Neuroscience and Biobehavioral Reviews 74 (2017) 310–320

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

In the search for integrative biomarker of resilience to psychological stress

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ARTICLE INFO

Article history:
Received 22 December 2015
Received in revised form 26 April 2016
Accepted 6 May 2016
Available online 11 May 2016

Keywords:
Resilience
Psychological stress
PTSD
Biomarkers

ABSTRACT

Psychological resilience can be defined as individual's ability to withstand and adapt to adverse and traumatic events. Resilience is traditionally assessed by subjective reports, a method that is susceptible to self-report bias. An ideal solution to this challenge is the introduction of standardised and validated physiological and/or biological predictors of resilience. We provide a summary of the major concepts in the field of resilience followed by a detailed critical review of the literature around physiological, neurochemical and immune markers of resilience. We conclude that in future experimental protocols, biological markers of resilience should be assesses both during baseline and during laboratory stressors. In the former case the most promising candidates are represented by heart rate variability and by *in vitro* immune cells assay; in the latter case—by startle responses (especially their habituation) during stress challenge and by cardiovascular recovery after stress, and by cortisol, DHEA and cytokine responses. Importantly, they should be used in combination to enhance predictive power.

Contents

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http://dx.doi.org/10.1016/j.neubiorev.2016.05.003
0149-7634/

1. Introduction

Psychological resilience has been variously defined as the process of positive adjustment to adverse events (Fletcher and Sarkar, 2013). In the context of exposure to potentially traumatic events an indicator of resilience would be considered the absence of psychiatric disorder symptoms, such as post-traumatic stress disorder (PTSD). The term "resilience" (or "resilience") was first used in this context by Jack Block in his 1950 doctorate dissertation (Block, 1950); however the concept could be traced back to Sigmund Freud's theory of personality where it had a name of "ego strength" (Freud, 1921). Over recent years, there has been a growing interest in resilience, particularly in its prophylactic properties in at risk populations, most notably first responders and military personnel. Despite the obvious potential, implementation of resilience training and monitoring programs has proven difficult, in large part because of the absence of accurate and rapid tools to assess resilience. Presently, psychometric approaches dominate the research landscape. While these approaches have value, self-report assessments are highly susceptible to self-report bias. This issue is well recognised in many areas of psychometrics but is especially pertinent in populations where low levels of resilience may result in temporary or permanent removal from front-line positions. An ideal solution to these challenges is the introduction of standardised and validated physiological and/or biological predictors of resilience. Such readouts are significantly less prone to subject manipulation and therefore offer the possibility of improved assessment accuracy. Given these facts, the aim of this review will be to provide a brief summary of the major concepts in the field of resilience before providing a detailed critical review of the literature around biological markers of resilience. We initially focus on the significance of assessing resilience; this is followed by a description of psychometric resilience scales and of potential physiological, neurochemical and immune markers of resilience. We conclude by canvassing the multiple pathways for future use of bioanalytic approaches for resilience research.

2. Significance of assessing resilience from the public health perspective

Human beings encounter a variety of stressors across the course of their lives, ranging from daily hassles to major life events. Experience of traumatic events has been found surprisingly common across communities, with estimates that most individuals experience a potentially traumatic event in their lifetime (Bonanno and Mancini, 2008; Kessler et al., 1995). There now appears to be compelling evidence to suggest that humans exposed to a common aversive or traumatic experience will exhibit a wide range of responses. Underscoring this point, it has been shown that only somewhere between 10–15% of veterans from the Vietnam conflict (1962–1975) went on to develop PTSD (*e.g.* (Barrett et al., 1988; Marmar et al., 2015)). While there are likely to be several factors that account for the fractional percentage of veterans that developed PTSD, the figure has widely been interpreted as suggesting that the majority of combat veterans could be characterized as resilient. This phenomenon has further been interpreted as indicating that the principal cause of affective disorders is not the traumatic event *per se*, but rather the way in which these events are psychological processed by the affected individual.

While cited studies underscore the importance of identifying vulnerable individuals in military servicemen and to enrol them in resilience-enhancing programs prior to deployment, the potential value of resilience measurements is much broader. Firstly, it is directly applicable to occupations associated with real life dangers such as defence or police forces. Secondly, and more importantly, assessing indicators of resilience at early age might appear to be an efficient mean in the prevention of depressive disorders that represent tremendous burden, both for the society as a whole and for individuals suffering from these disorders. Therapeutic strategy for managing these mental illnesses focuses on established cases; it has limited efficacy and high cost. It would be highly advantageous, from both economic and public health perspectives, to identify susceptible individuals prospectively, and to subject them to resilience-enhancing interventions. The major difficulty in this strategy is a lack of means to identify such vulnerable individuals. There are currently no established robust biomarkers of resilience, and all proposed biomarkers do not have discriminative power.

