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Physiological Response as Biomarkers of Adverse Effects of the Psychosocial Work Environment

Åse Marie Hansen[1,2], Annie Hogh[2] and Eva Gemzøe Mikkelsen[3]
[1]*The National Research Centre for the Working Environment, Copenhagen,*
[2]*University of Copenhagen, Copenhagen*
[3]*CRECEA A/S,*
Denmark

1. Introduction

Throughout medical history, measurement of hormones and other physiological parameters have been used in clinical settings with the purpose of detecting and monitoring progress of disease. During the past three or four decades, however, hormones and other physiological effect markers have been increasingly used in occupational settings for purposes of assessing the effects of psychosocial circumstances and of occupational stress. Accordingly, the focus has partly drifted from detecting and monitoring disease to including the detection and monitoring of precursors of disease and risk factors for poor health in otherwise healthy subjects before medical manifests. Because the majority of the workforce is in good health, differences in hormonal and other physiological parameters are often expected to be less pronounced than the differences that typically render clinical interest. Salivary cortisol has increasingly been used in the study of the responsiveness of the hypothalamic pituitary adrenal (HPA) axis in occupational stress studies and employed in both field studies and experimental studies (for review see (Chida & Steptoe, 2009)). The reason for the increasing use of salivary cortisol in occupational settings is that it is a simple, non-invasive, harm-free and pain-free measure that allows the longitudinal study of HPA-axis activity without substantial interference with the subject's normal habits and environment. Since cortisol in saliva is stable for at least two week, it provides the possibility of self-sampling and mailing the samples by post (Garde & Hansen, 2005b). This chapter will use salivary cortisol as an example of a biomarker of adverse effects of work stress.

The biological pathways linking stress and health need to be better investigated (Kudielka & Wüst, 2010). In the understanding of the adaptation processes and in the pathogenesis of chronic diseases and adverse psychosocial working environment endocrine factors have become increasingly relevant. Exposure to adverse psychosocial working environment initiates a number of physiological reactions, regulated by hormones (Henry, 1992). The locus coeruleus-noradrenaline/autonomic (sympathetic) nervous system (Chrousos & Gold, 1992) and the hypothalamus-pituitary-adrenal (HPA) axis are the major physiological stress response systems in the body (Chrousos & Gold, 1992; Gold et al., 1995; Heim et al., 2000;

McEwen, 1998; McEwen & Seeman, 1999; Raison & Miller, 2003; Tsigos & Chrousos, 2002). The characterization of an individual's HPA axis activity, reactivity pattern to psychosocial stress and inter- and intra-individual variability appear to be of major interest (Hellhammer et al., 2009; Mason, 1968). Measurement of hormones and other physiological parameters have been used in clinical settings with the purpose of detecting and monitoring progress of disease. During the past three or four decades, however, hormones and other physiological effect markers have been increasingly used in occupational settings for purposes of assessing the effects of psychosocial circumstances and of occupational stress. According to Selye "*stress is the nonspecific response of the body to any demand*" (Selye, 1975). The stress response may be identified as changes in physiological indicators, e.g. endogenous substances measurable in blood, urine or saliva. Physiological indicators are therefore potential intermediate biomarkers of effect as defined by the World Health Organization (WHO) (1993): '*Biomarker for effect: a measurable biochemical, physiological, behavioural or other alteration within an organism, that depending upon the magnitude, can be recognized as associated with an established or possible health impairment or disease'*. However, the majority of the workforce is in good health, and differences in hormonal and other physiological parameters are often expected to be less pronounced than the differences that typically render clinical interest, such as manifestation of disease.

The aim of the present chapter is twofold: One is to provide the reader with insight into the present evidence for how different physiological responses may be used as potential biomarkers of the psychosocial working environment and health. The other aim is to address and thereby bring to awareness to potential sources of variations and confounders.

2. Job stress theories

The Job Demand–Control model identifies two crucial job aspects: job demand and job control (Karasek & Theorell, 1990). Job demand refers to the workload, and has been operationalized mainly in terms of time pressure and role conflicts. Job control refers to the person's ability to control his or her work activities. The job content questionnaire (JCQ) has been used to characterize the psychosocial working environment according to the Job Demand-Control model (Karasek et al., 1998). The underlying theoretical explanation may be that low control causes chronic disease through chronic de-regulation of our highly integrated physiological systems (Karasek, 2006). The Effort-Reward Imbalance (ERI) model is a model of occupational stress, focusing on a negative trade-off between experienced 'costs' and 'gains' at work. In this model, high ratio of effort spent relative to rewards received in terms of money, esteem, job security, and career opportunities, elicits sustained stress responses and ill health (Siegrist et al., 2004).

