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## Long-lasting stress, burnout syndrome, aging, and risk of Alzheimer's Disease

Dariusz Mikołajewski<sup>1,2,3</sup>, Emilia Mikołajewska<sup>4</sup>

<sup>1</sup> Department of Teleinformatics, Institute of Mechanics and Applied Computer Sciences, Kazimierz Wielki University in Bydgoszcz, Poland

<sup>2</sup> Neurocognitive Laboratory, Centre for Modern Interdisciplinary Technologies, Nicolaus Copernicus University in Toruń, Poland

<sup>3</sup> Department of Neurophysiology and Psychiatry, Medical University in Lublin, Poland

<sup>4</sup> Department of Physiotherapy, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland

### Corresponding author:

Dariusz Mikołajewski *PhD Eng.*

Department of Teleinformatics

Institute of Mechanics and Applied Computer Sciences

Kazimierz Wielki University in Bydgoszcz, Poland

e-mail: [darek.mikolajewski@wp.pl](mailto:darek.mikolajewski@wp.pl) [dmikolaj@ukw.edu.pl](mailto:dmikolaj@ukw.edu.pl)

phone: +48 725-88-99-09

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## **Abstract**

Burnout is defined as an excessive stress reaction to environment characterized by emotional and physical exhaustion, coupled with a sense of frustration and failure. Work-related stress, especially low job control and low social support, may increase the risk of dementia, especially AD. Aim of the paper is a better understanding of the complex nature of the long-lasting stress and professional burnout to early symptoms of the AD onset. Identification of mechanisms underlying of such associations may help to develop more effective therapeutic strategies better tailored to patient's profile. Despite efforts of scientists and clinicians objective diagnostic criteria and influence of burnout syndrome to AD remain ambiguous, making it difficult to recognize transition to early stage of AD. Additional longitudinal research is needed for determining what mediates the stress, burnout, and AD association, including both genders and not yet known risk factors.

**Keywords:** burnout syndrome, elderly people, compensation, mental disorders, occupational diseases, prevention.

## **Introduction**

Burnout is defined as an excessive stress reaction to environment characterized by emotional and physical exhaustion, coupled with a sense of frustration and failure [1]. Professional burnout takes into consideration only influence of the occupational or professional environment. All European Union (EU) countries must have an action plan to prevent stress at the workplace and associated burnout syndrome. Quick pace of life causes increased risk of psychological disorders. Its influence to the health of workers increases in accordance with growing requirements on employees across various professions. Intervention may cause increased attention to social context and provision of meaningful roles for employees, and promotion of cognitive health. But only in 39% of the countries exists a possibility to acknowledge burnout syndrome as an occupational disease [2]. AD is a progressive neurodegenerative disorder characterized by the accumulation of  $\beta$ -amyloid peptides and neurofibrillary tangles in brain, resulting in neuronal death and loss of cognitive abilities. Longstanding psychological stress and burnout, including professional burnout, can result in neural degeneration and AD due to pathological alterations in the hypothalamic-pituitary-adrenal (HPA) axis. Work-related stress, especially low job control and low social support, may increase the risk of dementia, especially AD. Research of gender differences in risk of AD showed that women are more likely to suffer from stress-related psychiatric disorders, such as burnout syndrome [3].

Aim of the paper is a better understanding of the complex nature of the long-lasting stress and professional burnout to early symptoms of the AD onset. Identification of mechanisms underlying of such associations may help to develop more effective therapeutic strategies better tailored to patient's profile.

## **Methods**

Systematic review has been based on the published peer-reviewed articles. Literature search was conducted: three major databases (PubMed, Medline Complete, and EBSCO) were searched with following keywords: 'limbic system', 'elderly', 'aging', 'long-lasting stress', 'Alzheimer's Disease' and 'burnout'. The search period covered from 2010 to 2018 and searches were limited to English language. Fourteen papers meet inclusion criteria. The results of the review are discussed below.

## **Burnout in young and older**

Quick pace of life causes that stress and burnout may be observed even in young people. Even medical students of urban and rural origin with various personality structure tendencies (schizotypal, narcissistic and borderline) and gender presented aforementioned symptoms. Thanks to their knowledge two types of coping styles (avoidance and looking for social contacts) were significantly common, especially among females [4].