3. Current means for assessing resilience

3.1. Psychometric instruments and their inherent problems

Assessment of resilience has been approached using a number of psychometric tools. Although not exhaustive these include: Ego-Resilience scale (ER89, (Block and Kremen, 1996)), Connor-Davidson Resilience Scale (CD-RISC, (Connor and Davidson, 2003)), Adult Resilience Scale (ARS, (Friborg et al., 2003)), Brief Resilient Coping Scale (BRCS, (Sinclair and Wallston, 2004)), Dispositional Resilience Scale-15 (DRS-15, (Bartone, 2007)), Resilience Scales for Children and Adolescents (RSCA, (Prince-Embury, 2008)) and most recently developed Response to Stressful Experiences Scale (RSES, (Johnson et al., 2011)). Most commonly, these questionnaires determine subjective ratings of psychological factors, such as cognitive flexibility, spirituality, social support, self-efficacy, which lead to positive adjustment (see (Southwick et al., 2005) for a comprehensive review). It has been suggested that currently there is no 'gold standard' psychometric instrument for measurement of psychological resilience (Windle et al., 2011). However, questionnaires such as the Connor-Davidson Resilience Scale (CD-RISC, (Connor and Davidson, 2003)) present a promising approach.

The common problem of all psychometric tests derives from their subjective nature. Their results could be affected by non-intentional or intentional biases, especially in those respondents whose job perspectives and/or career advances depend on their resilience level. Objective measurements are devoid of these flaws, and it will be most advantageous to complement existing psychometric scales of resilience with objectively measurable biomarkers.

3.2. Concept of psychobiological allostatic load

In the review of psychobiological mechanisms of resilience and vulnerability (Charney, 2004) introduced the idea of "psychobiological allostatic load". It is based on the concept of allostatic load and on the knowledge of identified neurobiological factors potentially responsible for stress resilience and vulnerability. In their seminal article, (McEwen and Stellar, 1993) defined allostatic load as "the cost of chronic exposure to fluctuating or heightened neural or neuroendocrine response resulting from repeated or chronic environmental challenge that an individual reacts to

as being particularly stressful"; if the burden of allostatic load exceeds the capacities of physiological systems on the body, a state of disease occurs. So far the concept of allostatic load was largely applied to somatic consequences of psychological and physical stressors, and (Seeman et al., 1997) developed and validated a 10-point scale for its assessment. This scale comprised the following variables: overnight urinary cortisol, epinephrine and norepinephrine; serum DHEA-S levels; systolic and diastolic BP; HDL and total/HDL cholesterol; waste/hip circumference ratio and plasma glycosylated haemoglobin. Importantly, despite lack of correlation between any one of these biomarkers with the health outcomes of the study during the seven years follow-up, the total score of allostatic load appeared to be significantly associated with these outcomes. (Charney, 2004) suggested that "the analogous approach that involves the identification of a group of biological markers that will relate to psychobiological allostasis and psychobiological allostatic load, and consequently, to resilience and vulnerability to the effects of extreme psychobiological stress will be fruitful". He then proposed to use objective measurements of 11 identified stress resilience/vulnerability markers to construct individual profiles of psychobiological allostatic load (Charney, 2004). In the present manuscript we attempt to expand Charneys's ideas by: (i) adding the description of physiological biomarkers of resilience; (ii) focussing on recovery in addition to reactivity of physiological variables; and (iii) assessing which of available measurements are suitable for large-scale community studies and for repetitive testing during occupational resilience-enhancing training programs.

Many neurobiological factors responsible for psychological resilience are yet to be found; the field is however quickly expanding, and in his excellent and highly relevant review (Charney, 2004) has identified 11 potential neurobiological factors of resilience. They comprise three classical monoamine neurotransmitters (noradrenaline, serotonin and dopamine), neuropeptides (neuropeptide-Y, NPY and corticotropin-releasing factor, CRF), hormones (cortisol and dehydroepiandrosterone, DHEA) as well a polymorphism of 5-HT1A and alpha-2 adrenergic receptors. We would like to add to this list several additional candidates that became known during the last decade, including oxytocin and pro-inflammatory cytokines. We also focus on potential physiological biomarkers of resilience—cardiovascular reactivity and recovery, and heart rate variability.

3.3. Candidate neurobiological markers of resilience—physiological measures

Ideally, to assess links between biological markers and resilience to stresses, and to evaluate the predictive power of such markers, one would need to perform measurements before and after traumatic events, and compare the differences between those who resisted the psychological impact and those who developed PTSD and thus could be classified as low-resilient by the very nature of their condition. Remarkably, few studies indeed employed this prospective approach; however the vast majority of data in the field were acquired by different research strategies—by either correlating a given physiological or biochemical measure with self-rated resilience score in mentally healthy individuals, or by comparing measures obtained in PTSD patients with matched healthy controls. We have grouped the results presented in this review according to this division.

3.3.1. Acoustic startle response

Hyperarousal is a diagnostic criterion for the PTSD (DSM-IV, 2000), and physiological responses to acoustic startle probe (sudden loud sound) have been extensively studied in PTSD patients (Orr et al., 2004; Prins et al., 1995). Currently established view is that these pathological responses comprise elevated eyeblink EMG (Grillon et al., 1998a; Morgan et al., 1995; Seppala et al., 2014; Shalev et al., 2000), larger tachycardia (Carson et al., 2007; Metzger et al., 1999; Shalev et al., 2000) and higher and slower habituating skin conductance response (SCR) (Metzger et al., 1999; Shalev et al., 2000). Many studies however reported lack of potentiated eyeblink in PTSD patients (Carson et al., 2007; Jovanovic et al., 2009; Metzger et al., 1999), and after performing meta-analysis of 11 relevant publications (Pole, 2007) concluded that under more stringent tests for significance, PTSD was reliably related only to higher HR response and to slower SCR habituation. Moreover, the established view has been further challenged by (Zoladz and Diamond, 2013): thorough review of existing publications led them to conclusion that elevated startle responses reflect not hyperarousal *per se*, but rather the process of fear potentiation. Indeed, elevated startle responses in PTSD patients compared to controls were consistently found in those studies where the level of fear was manipulated by laboratory stressors (Grillon et al., 1998a,b; Pole et al., 2003).

