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Research paper

# Amygdala-frontal connectivity predicts internalizing symptom recovery among inpatient adolescents

Amanda Venta[a], Carla Sharp[b,*], Michelle Patriquin[c], Ramiro Salas[d], Elizabeth Newlin[c], Kaylah Curtis[c,e], Philip Baldwin[c,e], Christopher Fowler[c], B. Christopher Frueh[f]

[a] Department of Psychology & Philosophy, Sam Houston State University, Huntsville, TX, United States
[b] Department of Psychology, University of Houston, Houston, TX, United States
[c] Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, United States
[d] Menninger Department of Psychiatry and Behavioral Sciences, Michael E DeBakey VA Medical Center Department of Neuroscience, Baylor College of Medicine, Houston, TX, United States
[e] Michael E DeBakey VA Medical Center, Houston, TX, United States
[f] Department of Psychology, University of Hawaii, Hilo, HI, United States

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ABSTRACT

*Background:* The possibility of using biological measures to predict the trajectory of symptoms among adolescent psychiatric inpatients has important implications. This study aimed to examine emotion regulation ability (measured via self-report) and a hypothesized proxy in resting-state functional connectivity [RSFC] between the amygdala and frontal brain regions as baseline predictors of internalizing symptom recovery during inpatient care.

*Methods:* 196 adolescents (61% female; *M*age = 15.20; *SD* = 1.48) completed the Achenbach Brief Problem Monitor (BPM) each week during their inpatient care. RSFC ($n$ = 45) and self-report data of emotion regulation ($n$ = 196) were collected at baseline.

*Results:* The average internalizing symptom score at admission was high ($\alpha_o$ = 66.52), exceeding the BPM's clinical cut off score of 65. On average, internalizing symptom scores declined significantly, by 0.40 points per week ($p$ = 0.004). While self-reported emotion regulation was associated with admission levels of internalizing problems, it did not predict change in symptoms. RSFC between left amygdala and left superior frontal gyrus was significantly associated with the intercept—higher connectivity was associated with higher internalizing at admission—and the slope— higher connectivity was associated with a more positive slope (i.e., less decline in symptoms). RSFC between the right amygdala and the left superior frontal gyrus was significantly, positively correlated with the slope parameter.

*Conclusions:* Results indicate the potential of biologically-based measures that can be developed further for personalized care in adolescent psychiatry.

## 1. Introduction

The possibility of using biological measures to predict the trajectory of symptom change among psychiatric inpatients has important implications for public health issues including ideal length of stay, best clinical practices, recommendations for mandated care, and insurance reimbursements. Adolescents have a high rate of psychopathology (Merikangas et al., 2010) and are highly represented in mental healthcare settings. Inpatient care provides an opportunity to observe, assess, and treat adolescents who may otherwise be difficult to engage in treatment (Laget et al., 2006). However, inpatient hospitalization is the most costly treatment modality (Haggerty, 2014) and the availability of inpatient units has been reduced due to economic pressures (Blanz, 2000). Maximizing the impact of a limited number of inpatient beds requires that clinicians understand who benefits from inpatient care and what duration of hospitalization is needed. A recent emphasis on biologically-informed psychiatric care (Cuthbert, 2014; Glannon, 2015; Insel et al., 2013) warrants inclusion of biological measures when considering recovery trajectories. The aim of this study was to map the trajectory of internalizing symptom change among adolescents during the first month of inpatient psychiatric care in a naturalistic setting, while modeling the role of emotion regulation (ER) abilities, assessed

* Correspondence to: University of Houston, Houston, TX 77204, United States.
*E-mail address:* csharp2@uh.edu (C. Sharp).

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through self report and a hypothesized proxy of resting state functional connectivity (RSFC). The overall goal was to evaluate the utility of biological measures in predicting change trajectories alongside more traditional self-report measures.

We elected to focus on modeling the trajectory of internalizing symptoms—those related to anxiety and depression— due, firstly, to high rates of internalizing problems in clinical (Venta et al., 2012) and inpatient (Venta et al., 2012; Kovacs and Sharp, 2014) samples. Second, internalizing symptoms in adolescents are highly comorbid (Angold, 1999) with academic and social problems (Cutuli et al., 2013), substance use (Wills et al., 2007) and disordered eating (Siegel, 2002). Third, treatments targeting internalizing symptoms in adolescence show generalized improvements in externalizing pathology (Cutuli et al., 2013) bolstering our focus on internalizing symptoms as an outcome of interest. Finally, the possibility that internalizing problems capture shared latent vulnerability underlying psychopathology in the form of negative affectivity or neuroticism suggests this may be an important cross-cutting target for treatment (Watson and Clark, 1984).

