Adolescent male substance use disorder and the “with limited prosocial emotions” specifier: brain activation during decision associated with increasing other harm and self-benefit

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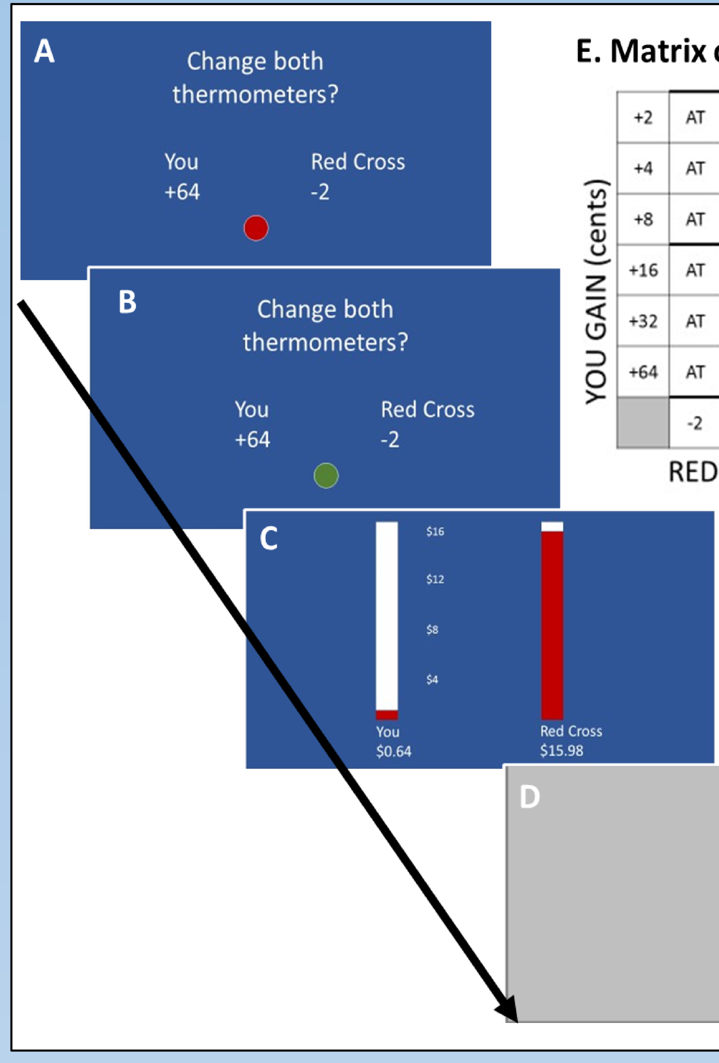
INTRODUCTION:

- Adolescent SUD is common and predicts increased risk of drug abuse, other behavioral problems and worse health outcomes in adulthood (SAMHSA. 2017 NSDUH Annual National Report 2017; Nelson SE et al.,2015).
- Adolescent SUD frequently co-occurs with conduct disorder (CD) and youth with SUD plus CD tend to have worse clinical outcomes and more persistent courses. (Hopfer C et al., 2013; Myers MG et al, 1995).
- DSM-5 also describes a “with limited prosocial emotions” (LPE) specifier identifying individuals who display high callous-unemotional traits, these adolescents may be at even greater risk of substance misuse (Baskin-Sommers AR et al., 2015).
- The neuroscience of social cognition is often conspicuously absent from biological models of addiction; the available literature supports that SUD is associated with deficits in social cognition (Uekermann J and Daum I, 2008).
- Adolescent prosocial behaviors and empathy have a negative association to adolescent substance use over time (Carlo G et al., 2011; Winters DE et al., 2020).
- Problem Statement: Very limited work has examined the association of social cognition and prosocial decision making with adolescent SUD/externalizing behavior problems in the MRI environment.
- Project Aim: We sought to better understand brain structures engaged during decisions which may be increasingly harmful to others and increasingly beneficial to self, and to identify group differences in brain activation patterns.
- Hypothesis: We hypothesize that all three groups will have measurable differences in the pattern of brain activation depending on whether the subject is behaving in a manner that is beneficial to self versus behavior harmful to others.