A major question in PTSD research is whether differences in startle-induced responsivity between resilient and vulnerable individuals are innate and exist pre-trauma or they represent the result of trauma-induced neural remodelling. Of major relevance and importance for this topic are results from the two prospective studies. In one of them conducted in fire fighters, magnitude of the pre-trauma skin conductance response, but not of eyeblink response to startle stimuli was a positive predictor of posttraumatic stress symptoms (Guthrie and Bryant, 2005). In contrast, no differences in physiologic responses to startle were found shortly post-trauma in survivors who later developed symptomatic PTSD (Shalev et al., 2000). It is of course not known what were responses to startle stimulation in this group pre-trauma. Equally relevant is a study of monozygotic twins discordant to combat exposure: authors argue that higher HR responses to startle in siblings with PTSD favour against innate mechanism (Orr et al., 2004). It is however questionable whether the reported difference in tachycardia (+0.32 bpm) is physiologically significant. On the other hand, in PTSD twins with and without trauma, SCR recovery was slower, suggesting that slower habituating SCRs to startle stimuli may be an innate vulnerability factor for PTSD. This possibility is not supported by results of (Schumacher et al., 2013) who found no differences in responses to startle between remitted PTSD patients and controls suggesting that heightened startle reactions were the consequence of trauma; and by finding that elevated startle responses in PTSD patients recede during treatment (Seppala et al., 2014). Lastly, (Costanzo et al., 2014) assessed physiological responses to startle in military servicemen with subthreshold PTSD; it was found that HR responses and, to a lesser extent, SCR, were associated with overall subthreshold PTSD symptoms. Of major importance, startle stimuli were presented during stressful videos related to combat trauma underscoring the role of fear in startle hyperresponsivity.

3.3.2. Cardiovascular reactivity during laboratory stressors

In the present section we focus on cardiovascular responses to standard laboratory stressors. These stressors could be separated in two groups: short-duration high-intensity stimuli (acoustic startle) and prolonged artificial distressing situations (Trier social stress test—preparation for and participating in a videotaped job interview; mental arithmetic; mirror tracing; anger recall; cold pressor test etc.). The information on cardiovascular responses to these stressors in humans is abundant, with the vast majority of studies considering the reactivity model; its major premise is that individuals with higher cardiovascular reactivity (response amplitude) have higher risk of cardiovascular morbidity. Cardiovascular reactivity to both startle and prolonged stressors was extensively studied in both healthy individuals and in patients with PTSD; overall results

could be characterized as controversial and inconsistent. While the meta-analysis of startle studies by (Pole, 2007) revealed significant effect of PTSD on the post-startle tachycardia, in some experiments this effect was not observed (Kibler and Lyons, 2004; Shalev et al., 1997).

Relationships between prolonged laboratory stressors and cardiovascular responses appear to be quite complex. Not surprisingly, war veterans, car crash survivors or victims of child sexual abuse with PTSD have higher tachycardic and pressor responses to audio or visual cues with specific trauma-related triggers (Blanchard et al., 1996; Blanchard et al., 1982). On the other hand, lack of consistency was found in cardiovascular responses to trauma-unrelated prolonged stressors: while some studies reported no difference between PTSD patients and healthy controls in HR and BP changes induced by mental arithmetic or cold pressor test (Jones-Alexander et al., 2005; Keary et al., 2009; Orr et al., 1998; Sahar et al., 2001), other researchers reported that PTSD was associated with *reduced* cardiovascular reactivity when responses to trauma-unrelated stressors were assessed (Blanchard et al., 1989; Keane and Lavori, 1998; McDonagh-Coyle et al., 2001). Interestingly, blunted cardiovascular reactivity to psychological stress prospectively predicted symptoms of depression in a large population study (Phillips et al., 2011).

3.3.3. Cardiovascular recovery after laboratory stressors

It may be that the speed of post-stress cardiovascular recovery (time of return to baseline) is equally if not more relevant for the development of stress-related pathology than the reactivity (rise from the baseline). Despite potential importance of the recovery measures, in their seminal review of 105 relevant studies, (Linden et al., 1997) pointed out that recovery was reported in less than a quarter of publications where it was recorded. The authors concluded that ". . . the case for studying recovery is further supported by studies using recovery protocols that revealed positive findings not apparent in reactivity comparisons only". More recently significance of assessing post-stress cardiovascular recovery was emphasized by (Brosschot et al., 2005).

There is now considerable experimental evidence linking prolonged post-stress recovery to psychological traits and/or states ascribed to the low-resilient individuals. Relevant studies could be split in three categories: (i) those conducted in individuals who developed psychopathology after traumatic experience; (ii) those conducted in healthy subjects; and (iii) those conducted during resilience-enhancing training programs, also in healthy individuals. While at the present time only two articles fall into the first category, they are of particular importance as the were conducted in Vietnam combat veterans who developed PTSD. In the first of these studies conducted in Vietnam veterans, BP recovery after anger recall was slightly but significantly higher compared to control group (Beckham et al., 2002). In the second study, (Kibler and Lyons, 2004) assessed cardiac responses to acoustic startle in veterans that were undergoing treatment for the PTSD. They found that HR recovery time (ranging from 1 to 30 s) was directly related to PTSD severity while the ability to cope (a psychometric resilience item) was inversely related to both HR recovery and PTSD severity. On the other hand, neither amplitude nor habituation to repetitive stimuli of tachycardic responses had any association with PTSD severity.

