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Salivary nerve growth factor response to stress related to resilience

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HIGHLIGHTS

- Nerve growth factor in saliva (sNGF) has been shown to respond to stress.
- We investigated how acute sNGF responses relate to markers of resilience.
- People with positive stress appraisals showed stronger sNGF reactivity and recovery.
- Agency and well-being are also related to dynamic sNGF reactivity and recovery.
- The sNGF response to stress may help explain differences in resilience.

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ABSTRACT

Salivary nerve growth factor (sNGF) has recently been shown to respond to psychosocial stress, but little is known about how individual differences in this neurotrophic marker relate to stress vulnerability vs. resilience. This study followed up on these initial findings by examining sNGF responses to interpersonal stress in relation to both well-being and state/trait factors that determine the way a person approaches and is impacted by stress. Young adults ($n = 40$) gave 5 saliva samples over the course of a laboratory session that involved an interpersonal conflict stressor, and all samples were assayed for sNGF. Participants also completed self-report measures of global well-being, stress appraisals before and following the conflict, and agency. Greater sNGF reactivity to conflict related to stronger appraisals of coping ability and agency. Post-conflict sNGF recovery related to lower anticipatory stress appraisals, and to higher agency and well-being. These results support the idea that dynamic sNGF responses are adaptive. Implications for the potential role of the neurotrophic system in stress resilience are discussed.

1. Introduction

Nerve growth factor measured in human saliva (sNGF) has recently been shown to respond to acute psychosocial stress, highlighting a neurotrophic component of the stress response system that may complement the more well-known sympathetic branch of the autonomic nervous system (ANS) and hypothalamic–pituitary–adrenal (HPA) axis [21]. However, little is known about how individual differences in neurotrophic response relate to stress vulnerability vs. resilience. The current investigation takes a critical step toward defining this system's adaptive value by relating young adults' sNGF responses to interpersonal stress to both well-being and state/trait variables known to reduce the negative impacts of stress.

Nerve growth factor is one of a larger class of neurotrophins that regulate neural differentiation and growth/plasticity [24]. NGF is expressed in both the brain and periphery, with the salivary glands representing the largest source of circulating NGF in rodent models [23]. To date, most of the evidence for NGF's acute stress-reactive properties comes from mice, which demonstrate brain and blood increases following social stress (e.g., [1,2,4]). The recent discovery that NGF measured in saliva responds to psychosocial (interpersonal conflict) stress, and that this response relates to both HPA axis and ANS responses, has opened the door for investigation of sNGF as part of the human stress response [21]. This initial study documented significant sNGF reactivity to a relationship conflict discussion, in contrast to nonsignificant changes in sNGF across the same time period for a control group of subjects not exposed to conflict stress. It further revealed significant associations between participants' sNGF response trajectories and both their cortisol (HPA marker) and salivary alpha-amylase (sAA; ANS marker) responses across the session, helping to validate this measure as part of a larger stress response. Finally, this research

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related sNGF reactivity to lower levels of negative emotion when confronting conflict stress, suggesting that it may be beneficial. The present study follows up on these early findings in the same dataset, moving from the basic question of whether sNGF responds to acute stress to the question of why this response matters—in particular, how does the sNGF response relate to more lasting markers of well-being?

There is a body of research relating blood and/or brain NGF levels to stress-related psychological difficulties, though these links are not straightforward. A neurotrophic deficit has been implicated in depression, which is reversed by successful antidepressant treatment (e.g., [18,25,36,41]). At the same time, increased neurotrophin (NGF and/or BDNF) levels were observed in animals subjected to early stress that later showed depression-like behaviors [7,10,11]. It seems that NGF does not directly influence mood, but rather plasticity and the ability to benefit from new learning experiences [9]. Humans in anxiety-inducing situations including a first parachute jump and caring for an ill spouse have also exhibited elevated blood NGF [3,15]. A study showing higher NGF among people in love [12] suggests that NGF may be increased by states of high arousal, rather than negative affect per se, consistent with an alternate interpretation of the parachute situation as inducing excitement (instead of or in addition to anxiety). Thus, there is evidence that both elevated and diminished NGF could underlie differences in well-being, but no information as yet about relations with acute stress responsiveness.