Measures Used: Inventory of Callous Unemotional Traits (ICU) (Frick PJ, 2004), the Diagnostic Interview Schedule for Children (Shaffer D et al., 2000), the Composite International Diagnostic Interview – Substance Abuse Module (Robins LN et al., 2000) and the Youth Self Report (Achenbach T, 1991). Parents completed the Child Behavior Checklist (CBCL, Achenbach, 1991), a race/ethnicity questionnaire, and a socioeconomic status measure.

Altruism-Antisocial (AlAn’s) Game:



E. Matrix of Active Trials

YOU GAIN (cents)						
+2	AT	AT	AT	AT	AT	AT
+4	AT	AT	AT	AT	AT	AT
+8	AT	AT	AT	AT	AT	AT
+16	AT	AT	AT	AT	AT	AT
+32	AT	AT	AT	AT	AT	AT
+64	AT	AT	AT	AT	AT	AT
	-2	-4	-8	-16	-32	-64

RED CROSS LOSES (cents)

Supplemental Figure 1. Description of AlAn’s Game. Participants must choose to either act in their self-interest at the expense of others or act beneficently at the expense of themselves. The entire game is composed of 144 offers, and each offer is presented to the subjects for a 5 second deliberation period after which they are given 1 second to accept or reject the offer. The game takes approximately 30 minutes to complete. **Panel A.** Showing an Active Trial - the subject will gain 64 cents and the Red Cross donation will go down by 2 cents (5 seconds). **Panel B.** When the ball turns from red to green the subjects accept or reject the offer (1 second). **Panel C.** Then the counters appear, showing both visually and numerically the amount of money the subject has taken, and the amount of money left in the charity donation. **Panel D.** Then a jittered fixation screen appears. **Panel E.** Shows the Active Trials included in the game. Y-Axis indicates the amount of money the subject will gain (in cents). X-Axis shows the amount by which the donation will be reduced (also in cents). All 36 Active Trials are presented to subjects twice while playing the game. Other trial types, which are not used in these analyses, are not discussed here.

METHODS:

Groups studied: (1) male patients with SUD+LPE, (2) male patients with SUD but without LPE and (3) male controls.

Inclusion:
- 15-18 years
- Male
- Estimated IQ ≥80
- ≥ 30 days sobriety
- English proficiency
- Right-handed

Exclusion:
- Current dangerousness
- Red Green color blindness
- Psychotic/bipolar/anxiety disorder
- Caffeine/nicotine withdrawal (refrain from use 12 hours prior to scan)
- Volunteered for/help from Red Cross
- Standard MRI exclusions

Sample:
Patients recruited from a University based treatment program for youth with substance and conduct problems (all had at least one non-nicotine substance use disorder). Controls recruited from same neighborhoods as patients and excluded for prior convictions (minor traffic and curfew violations permitted) or hx of substance related expulsion/treatment

66 adolescents (21 SUD patients with LPE; 21 without LPE and 24 controls) imaged in 3T MRI while playing AlAn’s game.

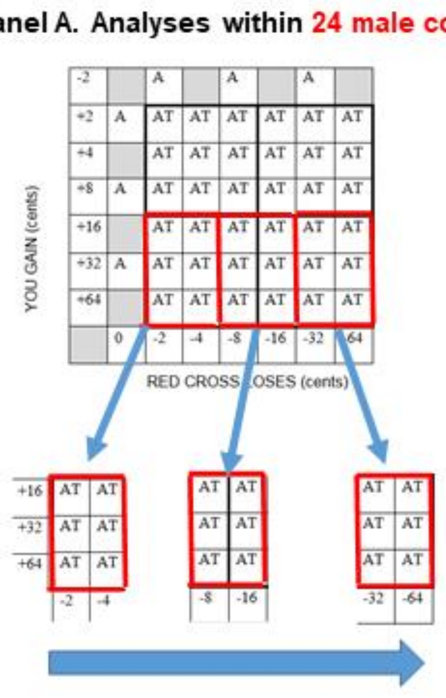
(The Colorado Multiple Institutional Review Board approved the study (COMIRB protocol 12-0117). For adolescents under the age of 18, parents gave consent and participants assent. Participants 18 years of age gave written consent to participation.)