Studies belonging to the second category (comparison of resilience with cardiovascular recovery in healthy individuals) are also represented by only two publications. The first one was conducted by (Tugade and Fredrickson, 2004); it compared resilience scores of 57 female participants with their post-stress recovery time, and found that trait resilience was negatively correlated to this index, indicating that high-resilient individuals recover faster. The reported mean recovery time was 30 s; however one serious difficulty in interpreting this value is that it represented averaged recovery time of six cardiovascular variables—heart rate, finger pulse amplitude, pulse transmission times to the finger and the ear, and systolic and diastolic blood pressure. Unfortunately authors did not present any graphic illustrations of their results, but from other studies it is known that there are quite dramatic differences between post-stress recovery in different physiological measures. For example, HR returns to the baseline within one minute after termination of the mental arithmetic task whereas blood pressure remains elevated for at least 10 min (Glynn et al., 2002). In a more recent study conducted in 50 peacekeepers after their deployment, (Souza et al., 2013) found significant correlation between trait resilience and HR recovery following laboratory stressors, and came to the same conclusion as (Tugade and Fredrickson, 2004)—that resilient individuals recover faster. Unfortunately authors did not provide any data regarding actual duration of HR recovery.

In the recent study by (Johnson et al., 2014), 147 US Marines underwent 8-week mindfulness training as a mean to enhance their resilience, and measurements of HR and respiratory rate were performed before, during and after stressful combat exercise lasting 30 min. Compared to control group, they had somewhat faster recovery of heart and respiratory rates. It must be acknowledged that these findings could not be directly compared with other results presented in this section because of combined physical/psychological nature of the stressor in Johnson's work: indeed, even after 10 min of recovery both physiological measures were still far away from the baseline. Unfortunately authors did not report what happened to the resilience scores that were assessed in both control and experimental groups; judging from their Fig. 4 showing changes in this score in a subsample of 25 subjects, there were more subjects whose score did actually decrease following mindfulness training.

In summary, despite small number of studies addressing relation between resilience rating and cardiovascular recovery from laboratory stresses, and despite some limitations of individual studies, a trend is becoming evident. It appears that those who rated themselves as having higher scores in the resilience items also have faster recovery of their physiological responses.

3.3.4. Mechanisms that may mediate slow post-stress cardiovascular recovery in low-resilient individuals

Several studies conducted in healthy individuals provide insight in psychobiological mechanisms of potentially slower cardiovascular recovery; these mechanisms may include ruminating thoughts and/or negative affect that possibly act in combination. Rumination could be defined as the presence of intrusive, repetitive, negative and non-constructive thoughts about past stressful situations (Gerin et al., 2006). Nearly 30 years ago (Roger and Jamieson, 1988) reported that HR recovery following Stroop test correlated with Rehearsal score in their Emotion Control Questionnaire. This item was defined as having thoughts of a kind "I get worked up just thinking about things that have upset me in the past" that clearly coincides with the definition of ruminations. Later (Glynn et al., 2002) introduced an elegant approach for controlling stress-induced rumination. It occurred that if immediately after stress subjects were distracted by a neutral attention-consuming task, their pressor responses returned to the baseline much faster compared to the control (no distraction) condition. The authors interpreted this observation as indirect evidence that those without distraction were ruminating during the post-task period. Later the same group obtained more direct confirmation of ruminative thoughts in post-stress recovery. Firstly, they found that distraction accelerated BP recovery following purely mental stressor (anger recall) (Gerin et al., 2006). Next, they directly assessed trait and state rumination by a questionnaire, and demonstrated that BP

recovered faster in low-ruminating subjects (Key et al., 2008). Shortly after the finding was confirmed by (Radstaak et al., 2011).

(Brosschot et al., 2006) introduced the concept of perseverative cognition and developed its theoretical model; in essence, its states that physiological responses to stressors could be separated into those that occur *during* stressful events and those that occur *after* its termination. Importantly, the latter do not simply represent return to the baseline but are the results of perseverative thoughts about stressor, and are likely mediated by the same limbic brain areas that are responsible for the direct stress-induced effects. In their concluding remarks, authors suggested that "...physiological reactions that occur while the stressor is actually taking place may not be as important as the cognitive, representational perseverations that may occur long after the stressor itself has ended" (Brosschot et al., 2006). Recently this group has published a very impressive meta-analysis that revealed associations between perseverative cognition and elevated systolic and diastolic blood pressure, heart rate and cortisol, and with lower heart rate variability (Ottaviani et al., 2016).

Non-resilient individuals are also characterized by a largely negative state affect (Southwick et al., 2005), and the relationship between the latter and slow recovery after stress exposure is now well established. This issue is comprehensively covered in the excellent meta-analysis of 161 articles conducted by (Chida and Hamer, 2008). Another review by (Pieper and Brosschot, 2005) also concluded that negative emotional episodes are related to prolonged cardiovascular responses; they noted that particular startling is the fact that cardiovascular response could be far away from the baseline long after the dissipation of the negative affect as was shown by (Brosschot and Thayer, 2003). These human findings are well supported by preclinical studies in rodents: it was demonstrated that while HR, BP and corticosterone levels rise to similar levels during territorial fights in rats, recovery of these physiological variable to the basal level occurs significantly faster in winners compared to losers (Koolhaas et al., 2011). Moreover, even among losers, those who exhibited a proactive coping strategy (and presumably had a positive appraisal of the conflict outcome) did recover faster and did not develop long-lasting behavioural and physiological disturbances (Meerlo et al., 1999). These findings form the basis of our suggestion that recovery rate of stress-induced changes reflect resilience level, and that those who have slow recovery may represent a risk group for developing depression and PTSD.

