MECHAMISMS UNDERLYING THE COMORBIDITY BETWEEN DEPRESSIVE AND ADDICTIVE DISORDERS IN ADOLESCENTS: INTERACTIONS BETWEEN STRESS AND HPA ACTIVITY (ON-LINE SUPPLEMENT)

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Method

Informed Consent Process and Overview of the Study

Prior to performing the research procedures, all adolescent participants signed a written assent form and parents signed an informed consent document, approved by the Institutional Review Boards at the University of California at Los Angeles and its affiliate institutions. The participants were recruited from local pediatric and mental health clinics and schools in Los Angeles, through advertisements in local news papers and by word-of-mouth. The study included initial screening to determine basic inclusion criteria. Eligible subjects then underwent a detailed diagnostic evaluation along with assessment of recent stressful experiences. Participants who continued to meet eligibility criteria underwent a physical examination and routine laboratory investigations following which they participated in the laboratory sleep and neuroendocrine study. The subjects received financial compensation for participation in the study, with payment prorated for each assessment.

Clinical Assessments

Standardized instruments were used for all assessments, and more details regarding each assessment are provided in the main paper. The interviewers were clinicians with Bachelor's or Master's Degree in Psychology and had a minimum of three months' training on the instruments. In addition, they had to demonstrate agreement (>85%) in coding all variables with previously trained raters prior to conducting the interviews. All interviews were audio-taped, and a random set of assessments was independently coded by the first author for reliability (κ = 0.88-1.00). During the course of the study, reliability checks between interviewers were repeated at 6-month intervals. All baseline interviews were conducted face-to-face. Majority of the follow-up assessments were conducted face-to-face. In the remaining cases when the participants moved out of town (e.g., leaving for college), telephone interviews were conducted.

In order to obtain information on recent stressful life experiences, a semi-structured interview developed in our laboratory was modified for use with adolescents (1, 2). The instrument probed about discrete, acute events with a clear period of onset and offset. Nine content areas (including family relationships, close friendships, romantic relationships, social life, school, work, finances, health of subject, and health of family members) were assessed. Only the adolescent served as an informant for this assessment (in contrast to diagnostic information where both adolescent and a parent were interviewed).

Narrative summaries of the life events were presented to a group of trained raters (see above for qualifications). The raters were blind to the participant's diagnostic status and reaction to the stressor. Consensus group ratings were given for the degree of stress for each event (1 = not at all stressful, and 5 = extremely stressful), independence of the event from the person's actions (1 = completely independent, and 5 = completely dependent), and whether the event was a positive, neutral or negative experience under the given circumstances. Symptom-related events were not scored. A random selection of the interviews was presented to an independent group of trained raters supervised by Dr. Hammen. Good inter-rater reliabilities have been established for the stress ratings (1, 3).

It is possible that retrospective reports of stressful experiences may be biased by memory effects. Care was taken to probe each social domain systematically and also timelines were provided for the occurrence of events (e.g., academic calendar, birthdays, holidays, etc.).

Results

Developmental Progression of Substance Use Disorder in Depressed and non-Depressed Adolescents

The developmental progression from initiation of alcohol/drug use to substance use disorder in the three groups is described in Table 1. The groups were comparable on the age at which initiation of alcohol/drug use occurred, first experience of intoxication, and regular

alcohol/drug use. There was a tendency for high-risk and depressed youngsters to develop substance use disorder at an earlier age than normal controls. These two groups progressed more rapidly from regular alcohol/drug use to substance use disorder than normal controls.

Insert Table 1 Here

Baseline Demographic and Clinical Features associated with Substance Use Disorder during Prospective Follow-up in Depressed Adolescents

The initial demographic and clinical characteristics of depressed adolescents who developed substance use disorder during prospective follow-up (n = 19) were compared with those of depressed youth who did not develop substance use disorder (n = 32). None of the demographic factors were associated with vulnerability for substance use disorder (see Table 2). Among the clinical variables, depressed adolescents who developed substance use disorder had longer recovery time from the index depressive episode than their counterparts who did not develop substance use disorder. Comorbid anxiety disorder also was associated with a higher likelihood of developing substance use disorder during prospective follow-up.

Insert Table 2 Here

Effect of Comorbid Psychiatric Disorders on HPA Activity in Depressed Adolescents

Both anxiety disorder and nocturnal urinary free cortisol concentration at intake were associated with the development of substance use disorder during follow-up. Therefore, the association between anxiety disorder and nocturnal urinary free cortisol concentration was examined. Depressed adolescents with comorbid anxiety disorder had higher nocturnal urinary

free cortisol concentration than their counterparts without anxiety disorder (see Figure 1). In contrast to this, there was a tendency for depressed adolescents with comorbid disruptive disorder to have lower nocturnal urinary free cortisol concentration than their counterparts without disruptive disorder (see Figure 1).