The prime candidates for assessing ER through biological measures are the amygdala and prefrontal cortex (Frank et al., 2014; Ochsner and Gross, 2004; Buckholtz and Meyer-Lindenberg, 2012). Kim et al. (2011) posit that it is the "coupling" between these regions that underlies ER—more so than the activity or structure of either region alone. Indeed, ER has been conceptualized as the prefrontal cortex exerting control over the amygdala; prefrontal activity is increased whereas amygdala activity is decreased (Geise et al., 2014; Hariri et al., 2000; Ochsner et al., 2002; Phelps, 2006; Wager et al., 2008). RSFC is a compelling method for assessing this "coupling," as it is a functional MRI technique measuring connectivity between brain regions at rest (Kim et al., 2011). Within the larger prefrontal cortex, the medial and lateral areas of the prefrontal cortex (Kim et al., 2011; Ochsner et al., 2002) have received the widest empirical support in the context of ER, though the specific prefrontal cortex regions of interest differ across studies (Phelps, 2006). While RSFC between the amygdala and frontal areas has been implicated in adolescent internalizing psychopathology (Pannekoek et al., 2014; Roy et al., 2013), it has not been used to predict treatment trajectories of any kind—a necessity if brain-based research is to inform clinical practice. In this study, RSFC between the amygdala and three prefrontal area (superior, medial, and inferior frontal gyri) were explored as potential biological measures of ER in order to test relations between amygdala and medial/lateral prefrontal regions that have identified in prior research (Kim et al., 2011; Ochsner et al., 2002) as well as examine amygdala-prefrontal connectivity more globally, as is necessitated by mixed findings in existing research (Phelps, 2006).

While perhaps less innovative, self-reported ER abilities have emerged as a predictor of treatment outcome in psychopathology across the lifespan (Gratz et al., 2014; Slee et al., 2008; Venta et al., 2015). Valuable in this regard has been Gratz and Roemer's (2004) model of ER, which is associated with the Difficulties in Emotion Regulation Scale (DERS; Gratz and Roemer, 2004). In this model, ER is defined as emotional awareness, in concert with having ER strategies and the flexibility to use them—abilities that are often considered central to therapy and recovery from psychopathology (Marroquín, 2011; Mennin and Farach, 2007). While the DERS has been widely used in adolescents, data in inpatient adolescent samples is sparse (Venta et al., 2015) and ER has not been examined in relation to change during inpatient care.

In sum, the present study aimed to model the trajectory of internalizing symptom change among adolescents during the first month of inpatient psychiatric care and assess the role of amygdala-frontal connectivity and self-reported ER in symptom reduction, while taking into account length of stay and demographics. In acknowledging the transdiagnostic potential of ER and the NIMH's call to apply neurobiological methods to the study of mental illness irrespective of current classification systems, the present study sought to evaluate internalizing symptom change broadly among all admissions, rather than constraining the sample to one diagnostic category. Therefore, a broad-band measure of internalizing symptoms was used upon admission and weekly for four weeks, allowing for a latent growth curve analytic approach and permitting the evaluation of symptom recovery *during* hospitalization. It was expected that internalizing symptoms would decrease during the first month of hospitalization and that adolescents with better emotion regulation abilities at admission would demonstrate greater improvement.

**Table 1**
Descriptive data at admission.

| Disorder | *n* | *% Positive* |
|---|---|---|
| Depressive | 123 | 62.8% |
| Bipolar | 10 | 5.1% |
| Eating | 19 | 9.7% |
| Externalizing | 81 | 41.3% |
| Anxiety | 118 | 60.2% |
| Substance Use | 32 | 16.3% |
| DERS Scale | *Mean* | *SD* |
| Nonacceptance | 16.71 | 7.48 |
| Goals | 18.59 | 5.33 |
| Impulse | 16.14 | 7.13 |
| Awareness | 19.09 | 5.95 |
| Strategies | 25.72 | 9.17 |
| Clarity | 15.42 | 5.50 |

*Notes.* Depressive = MDD, dysthymia; Eating = anorexia, bulimia; Externalizing = ADHD, ODD, CD; Anxiety = PTSD, GAD, SAD, specific phobia, social phobia, OCD, panic disorder, agoraphobia; Substance Use = alcohol, marijuana, nicotine, other substance abuse or dependence; DERS = Difficulties in Emotion Regulation Scale. Based on the baseline linear model, the average internalizing symptom score at admission was 66.52.