Relationships between perseverating cognition, negative affect and physiological response to stressors could be quite complex; as suggested by (Gerin et al., 2006), they may be reciprocally determined such that "...autonomic arousal could prolong anger and vice versa.....and the prolonged anger may promote ruminative thoughts and vice versa". Since both rumination (reflecting lack of cognitive flexibility) and negative affect are the characteristics of low-resilient individuals (Southwick et al., 2005), it is not unexpected if slow cardiovascular recovery after stress exposure will appear to be a suitable biomarker for their identification. In support, in patients with major depression, heart rate recovery was found to be substantially prolonged after termination of laboratory stressors; this was associated with task appraisal as more demanding, stressful and threatening, and with less ability to cope (Salomon et al., 2009). In line with this, slow post-stress HR recovery was associated with cognitive depressive symptoms in healthy subjects without (Gordon et al., 2012) or with elevated risk of depression (Salomon et al., 2009).

3.3.5. Heart rate variability and potential mechanisms of its reduction in PTSD

Heart rate variability (HRV) is a well validated ECG-based marker of cardiac autonomic outflow; it could be assessed in time or frequency domains Malik et al. (1996). We focus here on relevant publications that report results of parasympathetic cardiac influences that could be reliably assessed by quantifying vagally-mediated respiratory sinus arrhythmia (RSA). The relevant vagal indices include time-domain indices such as SDNN (SD of sequential R–R intervals) and RMSSD (square root of the mean squared difference between adjacent R–R intervals), and frequency domain index—high-frequency power (HF power or HF HRV).

Nearly all studies that addressed the link between RSA and resilience are represented by cross-sectional investigations of association of low cardiac vagal tone with PTSD symptoms. Their outcome is quite consistent in supporting the view that RSA is reduced in PTSD sufferers (see recent review by (Gillie and Thayer, 2014) that lists nine relevant publications). We were able to identify only one study where resilience and vagal activity were assessed during laboratory stressors in healthy subjects whose subjective resilience scores were also measured. The robust and important findings in this study were that: (i) pparticipants with higher level of resting RSA scored higher on the trait resilience scale; and (ii) participants with higher resting RSA recovered more efficiently from stressors (as assessed by both HR and RSA recovery) (Souza et al., 2013). Similar findings were made in the previous work from the same group (Souza et al., 2007).

The mechanisms underlying low cardiac vagal tone in PTSD are currently unknown. In the frame of their Neurovisceral Integration Model (Thayer and Lane, 2000), Gillie and Thayer (Gillie and Thayer, 2014) proposed that individual differences in RSA may reflect altered cognitive flexibility in PTSD patients, such that perseverative cognition (inability to suppress ruminating thoughts) is associated with reduced cardiac vagal tone. They substantiated this claim by reviewing results confirming link between RSA and cognitive abilities, in particular the ability to suppress unwanted memories. It is thus quite possible that perseverative cognition that is responsible for prolonged BP and HR recovery post-stress (see previous section), could be also involved in lowering resting RSA, and possibly for larger RSA suppression during psychological challenges.

3.4. Candidate neurobiological markers of resilience—biochemical measures

3.4.1. Cortisol

Cortisol and dehydroepiandrosterone (DHEA) are released from the adrenal cortex episodically and synchronously in response to fluctuating ACTH levels (Rosenfeld et al., 1971); release of both hormone increases substantially during psychological and physical stressors. Research literature on baseline cortisol and on cortisol responses to laboratory stressors is abundant; in the present section we limit our analysis to publications relevant to PTSD or to the risk of psychopathology. Many studies assessed plasma or salivary cortisol at baseline; their results are controversial and inconsistent, with reduction, increase and no change in PTSD patients being reported (see (Haglund et al., 2007; Hoge et al., 2007) for reviews). It is now unclear why these discrepancies were found; potential factors may include illness severity, timing of measurements and differences in measurement techniques. Somewhat more promising might be measuring cortisol-awakening response (CAR)—a 4-point hormone profile measured at awakening and 30, 45 and 60 min later. We were able to identify three publications where this response was evaluated in relation to resilience. In a cross-sectional study of mentally healthy adults with a constant psychological strain (parenting autistic children), no difference in CAR was found between high- and low-resilient subjects (Ruiz-Robledillo et al., 2014). In three prospective studies conducted in fire fighters, in military population and in police officers, CAR at the entry point consistently failed to pre-

dict later PTSD development (Heinrichs et al., 2005; Inslicht et al., 2011; van Zuiden et al., 2012). Thus it is unlikely that measurements of baseline plasma or salivary cortisol or CAR could represent a productive approach for identifying susceptibility to PTSD.

