Boosting stress resilience using flexibility as a framework to reduce depression risk

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1. Introduction

Individuals can have vastly different responses to the same situation. People experience stress when the situation exceeds their resources or ability to cope. Particularly intense or long-lasting periods of stress can morph into depression – a significant period of low mood or anhedonia that interferes with daily functioning. Although a major life event precedes most depression cases, a majority of people who experience a major life event do not develop depression (Hammen, 2005). Indeed, most people have a stable trajectory of healthy functioning, termed resilience, following a potentially traumatic event (Bonanno et al., 2011). Therefore, the question is: How can we further sever the tie between stress exposure and depression? Given that stress-induced physiological changes are one route to depression onset, perhaps the better, more specific question is: How can we lessen the physiological impact of stress to reduce depression risk? When looking at physiological responses to a single stressor, most prior research has focused on its magnitude. However, the duration of the response – including anticipation and recovery –, and the response’s alignment with stressor type and intensity matter as well. Two recent contributions to stress theory – the Perseverative Cognition Hypothesis and the Generalized Unsafety Theory – shift the focus to response duration, including anticipatory reactivity and poor recovery. Using these theories as framework, this article reviews evidence suggesting that psychological inflexibility, such as perseverative cognition, and the inability to recognize safety promote heightened and prolonged (i.e., inflexible) physiological stress responses. Moreover, interventions that increase psychological flexibility or safety recognition may foster more flexible physiological responses to psychological stress. By adopting the lens of flexibility to examine physiological responses to stress, PNI will speak the same language as clinical psychology, which has identified inflexibility as an etiological and maintenance factor of depression.

2. Defining physiological stress response flexibility

A flexible stress response mobilizes the physiological resources needed for an appropriate response, and thus it is proportional to the threat. In case of social stress, it prepares the body for possible attack...
because they may translate into a new, higher baseline. Particularly problematic in the context of frequent stress exposure, biomarkers to return to baseline. High frequency and poor recovery are hallmarks of in-rigid, stereotyped response does not differentiate between stressors, and adulthood (Danese and Lewis, 2017; Mondelli and Vernon, 2019). This mount an exaggerated in, threat is no longer present, and therefore it is time-limited. In contrast, an exible stress response does not align with the intensity or type of stressor. For instance, early life adversity can prime immune cells to inflammatory response to stressors even into adulthood (Danese and Lewis, 2017). A flexible stress response also returns to baseline once the threat is no longer present, and therefore it is time-limited. In contrast, an inflexible stress response is more important in the context of a repetitive stressor. When the stressor does not pose a threat to life or social inclusion, individuals should be able to habituate, such that they do not respond as strongly to subsequent provocations. Conversely, a failure to habituate to a repetitive stressor is a feature of inflexible stress responding. Chronic stressors, such as poverty or a troubled marriage, may ultimately preclude flexible stress responding even in other contexts, because they inherently tax the body to the point of exhaustion. Early life adversity is likely a major culprit for inflexible stress responding even into adulthood, as this stress occurs during a particularly sensitive period of development when children are learning to distinguish safe and unsafe environments.

The concept of flexible stress responding tangentially relates to the existing concepts of autonomic flexibility, allostatic load, and psychological flexibility. Autonomic flexibility is used to describe those with high resting heart rate variability (HRV; variation in the interval between heartbeats), which facilitates adaptation and appropriate responses to environmental challenges (Friedman and Thayer, 1998). Therefore, it overlaps with, but is distinct from, stress response flexibility, which focuses on the trajectory of the response itself. Allostatic overload occurs when physiological systems involved in adaptation are chronically over-or under-active, taking a toll on the brain and periphery (McEwen, 2004).

Stress response flexibility, on the other hand, refers to the specific biomarker trajectory following a single, time-limited stressor. It is a more micro-level concept that can provide a snapshot of an individual’s ability to adapt. Psychological flexibility refers to the ability to adapt to the changing environment, shift perspectives, and balance competing desires (Kashdan and Rottenberg, 2010). Its link with physiological stress response flexibility is discussed in more detail below, but there are many parallels, in that physiological stress response flexibility indexes the body’s ability to differentiate stressor types and intensities and mobilize adequate resources to respond appropriately to environmental challenges.

