seconds.

Within each face block, the interstimulus interval (ISI) varied (i.e., jitter) between 2, 4 and 6 seconds (mean ISI = 4). The mixed-trial design maximized both our detection efficacy of sustained activity (BOLD signal amplitude) over entire blocks and our estimation efficacy of trial-related transient activity (modeling of hemodynamic characteristics) for individual trials (Mechelli et al., 2003a; 2003b).

BOLD fMRI Acquisition Parameters—MRI scans were performed at the Brain Imaging Research Center (BIRC), located near the University of Pittsburgh campus. MRI images were acquired on a Siemens 3T Allegra Scanner (Siemens Medical Solutions, Erlangen, Germany) optimized for functional brain imaging. An automated shim procedure was applied to minimize possible magnetic field inhomogeneities. In-plane T2 structural images were acquired for visualization and normalization of functional imaging data. Blood oxygenation-level dependent (BOLD) functional images were acquired with a gradient echo EPI sequence oriented to the AC-PC line and encompassing the entire cerebrum and the majority of the cerebellum (TR/TE=2000/25 msec, FOV=24 cm, matrix=64x64). All scanning parameters were selected to optimize the quality of the BOLD signal while

maintaining a sufficient number of slices to acquire whole-brain data (34 slices). Before the collection of fMRI data for each subject, a reference EPI scan was collected and visually inspected for artifacts (i.e., ghosting) as well as for signal quality across the entire volume of acquisition, including the medial temporal lobes and ventromedial PFC.

Statistical Methods of fMRI Image Analysis—Analysis of our fMRI data was completed using Statistical Parametric Mapping software (www.fil.ion.ucl.ac.uk/spm). Images for each subject were realigned to the first volume in the time series to correct for head motion, spatially normalized into a standard stereotactic space (Montreal Neurological Institute template) using a 12-parameter affine model, and smoothed to minimize noise and residual differences in gyral anatomy with a Gaussian filter set at 6 mm full-width at half-maximum. Voxel-wise signal intensities were ratio normalized to the whole-brain global mean. Predetermined condition effects at each voxel within anatomically defined regions of interest including the bilateral amygdala and the ventromedial and dorsomedial prefrontal cortices were calculated using a t-statistic, producing a statistical image for the contrasts of interest for each subject. These individual contrast images were then used in second-level random effects models, which account for both scan-to-scan and subject-to-subject variability, to determine task-specific regional responses at the group-level for the entire sample (main effects of task) and paired t-tests (direct comparisons between groups). A statistical threshold of $P < 0.05$, with a region of interest correction (FDR) for multiple comparisons, was used to identify significant responses for all comparisons. Whole-brain image analyses for all predetermined condition effects also were calculated using second-level random effects models. A statistical threshold of $P < 0.05$, corrected for multiple comparisons across all supra-threshold voxels, were used for these whole-brain comparisons. The primary analysis of interest was the interaction between group (high risk versus low risk) and condition (faces versus shapes).

We also planned correlational analyses to determine whether any significant clusters of activation were related to the TLI and the Affect subscale of the DI.

Results

In the corticolimbic reactivity task, the main effect of condition (i.e., faces versus shapes) was statistically significant across the two groups, indicating that the task activated the amygdala as expected. The condition by group interaction also was statistically significant, as hypothesized. Compared with low risk adolescents, adolescents at high risk for SUD exhibited a cluster (maximum voxel coordinates $-20, 4, -20$) of significantly greater left amygdala activation during the presentation of affectively-laden facial expressions versus geometric shapes ($t=2.76, p=0.03$). See Figure 1 for the anatomical location of this cluster.

Pearson's r correlation coefficients were obtained for the maximum voxel of the significant cluster with the Transmissible Liability Index (TLI) and the Affect subscale of the DI (AFFECT). While the magnitudes would indicate moderate correlations (TLI: $r=0.51, p=0.20$; AFFECT: $r=-0.48, p=0.23$), neither of these correlations were statistically significant.

Discussion

These preliminary results indicate that adolescents at risk for SUD exhibited left amygdala hyper-reactivity in response to viewing affect-laden faces. Amygdala hyper-responsiveness may indicate impaired emotional regulation. These results provide neurobiological evidence for the hypothesis that compromised emotional regulation is present in adolescents at high risk for SUD before significant alcohol or other substance involvement. Amygdala hyper-reactivity may be an endophenotype predicting SUD.

Recent studies have implicated the corticolimbic system in general, and the amygdala in particular, in dysfunctional processing of emotionally laden information thought to be involved in the development of addiction. Using the same protocol as the current study, reduced rather than increased amygdala activation was found in young adults at risk for alcoholism relative to controls (Glahn, Lovullo, & Fox, 2007). The mean age in the Glahn study was 23–24, while the subjects in the current study were adolescents. Subjects in the Glahn study reported mild to moderate levels of alcohol use, while subjects in the current study had no previous exposure to alcohol. These two important factors may account for the differences between these two studies.

While amygdala reactivity was not significantly correlated with the Transmissible Liability Index (Vanyukov et al., 2009) or with the Affect subscale of the Dysregulation Inventory (DI), the magnitude of both correlations was greater than 0.45. The small sample size in this study compromised the statistical power needed to examine this correlation. If the relationship between amygdala hyper-reactivity and TLI/DI is replicated in larger, well-matched samples, it would validate amygdala hyper-reactivity as an endophenotype predicting SUD.