Imaging Parameters:
We obtained functional brain images with Blood Oxygenated Level Dependent (BOLD) contrast using a T2*-weighted gradient-echo echo-planar imaging (EPI) technique over a 64×64 matrix (TE/TR/TI (in milliseconds)): 26/2000/70; Flip angle: 70°; FOV: 220×220 mm^2 in axial acquisition.

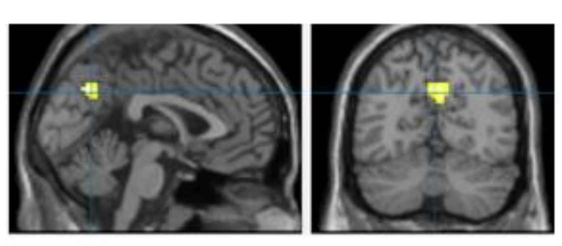
RESULTS:

Figure 1. What brain areas are engaged (more and less) as other harm increases (selecting high you-gain amounts 16, 32, 64 and examining changes between -2/-4, -8/-16 and -32/-64)

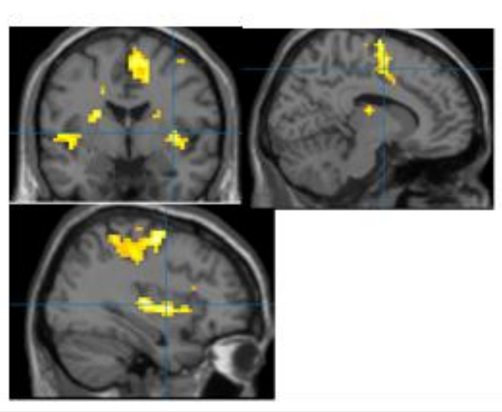
Panel A. Analyses within 24 male control adolescents.



As other harm increases, this brain region becomes <u>more</u> active: precuneus ↑ (1 cluster; 58 voxels)

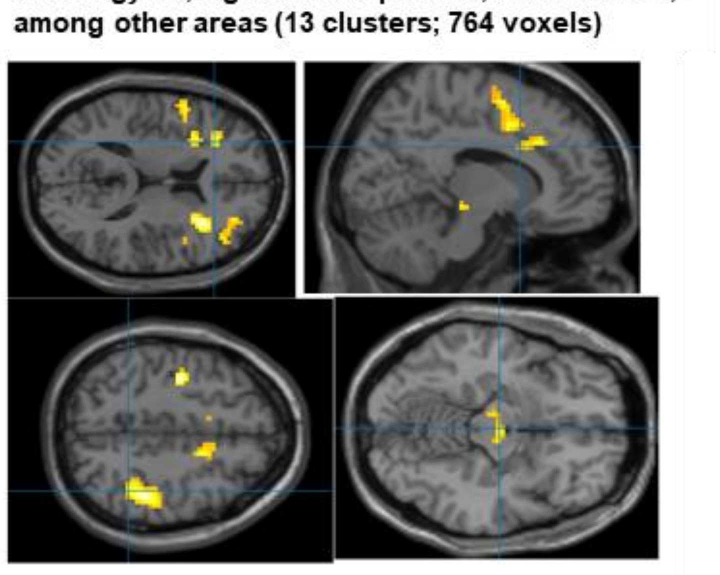


As other harm increases, these brain regions become <u>less</u> active: bilateral insula, right superior temporal and parietal regions, SMA, thalamus ↑ (8 clusters; 1091 voxels)



