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The differential influence of life stress on individual symptoms of depression

Fried EI, Nesse RM, Guille C, Sen S. The differential influence of life stress on individual symptoms of depression.

Objective: Life stress consistently increases the incidence of major depression. Recent evidence has shown that individual symptoms of major depressive disorder (MDD) differ in important dimensions such as their genetic and etiological background, but the impact of stress on individual MDD symptoms is not known. Here, we assess whether stress affects depression symptoms differentially.
Method: We used the chronic stress of medical internship to examine changes of the nine Diagnostic and Statistical Manual (DSM)-5 criterion symptoms for depression in 3021 interns assessed prior to and throughout internship.
Results: All nine depression symptoms increased in response to stress (all $P < 0.001$), on average by 173%. Symptom increases differed substantially from each other ($P < 0.001$), with psychomotor problems (289%) and interest loss (217%) showing the largest increases, and suicidal ideation (146%) and sleep problems (52%) the smallest. Symptoms also differed in their severities under stress ($P < 0.001$): Fatigue, appetite problems and sleep problems were most prevalent; psychomotor problems and suicidal ideation were least prevalent.
Conclusion: Stress differentially affects the DSM-5 depressive symptoms. Analyses of individual symptoms reveal important insights obfuscated by sum-scores.

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Key words: depressive symptoms; major depressive disorder; life stress; internship

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Significant outcomes

- While all MDD symptoms increase in response to internship stress, symptoms differ dramatically in magnitude of increases.
- MDD symptoms show pronounced prevalence differences under stress.

Limitations

- Internship stress is a particular stressor in a fairly homogeneous population, and extrapolation to the general population and other stressors should be performed with caution.
- This study did not assess the direction of depressive symptoms with complex natures (e.g. hypersomnia vs. insomnia).

Introduction

Major depressive disorder (MDD) is a highly heterogeneous disorder (1–3). The Diagnostic and Statistical Manual (DSM-5) (4) uses nine symptoms to define depression, three of which are comprised of opposite symptoms (e.g. 'insomnia *or* hypersomnia'), leading to 1497 unique symptom profiles that qualify for the same diagnosis (5). In line the with the National Institute for Mental Health (NIMH) strategic plan for mood disorder research (6), a growing body of evidence suggests that the analysis of individual depression symptoms is an untapped source of important and clinically relevant data. For instance, MDD symptoms differ from each other in their genetic (7–9) and

etiological (10) background, differentially impact impairment of psychosocial functioning (11) and show differential associations with important clinical variables such as demographic information, personality traits, life events and lifetime comorbidities (12).

Life stress is one of the most robust triggers for MDD (13,14). Elevated levels of depression after experiencing stress have been documented both in patients and general population samples (14,15), with depression rates 2.5–7 times higher for individuals exposed to serious stressors (16,17). Despite the overwhelming evidence that depression diagnoses are increased in the context of stress, we know little about the behaviour of individual depressive symptoms in response to stress.

Here, we prospectively investigate the impact of life stress on the nine DSM MDD criterion symptoms in a cohort study of interns. Internship is a well-established serious chronic stressor, and interns are faced with long work hours, sleep deprivation, loss of autonomy, as well as extreme emotional situations (18,19). In a previous longitudinal study of interns, depression levels increased from 3.9% at baseline to 25.7% during internship (20). Utilizing internship as prospective stress model offers the opportunity to assess depression symptoms in a large sample before and after the reliable onset of severe chronic stress.

Aims of the study

The present report uses a cohort of 3021 interns to examine whether internship stress impacts some depression symptoms more strongly than others, as well as the magnitude of potential differences.

Material and methods

Sample

Seven thousand and four hundred and twenty-nine interns entering internship programmes in the USA during the 2007–2012 academic years were invited to participate in the study; 59% (N = 4383) accepted the invitation. The institutional review boards at participating hospitals approved the study. Participating subjects provided electronic informed consent and were given $50 in gift certificates.

Assessment

All surveys were conducted through a secure online Web site designed to maintain confidentiality. Depressive symptoms were measured using the Patient Health Questionnaire (PHQ-9) (21). The PHQ-9 is a self-report component of the PRIME-MD inventory that screens for the DSM-5 criterion symptoms of depression. For each of the nine symptoms, subjects indicated whether, during the previous 2 weeks, the symptom had bothered them 'not at all', 'several days', 'more than half the days' or 'nearly every day'. Each item yields a score of 0, 1, 2 or 3. The nine symptoms assessed by the PHQ-9 are as follows: 'little interest or pleasure in doing things' (interest), 'feeling depressed or hopeless' (mood), 'sleep problems' (sleep), 'feeling tired' (fatigue), 'appetite problems' (appetite), 'feeling bad about yourself/that you are a failure' (self-blame), 'trouble concentrating on things' (concentration), 'moving or speaking slowly/being fidgety or restless' (psychomotor) and 'suicidal ideation' (suicide).