## 2. Method

### 2.1. Participants

This study was approved by the appropriate institutional review board. 241 admissions to an adolescent inpatient unit at a large private-pay psychiatric hospital were approached for consent. This hospital provides medication management, psychoeducation, therapy, and recreation for adolescents with a range of psychiatric disorders (see Table 1). If parent consent was granted, adolescents were approached for assent. Of those approached, 27 declined, 4 later revoked consent, and 14 were excluded (inclusion criteria were age 12–17 and English fluency; exclusion criteria were psychosis or intellectual disability). In the remaining sample of 196, 61% ($n$ = 120) was female and the average age was 15.19 years ($SD$ = 1.480). 7% stated that they were of Hispanic origin and the racial breakdown was as follows: 79% White, 3% Asian, 1% Black, and 17% Other.

### 2.2. Measures

#### 2.2.1. Achenbach brief problem monitor (BPM)

The BPM (Achenbach et al., 2011) was completed by adolescents upon admission and also each week after admission. The BPM contains 19 items rated on a 0, 1, or 2 Likert scale. In the present study, the Internalizing t-score was used as a measure of self-reported internalizing distress. A score above 65 on this measure indicates scores of clinical concern. Adequate test-retest reliability, internal consistency, and criterion-related validity have been reported for this measure (Achenbach et al., 2011). It should be noted that this measure is a shortened version of the popular Youth Self-Report, which has been widely used with adolescents, though, to date, no published works have reported on the BPM with inpatient adolescents. Prior research utilizing the Youth Self-Report has described mean Internalizing t-scores of, for example, 57.2 (Handwerk et al., 1999) and 64.41 (Venta et al., 2015) in inpatient samples.

**Table 2**
Relations between final growth model variables and growth parameters.

| | *Estimate* | *S.E.* | *p-value* |
|---|---|---|---|
| **Intercept** regressed on: | | | |
| Nonacceptance of emotional responses | 0.31 | 0.08 | < 0.001[a] |
| Difficulties engaging in goal directed behavior | 0.31 | 0.12 | 0.009[a] |
| Impulse control difficulties | − 0.16 | 0.08 | 0.05 |
| Lack of emotional awareness | − 0.13 | 0.09 | 0.15 |
| Limited access to ER strategies | 0.31 | 0.09 | < 0.001[a] |
| Lack of emotional clarity | 0.26 | 0.11 | 0.018[a] |
| Age | − 0.38 | 0.30 | 0.21 |
| Sex | − 0.10 | 0.92 | 0.91 |
| Length of Stay | − 0.01 | 0.03 | 0.83 |
| **Slope** regressed on: | | | |
| Nonacceptance of emotional responses | − 0.01 | 0.03 | 0.76 |
| Difficulties engaging in goal directed behavior | 0.01 | 0.04 | 0.86 |
| Impulse control difficulties | − 0.05 | 0.03 | 0.05 |
| Lack of emotional awareness | 0.01 | 0.03 | 0.68 |
| Limited access to ER strategies | 0.02 | 0.03 | 0.50 |
| Lack of emotional clarity | 0.01 | 0.04 | 0.80 |
| Age | − 0.16 | 0.10 | 0.10 |
| Sex | 0.41 | 0.30 | 0.17 |
| Length of Stay | 0.003 | 0.011 | 0.78 |

[a] Statistically significant relation between the growth parameter (i.e., intercept, slope) and the variable in question (e.g., non-acceptance of emotional responses).

#### 2.2.2. Difficulties in emotion regulation scale (DERS)

The DERS (Gratz and Roemer, 2004) is a self-report questionnaire that assesses emotion dysregulation. It consists of 36 items that are scored on a 5-point Likert scale, ranging from 1 “almost never (0–10%)” to 5 “almost always (91–100%).” A higher score indicates greater emotion dysregulation. The measure assesses six domains listed in Tables 1 and 2. In the measure's initial publication, the DERS displayed good internal consistency, construct and predictive validity, and test-retest reliability (Gratz and Roemer, 2004). The six-factor structure of the DERS has also received support in a sample of inpatient adolescents (Perez et al., 2012).