The cognitive theory of stress (CATS) offers a psychobiological explanation for the assumed relationship between stressful events and health (Reme et al., 2008; Ursin & Eriksen, 2004). CATS incorporate the cognitive evaluation of the situation and a core element in CATS is expectancy outcome. It is the person's experience and evaluation of demands and expectancies of outcomes that determine whether the demands cause a stress response which may affect the health. In CATS, coping with stressors is defined as positive outcome expectancy and is related to psycho-physiology. In a stressful situation, it is not enough with control. People must expect that this control leads to a good result. If this is not the case they may develop hopelessness (Reme et al., 2008).

According to the CATS a stress response is a general alarm in a homeostatic system, producing general and unspecific neurophysiological activation from one level of arousal to more arousal (Ursin & Eriksen, 2004). The stress response occurs whenever there is something missing, for instance a homeostatic imbalance, or a threat to homeostasis and life of the organism. The stress response, therefore, is an essential and necessary physiological response. The unpleasantness of the alarm is no health threat. However, if sustained, the response may lead to illness and disease through established pathophysiological processes ('allostatic load') (McEwen & Wingfield, 2003). It is the person's experience and evaluation of demands and expectancies of outcomes that determine whether the demands cause a stress response which may affect the health.

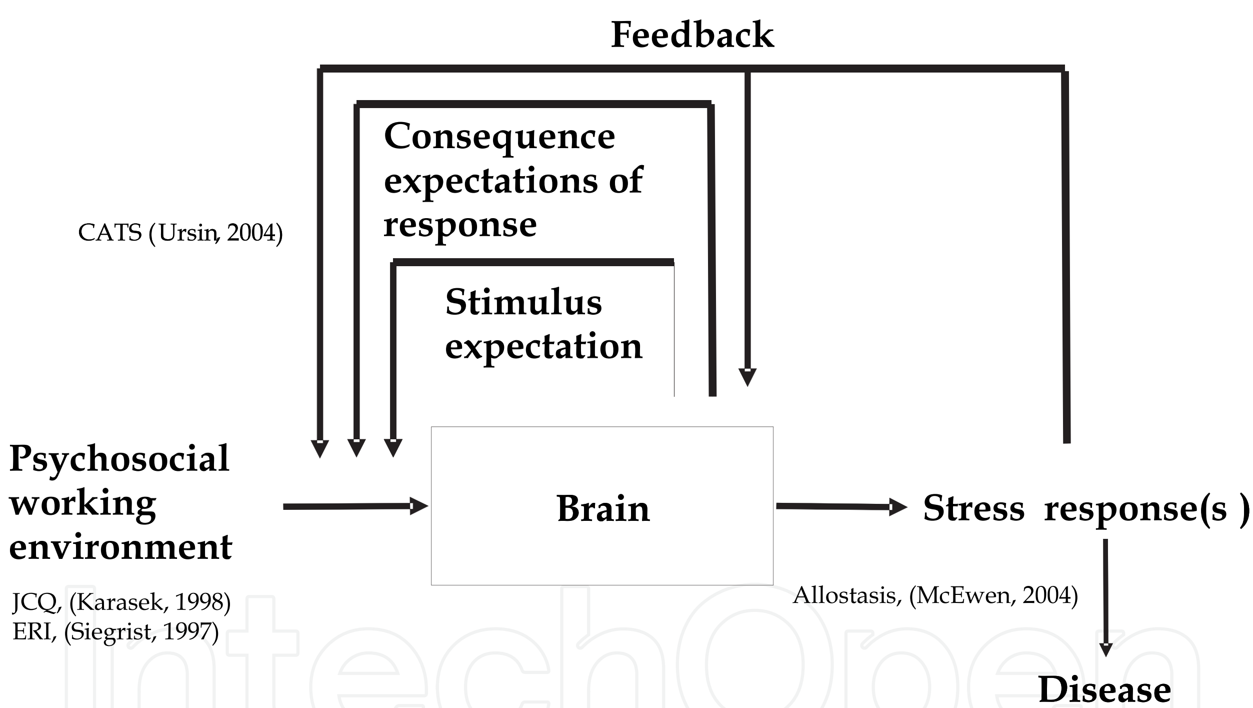

Fig. 1. A model of the association between the psychosocial working environment and disease.

