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Distinct CCL2, CCL5, CCL11, CCL27, IL-17, IL-6, BDNF serum profiles correlate to different job-stress outcomes

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ABSTRACT

Chronic psychosocial stress at workplace is an important factor in the development of physical and mental illness. Objective biological measures of chronic stress are still lacking, but inflammatory response and growth factors are increasingly considered as potential stress biomarkers. Therefore, we investigated the relationship between psychophysical strain and serum levels of 48 chemokines, cytokines and growth factors measured using a multiplex immunoassay, and serum brain-derived neurotrophic factor (BDNF) measured by ELISA. Severity of psychophysical strain was scored in 115 healthy hospital workers using specific scales for anxiety, depression-like emotion, gastrointestinal or cardiac disturbances, and ergonomic dysfunction. Multivariate analysis revealed that higher anxiety scale scores were correlated with lower serum chemokine C-C motif ligand-2 (CCL2/MCP-1), chemokine C-C motif ligand-5 (CCL5/RANTES), chemokine C-C motif ligand-27 (CCL27/CTACK), chemokine C-C motif ligand-11 (CCL11/Eotaxin) and interleukin-6 (IL-6); gastrointestinal disturbances correlated with increased levels of interleukin-17 (IL-17) and reduced CCL11/Eotaxin, CCL27/CTACK and CCL2/MCP-1; while cardiac dysfunctions associate only to reduced CCL27/CTACK, and ergonomic dysfunction correlated with increased BDNF and reduced CCL11/Eotaxin and CCL5/RANTES. Thus, these 7 serum factors may provide a distinct signature for each different stress-related psychophysical outcome giving indications on individual vulnerabilities.

1. Introduction

Real or perceived threats at job (i.e. stressors) can activate a network of behavioral, psychological and physical reactions in the individual (i.e. psychophysical strain), collectively known as work-related stress (Girardi et al., 2015). This chronic stress condition is a process that occurs when a person has or feels a high job demand having however low job control, thus feeling unable to cope with the requests (de Jonge et al., 2010). Another means driving this kind of chronic stress is the alteration in the effort-reward balance (Siegrist et al., 2004), in terms of salary, accomplishment or job perspectives in front of demanding tasks. Work-related chronic stress is an emerging factor in the development of physical and mental illness (such as depression) and many people experience physical and psychological symptoms related to stress (Ganster and Rosen, 2013; Nixon et al., 2011). Accordingly, psychophysical strain is associated with increased sickness absences and reduced job performance (Falco et al., 2013a, 2013b).

The pathophysiological events triggered by prolonged exposure to stress in humans are not completely characterized, but they involve the hypothalamus-pituitary-adrenal (HPA) axis involving stress hormones such as corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and glucocorticoids, the sympathetic-adrenal-medullary (SAM) axis as well as the endocrine system (Chandola et al., 2010; Dhabhar, 2014; Juster et al., 2010). Besides the above mentioned mechanisms, the recognition that immune alteration is a primary pathophysiological mechanism in chronic stress is one of the major scientific insights of the decade (Reiche et al., 2004; Schmidt et al., 2010; Segerstrom and Miller, 2004; Dhabhar, 2014; Siegrist and Li, 2017). Previous studies showed that sympathetic system stimulate inflammatory cytokine production (McEwen et al., 2015) which in turn augment glucocorticoid production, that has usually anti-inflammatory effects, but it can be also pro-inflammatory, in some cases (Munhoz et al., 2010). Inflammation has been hypothesized to be a biomarker of chronic psychophysiological stress, with interleukins 6 (IL-6),

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interferons (IFNs) and tumor necrosis factors (TNFs) as the most investigated candidates (Hansel et al., 2010). In addition, other studies reported a general immune suppression (Calcagni and Elenkov, 2006; Dhabhar et al., 2012), highlighting the complexity of interactions between brain and immune system. Chronic stress is known to increase susceptibility to infection and cancer, due to immune suppression, but it may also exacerbate allergic or autoimmune conditions involving a shift in cytokine balance from type-1 to type-2 response, meaning a decrease in cellular immunity in favour of a humoral immunity (Dhabhar, 2014; Glaser et al., 2001). Moreover, the stress response includes alterations in the levels of growth factors and neurotrophins, like the brain-derived neurotrophic factor (BDNF) (Bath et al., 2013; Mitoma et al., 2008). Indeed, decreased BDNF levels are associated with stress-related reduction in dendritic branching and spine density of CA3 neurons (Davidson and McEwen, 2012).