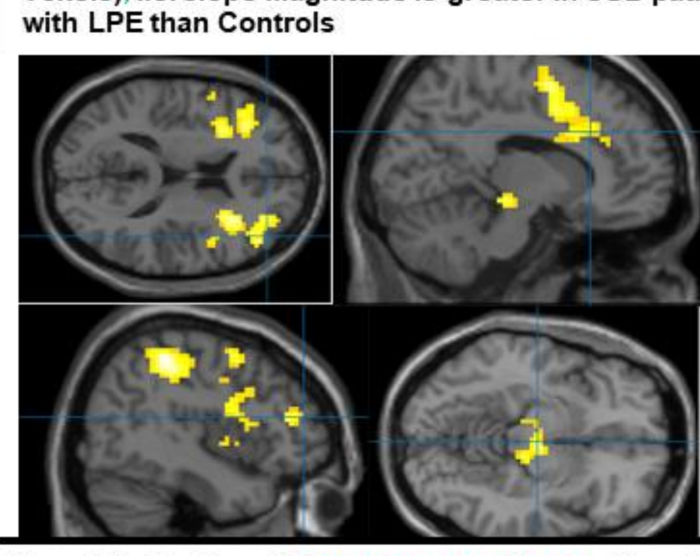
Panel B. Three-group ANCOVA – How do groups differ when other harm changes?

Significant F-test in bilateral insula and inferior frontal gyrus, right inferior parietal, and midbrain, among other areas (13 clusters; 764 voxels)



Panel C. Two-group analyses – How do groups differ when other harm increases?

SUD patients with LPE>Controls
Bilateral insula and inferior frontal gyrus, cingulate, right inferior parietal, midbrain (11 clusters; 1878 voxels), i.e. slope magnitude is greater in SUD patients with LPE than Controls



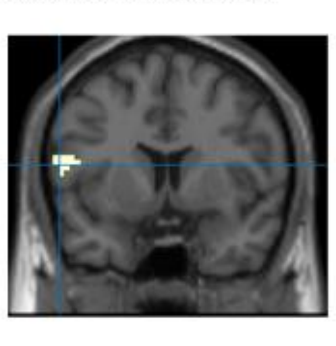
Panel C continued – Two-group analyses – How do groups differ when other harm increase?

Controls>SUD patients with LPE
NO AREAS OF SIGNIFICANT DIFFERENCE

Controls>SUD patients without LPE
NO AREAS OF SIGNIFICANT DIFFERENCE

SUD patients without LPE>with LPE
NO AREAS OF SIGNIFICANT DIFFERENCE

SUD patients with LPE>without LPE
Left inferior frontal gyrus (1 cluster; 29 voxels), i.e. slope magnitude is greater In SUD patients with LPE than those Without LPE



Panel C. Continued - Two-group analyses – How do groups differ when other harm increases?

SUD patients without LPE>Controls
Right insula, inferior/middle frontal regions, cingulate, right inferior parietal, and caudate (9 clusters; 431 voxels), i.e. slope magnitude is greater In SUD patients without LPE than Controls