There are numerous reports describing cortisol response to laboratory stresses, the latter most frequently being the Trier Social Stress Test, TSST. Blunted (Carpenter et al., 2007; Danielson et al., 2015; Morris et al., 2014), exaggerated (Giletta et al., 2015) and normal (Dienes et al., 2013) cortisol responses have been reported in several healthy but "at risk" populations. It could be that differences here were in the way how "at risk" was determined: childhood maltreatment (Carpenter et al., 2007) subjects with major depression in remission (Morris et al., 2014), young offspring of mothers with PTSD (Danielson et al., 2015), risk of suicidal ideations (Giletta et al., 2015) or negative-positive affect score (Dienes et al., 2013). No influence of ruminations on cortisol response was found in TSST (Young and Nolen-Hoeksema, 2001). Lack of effect of this and other resilience-related personality traits on stress-induced rise in cortisol is potentially due to the dominating influence of novelty (see (Kudielka et al., 2007) for review).

Similar to the situation with physiological data on post-stress recovery, only very minor number laboratory stress studies reported data on cortisol recovery. In their meta-analysis, (Burke et al., 2005) have identified seven such studies, all focussed on MDD patients. Authors concluded that MDD patients and healthy individuals exhibited similar baseline and stress-induced cortisol levels, but MDD patients had much slower recovery. Post-stress cortisol recovery in response to neutral laboratory stressors has not been tested in PTSD patients, and has not ben employed in prospective studies with occupational stress.

In two cases researchers employed the experimental stress paradigms to explore cortisol-resilience relationship; of those the most interesting is a prospective study of police officers. The salivary cortisol response to distressing video was initially determined during their training; their psychological health status was then monitored during the next four years of active service. The study revealed that in a subpopulation of low-resilient individuals (determined by presence of PTSD-like symptomatology), cortisol response during stressful video was severely blunted or rather absent (Galatzer-Levy et al., 2014). These results could explain apparently paradoxical finding that in healthy volunteers, 24 h urinary cortisol positively correlated with subjectively assessed resilience levels (Simeon et al., 2007). It may be that the latter reflects lower cortisol responses provoked by minor everyday stressors in low-resilient subjects. The police officers' cortisol findings however do not agree with results of (Mikolajczak et al., 2008) who reported no differences in cortisol response between low- and high-resilient subjects during speech test. The reasons for these differences is unclear; one noticeable issue is that in the former study the number of participants was much larger—234 *vs*. 28 in the latter one.

3.4.2. Dehydroepiandtrosterone and dehydroepiandrosterone sulphate

Dehydroepiandrosterone (DHEA) and its active metabolite dehydroepiandtrosterone sulphate (DHEA-S) are released during stressful challenge; they have anti-glucocorticoid action that may contribute to psychiatric symptoms associated with PTSD (reviewed by (Haglund et al., 2007; Rasmusson et al., 2003)). Similar to the situation with cortisol, measurements of baseline DHEA in PTSD patients produced controversial results. Elevation of DHEA has been reported in combat veterans and in refugees with PTSD (Sondergaard et al., 2002; Spivak et al., 2000; Yehuda et al., 2006), but not in pre-menopausal women with PTSD (Rasmusson et al., 2004). In another study of combat veterans, more severe PTSD was associated with higher DHEA levels (Butterfield et al., 2005). Anti-glucocorticoid action of DHEA prompted the idea that assessing cortisol/DHEA balance could play a role in the pathogenesis of PTSD, and thus a new index – cortisol/DHEA ratio – was introduced in the PTSD research. (Yehuda et al., 2006) reported that in PTSD patients this index was lower compared to healthy control; (Rasmusson et al., 2004) found no differences between the two groups.

There are several reports describing DHEA responses during laboratory stress tests. Significant rise in DHEA, with large inter-individual variation, was found in healthy subjects (Izawa et al., 2008; Lennartsson et al., 2012); and stress-induced changes in anxiety and negative affect were positively correlated with DHEA increases (Fang et al., 2014). Attenuated DHEA-S, but not DHEA, responses during laboratory stressors were found in subjects with high perceived work stress including those with clinical burnout (Lennartsson et al., 2013; Lennartsson et al., 2015).

Of interest, there have been two interventional studies with oral administration of DHEA that also brought somewhat controversial results. In a clinical trial conducted in depressed patients, DHEA was more efficient than placebo as antidepressant (Rabkin et al., 2006). On the other hand, DHEA supplementation during highly stressful military training did not affect the level psychological distress ratings (Taylor et al., 2012). Finally, in the only cross-sectional correlational study of the DHEA-resilience relationship, a positive association between resilience and the salivary hormone level has been reported (Petros et al., 2013).

3.4.3. Oxytocin

Oxytocin may have interest to the resilience field for its proven ability to reduce fear/anxiety and to increase social interaction, a resilience-enhancing trait (see (Marazziti and Catena Dell'osso, 2008; Olff et al., 2010) for reviews). Current data on the link between oxytocin and PTSD are limited. Several cross-sectional human studies examined association of plasma oxytocin levels with the severity of PTSD, depressive and anxiety symptoms. No such association was found in motor vehicle accident survivors with PTSD (Nishi et al., 2015), and a recent preliminary report stated that only anxiety scores, but not total PTSD score, were linked to PTSD in the earthquake survivors (Cao et al., 2014). Finally, in male, but not female police officers with PTSD plasma oxytocin level was reduced (Frijling et al., 2015). No change (Taylor et al., 2006) or increase (Pierrehumbert et al., 2010) in plasma oxytocin were reported in healthy individuals during laboratory speech test; and substantial post-stress fall was found in the at risk (child abuse) subjects (Pierrehumbert et al., 2010).