Figure 1 presents a model of how the psychosocial working environment in theory may lead to disease. Theoretically, stress reactions may affect health either by a direct biological, prolonged physiological activation and lack of restitution, or by affecting health through lifestyle and health behaviours. The stress response occurs when homeostasis is threatened or perceived to be threatened and is mediated by the stress system. Cortisol is an indicator of the responsiveness of the HPA axis. Cortisol is a natural energy-releasing hormone with a distinct diurnal rhythm being highest in the morning and decreasing to the lowest in the evening. The acute stress response is in that sense a healthy response that adapts the organism to handle a challenge. However, prolonged stress leads over time to wear-and-tear on the body (allostatic load) (McEwen, 2004). Hormones and other mediators, such as neurotransmitters, cytokines, and other hormones are essential for adaption to challenges of daily life as well a major life stressors. One potential pathway to disease is when hormones and other mediators are not turned off when the stress is over. (McEwen, 2004). Frankenhaueser and Johansson (1986) studied excretion of adrenaline in urine during the day and in the evening among office workers before during and after a period of overtime work. Urinary adrenaline was consistently elevated during the overtime period and 4 weeks after the overtime period ended (Frankenhaeuser & Johansson, 1986). Increased risk of cardiovascular diseases has been found among employees performing mentally straining work (Karasek et al., 1981; LaCroix & Haynes, 1984; Pieper et al., 1989), monotonous work (Christensen, 1986; Kristensen, 1989; Putz-Anderson et al., 1992), as well as a high pace and shiftwork (Kristensen, 1989). Debilitated immune defence system may lead to cancer, infections and allergy. Long-term stress has been shown to influence the immune system and susceptibility to infection (Cohen & Williamson, 1991).

3. Early indicators of psychosocial work environment and health – exposure to workplace bullying as an example

Stressful and poorly organized work environments as well as deficiencies in leadership may facilitate work-related bullying and negative behaviour either directly or by creating a work climate in which bullying can flourish. In Denmark, it has been estimated that 8.3% of the working population between 20 and 59 years of age has been subjected to bullying within the past year. Of these, 1.6% reported frequent bullying, that is, weekly or daily (Ortega et al., 2008). Similar results have been reported in other countries (Lallukka et al., 2011; Matthiesen & Einarsen, 2007; Niedhammer et al., 2009). The most studied health outcomes of bullying are psychological symptoms and emotional reactions such as depression, burnout, anxiety, and aggression. However, psychosomatic and musculoskeletal health complaints have also been in focus (Hogh et al., 2010).

Systematic negative behaviour at work such as bullying or mobbing may have devastating effects on the health and well-being of the exposed individuals. Previous research covers cross-sectional studies, a few case-control studies and clinical interviews, as well as recent longitudinal studies. The early cross-sectional studies found correlations between exposure to bullying and chronic fatigue, psychosomatic, psychological and physical symptoms, general stress, insomnia, and mental stress reactions etc. (for reviews see e.g., (Dofradottir & Høgh, 2002; Einarsen & Mikkelsen, 2003; Moayed et al., 2006)). Common symptoms such as musculo-skeletal complaints, anxiety, irritability and depression were reported by targets in different European countries (Einarsen et al., 1996; Niedl, 1996; O'Moore et al., 1998; Zapf et al., 1996). Some victims displayed a pattern of symptoms indicative of Posttraumatic Stress Disorder (PTSD) (Björkqvist et al., 1994; Einarsen et al., 1999; Leymann & Gustafsson, 1996; Mikkelsen & Einarsen, 2002). Self-hatred and suicidal thoughts have also reported (Einarsen et al., 1994; Thylefors, 1987). Qualitative studies (Kile, 1990; Mikkelsen & Iversen, 2002; O'Moore et al., 1998; Price Spratlen, 1995; Thylefors, 1987) have demonstrated consequences such as reduced self-confidence, low self-worth, shyness, an increased sense of vulnerability as well as feelings of guilt and self-contempt. Moreover, some targets reported that their physical health and mental well-being had been permanently damaged (Mikkelsen, 2001). Longitudinal studies offer the possibility of measuring exposure and effects at different time points thus making it easier to conclude on the direction of the association from exposure to effect. Two recent Norwegian longitudinal studies have found that bullying predicts mental distress two years later (Finne et al., 2011; Nielsen et al., 2011). A longitudinal Finnish hospital study of primarily female employees showed a much higher risk of cardiovascular disease for targets of prolonged bullying as well as a four times higher risk of developing depressive symptoms. The longer time the bullying had taken place the higher risk of depression. (Kivimäki et al, 2003). Two Danish studies showed long-term health effects of exposure to bullying. For instance that exposure to bullying behaviour such as nasty teasing may generate both early and long-term stress reaction as shown in a 5-year follow-up study of the Danish working population; and that being bullied during your education may have health effects one year later as demonstrated by a prospective study of health care workers in care of the elderly (Høgh et al., 2007). Finally, longitudinal studies have also shown an increase in sickness absence among bullied targets (Clausen et al., 2011; Kivimäki et al., 2000; Ortega et al., 2011), as well as a risk of ending up on early retirement pension (Dellve et al., 2003)

