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Perceived stress, health status, and the activity of neutrophils in undergraduates over one academic year

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Summary
Twenty-eight undergraduates participated in a 12-month (one academic year) study and were tested on six occasions to examine the effects of perceived stress on the activity of neutrophils. The six testing periods were selected to encompass variation in academic typical experiences over 1 year. At each time point, participants gave a small finger-stick sample of blood before completing standard measure of perceived stress and health. Activity of neutrophils was determined from the whole bloods' capacity to reduce nitro-blue tetrazolium (NBT) and was presented as percentage of NBT positive cells. Results showed that there were significant correlations between perceived stress levels and NBT positive cells ($p < 0.05$) at all six testing periods, with surprisingly large effects size. Further analysis (Fisher's Z averaging analysis) revealed the robust nature of this association. In addition, there were significant correlations between NBT positive cells and participants' current state of health on three of the six occasions: generally, as perceived stress increased the percentage of NBT positive neutrophils increased and health status decreased. The results support the hypothesis that stress may affect the activity of neutrophils, which in turn may influence health. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words
perceived stress; neutrophils; health status; nitro-blue tetrazolium (NBT) test; academic stress

Introduction

The potential stressors facing undergraduate students at university are many. In addition to academic demands, there are financial, interpersonal and domestic demands, and, generally being able to look after one's self. Many studies have shown that the stress of academic life can lead to immunosuppression and illness (Dorian et al., 1982; Glaser et al., 1992; Jemmott et al., 1983; Tomei, Kiecolt-Glaser, Kennedy, & Glaser, 1990).

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Glaser and Coworkers (Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986; Glaser et al., 1985) assessed immune parameters in a sample of second year medical students before, during and after examinations. Distress significantly depressed both number and cytotoxic activity of natural killer (NK) cells. In contrast, lymphocyte numbers and ability to respond were lower during the exam period when compared to baseline, as was the quantity of interferon produced by stimulated leukocytes. Follow-up studies (Glaser et al., 1992; Tomei et al., 1990) supported and extended these findings, indicating a variety of immune alterations at the time of exams.

Whilst there is considerable evidence to support the notion that stress has an immunosuppressive effect, few studies have investigated the effects of academic stress on components of the non-specific immune system. This is surprising as polymorphonuclear neutrophils (PMN) comprise 60–70 per cent of the leukocyte population and in an earlier study, it was demonstrated that even a short-term mental stressor modulated the activity of PMN (Ellard, Castle, & Mian, 2001). Further developmental work on the nitroblue tetrazolium (NBT) test method, used in this study, demonstrated that there was a significant positive association between perceived stress and the percentage of activated neutrophils in a student population indicating the need for more development work on this method (Ellard, Barlow, & Mian, 2004).

The health of students has been shown to be affected by the levels of stress they are experiencing. Jemmott and coworkers (Jemmott & Magloire, 1988; Jemmott et al., 1983) reported that academic stress reduced salivary immunoglobulin A (IgA) concentrations, leading to increased risks of upper respiratory illness. Cohen, Tyrrell, and Smith (1991, 1993) supported these findings demonstrating that high levels of perceived stress gave rise to increased susceptibility to the common cold. Anecdotal evidence from schools, colleges or universities supports the notion that during stressful periods, more students report 'feeling unwell'. However, perceptions of stress and health status of students throughout an academic year and the effect these may have on neutrophil activity has not been explored.

The aim of this study was to follow a group of university students through an academic year monitoring their perceived levels of stress, health status and leukocyte activity. Specifically, the association between perceived stress and the activation of neutrophils was examined, as was the association between perceived stress and heath status. It is hypothesized that as perceived levels of stress change during the year these will be reflected in changes in the percentage of activated neutrophils and higher levels of stress will result in reports of more illness.

Method

Participants

The sample was recruited from undergraduates attending lectures and tutorials at Coventry University (UK). The sample comprised 28 undergraduates (six males and 22 females, median = 21 years, standard deviation, SD = 3.28, range 19–37).

Procedure

Initial interview. Participants were briefed regarding the nature of the study (including an information sheet) and were invited to sign a consent form. A questionnaire was completed; giving basic demographic and contact details, and self-reports of current health status (e.g. chronic illnesses, smoking and exercise).