Insert Figure 1 Here

Discussion

Consistent with prior literature, depressed adolescents were more likely to develop substance use disorder during prospective follow-up compared to non-depressed youth (4, 5; also see the main paper). Moreover, once regular alcohol/drug use occurred, the progression to substance use disorder was more rapid in depressed youngsters (6). However, because of the modest sample sizes, these findings should be considered preliminary until they are replicated in a larger sample. Overall, there were few demographic or clinical predictors of substance use disorder. In particular, depressed youth with a protracted depressive episode, or those with comorbid anxiety disorder, were more likely to develop substance use disorder. It is possible that depressed youth might find temporary relief of anxiety/dysphoric mood when they experiment with alcohol and/or drugs. The alleviation of anxiety symptoms and/or dysphoric mood potentially leads to abuse of these substances. Continued use of addictive substances reciprocally could worsen depressive symptoms, thereby leading to a downward spiral of increased anxiety, depression and addictive behavior (5, 6).

From a neurobiological perspective, there is a tentative suggestion that the increased vulnerability for substance use disorder in depressed adolescents with comorbid anxiety disorder might be mediated/moderated by elevated HPA activity in this subgroup of patients (6).

Other investigations in adolescents and adults found that depressed persons with comorbid anxiety disorder exhibited greater HPA response to a standard psychosocial stressor compared to their counterparts without anxiety disorder (7, 8). It is not clear whether anxiety disorder and depressive episodes induce a change in HPA regulation, thereby increasing the risk for substance use disorder. Alternatively, genetic factors, early developmental stressors or their combination could sensitize the stress pathways in the central nervous system, thereby inducing HPA dysregulation (7, 9, 10). HPA dysregulation, in turn, might increase the risk for both anxiety and depressive disorders in persons who experienced stress in early-life (11, 12).

In contrast to the described associations among anxiety disorder, elevated HPA activity and vulnerability for substance use disorder in depressed adolescents (5), Moss and colleagues observed lower cortisol response to an anticipated stressor in pre-adolescent boys whose biological fathers had substance use disorder compared with boys whose fathers did not have substance use disorder (13). The lower cortisol response during pre-adolescence was associated with "regular" substance use during adolescence. Antisocial disorders mediated the risk for substance-related problems in the "high-risk" group (14). Although depressed youth with comorbid disruptive disorder exhibited lower HPA activity than their counterparts without disruptive disorder in the current study, extreme caution should be exercised in over-interpreting this observation due to the modest sample sizes. Other investigators also reported that antisocial behaviors/disorders contributed significant variance to the association between addictive and depressive disorders, possibly through common genetic and/or environmental factors shared by all three conditions (15). These findings suggest that there may be two subgroups of depressed youth at risk for developing substance use disorder, one subgroup with anxiety symptoms and high HPA function and a second subgroup with conduct symptoms, low HPA function and high density of substance use disorder in family members. Longitudinal investigation of at-risk youth from both diagnostic categories (including externalizing and internalizing disorders) will be helpful in determining the magnitude of risk for substance use

disorder in each subgroup of adolescents, as well as the underlying mechanisms of vulnerability. If the hypothesized relationships among these factors are demonstrated, it is likely that the two groups would benefit from different treatment strategies (for further discussion, see the main paper).

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Table 1: Progression of substance use (means and standard deviations) in adolescents that developed substance use disorder at follow-up

	Normal (n = 4)	High-Risk (n = 10)	Depressed (n = 19)	Statistic	p
Age of first use	14.0 ± 2.4	14.5 ± 2.6	14.1 ± 2.4	0.10	NS
Age of first intoxication	14.3 ± 2.2	14.8 ± 2.6	14.5 ± 2.2	0.11	NS
Age of regular use[1]	16.2 ± 1.0	16.0 ± 2.3	16.0 ± 1.7	0.03	NS
Age of SUD onset	19.5 ± 2.5	17.3 ± 2.9	16.6 ± 2.0	2.52	.10
Progression to SUD[2]	$3.3 \pm 2.0_a$	$1.3 \pm 1.3_b$	$0.6 \pm 0.4_b$	12.17	.0001

[1]Substance use at least twice/week for more than one-month duration

[2]Time interval between age of regular substance use and onset of substance use disorder (SUD) in years

Different subscripts denote significant differences among groups

Table 2: Demographic and clinical parameters at intake in depressed adolescents stratified by substance use disorder at follow-up