According to transactional stress models, the nature and severity of emotional reactions following exposure to bullying may be a function of a dynamic interplay between event characteristics and individual appraisal- and coping processes. Definitions of bullying at work commonly entail descriptions that emphasize prolonged exposure to interpersonal acts of a negative nature, with which the target is unable to cope. These negative acts may be person related and/or work related. Together, these factors are likely to make up a highly stressful situation characterized by lack of control. Attributions of control and predictability are salient features of the individual's appraisal processes (Joseph, 1999; Lazarus, 1999). In transactional models such as the cognitive activation theory of stress (CATS) (Ursin & Eriksen, 2004) and the allostasis model (McEwen, 2004) the link between cognitive processes and physiology is emphasized. Yet, until now only few studies have studied the physiological consequences of bullying.

The stress response is the activation of the autonomic nervous system and hypothalamo-pituitary-adrenal (HPA) axis. Activation is a normal response and as such not unhealthy. However, inadequate or excessive adrenocortical and autonomic function is deleterious for health and survival. It is when the "fight/flight" response occurs too frequently or is greatly prolonged that we begin to experience the negative effects of stress. This prolonged elevation may be due to anxiety, to constant exposure to adverse environments involving interpersonal conflict, and to changes in life-style and health-related behaviours that result from being under chronic stress (McEwen, 2007). Recent research has pointed to a functional link between stress, disturbed sleep, psychiatric disorders, ageing, and neuroendocrine dysfunctions. In particular, elevated plasma cortisol levels have been shown in physiological ageing and patients with psychiatric disorders. Salivary cortisol has increasingly been used to study occupational stress and the responsiveness of the HPA-axis in both field studies and experimental studies (Aardal-Eriksson et al., 1999; Evans & Steptoe, 2001; Kirschbaum et al., 1989; van Eck et al., 1996; Zeier, 1994).

A few studies have addressed the physiological consequence of workplace bullying with biological measurements among targets who were still working (Hansen et al., 2006; Hansen et al., 2011; Kudielka & Kern, 2004). Kudielka and Kern presented tentative evidence of an altered circadian cycle of cortisol secretion among targets. Likewise, Hansen and colleagues observed signs of an altered HPA-axis activity among 22 targets manifested as a lower excreted amount of salivary cortisol in the morning (Hansen et al., 2006) and in among 161 frequently and occasionally occupationally active bullied persons (Hansen et al., 2011). Recently results pointing in the same direction were reported among young adults in as much as salivary cortisol levels and systolic blood pressure were lower in male targets who reported having no feelings of anger about their experience compared to controls and those who did report anger (Hamilton et al., 2008). While these observations are interesting and potentially clarifying as regards to how bullying might get "under the skin", it is equally clear that the study designs and methods used have limitations. In the Hansen et al (2006) study the definition of bullying did not account for frequency or duration, which are often considered important aspects despite controversies as to how they should be incorporated in a definition (Leymann, 1996; Zapf & Einarsen, 2005). A recent study of a large number of occupationally active persons was designed to counter methodological weaknesses inherent in previous studies involving salivary cortisol (Hansen et al., 2011). Results showed that frequently bullied employees, irrespective of gender had poorer psychological health and a lower level of salivary cortisol compared to a non-bullied reference group. Occasionally bullied employees only had a poorer psychological health compared to a reference group. These findings underline results reported among young adults (Hamilton et al., 2008) where the most affected individuals showed long-term effects on salivary cortisol.