### 2.3. Procedures

Self-report assessments were conducted in private on the unit by doctoral psychology students and trained clinical research assistants. Internalizing symptom assessment timing was standardized such that assessments were conducted within four days of admission and then again one, two, three, and four weeks later. The average length of stay was 38 days ($SD$ = 13.41).

#### 2.3.1. Image data acquisition

A subset of 45 adolescents additionally received a RSFC fMRI; a 3T Siemens Trio MR scanner was used. First, a structural MPRAGE sequence was collected for approximately 4.5 min (TE = 2.66 ms, TR = 1200 ms, flip angle = 12°, 256 × 256 matrix, 160 one mm axial slices at 1 × 1 × 1 mm voxels). This was followed by a 5 min RSFC scan: TE = 40 ms, TR = 2 s, flip angle = 90°, 3.4 × 3.4 × 4 mm voxels. During the RSFC scan, a large “X” was presented on a screen in the scanner. Participants were instructed to relax and let their mid wander, be as still as possible, keep eyes open or closed, and not to sleep.

### 2.4. Data analysis

#### 2.4.1. Neuroimaging data

The CONN Matlab Toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) was used to preprocess RSFC images in SPM 8 (2009). Preprocessing included: realignment to the first time series image, slice-timing correction, segmentation and normalization to the MNI EPI template, and smoothing with a 8 mm full width at high maximum (FWHM) Gaussian smoothing kernel. Individual scans (outlier images) with excessive movement were removed using the software ART (Artifact detection Tools, http://web.mit.edu/swg/art/art.pdf) with default parameters. Thus, no patients were excluded in the final analysis only individual scans with excessive movement. The ART-based functional outlier detection identified the outlier scans, which were then entered as first-level covariates in the toolbox and removed from consideration during analysis. RSFC data were analyzed using the CONN Matlab Toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). Regions of interest were created using the Montreal Neurologic Institute atlas. Since CONN processing includes a gray matter segmentation step, no segmentation was performed during preprocessing. Movement files from preprocessing (3 translational files, 3 rotational files), CSF, and white matter signals were used as covariates of no interest. The data was filtered with a frequency range of 0.008–0.09 Hz. IN ROI to ROI analysis, after processing the data through CONN, the Fisher-transformed correlation coefficients between the different seeds for each subject were identified. For amygdala to whole brain analysis, we used a similar procedure as in Ambrosi et al. (2017). The right and left amygdala seeds were not smoothed, but the rest of the brain was (8 mm FWHM).

#### 2.4.2. Behavioral data

Latent growth curve analyses were used to model the trajectory of internalizing symptom recovery across the first month of hospitalization. This method specifies parameters of change (e.g., linear and quadratic) to form a baseline model of change across time. Predictors of change are added to this baseline model. Consistent with the approach described in prior research (Bollen, 2004; Clapp et al., 2013), this study first estimated a baseline model of expected reduction in internalizing symptoms, comparing quadratic and linear models. Then, ER abilities were incorporated to form a final model. Intercept and slope parameters were extracted and correlated with RSFC data. Analyses were conducted using MPLUS 7 and SPSS. The comparative fit index (CFI), Tucker-Lewis Index (TLI), and root-mean-square error of approximation (RMSEA) were used to assess model fit. CFI and TLI > 0.90 and RMSEA < 0.08 were considered evidence of adequate fit (Bentler, 1990; Browne and Cudek, 1992; Kline, 2011); CFI and TLI > 0.95 and RMSEA < 0.06 were considered evidence of close fit (Hu and Bentler, 1999).

## 3. Results

### 3.1. Preliminary analyses

Data analyses were conducted on a sample of 196 adolescents. No evidence of problematic skewness (all smaller than ± 1) or kurtosis (all smaller than ± 2) was noted in baseline data (i.e., BPM and DERS subscales). Little's test indicated that data was missing at random ($Chi\text{-}Square$ = 70.99; $p$ = 0.23); thus, maximum likelihood estimation was appropriate. RSFC analyses were based on a reduced sample of 45 adolescents, which did not differ from the broader sample regarding age ($p$ = 0.32), sex ($p$ = 0.59), length of stay ($p$ = 0.73), or internalizing ($p$ = 0.18). Diagnostic data and self-reported ER abilities at admission appear in Table 1.

