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Research paper

Amygdala-frontal connectivity predicts internalizing symptom recovery among inpatient adolescents

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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 (α_0 = 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

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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.