To understand how neurotrophic responses relate to stress adaptation, relations not only with the outcome of such adaptation (i.e., well-being), but also with individual difference factors driving adaptation, must be explored. Both state and trait differences in the ways people approach stress are known to contribute to well-being, with resilience depending on a host of cognitive and personality factors. For example, appraising a stressor as non-threatening (low primary appraisal) and oneself as having the power to control the situation (high secondary appraisal) reduces distress and promotes positive coping, which in turn protects against mental disorder [40]. At the dispositional level, people higher in agency—i.e., instrumental personality characteristics related to mastery and a strong, independent self—similarly show superior coping and mental health outcomes [16]. Although these factors are known to impact other aspects of stress physiology (i.e., the ANS and HPA axis; [13]; [42]; [37]), their role in neurotrophic responses to stress is unknown.

The current study was designed to follow up on our initial discovery that sNGF responds to psychosocial stress in humans with tests of resilience-related individual differences in sNGF before and following interpersonal conflict stress. In particular, we examined relations between sNGF reactivity/recovery patterns and well-being, stress appraisals, and agency, in the same sample of young adults we reported on previously [21]. Based on indications from prior human and animal research involving circulating NGF levels, we hypothesized that resilience—evidenced by higher well-being and agency, as well as lower primary and higher secondary stress appraisals—would be associated with greater sNGF reactivity and higher post-stress levels. Absent previous research on post-stress dynamics, we made no hypotheses about sNGF recovery.

2. Method

2.1. Participants and procedures

Participants for this study were 40 (17 male, 23 female) healthy young adults (M age = 21.56, SD = 5.89), drawn from a larger study of romantic couples recruited from a departmental human subject pool and community fliers. All participants gave informed consent prior to completing the study, which was approved by the University of Wyoming Institutional Review Board. During a two-hour laboratory session, participants confronted a validated psychosocial stressor—discussing an unresolved conflict with their romantic partner—known to induce physiological (HPA) reactivity. In particular, the task was modeled after the task found by Kiecolt-Glaser and colleagues (e.g., [20]) to elicit both subjective and physiological stress responses, the magnitude and/or duration of which may vary according to individual differences in psychosocial adjustment (i.e., negative emotionality, attachment security, trauma symptoms—see [22,30,31]). They also gave a series of saliva samples to index physiological stress trajectories.

All sessions began at 4 pm to control for diurnal variations in stress systems.[1] Following a set of initial questions to determine compliance with study conditions—i.e., no current illness, no smoking or other drug use that day, no heavy exercise or brushing teeth in the past 3 h, no eating/drinking in the past hour—participants gave the first saliva sample (entry). The second sample, collected 20 min after receiving a vivid description of the conflict task and shortly before the discussion, measured stress anticipation. Each partner nominated an unresolved issue that had caused an argument or fight recently, and one was selected by coin toss. Participants were given 15 min to discuss and attempt to resolve the selected conflict. Three post-stress samples were collected 10, 25, and 40 min after the conclusion of the discussion. Whole unstimulated saliva samples were collected using passive drool and stored at −20 °C prior to shipment on dry ice to Salimetrics for assay.

2.2. Measures

2.2.1. sNGF

As detailed in [21], all saliva samples were assayed for NGF in triplicate using a commercially available enzyme immunoassay kit (Promega NGF E_{max} Immunoassay System Cat.# G7631; Madison, WI) modified for use with saliva. The NGF salivary test method was developed by Salimetrics (State College, PA) using the commercially available Promega NGF E_{max} Immunoassay System. Coating buffers, sample diluent and wash buffer were developed and optimized for accurate and precise detection of NGF in saliva. The coating buffer is comprised of 27 mM carbonate–bicarbonate. Sample diluent is phosphate buffered saline with bovine serum albumin and a preservative. The wash buffer is phosphate buffered saline with 0.05% Tween-20.

Saliva samples with varying levels of NGF were used during validation to ensure accuracy and precision and lack of matrix effects. Method accuracy was assessed by measuring the recovery of exogenous NGF added to saliva, which was found to be 100.3% for recovery of 30 pg/mL and 97.6% for recovery of 100 pg/mL. Intra-assay precision was 16.5% (134.5 pg/mL) and 12.6% (36.9 pg/mL) as determined by running 20 replicates within one plate. Inter-assay precision was 11.9% (133.57 pg/mL) and 19% (20.98 pg/mL) as determined by the mean of average results of 6 runs. Linearity of dilution was used to assess matrix effects from saliva. Admixtures of a high (134.5 ng/mL) and low (37 pg/mL) NGF saliva samples were prepared and tested according to NCCLSEP6-A. The average recovery from across the range was 102.7% with a range of 82.3% to 127.2%. All saliva samples were assayed in the Salimetrics CLIA approved testing facility with trained operators and technicians. Saliva samples were tested for NGF in triplicate after being diluted 1:4 prior to testing. The assay standard curve range is 3.9 to 250 pg/mL. For this investigation, five samples were obtained from each subject and all were run on the same assay plate in triplicate.