### 3.2. Baseline model of internalizing symptom change

Baseline linear and quadratic models were examined in the entire sample to determine the overall trajectory of internalizing symptom change beginning at admission (time point 0) and each week during the first month of hospitalization (time points 1, 2, 3, and 4). The baseline linear model demonstrated close fit (RMSEA = 0.06, CFI = 0.99, TLI = 0.99). The baseline quadratic model evidenced adequate fit (RMSEA = 0.07, CFI = 0.99, TLI = 0.98) but was not a significant improvement ($\Delta Chi\text{-}Square$ = 4.26, $\Delta df$ = 4, $p$ = 0.37), which was therefore selected for further examination.

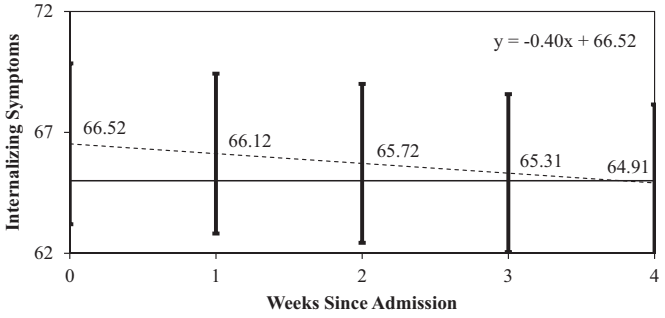


**Fig. 1.** Expected internalizing symptom trajectory. *Notes.* Dotted line indicates expected internalizing symptom trajectory. Vertical bars indicate 95% confidence bands. Horizontal bar at 65 indicates the BPM clinical cut-off.

Regarding the baseline linear model, as would be expected for an inpatient sample, the average internalizing symptom score at admission was high ($\alpha_0 = 66.52$), exceeding the BPM's cut off score of 65, and there was significant variability in these scores at admission ($\psi_{00} = 45.61, p < .001$). On average, internalizing symptom scores declined by 0.40 points per week ($\alpha_1 = -0.40$) and this decrease was significant ($p = 0.004$). Symptom change (i.e., slope) did not significantly vary ($\psi_{11} = 0.53, p = 0.19$), indicating that all individuals changed over time at approximately the same rate. Expected internalizing symptom trajectory appears in Fig. 1; by the fourth week, internalizing symptoms had fallen below the clinical cut-off (*Est* = 64.91).

### 3.3. Role of self-reported emotion regulation in symptom change

The six DERS subscales were added to the baseline linear model. Age, sex, and length of stay were added to the model as covariates. The augmented model demonstrated close fit (RMSEA = 0.04, CFI = 0.99, TLI = 0.98). Relations between predictor variables measured at admission and growth parameters appear in Table 2.

The DERS subscales differentially related to the intercept and slope parameters. Regarding the intercept parameter, increased Non-acceptance of emotional responses, Difficulties engaging in goal directed behavior, Limited access to ER strategies, and Lack of emotional clarity were associated with increased internalizing symptoms at admission. No DERS subscale was significantly associated with symptom reduction (i.e., slope).

### 3.4. Role of amygdala-frontal gyri RSFC in symptom change

A subsequent addition to the aforementioned protocol was sought to conduct fMRI scanning. Of the 196 enrolled in this study, 127 were approached for parental consent and adolescent assent; of these, 45 adolescents completed the additional consent/assent and underwent fMRI scanning. In this reduced sample, symptom change latent growth parameters (i.e., intercept and slope) were extracted and correlated with RSFC related to the amygdala and prefrontal areas. RSFC data was not included in growth curve models due to the limited sample size. Bivariate correlations appear in Table 3 and are graphically displayed in Fig. 2. RSFC between left amygdala and left superior frontal gyrus was significantly associated with the intercept—higher connectivity was associated with higher internalizing at admission. RSFC between the same regions was significantly, positively correlated with the slope— higher connectivity was associated with a more positive slope (i.e., less decline in symptoms). RSFC between the right amygdala and the left superior frontal gyrus was significantly, positively correlated with the slope parameter.

RSFC between these regions was also examined in relation to DERS ratings. RSFC between the left amygdala and the left superior frontal gyrus was significantly correlated with Difficulties engaging in goal-directed behavior ($r = 0.38, p = 0.009$) and Impulse control difficulties ($r = 0.34, p = 0.02$). RSFC between the right amygdala and the left superior frontal gyrus demonstrated a near-significant correlation with Difficulties engaging in goal-directed behavior ($r = 0.28, p = 0.06$).