Study procedure. Upon arrival at the laboratory a heart rate transceiver (Polar, heart rate monitor) was attached directly to the chest and heart rate was monitored. Participants were then asked to make themselves comfortable on the couch (laying with back propped at approximately 45 degrees), close their eyes and breathe orthonasally, for a period of at least 5 minutes in order to minimize possible stress levels experienced prior to, or, upon arrival at the laboratory. Previous work has demonstrated that this period of time, for relaxation, gives a baseline free of any effect of current acute stressors (Ellard et al., 2001). At the end of this time, baseline heart rates were recorded and blood pressure taken. A finger-stick blood sample was then taken and treated with NBT as per sample protocol (Ellard et al., 2004; Ellard et al., 2001).

Briefly, finger-stick blood samples (20 µl) were mixed with an equal quantity of NBT diluted at 1 mg/ml with phosphate buffered saline 0.9 per cent. This sample was placed on a microscope slide, incubated at 37°C for 10 minutes, and then

air-dried (two samples were made for each participant at each time point). Once dry, the samples were flooded with Accustain Wright stain modified (0.3%w/v buffered at pH 6.9 in methanol) and rinsed with distilled water. At least 100 cells were counted on each slide, a percentage 'activated' enumerated and a mean of the two slides calculated. Samples were enumerated 'blind' and a random sample of the slides was checked by another person to investigate reliability of the measure. These checks showed a consistency of between 95 per cent and 98 per cent across the sample.

Heart rate and blood pressure were again recorded to compare with baseline in order to evaluate any stress inducing effects of the procedure. Participants were then asked to sit at a table and complete the questionnaires.

Before leaving the laboratory the participants were rewarded with a small chocolate bar and asked to make an appointment for the next testing session.

Measures. Two psychological measures were used; perceived stress scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983) and a health questionnaire used in a previous study of neutrophil activity (Ellard et al., 2004).

The PSS is a reliable measure of stress that has been used in similar studies (Lacey et al., 2000; Maes et al., 1998; Skirka, 2000). The 10-item PSS (PSS10) was used here. Cohen and Williamson (1988) suggest that the PSS10 has better internal reliability than PSS14, and provides an adequate measure of perceived stress. Each of the 10 questions begins 'In the last month, how often have you. . . .' And is rated using a five-point response format (i.e. 0 = never, 1 = almost never, 2 = sometimes, 3 = often, 4 = very often). The 10 items are summed to produce a total score (range 0–40) with higher scores indicating more stress. Cohen and Williamson (1988) state that the 'normal' mean score for a student population is 15.3 (SD = 6.6).

The health questionnaire assesses general health and health behaviours between each testing point. Participants are asked to report any illness since their last visit, including those not needing medical attention.

Testing periods. The six testing periods were selected in order reflect the variations in academic demands placed on students during an academic year, thus reflecting variation in potential stress. Testing commenced early in the academic year and encompassed periods of low pressure (e.g. directly after Christmas) and periods of higher demand (e.g. just prior to exams). These testing periods are shown in Table II.

Each participant made an appointment during the 'testing week'. One week prior to these appointments reminders were sent via electronic mail to each participant.

Analyses. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, USA). One-way ANOVAs were carried out on the physiological data (heart rate and blood pressure) comparing the pre and post finger-stick levels. Kruskal–Wallis tests were carried out on the PSS and percentage NBT data over the six time points, *post hoc* Mann–Whitney U tests were used to explore differences between testing periods. Bivariate correlations (Spearman's RHO) were performed between PSS scores, the percentage activation of neutrophils, illnesses reported and current state of health for each of the six tests. Scatter-plots were carried out for all correlations to ascertain the validity of any associations. *Post hoc* analysis (Fisher's Z averaging analysis) was carried out on the correlations to ascertain their robustness. Case summaries and descriptive statistics were carried out on the self-report health data and are shown as number or percentage of cases.

Results

Table I shows the characteristics and initial health status of participants. The sample comprised a higher proportion of female undergraduates (22) than males (6); all participants reported that they were in good health at the initial interview.

Perceived stress scores (PSS) and percentage of NBT positive neutrophils

Table II presents PSS scores and percentage of NBT positive neutrophils for each of the six testing periods. The lowest PSS score and percentage of NBT was in period 4 (mean 18.39 ± SD 5.44 and 46.07 ± SD 8.59, respectively), and the highest was in period 5 (mean 22.07 ± SD 6.27 and 51.86 ± SD 9.62). Analysis of PSS and percentage of NBT (Kruskal–Wallis tests) revealed no significant differences overall. *Post hoc* analysis

(Mann–Whitney tests) of the differences between periods 4 and 5 do reveal significant differences for both variables. The median percentage of NBT positive cells during periods 4 and 5 were 43.79, (range 32.77–66.03) and 53.09 (range 37.31–70.14), respectively ($p = 0.035$). The median PSS scores for periods 4 and 5 were 16.5 (range 12–32) and 23 (range 8–32), respectively.