Associations with salivary flow rate (mL/min) were nonsignificant, so flow rate was not included in model testing. sNGF values above the

[1] As reported previously [22], a control sample of 20 participants was recruited to give saliva samples at the same times as study participants, but without undergoing a stress task. Nonsignificant changes in control participants' sNGF suggested that there were no diurnal effects, at least in the late afternoon period during which the study occurred.

assay's sensitivity range (17%) were assigned to the upper limit of the range (1000 pg/ml); deleting these cases yielded essentially unchanged results. In the absence of substantial skewness (<1.5), raw scores were used in analyses. Within-person stability of measured sNGF was high (*M* correlation = .89, ICC = .90). Fig. 1 shows sample means and standard errors for sNGF across samples.

2.2.2. Resilience measures

The World Health Organization Well-Being Scale (WHO-WB; [6]) assessed participants' overall well-being ($\alpha = .78$). Primary and secondary stress appraisals were assessed with scales used in previous psychosocial stress research. Primary appraisals tapped perceptions of the stressor as threatening and challenging. Secondary appraisals tapped perceived ability to cope with the stressor and control over the situation. Directly before the conflict task, participants completed the Primary Appraisal Secondary Appraisal (PASA; [14]) scale, and directly following the task they completed the Visual Analog Scales (VAS; see [14]). Each of these measures yielded separate scores for primary and secondary stress appraisals (α's = .80 and .64 pre-task, .83 and .77 post-task). Finally, the Personal Attributes Questionnaire (PAQ; [38]) measured participants' self-endorsement of agentic qualities on a 5-point bipolar scale (e.g., "stands up well under pressure" vs. "goes to pieces under pressure"; $\alpha = .68$).

2.3. Analytic strategy

Hierarchical linear modeling (HLM; [32]) was used to model sNGF response trajectories. This approach separates within-person variability in sNGF over time (Level 1) from between-person differences in sNGF response (Level 2). A piecewise growth model estimated each participant's sNGF reactivity slope (from samples 1 to 3), post-stress sNGF level (sample 3 intercept), and recovery slope (from sample 3–5) at Level 1. At Level 2, participant resilience characteristics were used to predict differences in each of these response components (i.e., slopes and intercepts).

3. Results

3.1. Baseline model

The baseline model containing no predictors demonstrated a significant sNGF reactivity slope ($\beta = .13$, $p = .001$), but a nonsignificant recovery slope ($\beta = .003$, *ns*). This means that, overall, participants tended to show a rise in sNGF from study entry to the first post-conflict sample, with no change in sNGF during the recovery period. At the same time, significant between-person variability in each of these parameters ($\chi^2[38] = 69.86–943.26$, all p's $\leq .001$) suggested individual differences in trajectories that could be explained by adding Level 2 predictors. Because males showed evidence of higher post-stress sNGF levels than females ($\beta = .30$, $p = .063$), consistent with rodent NGF and emerging human sNGF research [33], sex was included as a control variable in further analyses.

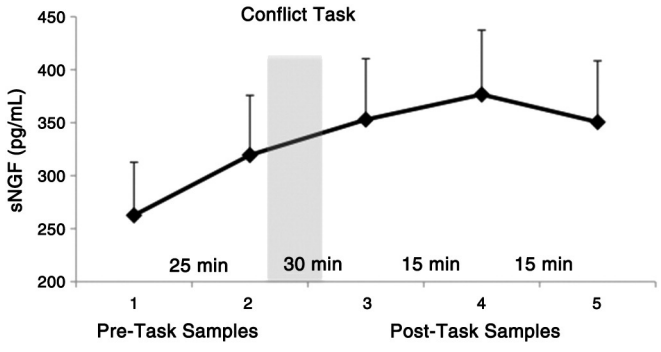

Fig. 1. Observed sNGF levels across samples (bars represent standard errors).