**Table 3**
Correlations between internalizing trajectory parameters and RSFC.

| RSFC areas | Intercept | | Slope | |
|---|---|---|---|---|
| | *r* | *p* | *r* | *p* |
| Left Amygdala with | | | | |
| Left Inferior Frontal Gyrus | 0.02 | 0.87 | 0.03 | 0.86 |
| Left Medial Frontal Gyrus | 0.26 | 0.07 | 0.20 | 0.19 |
| Left Superior Frontal Gyrus | 0.35 | 0.02 | 0.36 | 0.01 |
| Right Inferior Frontal Gyrus | − 0.08 | 0.62 | − 0.13 | 0.40 |
| Right Medial Frontal Gyrus | − 0.01 | 0.97 | − 0.04 | 0.81 |
| Right Superior Frontal Gyrus | 0.09 | 0.53 | 0.06 | 0.69 |
| Right Amygdala with | | | | |
| Left Inferior Frontal Gyrus | 0.13 | 0.37 | 0.18 | 0.22 |
| Left Medial Frontal Gyrus | 0.20 | 0.17 | 0.22 | 0.15 |
| Left Superior Frontal Gyrus | 0.26 | 0.08 | 0.31 | 0.04 |
| Right Inferior Frontal Gyrus | 0.18 | 0.23 | 0.13 | 0.40 |
| Right Medial Frontal Gyrus | 0.09 | 0.55 | 0.06 | 0.69 |
| Right Superior Frontal Gyrus | 0.13 | 0.38 | 0.11 | 0.46 |

Notes. RSFC = Resting state functional connectivity. Intercept and slope are extracted latent growth parameters based on a reduced sample of 45. Correlations control for age, sex, and length of stay.

A supplemental whole brain amygdala connectivity analysis was also conducted. Specifically, we examined the RSFC between right and left amygdala regions of interest (ROI) and each voxel of the brain. The mean signal time course from the seeds were extracted and the Pearson's correlations coefficients with the time course of all other voxels of the brain were calculated. Correlation maps were calculated for each subject and correlation coefficients were then converted to normally distributed z-scores using the Fisher transformation in order to perform General Linear Model analyses using symptom change latent growth parameters (i.e., intercept and slope) and DERS as regressors of interest. A voxel statistical height threshold of $p < 0.001$ with a cluster threshold of $p < 0.05$ False Discovery Rate (FDR) corrected was used. The results were considered significant if $p < 0.05$ FDR corrected. Regarding the right amygdala, RSFC with the Precuneous Cortex (only) was a positive predictor of both symptom change parameters—the intercept ($p = 0.0005$, *p-FDR* = 0.009) and the slope ($p = 0.0003$, *p-FDR* = 0.006). No evidence of a significant relation to DERS total score was noted. Regarding the left amygdala, no evidence of significant relations to symptom change parameters or DERS total score was noted.

## 4. Discussion

The present study aimed to model the trajectory of internalizing symptom change among adolescents during the first month of inpatient psychiatric care and assess the role of baseline biologically-based and self-report ER abilities. Findings indicated high internalizing symptoms at admission and a significant decrease in symptoms resulting in an average subclinical score by the fourth week of hospitalization, providing evidence that a medium length of stay is appropriate for significant symptom reduction and echoing the findings of Kaminer et al. (1992) who reported a significant change in symptoms between the third and fourth weeks of inpatient treatment and Venta et al. (2015) who documented a decrease in internalizing symptoms over a one-month hospitalization. Though symptom reduction has also been reported for shorter and longer (Barber et al., 2002; Walter et al., 2010) lengths of stay among adolescents, the present study adds data in support of medium-length inpatient treatment and is one of only two studies with adolescents (Kaminer et al., 1992) to examine symptom change *during* treatment. Evidence of significant relations between demographic variables and growth parameters was not noted, implying that treatment was uniformly effective.