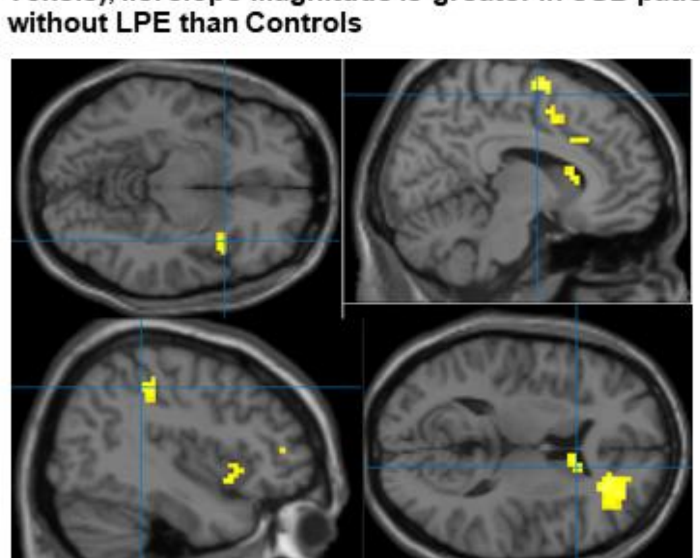
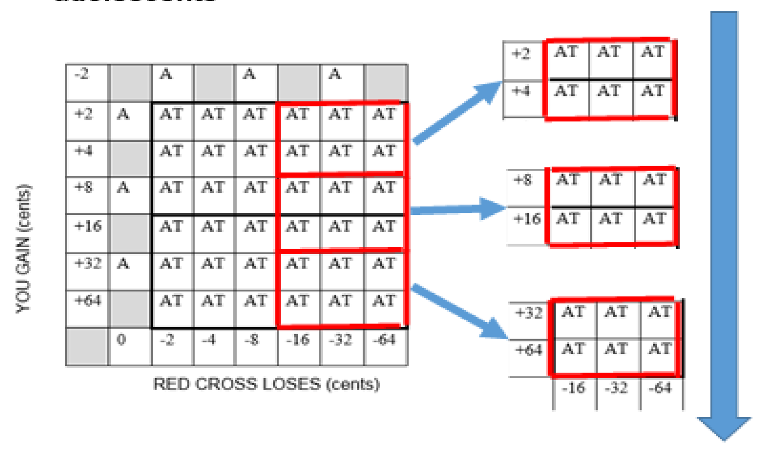
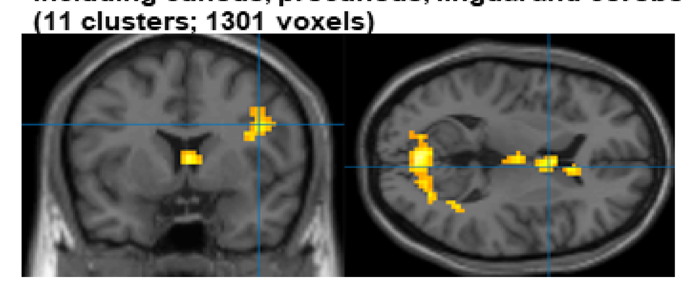


Figure 2. What brain areas are engaged (more and less) as benefit-to-self increases (selecting high Red Cross loss trials and examining you gain amounts of +2/+4, +8/+16, +32/+64)

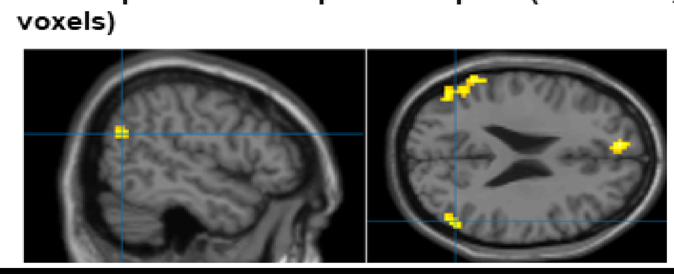
Panel A. Analyses within 24 control adolescents



As benefit-to-self increases these regions become <u>more active</u>: caudate, midbrain, right middle frontal gyrus, along with thalamus, and posterior regions including cuneus, precuneus, lingual and cerebellum (11 clusters; 1301 voxels)

