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Review article

Exposed to events that never happen: Generalized unsafety, the default stress response, and prolonged autonomic activity

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ABSTRACT

Based on neurobiological and evolutionary arguments, the generalized unsafety theory of stress (GUTS) hypothesizes that the stress response is a default response, and that chronic stress responses are caused by generalized unsafety (GU), independent of stressors or their cognitive representation. Three highly prevalent conditions are particularly vulnerable to becoming 'compromised' in terms of GU, and carry considerable health risks:

(1) 'Compromised bodies': in conditions with reduced bodily capacity, namely obesity, low aerobic fitness and older age, GU is preserved due to its evolutionary survival value;
(2) 'Compromised social network': in loneliness the primary source of safety is lacking, i.e. being part of a cohesive social network;
(3) 'Compromised contexts': in case of specific stressors (e.g. work stressors), daily contexts that are neutral by themselves (e.g. office building, email at home) may become unsafe by previously being paired with stressors, via context conditioning.

Thus, GUTS critically revises and expands stress theory, by focusing on safety instead of threat, and by including risk factors that have hitherto not been attributed to stress.

Contents

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1. The problem of chronic stress responses and its new hypothesized solution

Psychosocial stress, including chronic anxiety, is a major risk factor for somatic disease, including cardiovascular disease (Kiecolt-Glaser et al., 2002; Krantz and McCeney, 2002; Kubzansky and Kawachi, 2000; Roest et al., 2010; Rosengren et al., 2004; Searle and Bennett, 2001; Tully et al., 2013). The stressors for which this is best documented are work stress (Bosma et al., 1998; Matthews and Gump, 2002; Chandola et al., 2008), marital stress (Matthews and Gump, 2002; Orth-Gomer et al., 2000) and bereavement (Lee et al., 2003; Vitaliano et al., 2002). Still, the underlying psychophysiological mechanisms remain poorly specified. It is widely agreed that *chronic physiological stress responses* are the crucial causal factor leading to disease, but despite more than half a century of research, the precise causes of these chronic responses have not yet been sufficiently revealed. Conventional stress theories still embrace the reactivity hypothesis that holds that multiple intense responses during stressors are important. These theories neglect a crucial aspect: the duration of the exposure that often outlasts the stressful events themselves. We previously hypothesized that actually occurring stressors are far less important than what happens in people's thoughts, that is, their cognitive representations of stressors, termed '*perseverative cognition*' (PC; Brosschot et al., 2006; see also Fig. 2a). PC may even be largely unconscious (Brosschot, 2010; Brosschot et al., 2010) but still leads to prolonged physiological stress responses (ibidem). PC is not only a core element chronic stress, but also in chronic anxiety, and the latter can be easily conceptualized as a chronic psychobiological stress response in the absence of realistic stressors (e.g. Hoehn-Saric et al., 2004; Licht et al., 2009; Thayer et al., 1996). Despite growing evidence that PC causes prolonged physiological responses, especially for cardiovascular and endocrine (i.e. cortisol) activity (Brosschot et al., 2006; Ottaviani et al., 2015; Verkuil et al., 2010; Zoccola and Dickerson, 2012), it is still far from explaining most of, let alone *all* of, the often extremely protracted stress responses associated with chronic stressors such as work stress, marital stress or loneliness, chronic anxiety, and their psychophysiological concomitants such as continuously increased rest levels of blood pressure, cortisol or low heart rate variability (HRV; Robles and Kiecolt-Glaser, 2003; Thayer et al., 2010). What causes these, often truly chronic, responses, which over time will result in biological dysregulation (Brosschot et al., 2006), or 'allostatic load' (McEwen and Seeman, 1999)? It seems unlikely that people think incessantly about their stressors, either consciously or unconsciously (this problem is illustrated in Fig. 1a–c). But if PC cannot sufficiently explain truly chronic responses what else explains them? In this article, we take a radically different viewpoint by posing that not PC but the automatic (i.e. largely unconscious) '*generalized perception of unsafety*' is the crucial explanatory mechanism. How might this new idea solve the problem of what causes chronic physiological responses that, in the long run, lead to disease? Using a new theoretical approach, called the "*Generalized Unsafety Theory of Stress*" (GUTS), we propose that the solution lies in the fact that the way in which the problem is phrased is wrong.

2. The generalized unsafety theory of stress (GUTS)

Current neurobiological evidence (e.g. Ahern et al., 2001; Amat et al., 2005; Motzkin et al., 2015; Grupe and Nitschke, 2013; see below) and evolutionary reasoning (e.g. Nesse, 2005; Trimmer et al., 2013 see below) imply that the stress response is a *default response of the* organism, and that it is the response the organism *automatically* falls back upon when *no other information* is available. So, the problem should not be formulated as: "what causes chronic stress responses?" but as "what mechanism allows the *default stress response* to be turned off?—and when does this 'switch off' mode fail to work?" To answer this last question is the chief goal of this article. We hypothesize that the mechanism that explains most chronic stress responses in daily life is the *generalized perception of unsafety* (GU), that is largely automatic (and as a result mainly unconscious). The argument in a nutshell: GU causes the default stress response to remain activated, whenever our phylogenetically ancient mind-body organism fails to perceive safety in a wide range of situations in modern society that are not intrinsically dangerous. This new explanation forms a radical shift from current stress theory – including our own PC hypothesis – that focuses on stressors and PC. It comprises a completely new theory called, as mentioned, the "Generalized Unsafety Theory of Stress" (GUTS). A key principle of GUTS is that not being able to switch off, or inhibit the default stress response is *not dependent on actual stressors* or PC: perceived GU is sufficient, GU is the crucial element here. Due to GU, chronic stress responses occur in an objectively safe world, with no threatening information. The GUTS has a far greater explanatory ability than other current stress theories. Most esentially, as we will explicate below, it predicts how prolonged and even chronic stress responses occur when no actual stressors (threats) are present at all, or even cognitive representations of stressors, because of the continuous failure to perceive safety. Therefore, it can explain a much higher number of hypothetical situations in which stress responses may occur. For large groups of people, this means *all* situations, e.g. in people with a so called 'compromised' body or social network, as we shall explain below. *GUTS is thus likely to be far better at explaining prolonged or chronic stress-related physiological activity*. With increasing chronic stress as well as booming health care costs in our society it is very timely to test this new theory. We will further detail the hypotheses of GUTS below.

Before doing so, we would like to point out that these hypotheses pertain not only to stress but also to anxiety and its (neuro)physiological concomitants. As mentioned above, in terms of stress theory anxiety can be viewed as a stress response without actual stressor, and neuroscientists commonly treat stress and anxiety as the same subject because of their shared neurobiology. We have discussed the relevance of GUTS for anxiety in more detail elsewhere (Brosschot et al., 2016).

3. Feeling unsafe in a safe world: the neurobiological and evolution-theoretical basis of GUTS

It might feel somewhat counterintuitive that an intensely powerful and primary survival mechanism such as the chronic stress response is sparked off by the mere absence of something like *perceived safety*, instead of the presence of something profound like a threatening situation, or disturbing thoughts thereof. Yet, precisely because the stress response is a primary survival mechanism, it should be the response to *automatically and immediately fall back upon when the only information that could stop it*, i.e. *proof of safety is not available*. Organisms have survived in evolution not by waiting for more evidence of threat but instead by erring on the side of caution (e.g. Nesse, 2005; Trimmer et al., 2013), or, popularly