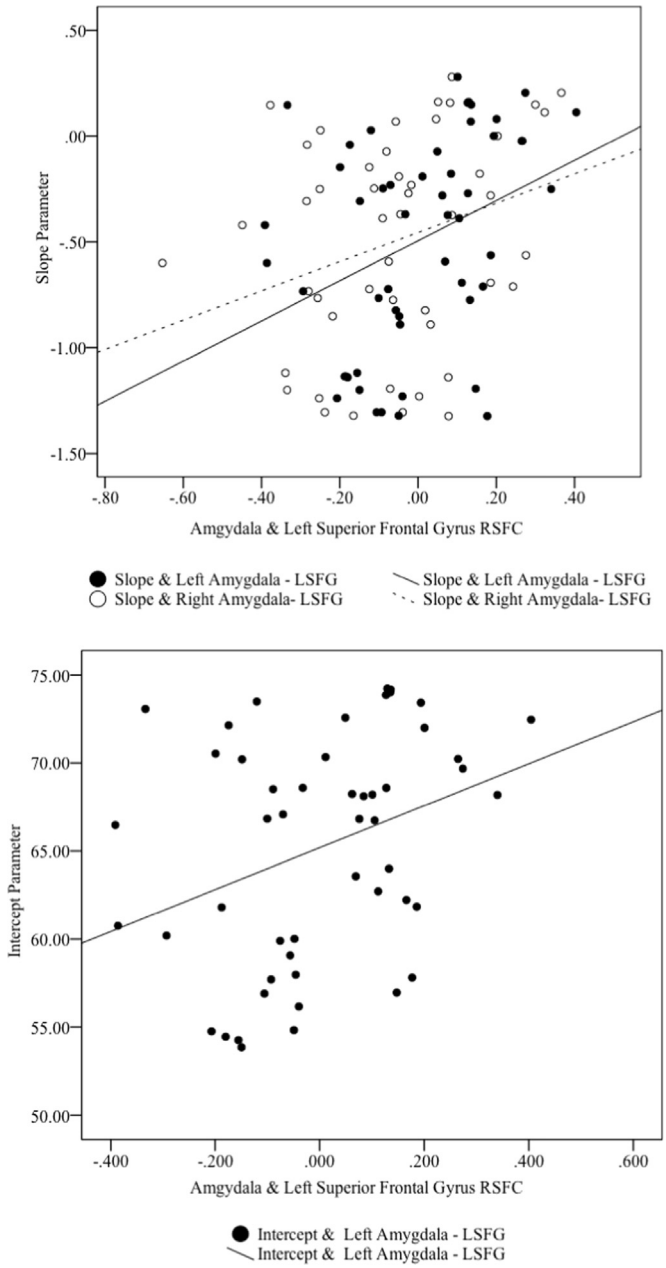


**Fig. 2.** Scatterplot of RSFC and internalizing trajectory parameters.

Regarding the role of self-reported ER, higher internalizing symptoms at admission were associated with several domains including increased Non-acceptance of emotional responses, increased Difficulties engaging in goal directed behavior, increased Limited access to ER strategies, and increased Lack of emotional clarity. Prior evidence documents significant correlations among the DERS subscales (Gratz and Roemer, 2004) and a number of conceptual models and empirical studies (Eastabrook et al., 2014; Izard et al., 2011; Mayer, 2001) point to relations between difficulties with emotional awareness and the regulation of those emotions, highlighting the role of *both* constructs in relation to internalizing distress. The findings of the current study echo the growing body of research highlighting associations between internalizing symptoms and multiple facets of ER.

Critically, findings did not support a relation between self-reported ER and internalizing symptom change, whereas RSFC data between areas forming an amygdala-frontal ER circuit (Kim et al., 2011) proved significant in this regard (as well as in relation to internalizing symptoms at admission). Increased RSFC between left and right amygdala and the left superior frontal gyrus was associated with less symptom reduction. A link identified between increased RSFC between these areas and increased emotion dysregulation (i.e., Impulse control difficulties and Difficulties engaging in goal-directed behavior) suggests that increased amygdala-frontal RSFC may serve as a biomarker of emotion dysregulation that significantly predicts treatment trajectory where self-reported ER falls short. The left superior frontal gyrus has been cited in what Soh and colleagues (2015) call “intentional emotional control.” Indeed, gray matter in this area was very recently linked to inhibition in children and activation was significantly correlated with ratings of impulsivity in adolescents (Soh et al., 2015; Ding et al., 2014). Closer inspection of the DERS subscales that demonstrated a significant relation to amygdala-frontal RSFC in this study reveals that these ER factors indeed reflect impaired inhibition/impulse control. Certainly the Impulse control difficulties subscale reflects these constructs and, likewise, the Difficulties engaging in goal-directed behavior subscale reflects difficulty inhibiting “upset” emotions. The findings of the present study suggest that, in adolescents with psychiatric diagnoses, excess connectivity between emotion and inhibitory regions of the brain serves as biomarker of emotional dysregulation that is predictive of poor treatment response.