Aforementioned situation may cause worsening of the general health-status and increased risk of dementia (especially AD) as far as their earlier onset in increasing population of elderly people. There were observed relationship between long-standing midlife psychological distress and late-life brain atrophy and white matter lesions in elderly. Neuroticism in midlife was associated with increased risk of AD dementia and long-standing distress over 38 years. Association between personality and AD is not clear: despite neuroticism/low extraversion showed the highest risk of AD, neuroticism may be associated with long-standing distress, but extraversion is associated with a lower degree of long-standing distress, but had no impact on AD. According to the current studies long-standing stress stimulates unspecific neurodegenerative processes, but not the core processes within early phase of AD [5-10].

Current research on ageing neurobiology show that involvement of life stress in Late-Onset Alzheimer's Disease (LOAD) may be influenced by catecholamine and corticosteroid systems. Role of noradrenergic signalling, previously demonstrated by childhood nucleus caeruleus degeneration for LOAD tauopathy, still remains unclear [11].

Moreover interactions between social and genetic risk factors of stress and burnout may be key for deeper understanding of multifactorial diseases such as AD. Negative impact of unfavourable social and economic conditions on health and longevity is well known. Taking into consideration work environment factors such as work control, support, psychological demands, physical demands and job hazards may be key part of the future studies. Especially work environment may significantly influence risk of dementia in males [12].

## **Neural correlates of burnout syndrome**

There is still a few research on neural correlates of burnout syndrome. Deeper understanding of relationship between burnout and limbic system function can provide better insight into brain structures associated with the burnout syndrome. Research on HPA axis in healthy and burnout patients put particular attention to activity of HPA axis and neuroimaging of the limbic brain structures, taking into consideration:

- impact of the chronic occupational stress on the limbic structures in terms of HPA dysregulation,
- a decrease of brain-derived neurotrophic factor (BDNF),
- impaired neurogenesis,
- limbic structures atrophy,
- and other factor, not mentioned previously, such as damaging results of lifestyle or another problems (e.g. influence of everyday stress of working exhausted caregivers of disabled family members - both children and elderly).

No doubt chronic stress:

- inhibits the feedback control pathway in the HPA axis,
- decreases BDNF,
- impairs neurogenesis,
- causes faster neuron atrophy [13].

Novel technologies such as EEG source localization using the photogrammetry station and the sLORETA algorithm associated with indication of the most active Brodmann areas may

provide another breakthrough in the aforementioned research on neural correlates of the burnout syndrome [14, 15].

Research on microglial phenotypes observed in patients with both chronic stress and AD may provide novel evidences as far opportunities for development of new diagnostic methods and well-targeted therapeutic interventions. Microglia constitute predominant immune cells of the central nervous system (CNS) responsible for maintaining CNS homeostasis in response to chronic stress (also related to burnout), as well as mediating neuroplasticity, learning and memory. Chronic stress constitutes important environmental risk factor modulating microglia function, and certain microglial phenotypes are associated with neuroprotection in AD [15].

## **Discussion**

Main limitation is caused by a few studies in the area of stress and burnout influence to the onset and severity of dementia and AD symptoms in elderly people. No doubt common psychosocial stressors, including workplace burnout, may have severe and long-standing physiological and psychological consequences, including more severe or earlier AD onset. Moreover problem of high levels of stress among mid-life and elderly people is a real problem of high scientific, clinical, social and economic relevance. Its prevalence and mechanisms have not been fully explored so far. Various factors may influence aforementioned processes including experience, co-occurrence of risk factors, coping styles and personality tendencies but also urban and rural settings [16]. The precise description of the objective methodology and research protocol for collecting medical imaging, EEG and neuropsychological data as well as the roadmap of future investigations in this area are needed. Aforementioned process may enhance looking for quantitatively biomarkers of the burnout syndrome in elderly people in order to support the process of diagnosis and hopefully choose most appropriate medical treatment later. Despite efforts of scientists and clinicians objective diagnostic criteria and influence of burnout syndrome to AD remain ambiguous, making it difficult to recognize transition to early stage of AD. Additional longitudinal research is needed for determining what mediates the stress, burnout, and AD association, including both genders and not yet known risk factors.

## **Conclusions**

Despite the number of people with AD has increased dramatically with global ageing underlying risk-factors are not clearly understood. Current studies have confirmed association between psychological stress (especially in middle-aged women) and development of dementia, including AD. Influence of the professional burnout to this situation is still unclear. More studies are needed to study neuropathological mechanisms of the aforementioned changes and provide targeted therapeutic approach.

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