The primary limitation here was the small sample size. These preliminary findings need to be replicated and extended in larger, well-matched samples. While the mechanism of the enhanced corticolimbic response might be construed to involve heritable transmission, environmental factors may also influence this response.

These results indicate that adolescents defined as being at high risk for SUD exhibit amygdala hyper-reactivity during affectively laden situations. If replicated and extended in larger, well matched samples, these results will inform prevention efforts. To the extent that emotional dysregulation and its underlying neural substrates are amenable to change, prevention efforts could be targeted toward this characteristic.

Acknowledgments

Funding for this study was provided by NIH grants P50DA005605, R21AA017312, K01DA018698, K02AA00291 and “Reducing the Cognitive Consequences of Cannabis Use by Adolescents” from the Pennsylvania Department of Health.

References

- Clark DB, Cornelius JR, Kirisci L, Tarter RE. Childhood risk categories for adolescent substance involvement: A general liability typology. *Drug and Alcohol Dependence*. 2005; 77(1):13–21. [PubMed: 15607837]

- Clark DB, Thatcher DL, Tapert SF. Alcohol, psychological dysregulation, and adolescent brain development. *Alcoholism: Clinical and Experimental Research*. 2008; 32(3):1–11.
- Costafreda SG, Brammer MJ, Venicio R, Mourao ML, Portela L, Campi de Castro C, et al. Multisite fMRI reproducibility of a motor task using identical MR systems. *Journal of Magnetic Resonance Imaging*. 2007; 26:1122–1126. [PubMed: 17896376]
- Ekman, P.; Friesen, WV. *Pictures of Facial Affect*. Palo Alto, CA: Consulting Psychologists Press; 1976.
- Glahn DC, Lovaglio WR, Fox PT. Reduced amygdala activation in young adults at high risk of alcoholism: Studies from the Oklahoma Family Health Patterns Project. *Biological Psychiatry*. 2007; 61:1306–1309. [PubMed: 17306772]
- Hariri AR, Gorka A, Hyde LW, Kimak M, Halder I, Ducci F, et al. Divergent effects of genetic variation in endocannabinoid signaling on human threat-and reward-related brain function. *Biological Psychiatry*. 2009; 66:9–16. [PubMed: 19103437]
- Hariri AR, Holmes A. Genetics of emotional regulation: The role of the serotonin transporter in neural function. *Trends in Cognitive Science*. 2006; 10(4):182–191.
- Hariri AR, Tessitore A, Mattay VS, Fera F, Weinberger DR. The amygdala response to emotional stimuli: A comparison of faces and scenes. *NeuroImage*. 2002; 17(1):317–323. [PubMed: 12482086]
- Mechelli A, Henson RN, Price CJ, Friston KJ. Comparing event-related and epoch analysis in blocked design fMRI. *Neuroimage*. 2003a; 18(3):806–810. [PubMed: 12667857]
- Mechelli A, Price CJ, Henson RN, Friston KJ. Estimating efficiency a priori: A comparison of blocked and randomized designs. *Neuroimage*. 2003b; 18(3):798–805. [PubMed: 12667856]
- Mezzich AC, Tarter RE, Giancola PR, Kirisci L. The dysregulation inventory: A new scale to assess the risk for substance use disorder. *Journal of Child and Adolescent Substance Abuse*. 2001; 10:35–43.
- Salzman CD, Fusi S. Emotion, cognition, & mental representation in amygdala and prefrontal cortex. *Annual Review of Neuroscience*. 2010 Advance online publication.
- Schwartz CE, Wright CI, Shin LM, Kagan J, Whalen PJ, McMullin KG, et al. Differential amygdalar response to novel versus newly familiar neutral faces: A functional MRI probe developed for studying inhibited temperament. *Biological Psychiatry*. 2003; 53:854–862. [PubMed: 12742672]
- Sowell ER, Trauner DA, Gamst A, Jernigan TL. Development of cortical and subcortical brain structures in childhood and adolescence: A structural MRI study. *Developmental Medicine & Child Neurology*. 2002; 44:4–16. [PubMed: 11811649]
- Tarter RE, Kirisci L, Habeych M, Reynolds M, Vanyukov MM. Neurobehavior disinhibition in childhood predisposes boys to substance use disorder by young adulthood: Direct and mediated etiologic pathways. *Drug and Alcohol Dependence*. 2003; 73:121–132. [PubMed: 14725951]
- Tarter RE, Vanyukov MM. Introduction: Theoretical and operational framework for research into the etiology of substance use disorders. *Journal of Child & Adolescent Substance Abuse*. 2001; 10(4): 1–12.
- Vanyukov MM, Kirisci L, Tarter RE, Ridenour TA, Reynolds MD, Maher B, et al. Measurement of the risk for substance use disorders: Phenotypic and genetic analysis of an index of common liability. *Behavior Genetics*. 2009; 39:233–244. [PubMed: 19377872]
- Wright CI, Martis B, Schwartz CE, Shin LM, Fischer HH, McMullin K, et al. Novelty responses and differential effects of order in the amygdala, substantia innominata, and inferior temporal cortex. *Neuroimage*. 2003; 18:660–669. [PubMed: 12667843]

Faces: Significant Voxels High > Low Risk

Figure 1.

Compared with Low Risk adolescents, High Risk adolescents exhibit enhanced BOLD response during affective face trials versus geometric shape trials.