Stronger RSFC in this ER circuit being negatively associated with treatment gains and ER abilities may appear somewhat paradoxical, as functional neuroimaging studies have often shown decreased activation in prefrontal regions signaling a failure to inhibit depressed mood. However, the present findings mirror several prior RSFC studies in depression, which have demonstrated *increased* RSFC in the cognitive control network (Zhou et al., 2010; Sheline et al., 2010), in contrast with earlier studies that found decreased task-based activity. The divergence in the cognitive control network between increased resting-state activity and decreased task-based activity might be explained by the presence of higher, more volatile activity in these regions at rest, which in turn could lead to smaller increases during tasks (Sheline et al., 2010). Consistent with Sheline et al. (2010) and Cullen et al. (2014), we suggest that increased connectivity between frontal regions and the amygdala at rest may be related to reduced frontal activity in controlling the cascade of negative mood in adolescent internalizing symptoms that appears to be elicited by negatively valenced tasks. This finding echoes the hyperconnectivity hypothesis of depression, which posits that increased RSFC coupling between prefrontal cortex, precuneus, and amygdala is associated with increased risk for internalizing disorders (Schilbach et al., 2014; Perrin et al., 2012).

A limitation in this study's main analyses is that the amygdala-frontal ER circuit was explored at the exclusion of other brain regions, when other brain regions also warrant investigation—connection between the amygdala and hippocampus, parahippocampus, and brainstem (Cullen et al., 2014); between the amygdala and precuneus (Cullen et al., 2014); and between the amygdala and the anterior cingulate cortex (Connolly et al., 2013) have also been linked to adolescent internalizing. Thus, a supplemental whole brain amygdala connectivity analysis was conducted examining RSFC between right and left amygdala and each voxel of the brain. The only significant relations to emerge regarded connectivity between the right amygdala and precuneous, which was a positive predictor of both symptom change parameters. Specifically, increased connectivity between these two regions was associated with increased internalizing symptoms at admission as well as a more positive slope (i.e., less symptom decline during treatment). This link between amygdala-precuneous RSFC and internalizing symptoms mirrors the findings of Cullen et al. (2014) who noted the same effect in adolescents with Major Depressive Disorder. The authors hypothesize that the coupling of these functionally opposite regions during rest (as in the current study) may (a) underlie a failure to suppress negative self-thoughts or (b) contribute to disproportionate emotional salience of self information processing, thereby serving as mechanisms in internalizing psychopathology. Likewise, several studies conducted in adults have previously linked

increased amygdala-precuneous RSFC to other internalizing symptoms like panic (Pannekoek et al., 2013) and social anxiety (Liao et al., 2010). To our knowledge this is the first study to also link connectivity between these regions to reduced symptom change during treatment.

Anomalous RSFC between these regions should be examined in future research, though the advantage of focusing on one circuit is reduced multiple comparisons.

Several additional limitations should be noted. First, RSFC is not without limitations; Stevens and Spreng (2014) cite concerns regarding technical artifacts, like head motion. Additionally, the present study did not control for specific aspects of treatment (e.g., number of therapy sessions) and sample sizes with RSFC data were insufficient to constrain analyses to individual diagnostic categories. In order to inform optimal healthcare decision-making, future research must isolate the mechanism of recovery and model that trajectory in relation to self-report and biologically-based variables. Additional limitations include the atypicality of this medium-stay unit relative to typical inpatient settings in the U.S. and limited ethnic and racial diversity in this sample. Likewise, the private-pay nature of this facility limits generalizability.

Notwithstanding these limitations, the present study is the first to examine internalizing symptom change *during* inpatient treatment in a large group of adolescents and adds to prior research by examining the role of baseline ER abilities from both self-report and biologically-based perspectives. Findings are strengthened by a latent growth curve modeling approach, allowing examination of change across one-week increments. Finally, findings point, preliminarily, to an RSFC-based biomarker of emotion dysregulation with potential predictive value regarding treatment trajectory for adolescents with severe psychopathology—an important indicator of the value of brain data in personalized psychiatric care.

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