3. Depression and inflexible physiological stress responses

A growing literature shows that depressed individuals have different physiological responses to stress than their non-depressed peers. Stressors, particularly social stressors, which are especially relevant to depression (Slavich, 2020), may evoke biomarker abnormalities that are not evident at baseline. In this vein, the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993), in which participants prepare and deliver a speech and then complete a serial subtraction activity out loud in front of a panel of judges who maintain neutral faces, is a common social-evaluative stress paradigm in PNI research. There is a bidirectional relationship between inflexible stress responses and depression: Depressed people have heightened inflammatory reactivity to the TSST (Fagundes et al., 2013; Pace et al., 2006), and elevated and prolonged inflammatory reactivity precedes depressive symptom increases (Aschbacher et al., 2012; Madison et al., accepted). There is also evidence of greater cardiovascular and autonomic reactivity (e.g., Hu et al., 2016) and impaired cortisol recovery (Burke et al., 2005) in depression. The combination of heightened reactivity and poor recovery indicates that depression coincides with inflexible physiological stress responding.

An inflexible stress response may increase risk for depression, especially when considered alongside the typical frequency and intensity of an individual’s stress exposure. My colleagues and I found that a composite of both initial and sustained inflammatory reactivity to laboratory social stressors (i.e., a 20-min marital conflict and the TSST) predicted depressive symptom worsening, and more frequent interpersonal stress strengthened this relationship (Madison et al., accepted). We also found that the pro-inflammatory cytokine IL-6, which reliably responds to psychosocial stress, was elevated even 5 h post-stress (Madison et al., accepted). Past PNI research measured inflammatory reactivity up to 2 h post-stress (Marland et al., 2017), which may not fully track recovery. Researchers must align measurement timepoints with the biomarker’s kinetics, in that faster-moving markers (i.e., cardiovascular, autonomic, and catecholamines) need to be measured more frequently and for a shorter duration than slower-moving markers (cortisol, inflammatory

Fig. 1. Annelise Madison, MA. Annelise Madison is a PhD Candidate in Clinical Psychology at The Ohio State University (OSU). She studies psychoneuroimmunity under the mentorship of Dr. Jan Kiecolt-Glaser at the Institute for Behavioral Medicine Research. In her 13 first-authored and 10 co-authored publications, as well as during seven national and international conference presentations, she has examined the physiological correlates of stress and depression, encompassing inflammation, vaccine responses, acute stress reactivity, and the gut-brain axis. Ms. Madison is currently funded through the National Institute of Health’s T11 Mentored Clinical Research Training Program to study associations between gut microbiota diversity and emotional reactivity and rumination following a laboratory psychosocial stressor. As part of this training program, she has completed OSU’s Interdisciplinary Specialization in Biomedical Clinical and Translational Science. Ms. Madison’s clinical training fuels her research questions, as she has treated both inpatients and outpatients with psychiatric and physical comorbidities using multiple evidence-based modalities, including cognitive-behavioral therapy and mindfulness-based stress reduction. Additionally, her record of teaching and mentoring undergraduate students is strong. She was Instructor of Record for two Introduction to Psychology courses, and she has mentored two undergraduate students on successful fellowship applications through the completion of their research projects. She has received several grants, fellowships, and awards, including OSU’s prestigious Dean’s Distinguished Fellowship, Trainee Scholar Awards from the American Psychosomatic Society and the Psychoneuroimmunity Research Society, NCAA Division III Academic All-America Award, and the National Merit Scholarship. During her time at OSU, she has served on two Dean’s Student Advisory Boards and one search committee. Ms. Madison plans to complete her clinical internship in Summer 2024. Ultimately, she will continue to explore individual difference variables and related interventions that promote resilience to acute psychosocial stress, thereby reducing depression and chronic disease risk.
4. Shifting focus from initial reactivity to duration of response