Subjects completed a baseline survey 1–2 months prior to commencing internship that assessed general demographic factors (age, sex) and depressive symptoms (PHQ-9). Participants were contacted via email 3, 6, 9 and 12 months into their internship year and asked to complete the PHQ-9 again.

Statistical analysis

We compared symptom severity at baseline with average symptom severity during the four measurements across the internship. This approach has been used in previous publications based on this dataset (10,20) and has the advantage of increased reliability of symptom assessment within internship through repeated measurement. When averaging the within-internship symptom scores, 1362 (31.1%) of the 4383 subjects were dropped via listwise deletion because they had missing data on two or more time points, leaving 3021 interns in the analytic sample.

Overall, three analyses were performed. First, we investigated whether PHQ-9 symptoms increased with stress. We used one paired samples t-test per symptom to compare severities and adjusted P-values for multiple testing using the Bonferroni correction.

Second, we tested whether symptoms differed from each other in response to stress, a test to assess whether stress had differential impacts on specific depressive symptoms. Instead of performing 36 individual tests comparing each symptom increase against all other symptom increases, we conducted one omnibus test. We fitted two longitudinal mixed models to the data with the subject variable as a random effect, using the *lmer* function of the R-package *lme4* (22). In model I, symptom increases from baseline to the stress condition

were allowed to be freely estimated, whereas increases were constrained to be equal in model II (i.e. slopes were forced to be equal). We then examined whether the constrained model II showed significantly decreased model fit compared with model I, as would be expected if symptoms increased differentially in response to stress. We compared models using a chi-squared difference test and used the Bayesian information criterion (BIC) (23) as goodness-of-fit statistic (the lower the value, the better the fit).

Third, we examined the stress condition symptom score to see whether the nine depressive symptoms differed in their severities after stress onset. Similar to analysis two, we performed one omnibus test by fitting two mixed models to the cross-sectional data of timepoint two using the *LMER* function of the R-package *LME4*, once again using the subject variable as random effect. Model I allowed for a free estimation of symptom severities, while model II constrained all symptoms to have equal severities. Model fit was compared similar to analysis two.

Lastly, we provide detailed descriptive information about symptom severity and increases. Analysis one was performed using SPSS v21.0 (24) and analyses two and three with R v3.1.0 (25). We consider *P*-values of <0.05 significant.

Results

Sample characteristics

Three thousand and twenty-one individuals were included in the analyses; 48.4% of the study participants were males, and the mean age was 27.5 (SD = 2.7) (Table 1). Participants that were dropped due to missing values did not differ significantly from the retained participants regarding the variables age, sex or history of depression (all $P > 0.05$).

Symptom increases

All symptoms increased significantly over time (*t*-values between 12.3 and 57.6, all $P < 0.001$) (Table 2) (Fig. 1). Symptoms increased by an average of 173.4%, ranging from 51.5% (*sleep*) to 289.2% (*psychomotor*) (Fig. 2).

Symptoms differed in their increases: Model I (variable symptom increases across time) fits the data significantly better than model II (equal symptom increases across time) ($\chi^2_{diff} = 2652$, $df_{diff} = 8$, $P < 0.001$) (Table 3). This means that stress had differential impact on the nine depressive symptoms.

Table 1. Demographic characteristics of study participants

Variable	Number (%)
Sex	
Male	1462 (48.4)
Female	1559 (52.6)
Age, years	
≤25	536 (17.7)
26–30	2146 (71)
31–35	281 (9.3)
>35	58 (<0.1)
History of depression	
Yes	1326 (43.9)
No	1693 (55.1)
Specialty	
Internal medicine	1106 (36.6)
Other	394 (13)
Pediatrics	350 (11.6)
General surgery	306 (10.1)
Psychiatry	217 (7.2)
Emergency medicine	197 (6.5)
Family medicine	137 (4.5)
Obstetrics/gynecology	123 (4.1)
Internal medicine/pediatrics	73 (2.4)
Neurology	48 (1.6)
Transitional	43 (1.4)
Missing	27 (0.9)