Table I. The initial health status of participants ($n = 28$).

		No.
Gender	Male	6
	Female	22
Smoker?	Yes	10
	No	18
Reported illnesses diagnosed by medical practitioner[a]	No Illness	21
	Asthma	5
	Diabetes	1
	Skin condition	1
Prescription and 'over the counter' medications used in general health[b]	None taken	10
	Oral contraceptive	10
	Vitamins	4
	Oral contraceptives & vitamins	4
Exercise status	None	10
	Once a week	10
	Twice a week	6
	More than twice a week	2

[a] All participants reported that they were currently in good health. Those with 'diagnosed' illnesses reported they were currently in a stable state.
[b] Not including treatments for 'diagnosed' illnesses.

Heart rate and blood pressure

No significant differences were found between base-line and post finger-stick blood test at any of the six test periods (data not presented), indicating that levels of arousal did not increase whilst blood samples were being taken. Participants' heart rates ranged between 68 and 101 bpm (mean 81.2, SD 7.81). Systolic blood pressures ranged between 113 and 141 mmHg (mean 123.56, SD 7.26), diastolic blood pressures ranged between 58 and 83 mmHg (mean 68.43, SD 6.88).

PSS, the activity of neutrophils and health status

The intercorrelations between PSS, percentage of activated (NBT positive) neutrophils, illnesses reported and current state of health, for the six test periods are shown in Table III. There is a consistent and significant relationship between PSS and the percentage of activated neutrophils, with correlations ranging from ($r = 0.507$, $p = 0.0059$) in period 2 to ($r = 0.810$, $p < 0.0005$) at period 4, thus indicating that as the level of perceived stress

Table II. When testing was carried out during the academic year, including an indication of the academic demands upon the participants at this time and the mean perceived stress scores for each time point.

Testing week	When testing was carried out	What's going on academically	Perceived stress sacores (PSS)		Percentage of NBT positive neutrophils	
			Mean	SD	Mean	SD
1	Mid November	End of 1st month at university	20.43	6.69	51.20	10.66
2	Early December	Prior to Christmas, heavy coursework load	18.79	6.64	50.99	8.98
3	Mid January	Immediately after Christmas break	19.21	7.35	47.25	9.31
4	Early February	Steady period between Christmas and Easter	18.39	5.44	46.07	8.59
5	End March	Coursework building up, just prior to Easter break	22.07	6.27	51.86	9.62
6	End May	Revision, weeks leading up to final exams	19.14	5.58	46.33	9.66

Table III. Intercorrelations between perceived stress scale scores, percentage of NBT positive neutrophils and self-reported health status scores.

	Perceived stress score (PSS)	Percentage of NBT positive neutrophils	Reported illnesses
Testing period 1			
Percentage of NBT positive neutrophils	0.676***		
Reported illnesses	0.334	0.268	
Current state of health	0.436*	0.492**	0.461*
Testing period 2			
Percentage of NBT positive neutrophils	0.507**		
Reported illnesses	–0.227	–0.081	
Current state of health	0.183	0.084	0.108
Testing period 3			
Percentage of NBT positive neutrophils	0.634***		
Reported illnesses	–0.190	–0.155	
Current state of health	–0.014	–0.086	0.463*
Testing period 4			
Percentage of NBT positive neutrophils	0.810***		
Reported illnesses	0.031	–0.018	
Current state of health	0.468*	0.346	0.503**
Testing period 5			
Percentage of NBT positive neutrophils	0.724***		
Reported illnesses	0.317	0.256	
Current state of health	0.241	0.142	0.893**
Testing period 6			
Percentage of NBT positive neutrophils	0.563**		
Reported illnesses	–0.060	0.092	
Current state of health	0.161	0.399*	0.488**

* $p < 0.05$ (two-tailed).
** $p < 0.01$ (two-tailed).
** $p < 0.0005$ (two-tailed).

increases so too does the percentage of activated neutrophils. The consistently large effect sizes were very surprising. Analyses of the resulting scatter-plots for each period reveal that there were no 'outliers' that could be influencing the results.