Both magnitude and duration are critical components of stress response flexibility. However, for many years, PNI research has focused on the magnitude of initial reactivity. Initial reactivity is easier, quicker, and cheaper to collect, but these may not be the limiting factors so much as precedence. In a two-year period, 63% of lab stress paradigms measuring physiological responses collected recovery data, but only 23% reported it (Linden et al., 1997). The untested assumption was that greater initial reactivity, especially in the face of repetitive stress, predicts worse physical and psychological health over time. More recent research has supported this hypothesis to an extent (Kiecolt-Glaser et al., 2020). For example, those with larger fibrinogen and TNF-alpha responses to two moderately stressful behavioral tasks had greater carotid artery stiffness three years later (Ellins et al., 2008). Even so, abnormally low stress responses also predict poor health outcomes (Turner et al., 2020) – complicating the literature. Also, strong inflammatory and cortisol reactivity might not always be harmful (Chen et al., 2017; Heponiemi et al., 2007). In fact, greater initial reactivity to stress may help to protect against acute infection (Marsland et al., 2017). However, it is possible that over time, this pattern of reactivity – especially combined with frequent stress exposure, a low threshold for reactivity, and poor recovery – may propagate chronic disease (Marsland et al., 2017).

Of the research that has included recovery, most has focused on cardiovascular, autonomic, and endocrine recovery, and poor recovery of these systems is indeed a risk factor for worsening mental and physical health trajectories, and even mortality. For example, slower heart rate recovery following a standardized exercise test predicts mortality (Cole et al., 1999). Poor physiological recovery from psychological stress may be even more harmful at a vascular and cellular level than poor recovery from a physical challenge, in that psychological stress does not often warrant a physical response like fighting or fleeing and therefore the body may not use the resources that the stress response mobilizes (e.g., glucose). Poor cardiovascular recovery after two moderately-stressful behavioral tasks predicted blood pressure increases over the subsequent three-year period (Steptoe and Marmot, 2005).

5. Explaining prolonged stress responses

Two relatively recent contributions to stress theory, the Perseverative Cognition Hypothesis and the Generalized Unsafety Theory, draw attention to stress response duration and explain prolonged responses (Brosschot et al., 2005, 2017). Perseveration, or recurrent, intrusive thoughts that precede or follow a stressor, extend the psychological and physiological consequences of a stressor. Indeed, those who were distracted after a laboratory speech stressor had better post-stress physiological consequences of a stressor (Zoccola et al., 2014). Poor meta-analytic evidence suggests that greater perseverative cognition predicts lower HRV, and higher blood default state of the brain attention to stress response duration and explain prolonged responses to stress. One corollary is that psychological flexibility and safety recognition may correspond to flexible stress responses. Indeed, those with high HRV, indicating an enhanced ability to suppress the default stress response and recognize safety, had improved cardiovascular, autonomic, and inflammatory recovery following a stressor (Weber et al., 2010) – a central aspect of stress response flexibility. The Generalized Unsafety Theory is relatively new but provides fodder for much more research into the connection between safety recognition, a largely unconscious process, and physiological stress reactivity.

Conscious processes – such as thinking styles – can also help to determine stress response trajectories. Perseveration promotes a perseverative physiological response, and psychological flexibility may promote a more flexible physiological response. When asked to give a speech, someone who can reframe their initially distressing thought of, “I will fail” to a more neutral and accurate thought (e.g., “I might make a mistake, but even so there will not be any major ramifications”) may have less of an anticipatory physiological response than someone who perseverates on the initial thought, or, even worse, spirals to other more distressing thoughts. Psychological flexibility fosters detachment from the initial distressing thoughts and re-evaluation of the situation from a different, often more holistic, perspective, thereby promoting healthy psychological reactivity that aligns with the stressor’s demands and does not persist long after the stressor ends. Importantly, psychological flexibility buffers against the depressogenic effect of major life stressors (Fonseca et al., 2020). One meta-analysis showed that those who tend not to ruminate were more resilient and had better mental health trajectories following early-life adversity (Fritz et al., 2018). In short, the manner and length of time that people think about stressors can partly determine stress response flexibility.

In the other direction, less flexible physiological responses to stress may promote psychological inflexibility. People are less able to think flexibly during stress, likely due to an influx of catecholamines, as beta-adrenergic antagonism rescues the ability to think flexibly (Alexander et al., 2007). Thus, those who have greater sympathetic-adrenomedullary responses to acute stress may have less cognitive flexibility during the stressor, which could limit problem-solving abilities and the ability to reframe intrusive, distressing thoughts – thereby prolonging the actual or perceived threat. A hypothesis worth testing is that high initial reactivity, when accompanied by reduced psychological flexibility, slows recovery, especially of cortisol and inflammatory cytokines, which are primary drivers of stress-related disease.