Since social support provides protection against affective disorders (see (Ozbay et al., 2007) for review), it may be that appropriate levels of oxytocin exert the resilience-enhancing action by facilitating social interaction. Indeed, experimental animal work that has just appeared provides direct evidence that oxytocin system promotes resilience to the effects of neonatal isolation (a model of child neglect) (Barrett et al., 2015).

3.4.4. Testosterone

Association of elevated gonadal testosterone with aggression and violence is well established (Rosell and Siever, 2015); transitory rise of the hormone is linked to the feeling of dominance or experience of success (Suay et al., 1999), and its transient fall occurs during psychological stress (Morgan et al., 1995). Reduced level of testosterone was suggested as causative factor for more frequent incidence of depression in aged men (McIntyre et al., 2006; Shores et al., 2004; Wainwright et al., 2011), and testosterone replacement therapy is partially efficient in improving depression symptoms in this population (Pope et al., 2003; Seidman and Rabkin, 1998; Zarrouf et al., 2009). Not surprisingly, such ample

evidence of association between testosterone and psychological wellbeing provoked interest in elucidating its role in maintaining resilience. Results obtained so far are however quite controversial: while some studies reported lower testosterone levels in PTSD subjects compared to controls (Mulchahey et al., 2001), most relevant publication did not find such difference in political refugees with PTSD (Bauer et al., 1994) or in patients with combat-related PTS D(Karlovic et al., 2012; Spivak et al., 2003). It may be thus safely concluded that existing data do not provide substantial evidence for participation of testosterone in resilience to psychological stresses.

3.5. Candidate neurobiological markers of resilience—immunological measures

3.5.1. Inflammatory markers

Inflammatory markers (*e.g.* cytokines and interferons) are chemical signals produced by activated immune cells both in the CNS and in the periphery, and their involvement in various disorders, including mental disorders, are actively investigated (Dantzer, 2009; Tabas and Glass, 2013). Cytokines were measured in PTSD patients by numerous authors, with mixed results. Our task in reviewing this topic is substantially simplified by an excellent meta-analysis in which 20 relevant studies were selected from more than 8000 publications (Passos et al., 2015). The authors came to the following conclusions: (i) levels of IL-1β, IL-6, interferon γ and TNFα are higher in patients with PTSD than in healthy controls; (ii) IL-1β is a potential biomarker of illness duration; and (iii) IL-6 is a potential biomarker of illness severity. Furthermore, the study identified four factors that could explain the heterogeneity of results reported by different authors: presence of comorbid major depressive disorder, use of psychotropic medication, type of assay used, and time of blood collection.

In a prospective study of motor vehicle accident survivors, serum IL-6 concentrations measured within the first 24 h after the accident were higher in children who developed PTSD six months later than those who did not and those of the control group (Pervanidou et al., 2007). Of course initial measure here does not represent baseline level of the cytokine. There is now a compelling evidence that acute stressors cause elevation in the circulating levels of pro-inflammatory cytokines (see review and meta-analysis by (Steptoe et al., 2007)), but it is still unknown whether stress-induced cytokine responses are different in PTSD patients, or whether they could predict susceptibility to PTSD. The only relevant study that we were able to identify reports that in healthy adults who were maltreated in the childhood, IL-6 increase in response to a speech test was higher compared to controls (Carpenter et al., 2010).

Mechanistically, relevance of inflammatory markers is supported by pre-clinical studies revealing that microglia – a major source of cytokines secreted in the brain – becomes activated in the prefrontal cortex in the course of chronic stress (Tynan et al., 2010), more so in non-resilient animals (Couch et al., 2013). Most human studies published in this field provide evidence that elevated pro-inflammatory cytokine levels might be an index of *ongoing* psychopathology; some recent publications however indicate that lower cytokine reactivity in response to laboratory stressors is associated with better cognitive control (Shields et al., 2015), a recognised psychological resilience-enhancing factor (Southwick et al., 2005). Moreover, it was shown that pre-existing differences in stress-induced cytokine reactivity functionally contribute to stress-induced behavioural abnormalities (Hodes et al., 2014). Taken together, these data suggest that cytokine reactivity might represent a valuable addition to the list of potential biomarkers of resilience.

3.5.2. In vitro immune cell reactivity

A promising approach was proposed by a Dutch group of researchers who explored immune cell reactivity in military personnel of the Dutch Armed Forces deployed to Afghanistan. They initially reported that pre-deployment, glucocorticoid receptor (GR) numbers on leukocytes were higher in participants who reported higher PTSD symptoms 6 months after deployment. (van Zuiden et al., 2011). In the follow-up study, it was demonstrated that the sensitivity of leukocytes for glucocorticoids prior to deployment is a predictive factor for the development of PTSD, depressive and fatigue symptomatology in response to deployment. Specifically, two immune measures were differentially linked to three clusters of stress-induced symptoms, such that: (i) post-deployment fatigue was associated with low dexamethasone sensitivity of TNF-alpha production by monocyte (a measure of innate immunity) before deployment; (ii) post-deployment depressive symptoms were associated with a low dexamethasone sensitivity of T-cell proliferation (a measure of adaptive immunity); and (iii) PTSD symptoms after deployment were associated with a high dexamethasone sensitivity of T-cell proliferation before deployment (van Zuiden et al., 2012). These findings were confirmed in a recent prospective study, where GR sensitivity of immune cells and depressive, PTSD and fatigue symptoms were assessed at 3 points—pre-deployment and 1 and 6 months post deployment (van Zuiden et al., 2015). Authors concluded that their immune measures may represent a persistent biological vulnerability factor for development of stress-related disorders.