There were no significant relationships between NBT positive neutrophils and reports of illnesses. At testing periods 1 and 6 there were significant positive associations between NBT positive neutrophils and current state of health ($r = 0.492$ and $r = 0.399$, $p < 0.05$, in both cases).

There were, with two exceptions, no significant relationships between PSS and reported illnesses and current state of health. This suggests that, in this sample, reported levels of stress were not due, in most cases, to health issues. The majority of illnesses reported were only minor and the majority of participants reported their health as either being the same as normal or better than normal (see Table V).

There is a significant relationship between the reported illnesses and current state of health at five out of the six testing periods, with correlations ranging from ($r = 0.461$, $p = 0.014$) in period 1 to ($r = 0.893$, $p < 0.0005$) in period 5.

Exploration of the differences in associations between PSS and NBT positive cells, over the six periods, did not reveal any clear patterns.

Table IV. Correlations resulting from mean Fisher's Z score transformation of the sets of data for each participant at each time point.

	Perceived stress score (PSS)	Percentage of NBT positive neutrophils	Reported illnesses
Percentage of NBT positive neutrophils	0.818***		
Reported illnesses	0.169	0.125	
Current state of health	–0.051	–0.068	0.224

*** $p < 0.0005$ (two-tailed).

Table V. The percentages of illnesses reported and state of health at each of the testing periods.

	Period 1 (per cent)	Period 2 (per cent)	Period 3 (per cent)	Period 4 (per cent)	Period 5 (per cent)	Period 6 (per cent)
Illnesses reported						
None reported	25	21	18	46	7	46
Minor, but no medical treatment	54	68	71	43	50	39
Minor, treated by doctor	14	4	4	11	36	15
Major, needing treatment	7	7	7	0	7	0
Current state of health						
Better than usual	21	7	7	7	7	11
Same as usual	29	54	54	64	43	61
Worse than usual	43	39	29	29	46	21
Much worse than usual	7	0	10	0	4	7

Fisher's Z averaging analysis

The 28 sets of correlation coefficients, a set for each participant, were transformed to Fisher's Z values to normalize their typically skewed distribution for statistical testing (Cohen & Cohen, 1975; Stone, 1981). Mean correlations were computed by averaging the Fisher's Z values and transforming the resulting means back to correlations. These mean correlations are presented in Table IV.

Table IV shows that when all scores are standardized the robust nature of the association between NBT and PSS is maintained ($r = 0.818$, $p = 0.01$). However, no other significant associations were found.

Reported illnesses

In Table V it is shown that the majority of illnesses reported over the year were minor and did not require medical intervention (e.g. headaches, colds, sore throats and coughs). The highest number of illnesses was reported at time period 5, the period before Easter when academic demand on students is high. Also at this time the severity of the illnesses reported is greatest with a 36 per cent having conditions that needed medical treatment. At period 4, when academic demands are lower, more of the sample reports no illnesses (46 per cent) and these were usually minor (43 per cent). Prior to Christmas (period 2), when academic demand is high, only a few students report no illnesses at all (21 per cent), and the majority are only reported minor illnesses that do not require treatment.

Current state of health

The data indicate that there are few trends on the state of health that the students report over the year. Most report feeling the 'same as usual'; feeling 'worse' or 'much worse' is reported by 50 per cent of participants at periods 1 and 5 when reported illnesses are also high.

Oral contraceptives

All data were examined to determine whether there were any differences due to the use of oral contraceptives. No differences were found (data not included).

Discussion

Results reveal a consistent positive relationship between perceived stress and the percentage of NBT positive neutrophils suggesting that as perceptions of stress increase so too does the activity of neutrophils. The results of the averaging analysis confirmed this finding. Together, these results support and extend earlier work, which demonstrated that short-term stressors increased neutrophil activity (Ellard et al., 2001) and consistency in the positive association between PSS and percentage of NBT positive neutrophils (Ellard et al., 2004). Neutrophil activity was not associated with the illnesses reported. However, the majority of reported illnesses in this study were minor, requiring no medical care, and thus may not have elicited a stressful response. There was no consistent association between the NBT positive neutrophils and current state of health. The few positive associations between the neutrophils and health status may have been due to low-level infections that the participants may not have been aware of.