Table 2. Symptom severities and increases

	Baseline		Under stress		Increases	
$n = 3021$	Mean	SD	Mean	SD	%	*P*
Interest	0.21	0.48	0.66	0.57	216.5	< 0.001
Mood	0.24	0.48	0.64	0.59	168.3	< 0.001
Sleep	0.54	0.73	0.82	0.71	51.5	< 0.001
Fatigue	0.57	0.69	1.40	0.70	145.4	< 0.001
Appetite	0.35	0.64	0.93	0.77	164.4	< 0.001
Self-blame	0.21	0.50	0.58	0.64	175.0	< 0.001
Concentration	0.17	0.47	0.52	0.62	204.4	< 0.001
Psychomotor	0.06	0.29	0.23	0.42	289.2	< 0.001
Suicide	0.04	0.21	0.10	0.27	146.0	< 0.001

Symptoms under stress

Model I (variable symptom severities under stress) showed a superior fit compared with model II (equal symptom severities under stress) ($\chi^2_{diff} = 13\,644$, $df_{diff} = 8$, $P < 0.001$) (Table 3). The three symptoms *fatigue* (Mean = 1.40), *appetite* ($M = 0.93$) and *sleep* ($M = 0.82$) showed the highest mean severity under stress, while the two symptoms, *suicide* ($M = 0.10$) and *psychomotor* ($M = 0.23$), showed the lowest mean severity.

Discussion

The present study examined the impact of chronic stress on the nine DSM-5 criterion symptoms for depression by prospectively assessing a population

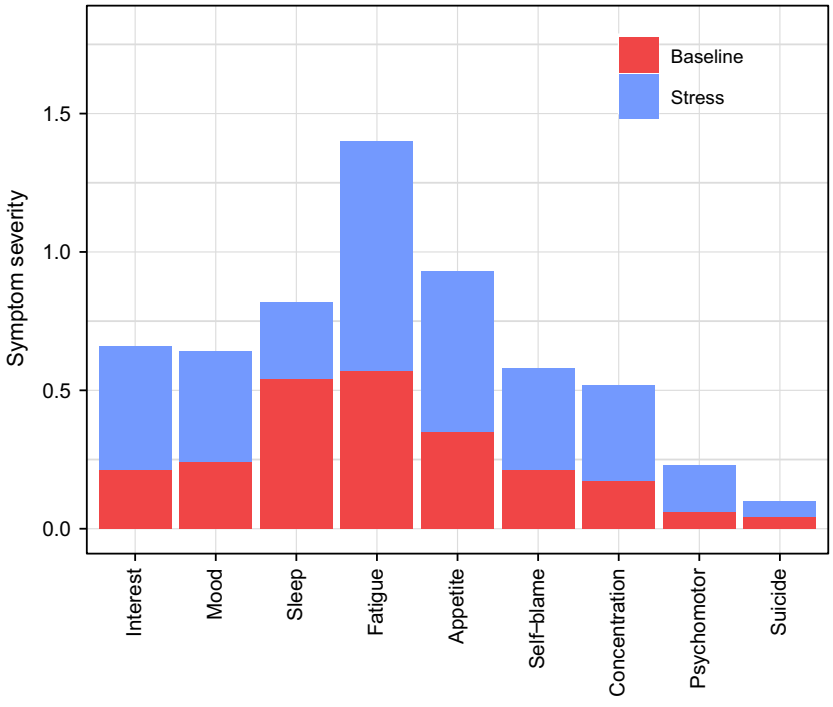

Fig. 1. Depression symptoms at baseline and under stress.

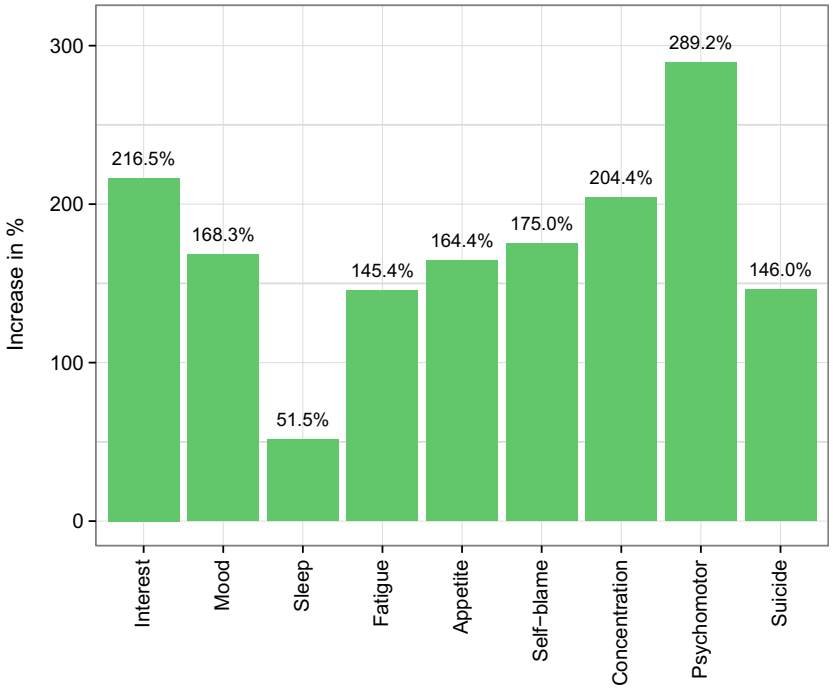

Fig. 2. Symptom change over time.