	No SUD (n= 32)	SUD (n= 19)	Statistic	p
Age at recruitment (years)	15.0 ± 1.6	15.2 ± 1.2	0.74	NS
Gender			2.69	.09
male	11(34.4)	11 (57.9)		
female	21 (65.6)	8 (42.1)		
Ethnicity	17 (53.1)	9 (47.4)	0.16	NS
Caucasian	15 (46.9)	10 (52.6)		
Non-Caucasian				
Socioeconomic score	42.3 ± 10.3	37.4 ± 12.7	1.50	NS
Follow-up interval (years)	3.8 ± 1.2	3.7 ± 1.0	0.87	NS
Hamilton Depression Rating Scale	19.9 ± 3.9	19.0 ± 3.8	0.78	NS
Beck Depression Inventory	18.7 ± 7.3	19.3 ± 9.1	0.25	NS
Children's Global Assessment Scale	52.2 ± 8.1	50.6 ± 6.8	0.77	NS
Duration of depressive episode (weeks)	22.0 ± 10.9	30.7 ± 10.3	2.84	.007
Lifetime substance use (n = 8)	3 (9.4)	5 (26.3)	FET	NS
Anxiety disorder (n = 18)	7 (21.9)	11 (57.9)	5.29	.02
Disruptive disorder (n = 7)	3 (9.4)	4 (21.1)	FET	NS
Depression history in parent (n = 26)	17 (53.1)	9 (47.4)	0.16	NS

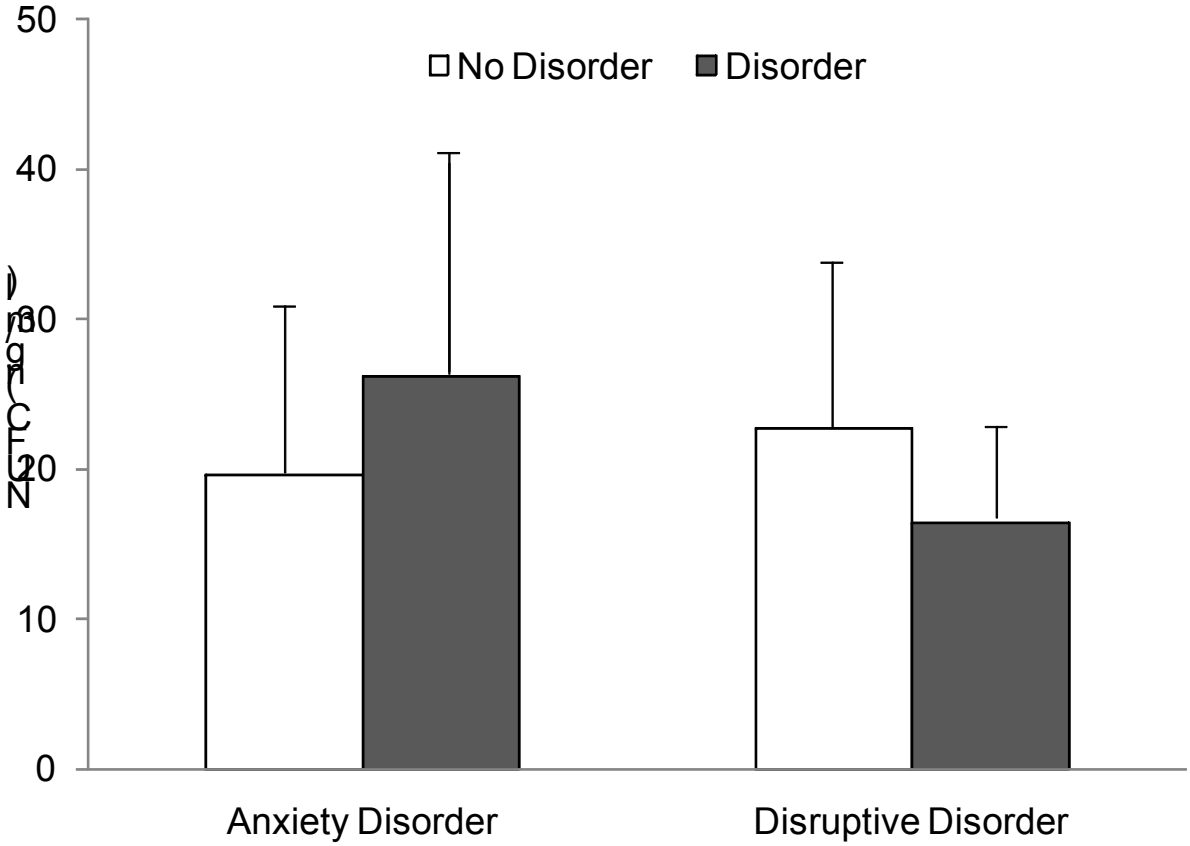
SUD = substance use disorder

Data are presented in Means and standard deviations, or as raw numbers and percentages (in parentheses)

FET = Fisher's Exact Test, two-tailed

Figure Legend

Figure 1: Nocturnal urinary free cortisol (NUFC) concentration measured at intake in depressed adolescents stratified by comorbid disorders.


50
40
30
20
10
0
No Disorder
Disorder
Anxiety Disorder
Disruptive Disorder