Cohen and Williamson (1988) demonstrated that there is an association between perceived stress and illness and that the higher the levels of perceived stress, the more illness is reported. Recent studies have shown that susceptibility to viral disease is linked to levels of perceived stress (Rozlog, Kiecolt-Glaser, Marucha, Sheridan, & Glaser, 1999). In our study there was no confirmation by doctors for most of the illnesses reported and they appeared to be minor in nature.

Evidence suggests that the 'acute' stressor of an academic examination can lead to increased risk of upper respiratory infections (Cohen et al., 1991, 1993; Jemmott & Magloire, 1988; Jemmott et al., 1983). Our findings show that at all times the reported levels of stress are significantly higher than the 'normal' scores for a student population and the highest mean PSS is reported at peroid 5 when there is a heavy 'coursework' demand on the students. However, comparison with 'norms' based on US data that are over 15 years old, may not be valid in a UK population.

The link between the type of illnesses reported in this study and the activity of neutrophils is tenuous. There is more evidence for a down-regulation of the immune system than there is for increased activity of PMN, evident in the types of illnesses reported which are viral in nature (colds and flu). However, in three of the six test periods there was a significant correlation between neutrophil activity (percentage of NBT positive cells) and health status. Suggesting that there may be some relationship dependent on the actual state of health of the participants but again the link is tenuous and no causal effect is inferred.

Ellard et al. (2004, 2001) propose that the activity of the neutrophils indicated by the NBT method is activity that is 'inappropriate' and not the cells 'normal' phagocytic activity and results in the release of radicals and enzymes from the cell into surrounding tissues. Increased activation of neutrophils results in a greater production of reactive oxygen species (ROS) via the nicotine adenine dinucleotide phosphate (NADPH) oxidase system. During these respiratory bursts, granules containing protolytic enzymes are released and along with the ROS, can directly attack host tissues (Weiss, 1989).

The number and distribution of leukocytes, including neutrophils, is known to change as a result of both physical (e.g. exercise) and mental (e.g. examinations) stressors (Kang, Coe, & McCarthy, 1996; Shepard & Shek, 1996). Kang et al. (1996) found that during an examination stressor superoxidase production is increased yet the phagocytic capacity of the cells is reduced. Recent studies have shown changes in levels of important pro-inflammatory cytokine production (interleukin 8, IL8 and interleukin 1, IL1), with decreased production as perceptions of stress increase (Glaser et al., 1999; Marucha, Kiecolt-Glaser, & Favagehi, 1998). These studies show that the recruitment of neutrophils to the site of an injury is the same in those reporting high levels of stress when compared to control, whilst, cytokine production is decreased. IL8 is an important mediator in the wound healing process and is released from neutrophils. It is therefore possible that the stress-induced activity of neutrophils demonstrated by our study may lead to this down-regulation and production of metabolites and protolytic enzymes may cause tissue damage, which helps to prolong the healing process. Therefore, inappropriate stress-induced neutrophil activity and down-regulation may also hinder recovery from coughs and colds. However,

this is only a speculative observation; much more work needs to be undertaken in this area before the situation is clear.

Limitations of this study are the small sample size, the uneven mix of males and females, and the lack of a reliable measure of individual 'academic demand' upon participants. At the beginning of this study, large numbers of students expressed an interest in participating. However, the commitment to repeated visits proved to be too much for many and in particular male students did not like to 'commit' to specific appointment times. Generally, academic stressors like coursework and examinations occur at specific times of the year but this does not tell us how each participant is perceiving this demand and some individuals may have 'more' to do than others, possibly dependant on their diligence and organizational skills. Also, stress is an individual appraisal and some may have more coping resources than others. The fact that in this sample levels of perceived stress and percentage of NBT positive neutrophils are only significantly different at one point in time is both a strength and a weakness in this study, a weakness because it does not show if the academic demands over the year result in greater stress for the students. However, it does demonstrate that the NBT and PSS methods are consistent over time and also that life at university is not just about academic demands, life in general also has a role to play. Future work would need to address these issues and expand these findings. A strength of the study was examination of the relationship between stress, neutrophil activity and health status in a natural setting on the same group of individuals at six points in time.

In conclusion, results of this study extend previous findings by examining the 'lives' of students over an academic year and illustrating changes in perceived stress, health status and the activity of neutrophils at the cellular level. Results show a significant and robust link between perceived stress and the percentage of NBT positive neutrophils and some links between these and reported health status. Neutrophils have many roles to play within the body. This study presents important and novel findings, about the neutrophil, that warrant further investigation.

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