3.2. Explanatory models

Resilience-related predictors were added in a series of models addressing (a) well-being, (b) state factors (stress appraisals), and (c) trait factors (agency). Global well-being was associated with sNGF recovery slopes; participants reporting greater well-being showed a post-task decline in sNGF (Table 1, panel A). This model explained 16.3% of the variance in sNGF recovery slopes. Pre-task primary stress appraisals predicted sNGF recovery slopes, and post-task secondary stress appraisals predicted sNGF reactivity slopes (Table 1, panel B). Participants who anticipated the conflict task as more threatening/challenging showed a continued increase in sNGF after the conflict task was over. Participants who showed a greater task-related increase in sNGF had a higher assessment of their coping abilities during the task. These models explained 29.8% of the variance in sNGF reactivity slopes, and 33.2% of the variance in recovery slopes, respectively. Finally, agency was associated with a stronger task-related increase and greater post-task decrease in sNGF (Table 1, panel C). This model explained 28.6% of the variance in sNGF reactivity, and 5.5% of the variance in recovery slopes.

4. Discussion

This study adds an important piece to the foundation of sNGF stress research by relating individual differences in sNGF response to acute stress to markers of psychological resilience. In particular, the current results support the value of a dynamic neurotrophic response to psychosocial stress. Greater sNGF reactivity was associated with a sense of successful coping and agency, and greater recovery was associated with global well-being and agency. Conversely, failure to recover (i.e., an ongoing increase in sNGF) was associated with negative anticipation of stress. Below, we consider what these findings mean in the context of previous NGF research and propose next steps in the investigation of neurotrophic stress responses.

In line with previous research relating neurotrophins to emotions and mental health, we found an association between sNGF and well-being. The present results suggest that an adaptive sNGF response is not necessarily characterized by higher or lower absolute levels, but rather by the dynamics of stress-related reactivity and recovery. Multiple measures of salivary NGF release before and after the stress task allowed us to detect these effects, which paralleled findings based on other stress system outputs such as cortisol—i.e., a healthy response includes both task-related reactivity and timely post-task recovery [34]. Elevated NGF following early life stress has been proposed to shape later neurobiological vulnerability to stress and disorder [10], and an efficient recovery mechanism may head off such detrimental stress-related remodeling. More broadly, the sNGF-well-being link detected here supports the proposal that an acute neurotrophic response to stress has an adaptive function.

Table 1
Explanatory models for sNGF response trajectories.

Model predictors	Reactivity slope		Post-task level		Recovery slope	
	β	p	β	p	β	p
A. Well-being	.044	.157	−.115	.474	**−.075**	**.046**
B. Stress appraisals						
Pre-task primary	−.022	.512	−.086	.624	**.091**	**.024**
Pre-task secondary	.010	.760	−.107	.517	.066	.075
Post-task primary	.011	.731	−.037	.806	.045	.373
Post-task secondary	**.042**	**.020**	−.027	.825	−.002	.921
C. Agency	**.061**	**.023**	.024	.856	**−.046**	**.047**

Note. Significant effects ($p < .05$) highlighted in bold.

Attention to stress-related cognitions and personality attributes aids in understanding the short- and long-term processes giving rise to adaptive stress responding. Appraisals immediately preceding and following the conflict task were related to different aspects of the sNGF response. Whereas sNGF reactivity appeared to enable a better sense of coping in the actual conflict, cognitive anticipation of stress created ongoing reactivity after the task was completed. To be confident about this particular sequence of effects, replication and more fine-grained investigation of forward- and backward-lagged relations between stress-related cognitions and sNGF are needed. Still, these results suggest that sNGF response can be influenced for better or worse by the way a person thinks about a given stressor and his/her ability to cope with it. The fact that such coping appraisals explained a sizeable proportion of the variance in stress responses has important practical implications. Specifically, cognitive interventions that target both exaggerated stress anticipation and weak secondary appraisals following the stressor could be used to build stress resilience.

At the level of stable dispositional characteristics, similarly, more resilient (agentic) participants were characterized by strong sNGF reactivity and recovery. The current findings offer a new potential explanatory mechanism for well-established links between agency and mental health; the self-sufficient, mastery-oriented qualities comprising agency may promote (and/or be promoted by) adaptive neurotrophic responses to stress. As suggested by research documenting NGF increases in patients treated for depression (e.g., [17,18]), maintaining mental health in the face of stress may depend on the ability to generate an adequate neurotrophic response. At the same time, the ability to reduce neurotrophic activation following stress appears important for maintaining well-being over the long-term. Taken together, these results provide initial support for the idea that the neurotrophic response measured by salivary NGF constitutes a biological marker of resilience.