6. Safety recognition, psychological flexibility, and flexible physiological stress responses

Both the Perseverative Cognition Hypothesis and the Generalized Unsafety Theory help to explain prolonged physiological responses to stress. One corollary is that psychological flexibility and safety recognition may correspond to flexible stress responses. Indeed, those with high HRV, indicating an enhanced ability to suppress the default stress response and recognize safety, had improved cardiovascular, autonomic, and inflammatory recovery following a stressor (Weber et al., 2010) – a central aspect of stress response flexibility. The Generalized Unsafety Theory is relatively new but provides fodder for much more research into the connection between safety recognition, a largely unconscious process, and physiological stress reactivity.

7. Psychological and behavioral interventions that increase flexible stress responding

Flexibility’s link with wellbeing – and inflexibility with psychopathology – is well-established in clinical psychology. Psychological inflexibility correlates with transdiagnostic etiological and maintenance
factors, or be a transdiagnostic factor in and of itself (Morris and Mansell, 2018). The benefits of boosting psychological flexibility may reverberate in the body. Emerging evidence suggests that psychological interventions can promote a more flexible physiological stress response. Acceptance of the present experience is the heart of psychological flexibility, and a dismantling randomized, controlled trial of mindfulness training showed that a 15-lesson smartphone-based training in both acceptance and awareness reduced cortisol and systolic blood pressure reactivity to and hastened recovery following the TSST, compared to lessons on awareness only or lessons on coping (Lindsay et al., 2018). Similarly, among those with Generalized Anxiety Disorder, an 8-week Mindfulness-Based Stress Reduction program reduced HPA-axis and inflammatory reactivity to the TSST, compared to an attention control training program (Hoge et al., 2013). Also, long-term meditators had lower amygdala reactivity to negative pictures than those without a meditation practice, and short-term mindfulness training enhanced functional connectivity between the ventral-medial prefrontal cortex and amygdala (Kral et al., 2018) – essential for top-down regulatory control.

As the Generalized Unsafty Theory suggests, increasing physical health via behavioral interventions also promotes more flexible physiological stress responses. We found that four months of omega-3 supplementation reduced cortisol and IL-6 levels during and after a social-evaluative stressor (TSST) and boosted cellular repair mechanisms (IL-10) and IL-6 levels during and after a social-evaluative stressor (TSST) and boosted cellular repair mechanisms (IL-10 and telomerase) during stress recovery (Madison et al., 2021), thereby fostering a healthier return to baseline. Short-term physical challenges within an individual’s control, such as exercise, may train the body to react to and recover from psychological stress more expediently. For instance, physical activity blocked rumination’s effect on cortisol reactivity and recovery from the TSST, in that rumination predicted higher cortisol reactivity and delayed recovery only among those who reported low levels of vigorous activity (Puterman et al., 2011). More flexible physiological stress responses may be one mechanism linking physical activity with improved health outcomes. Vigorous activity may also boost flexible thinking: In one study among older adults, high-intensity interval training improved cardiorespiratory fitness and reaction time when rules changed on a test of executive function (Mekari et al., 2020).

8. Conclusion

Current evidence points to the centrality of flexibility – psychological and physiological – especially in response to stress, as a predictor of physical and mental health. By widening its focus from magnitude of reactivity to include other relevant factors, such as duration, frequency, and proportionality to the threat, the field of PNI can begin to view stress responsivity through the lens of flexibility – a research and treatment target that may be more relevant to health outcomes. Importantly, this article has focused on the concept of physiological stress response flexibility as it relates to depression, but it is also a relevant construct for other forms of psychological and physical pathology. Also, there are many other social, behavioral, cognitive, and emotional factors that can boost stress response flexibility on a micro level, and ultimately resilience on a macro level, that are worth exploring (Fritz et al., 2018). As a trans-diagnostic risk factor, inflexibility may echo throughout the mind and the body, and stress exposure may reveal well-concealed inflexibility – pointing to the centrality of PNI research to the field of clinical psychology. Interventions that promote flexible physiological and psychological responses to stress can help to break the link between stress exposure and depression.

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Declaration of competing interest

I declare no conflicts of interest.

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