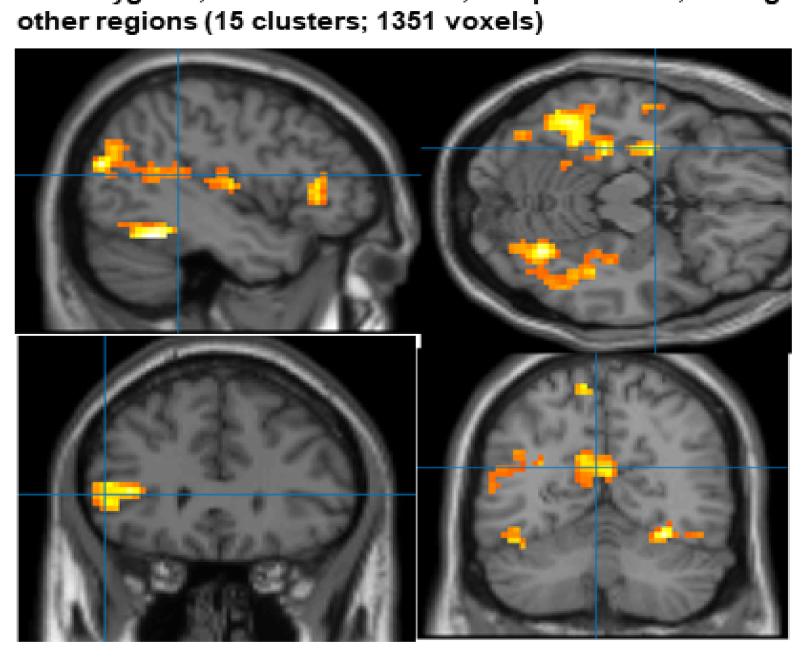


As you gain increases these regions become <u>less</u> active: superior frontal, orbitofrontal, posterior insula, inferior parietal and superior temporal (6 clusters; 621 voxels)



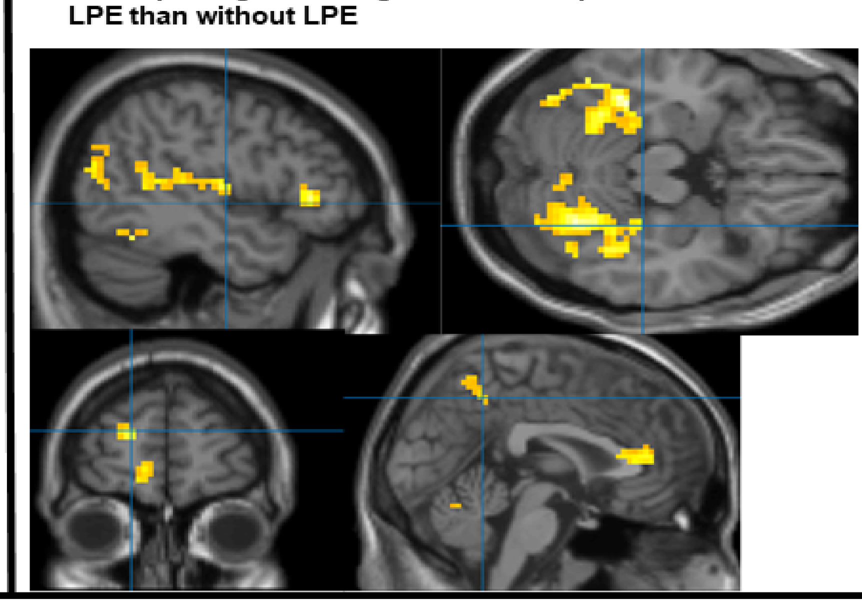
Panel B. Three-group ANCOVA – How do groups differ when benefit-to-self increases?

Significant F-test in left superior temporal gyrus into inferior parietal regions, fusiform into parahippocampal and amygdala, left inferior frontal, and precuneus, among other regions (15 clusters; 1351 voxels)



Panel C. Two-group analyses – How do groups differ when benefit-to-self increases?

SUD patients with LPE>without LPE
Bilateral superior temporal gyrus and left inferior parietal, prominent fusiform, some parahippocampal, left superior and inferior frontal, anterior cingulate, precuneus, among others (15 clusters, 1598 voxels); i.e. slope magnitude is greater in SUD patients with LPE than without LPE



Panel C continued – Two-group analyses – How do groups differ when benefit to self increases?