Psychophysical strain is usually evaluated by the worker himself (i.e., through self-report questionnaires) or by occupational physicians with the aid of ad-hoc questionnaires, which allow quantitative assessment of specific dimensions of psychophysical strain (Falco et al., 2013a). However, in addition to the valuable function of these questionnaires, it would be very useful to include in the assessment also objective biological measures, which are still lacking. In this study, we tested the hypothesis that psychophysical strain may affect blood levels of cytokines, chemokines and growth factors, including BDNF and that these relationships might be stronger in females than in males (Evolahti et al., 2006). From a psychological standpoint, gender may influence in several ways the stress process. For example, previous research has shown that women, compared to men, may perceive work situations as more stressful, engage more frequently in less adaptive coping strategies (e.g., emotion-focused), and also experience higher levels of psychophysical strain (Day and Livingstone, 2003; Eaton and Bradley, 2008; Tytherleigh et al., 2007). From a methodological point of view, we examined the relationship between the severity of different psychophysical strain and blood levels of cytokines, chemokines and growth factors in healthy volunteers working at a hospital. To this aim, we have taken benefit of proteomic analysis using a multiplex immunoassay built on magnetic beads for the quantitation of multiple analytes within a single assay (Zanin et al., 2012). Using this technique, we assessed a panel of 48 chemokines, cytokines and growth factors, aiming to test the hypothesis that serum concentrations of pro-inflammatory cytokines and growth factors are upregulated, and immune defense related chemokines and growth factors are decreased in relation to prolonged psychosocial stress (Segerstrom and Miller, 2004). In addition, we measured the neurotrophin BDNF with an ELISA assay, which we recently validated to be the most reliable among six commercial assays (Polacchini et al., 2015), and we hypothesized that it could be decreased in relation to chronic work-related stress.

2. Material and methods

2.1. Participants

The study, conducted as part of larger project aimed at assessing work-related stress risk, was performed examining a sample of workers in an Italian healthcare organization. Workers were informed beforehand by management and participated voluntarily to the study. Workers completed a self-report questionnaire aimed at determining psychophysical strain. Before the questionnaire was administered, the purpose of the present study was explained by a member of the research team, who emphasized that participants should report only psychophysical symptoms attributable to work-related stressful situations (i.e., not imputable to other stressful life events, such as, for example, providing care for a family member or financial difficulties). The questionnaire was completed by 115 subjects who agreed to participate to a clinical interview followed by a blood sample withdrawal. Then, blood samples were collected and sera isolated as previously described (Polacchini et al., 2015). Subjects reporting mood and anxiety disorders, neuroendocrine diseases, non-pharmaceutical drug abuse or dependence, according to DSM-IV-TR criteria, were excluded from the enrollment. Therefore, the study sample comprised 115 workers, of which 71.3% were women. Regarding the work position, 16.7% were managers-doctors, 63.3% were doctors or head nurses, 20% were nurses. Most respondents had a permanent contract (95.9%) and were working in the hospital for more than 8 years. All participants gave their written, informed consent, and the study was approved by the local ethics committee according to the recommendations of the Declaration of Helsinki.

2.2. Work-related stress assessment

Subjects were assessed for psychophysical strain using five scales taken from the Q-BO test, an instrument standardized for the Italian context (De Carlo et al., 2008; Falco et al., 2012). The first part of the questionnaire asked respondents to indicate how often, over the past six months, the psychophysical symptoms (see list below) attributable to work-related stressful events, had appeared or exacerbated. The six psychophysical strain dimensions assessed were: anxiety, emotion (depression-like), gastrointestinal disturbances, cardiac disturbances, ergonomic dysfunction at the workplace. The six point response scale ranged from 1 (never) to 6 (every day). The overall strain score was estimated by averaging the scores of each subscale. Both the self-report version of the questionnaire (the one adopted in this study, see Trifiletti et al., 2013) and the form developed for the administration by the occupational physician (Falco et al., 2013b) showed good psychometric properties. Additionally, Cronbach's alpha in the present study was 0.80 for the anxiety subscale, 0.80 for emotion (depression-like) symptoms, 0.78 for gastrointestinal disturbances, 0.66 for the cardiac disturbances, and 0.80 for ergonomic dysfunction.

The Q-Bo test consists of various scales, reformulated and reduced in the most recent release to about 200 items (from 350 of the original version) - thanks to an experiment conducted on over 30,000 workers - and with a delivery time of about 1 h. The protocol can be adapted to the different needs of organizations in the various public and private contexts both for modules and for specific constructs as well as social and personal information. In particular, sets of scales integrated with each other are available in function of the different types and sizes of the organizations object of survey. The main test configurations are directed specifically to those areas: Education/Training, Manufacturing, metal working industries, Public Administrations and Public Services, Health Sector, Financial Services/Insurance, Social Services. For the different sectors, in a benchmarking perspective, specific reference samples are available (normative values). The scales were developed based on the most extensive international literature, on the needs created by the Italian legislation and the requirements of European and global organizations working in the field of health and safety at work. Thanks to the adoption of a systemic approach, the multidimensional model is used to detect a broad spectrum of work, organizational and individual factors representing potential sources of risk. In particular, by means of the proposed dimensions, the model aims at assessing behavioural, physiological and psychological stress/strain (with particular reference to burnout). These dimensions are in fact designed in order to take into account factors, such as the quantitative and cognitive workload, the degree of control/autonomy, the social rewards in terms of support from the organization, the professional growth, the organizational equity and justice, and the various forms of conflict including conflicts work/life, person-role, with colleagues, between groups/departments of the same organization, with superiors and co-workers, changes, no clear definition of responsibilities. These elements can have negative consequences for the health of the worker and can cause at the same time a deterioration of corporate performance. Another section of the test is dedicated to the detection of psychological and physical symptoms (such as irritability,