of 3021 individuals before and after the onset of medical internship. While all symptoms increased during internship, the impact of stress varied dramatically across symptoms, with some symptoms increasing substantially more than others; especially, psychomotor problems, loss of interest and concentration problems exhibited pronounced increases. The somatic symptoms fatigue, appetite and sleep problems were most prevalent under stress.

Prior studies have focused on the relationship between stress and depression subtypes, but no clear pattern has emerged (26–28). This inconsistency is likely due to problems pertaining to the validity of MDD subtypes (29,30), a reliance on retrospective self-report of life stress that can be substantially biased (31,32), and a cross-sectional design that confounds the bidirectional influences of life stress and depression (14). The current study addresses these limitations, with a prospective

Table 3. Chi-squared difference tests for the two model comparisons

	df	BIC	χ^2_{diff}	df_{diff}	*P*
Differential symptom change					
Model I†	20	275 106			
Model II‡	12	277 680	2662	8	<0.001
Differential symptom severity					
Model I§	11	137 110			
Model II¶	3	150 530	13 502	8	<0.001

df, degrees of freedom; BIC, Bayesian information criterion; χ^2_{diff} , chi-squared statistic of the chi-squared difference test; df_{diff}, degrees of freedom of the chi-squared difference test; *P*, *P*-value of the chi-squared difference test.

†Variable symptom increases across time.

‡Equal symptom increases across time.

§Variable symptom severities after stress onset.

¶Equal symptom severities after stress onset.

design that allows for a causal interpretation: Stress leads to substantial and heterogeneous increases of depressive symptoms.

Implications

The present report documents substantial variability in symptom change across time and symptom severity under stress. This work adds to a growing body of evidence illuminating important differences between individual symptoms of depression (7,10,33) and indicates that the reliance on sum-scores and thresholds obfuscates crucial information about the nature of depressive symptoms. This covert heterogeneity may help to explain recent 'disappointing' findings such as low reliability for MDD diagnoses in the DSM-5 field trials (34), low antidepressant efficacy compared with placebo response (35), lack of common genetic markers associated with antidepressant response (36) and failure to detect even small genetic effects with depression diagnosis in large genomewide association studies (37).

The investigation of individual symptoms reveals clinically useful insights. For instance, about 72% of the interns in our study reported sleep problems on at least several days per week under stress. Sleep problems are a well-established predictor for the development of future episodes of depression (38), decrease treatment efficacy (39,40), and directly targeting sleep problems in depressed patients may increase overall depression improvement (41,42). We believe that utilizing symptom information is a crucial step toward the development of more efficient prevention and intervention strategies and may help us understand underlying biological processes better than diagnosis level analyses.

The DSM criterion symptoms assessed in this study are only a small subset of potential MDD symptoms (43) and were largely determined by clinical consensus instead of empirical evidence (12). Various other symptoms, including anxiety, irritability and anger, are prevalent among individuals diagnosed with MDD and may have great value in predicting the course of the disease (44,45). Assessing symptoms outside of traditional DSM criteria could advance future studies of stress and depression as well as treatment of patients, and is in line with the National Institute of Mental Health finding that strictly adhering to DSM diagnostic criteria may be inhibiting progress in elucidating the biological roots of mental illness (46). A recent study also documented that specific dimensions of rating scales for depression, such as the 6-item melancholia subscale of the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) (47,48), are more sensitive to treatment response than large multidimensional scales (49). The authors concluded that such subscales may possess greater biological validity and thus circumvent problems of heterogeneity inherent to most depression rating scales.

Limitations

The present report has three limitations. First, we only investigated symptom change in response to one specific stressor. While the particular pattern of symptom change is likely to be different with different stressors, the results of this study and others (50–52) suggest that it is unlikely that other stressors will uniformly increase the prevalence of all depressive symptoms equally. Second, interns are not a representative sample, so extrapolation to the general population should be performed with caution. Third, the PHQ-9 neither assesses the direction of depressive symptoms with complex natures (e.g. hypersomnia or insomnia instead of sleep problems) nor MDD symptoms outside of the DSM-5 criteria.

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Declarations of interest

All authors declare that they have no conflict of interests.

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