Notably, this study related sNGF to the presence of positive psychological characteristics (i.e., well-being, agency, coping appraisals) and not simply the absence of negative characteristics (i.e., threat appraisals). Although the concept of resilience itself implies a positive orientation, much of the research on the topic has characterized resilience through the absence of mental disorder following stress. In keeping with this operationalization, efforts to understand neurobiological mechanisms in resilience have focused largely on control of negative emotion and associated physiological stress responses (see [35] for a recent review). However, findings such as those reported here help shift the focus to generating and constructively using a (neurotrophic) component of the stress response to support adaptive functioning.

Measurement of salivary NGF in humans is a recent innovation, and we are still at the early stages of understanding what variation in this measure does and does not mean. Based on both this sample and (as yet unpublished) work in several other human samples, it appears that sNGF responds to acute psychosocial stress, that this response does not represent diurnal variation, and that individual differences in sNGF response relate to psychological adjustment. What we do not yet know is how changes in NGF in saliva relate to changes in other physiological systems that could impact psychological function. Experimental research in animals suggests possible central and peripheral routes of neurotrophic influence. NGF release in the brain aids in neural plasticity and protection/repair processes, and circulating NGF modifies stress responding via the size and activity of the adrenal gland [5,10,29]. Thus, NGF reactivity may buffer critical brain areas such as the hippocampus from stress-related increases in cortisol, whereas rapid recovery prevents neural/neuroendocrine stress sensitization from taking place as suggested above. The buffering effect of NGF may also involve the release of dehydroepiandrosterone sulfate (DHEAS), an adrenal androgen with antagonistic effects against cortisol, whose levels have been positively associated with sNGF at rest and under stress ([39]; Taylor et al., submitted). Controlled studies in humans and animals probing associations between salivary NGF and both blood and brain levels during stress exposure, including possible lagged effects and associations with DHEAS, will ultimately help to clarify these mechanisms. In the near term, further study of the human sNGF response and how it relates to different domains of psychological function will help to define its role in stress adaptation.

Future research should explore whether sNGF reactivity occurs, and whether similar responses can be considered adaptive, with different types of stressors (i.e., performance tasks, more severe/extended psychosocial challenge). Our ability to detect further effects, including associations between resilience variables and sNGF levels (as opposed to reactivity/recovery slopes), was likely limited by the modest sample size and resulting power limitations in this study. We were also restricted in the measurement of resilience (i.e., to a global well-being measure and several state/trait predictors), precluding strong statements about impacts on mental health vs. disorder. Clinical samples involving people suffering from past and/or present depression and anxiety should be studied to further define mental health implications of acute sNGF response patterns. Longitudinal research on stress exposure during critical developmental periods and both immediate and long-term neurotrophic consequences would further help to define paths to stress vulnerability vs. resilience.

The Promega assay used in this study to estimate sNGF is the current state of the art, selected because it is the most commonly employed assay to date for measuring NGF in saliva samples (e.g., [19,28,39]). Our subsequent work with this assay reveals an issue overlooked by prior research—the antibody used in this assay system cross-links with sIgA. We have reason to believe that the current results were not driven by this immune system marker. In particular, previous research has demonstrated a divergence of sIgA from cortisol responses to psychosocial stress (e.g., [8,26,27]). By contrast, the sNGF measure in this study showed concordance with cortisol responses, as would be expected based on known HPA–NGF associations (see [21] for further detail on sNGF-cortisol response coordination in this sample). Still, to fully explore the meaning of variation in sNGF, the next generation of research will need to improve upon this measurement strategy. Finally, as noted above, knowledge of mechanisms by which sNGF release may impact neural and neuroendocrine systems in humans is very limited, and research addressing basic questions about the nature and timing of connections across salivary and blood levels is needed.

Although further basic and applied research will be needed to follow up on these findings, the present study takes an important step in marking out both what an adaptive response of this novel neurotrophic stress marker looks like, and what gives rise to it. At both a theoretical and a practical level, sNGF promises to expand our understanding of how stress-responsive biological systems contribute to resilience.

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