Controls>SUD patients with LPE
NO AREAS OF SIGNIFICANT DIFFERENCE

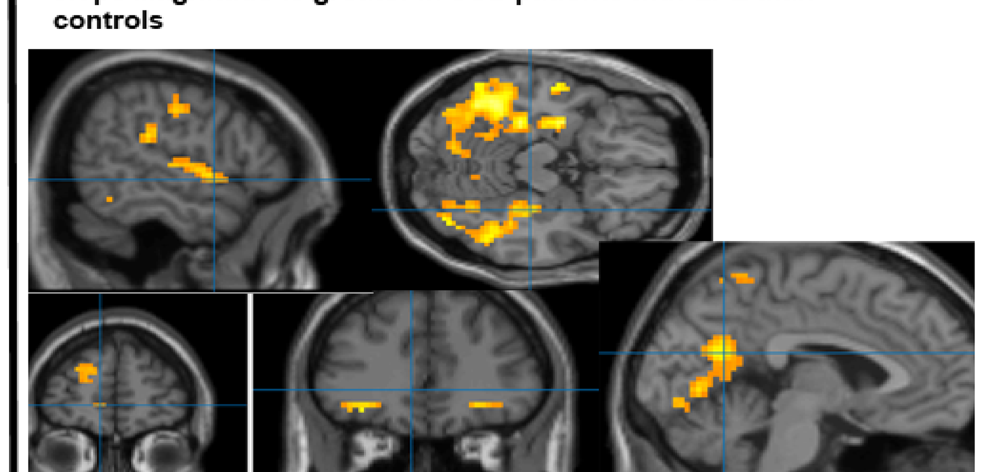
Controls>SUD patients without LPE
NO AREAS OF SIGNIFICANT DIFFERENCE

SUD patients without LPE>with LPE
NO AREAS OF SIGNIFICANT DIFFERENCE

SUD patients without LPE>Controls
NO AREAS OF SIGNIFICANT DIFFERENCE

Panel C. Two-group analyses – How do groups differ when benefit to self increases?

SUD patients with LPE>Controls
Bilateral superior temporal gyrus and inferior parietal lobule, and fusiform to parahippocampal gyrus, left superior frontal, orbitofrontal, and prominent posterior regions (occipital, precuneus, posterior cingulate) (19 clusters; 2425 voxels); i.e. slope magnitude is greater in SUD patients with LPE than controls



DISCUSSION/CONCLUSION:

- Our methods allow modeling of engagement of brain regions based on trial content (e.g., as there is increasing harm to a beneficent other, what brain regions become more active during decision).
- The three-group design allows examining what differences are related to SUD patient status (regardless of LPE) and what may be more specifically related to LPE.

AS OTHER HARM INCREASES:
Regions engaged in controls include:
↑ precuneus
↓ the bilateral insula, right superior temporal gyrus, parietal cortex, the supplementary motor area and thalamus
Group differences are primarily between controls and SUD patients and show differences in regions implicated in:
-Affective empathy, anticipatory guilt (insula, cingulate; Seara-Cardoso et al., 2016)
-Theory of Mind (temporal-parietal junction; Tusche et al., 2016)
-Reward sensitivity (midbrain and head of the caudate)

AS YOU GAIN INCREASES:
Regions engaged in controls include:
↑ caudate, midbrain, right middle frontal gyrus, thalamus, cuneus, lingual gyrus, and cerebellum
↓ superior frontal gyrus, orbitofrontal, posterior insula, inferior parietal, and superior temporal
Group differences relate to LPE and show differences in regions implicated in:
-Theory of Mind (temporal-parietal junction; Tusche et al.,2016)
-Executive control (superior frontal)
-Internal mentation (precuneus, posterior cingulate; Dalwani et al., 2014)
-Facial recognition and social context/self awareness (fusiform, parahippocampal; Chavoix & Insausti, 2017)

Limitations: Our study focuses on male adolescents but cannot inform us about differences in females, younger children, or adults.