4. The physiological response and the psychosocial working environment

Exposure to psychosocial stressors initiates a number of physiological reactions, regulated by hormones. Endocrine factors have become increasingly relevant for the understanding of the adaptation processes and in the pathogenesis of chronic diseases caused by occupational stressors. An intricate network of hormones and hormone-like activities is implicated in the stress response. Until now, neuro-endocrinological parameters have been widely used to estimate the biological effects of stress in field research.

A recent review compiled the literature on the psychosocial working environment and biological measures in blood and urine (Hansen et al., 2009). Job demands and job control were the most intensely studied factors of the psychosocial work environment. The result was clearest on HbA_{1c}, where all studies reported positive associations to both job demands (Cesana et al., 1985; Grossi et al., 2003; Hansen et al., 2003a; Kawakami et al., 2000) and job control (Grossi et al., 2003; Hansen et al., 2003a; Kawakami et al., 2000; Riese et al., 2000). Concentrations of testosterone were negatively associated with job demands (Hansen et al., 2003b) and job control (Berg et al., 1992; Hansen et al., 2003a; Theorell et al., 1990), whereas concentrations of fibrinogen were positively associated with job demands in all population based studies (Clays et al., 2005; Kittel et al., 2002; Steptoe et al., 2003; Tsutsumi et al., 1999), but not in workplace studies (Ishizaki et al., 2001; Riese et al., 2000). The result were mixed when evaluating prolactin in blood where both negative associations to job demands (Hansen et al., 2003b; Ohlson et al., 2001; Su, 2001), and positive associations between prolactin and job control were found (Berg et al., 1992; Hansen et al., 2003a; Ohlson et al., 2001; Su, 2001; Theorell et al., 1990; Theorell et al., 1993).

Only few studies were included on the effort reward model with mixed effect. One of two studies found cholesterol to be positively associated with effort reward (Kobayashi et al., 2005; Vrijkotte et al., 1999). No association between cortisol, fibrinogen and effort reward were found (Irie et al., 2004; Vrijkotte et al., 1999).

Concerning leadership five studies found a positive association with cortisol, one study when reporting poor leadership (Härenstam & Theorell, 1990), three when lacking of social support (Härenstam & Theorell, 1990; Payne et al., 1984; Schnorpfeil et al., 2003) and a single study on low job satisfaction (Payne et al., 1984). A positive association with concentrations of HbA_{1c} was found in three studies of poor social support (Grossi et al., 2003; Hansen et al., 2003a; Kawakami et al., 2000) and one of low job satisfaction (Kawakami et al., 1989).

Six studies found a positive association of catecholamines with organisational factors; two associated monotony and high work pace to catecholamines (Lundberg et al., 1989; Timio et al., 1979) where four studies found a positive association between catecholamines and having shift work (Fujiwara et al., 2004; Fujiwara et al., 1992; Levitt & Derrick, 1991; Mulders et al., 1982). Positive associations with HbA_{1C} were found for both having shift work (Cesana et al., 1985) and organizational changes where the participants rated their psychosocial working environment poorer at follow-up (Netterstrøm & Hansen, 2000). Low testosterone was found among employees having shift work (Axelsson et al., 2003; Touitou et al., 1990).

In summary the above mentioned studies point in the direction of adverse psychosocial working environment being associated with increased HbA_{1c} and fibrinogen in blood and decreased serum testosterone indicating an increased catabolic activity and decreased anabolic activity.

5. Potential variation and confounders in physiological response to adverse psychosocial working environment – cortisol used as an example

Biological measures will also reflect normal cyclic biological variations (e.g. diurnal and seasonal variations), effects of lifestyle factors, as well as the performance of the selected analytical methods and errors (Hansen et al., 2008). The magnitude of variations can, however, be estimated, statistically modelled and attributed to variations within the individual (intra-individual variation) as well as variations between individuals (inter-individual variation) (Costongs et al., 1985; Fraser et al., 1989; Garde et al., 2000; Hansen et al., 2001; Maes et al., 1997; Nicolau et al., 1984).