4. Conclusions and perspectives

The above presented data provide quite a long list of neurochemical, physiological and immune biomarkers of resilience: brain and circulating levels of monoamine neurotransmitters (noradrenaline, serotonin and dopamine), neuropeptides (NPY, CRF, oxytocin) and hormones (cortisol and DHEA); polymorphism of 5-HT1A and alpha-2 adrenergic receptors; acoustic startle responses; cardiovascular reactivity and recovery; heart rate variability (specifically RSA); inflammatory markers; response of immune cells to glucocorticoids. We now attempt to limit this list to the most relevant items, and to provide a sensible research strategy for their usage. In the current section we are dealing with three issues: (i) selection of most adequate markers; (ii) discriminative power; and (iii) their predictive power and casual/temporal relations between traumatic events and biological changes.

Our vision is that resilience markers would be most useful if they could serve at least one of the three following aims: (i) for conducting large-scale cross-sectional population studies aiming at early identification of individuals who are at risk of developing PTSD or depression; (ii) for assessing resilience levels during resilience training programs; and (iii) for identifying preclinical forms of PTSD. To satisfy these demands, measurement procedures should be cost-effective, relatively simple, preferentially non-invasive, and, most importantly, possess discriminative power. For the first three reasons, detection of receptor density or binding in the CNS, or assessing substance release in it are not suitable as this would require expensive and complicated brain imaging procedures. Measurement of substance spillover from the brain is possible but requires invasive administration of radioactive tracers and blood sampling from the jugular vein. Measurement of brain-released substances in plasma as a marker of their release in the brain does not seem to be a productive solution for those of them that are released *both* centrally and peripherally (*e.g.* norepinephrine, serotonin or NPY). Considering these limitations, measurements of serotonin and its receptors density, of norepinephrine, of dopamine, of NPY and of CRH that

are useful for mechanistic understanding of susceptibility and resilience to psychological stressors and of its association with cardiovascular pathology, are unlikely to be selected as routine measurements for the purposes outlined above. Further, controversial and inconsistent results with oxytocin and of cardiovascular reactivity favour their exclusion. We thus have in a remainder the following candidates: startle response (especially during provoked fear); post-stress cardiovascular recovery and HRV as physiological measures; and cortisol, DHEA and pro-inflammatory cytokines that could be readily performed non-invasively using salivary samples; *in vitro* assessing of immune responses seems to be very promising but would require blood sampling.

Speaking of discriminative power, it is unlikely that any single biomarker would be able to reliably differentiate low-resilient subjects from the norm; indeed a common feature of all studies cited here is lack of discriminative power: while group means were significantly different, in all instances individual data points in the groups substantially overlapped. This difficulty could be potentially overcome by using the psychobiological allostatic load approach, *i.e.* developing an index based on multiple measures as proposed by (Charney, 2004). The minimal study protocol thus would include laboratory stressors, with assessing baseline HRV and post-stress cardiovascular recovery, with superimposed startle measurements, and with saliva sample collection for measuring adrenal hormones and cytokines.

As follows from the reviewed material, most authors explored biomarkers of resilience in cross-sectional studies—in either mentally healthy subjects alone, or by comparing data obtained in PTSD patients and matched healthy controls. Consequently, one unresolved causal/temporal issue in resilience research is whether differences in physiological, neurochemical or immune markers found between PTSD patients and healthy subjects are a result of psychological trauma or are they a characteristic of low-resilience phenotype and were already present before the traumatic event. The only way to answer this question is to conduct prospective studies, and correlating pre-trauma measurements with subsequent development of PTSD symptomatology. Only a few of above described studies fall in this category: severely blunted cortisol response to laboratory stressor predicted development of PTSD symptoms in police officers (Galatzer-Levy et al., 2014), and immune cells sensitivity to glucocorticoids predicted post-deployment PTSD symptoms in military personnel (van Zuiden et al., 2011, 2012, 2015). Some measures such as elevated plasma IL-6 levels measured 24 h after the trauma predict PTSD during the follow-up (Pervanidou et al., 2007), and thus might be useful to identify vulnerable individuals shortly post-trauma. Finally, two prospective studies reporting lack of predictive power of the cortisol awakening response are equally important (Heinrichs et al., 2005; van Zuiden et al., 2011 #116).

Future studies on biomarkers of resilience should take into consideration some individual characteristics such as age or gender, and even some personality traits. Studying the sensitivity and specificity of biomarkers might improve the knowledge of etiology, prognosis and treatment of stress-induced disorders. The complexity of this bidirectional relation between biomarkers and underlying mechanisms makes it important to take into account the temporal dimension in a way that some biomarkers may reflect phenotype that precedes disease (including subclinical forms) while others may signify exposure to trauma.

In conclusion, biological markers of resilience could be assesses both during baseline and during laboratory stressors. In the former case the most promising candidates are represented by HRV and *in vitro* immune cell assays; in the latter case—by startle responses (especially their habituation) during stress challenge and by cardiovascular recovery after stress, and by cortisol, DHEA and cytokine responses. Of note and importance, they should be used in combination to enhance predictive power.

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