Measurement of saliva cortisol has been found to be an excellent indicator of unbound concentrations of cortisol in serum (Ahn et al., 2007; Neary et al., 2002; Putignano et al., 2001). The studies find a good correlation between mean saliva cortisol and mean serum cortisol (approx. r = 0.6) and that concentration of cortisol in serum was 10-20 times higher than measured in saliva. Also similar circadian fluctuations has been reported for cortisol in saliva and plasma (Umeda et al., 1981). It is however not only the total concentrations of cortisol that have rendered interest. A number of derived measures that are thought to better describe the dynamics of the stress response have been invented and put into common use. The two most common examples are the awakening response (ACR) and recovery (Kudielka et al., 2007). The ACR is sometimes called reactivity and recovery is sometimes referred to as "fall-during–the-day". The ACR is typically defined as the difference between concentrations of cortisol in the first saliva sample in the morning and the second sample. Recovery is typically defined as the difference between the highest concentration of cortisol in morning samples and the evening sample. Another derivate measure is the area under the curve, which is used as a proxy for the total concentrations during a pre-defined time period.

An important factor of compliance is the time of sampling. Some studies have used electronic devices to track when participants actually accessed the cotton swab, or tampon. In one study it was observed that 74% of the participants accessed the tampon according to the study protocol, whereas 26% failed to access the tampon on the proper time at least with one out of six samples. Of this latter group of non-compliants, 55% failed to take the second morning sampling correctly after 30 minutes. Participants, who were not informed that their sampling was being tracked, were significantly less compliant than informed participants (Kudielka et al., 2003). In another study that examined participant adherence found that 71% of participants, which were unaware they were being monitored, correctly followed the protocol. Their self-reported compliance was however 93%. Among the persons who were aware of being monitored, the objective compliance was 90%, consistent with the self-reported compliance of 93% (Wright & Steptoe, 2005). In both studies, the non-adherent participants had significantly lower morning cortisol values than the adherent participants.

In research projects, samples are often required to be stored for longer periods of time either because of the protocol of the project or because of lack of funding for analysis. A study on long-term storage found no effects on cortisol concentrations after storage of saliva at 5 degrees C for up to 3 months or at -20 degrees C and -80 degrees C for up to one year. In contrast, concentrations of cortisol were found to decrease by 9.2% (95% confidence interval (CI): 3.8%; 14.3%) per month in samples stored at room temperature. Repeated freezing and thawing of samples up to four times before analysis did not affect the measured concentrations of cortisol. Centrifuged saliva samples for analysis of cortisol may be stored at 5 ºC for up to 3 months or at -20 ºC or -80 ºC for at least one year. However, long-term storage at room temperature cannot be recommended. Repeated cycles of freezing and thawing did not appear to affect the concentrations of cortisol (Garde & Hansen, 2005a; Hansen et al., 2005).

In summary it is important to reduce unnecessary variability in the study design (diurnal and seasonal variation), and to provide suggestions for dealing with variability in cases where such influences are unavoidable. Some examples are given for using salivary cortisol, which may not be relevant for other biomarkers.

6. Conclusion

The present chapter provides the reader with insight into the existing evidence on how different physiological responses may be used as potential biomarkers of the adverse effects of the psychosocial working environment. Adverse psychosocial working environment was found to be associated with increased HbA_{1c} and fibrinogen in blood and decreased serum testosterone indicating an increased catabolic activity and decreased anabolic activity. Further when using and interpreting the measured physiological response it is important to be aware of potential confounders directly addressed to the selected biological measure. In this context it is also important to reduce unnecessary variability in the study design (diurnal and seasonal variation), and to provide suggestions for dealing with variability in cases where such influences are unavoidable.

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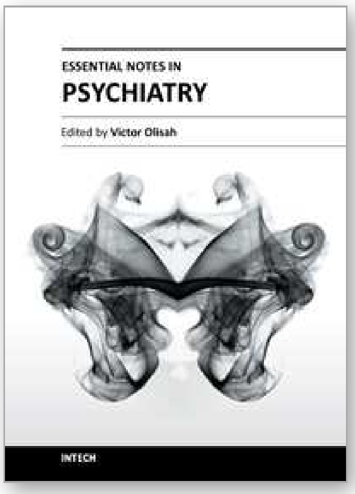

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