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COMPREHENSIVE REVIEW

WILEY

Investigating the stress-related fluctuations of level of personality functioning: A critical review and agenda for future research

Roland Sinnaeve^{1,2} | Thomas Vaessen^{2,3} | Ilse van Diest⁴ |
Inez Myin-Germeys³ | Louisa M. C. van den Bosch⁵ | Elske Vrieze^{1,2} |
Jan Henk Kamphuis⁶ | Stephan Claes^{1,2}

¹University Psychiatric Center KU Leuven, Kortenberg, Belgium

²Department of Neurosciences, Mind Body Research, KU Leuven, Leuven, Belgium

³Department of Neurosciences, Contextual Psychiatry, KU Leuven, Leuven, Belgium

⁴Faculty of Psychology and Educational Sciences, Health Psychology Research Group, KU Leuven, Leuven, Belgium

⁵Dutch Treatment Center Dialectical Behaviour Therapy, Harderwijk, The Netherlands

⁶Faculty of Social and Behavioural Sciences, Programme group Clinical Psychology, University of Amsterdam, Amsterdam, The Netherlands

Correspondence

Roland Sinnaeve, University Psychiatric Center KU Leuven, Leuvensesteenweg 517, Kortenberg 3070, Belgium.
Email: roland.sinnaeve@kuleuven.be

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Abstract

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the International Classification of Diseases (ICD-11) proposed a dimensional approach to the assessment of personality disorders (PDs). Both models dictate that the clinician first determines PD severity before assessing maladaptive traits, invoking the level of personality functioning (LPF) construct. We consider LPF a promising dimensional construct for translational research because of its clinical importance and conceptual overlap with the Research Domain Criteria (RDoC) Social Processes. We aim to identify biomarkers that co-vary with fluctuations in LPF in adulthood, ultimately to predict persistent decrease in LPF, associated with suicidality and morbidity. However, a theoretical framework to investigate stress-related oscillations in LPF is currently missing. In this article, we aim to fill this hiatus with a critical review about stress and LPF. First, we discuss acute stress and LPF. We briefly present the basics of the neurophysiological stress response and review the literature on momentary and daily fluctuations in LPF, both at a subjective and physiological level. Second, we review the effects of chronic stress on brain function and social behaviour and recapitulate the main findings from prospective cohort studies. This review underlies our suggestions for multimethod assessment of stress-related oscillations in LPF and our theoretical framework for future longitudinal studies, in particular studies using the experience sampling method (ESM).

KEYWORDS

ambulatory monitoring, level of personality functioning, longitudinal studies, physiological stress, social processes

1 | INTRODUCTION

Personality disorders (PDs) are mental disorders characterized by an enduring pattern of experiences and behaviours, which deviates markedly from cultural expectations (American Psychiatric Association [APA], 2013; World Health Organization [WHO], 2019). It is

estimated that PDs affect 6% of the world population (Huang et al., 2009). In western populations, the prevalence rate of PDs exceeds cardiovascular diseases and depression (Volkert et al., 2018). Having a PD is associated with increased mortality (natural and unnatural causes), social impairments, substance abuse, psychiatric comorbidity, deleterious health outcomes, and stigmatization

(Björkenstam et al., 2016; Dixon-Gordon et al., 2015; Fok et al., 2012; Moran et al., 2016; Sheehan et al., 2016). The medical costs and productivity losses are substantially higher than in other psychiatric disorders (Soeteman et al., 2008). This high burden emphasizes the need for effective treatments.

Progress in the efficacy of treatment has been slow, which is partly due to interrelated problems in research and diagnostic classification (Bateman et al., 2015; Storebø et al., 2020). Until recently, the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) used a categorical approach for the assessment of PDs (APA, 2013; WHO, 1992). The categorical approach facilitated communication and the development of empirically supported treatments and resulted in excessive co-occurrence, phenotypic heterogeneity, inadequate coverage, and arbitrary distinctions with “normal” personality functioning (First et al., 2002; Frances, 1993; Krueger et al., 2008). These validity issues, in turn, have contributed to repeated failures to identify PD-specific pathophysiology (Kozak & Cuthbert, 2016; Lilienfeld & Treadway, 2016; Treadway & Leonard, 2016). Distinct PDs and their comorbid disorders share neurobiological signatures. At the same time, studies report contradictory results within the same PD category (see, e.g., Ma et al., 2016; Schulze et al., 2016; White, Conway, & Oltmanns, 2020; Witt et al., 2017). As the validity issues of the categorical model for the diagnosis and classification of PDs became widely recognized, support for a shift towards a dimensional model increased.

This resulted in two new conceptualizations of PD: the Alternative DSM-5 Model for PD (AMPD) in DSM-5 section III (APA, 2013) and more recently an adapted chapter on PD and related traits in the ICD-11 (WHO, 2019). Both models dictate that the clinician first determines PD severity before assessing maladaptive traits (APA, 2013; WHO, 2019). In the AMPD, the PD severity dimension is level of personality functioning (LPF), defined as the degree of disturbances in self- and interpersonal functioning across various contexts and relationships, with high LPF indicating a low level of impairment (APA, 2013) (Table 1). While LPF is rooted in psychodynamic literature, specific elements of LPF lie at the heart of well-studied treatments such as dialectical behaviour therapy (DBT), targeting emotion regulation, and mentalization-based treatment (MBT), targeting tolerance of differing perspectives and attachment (Clarkin et al., 2006; Fonagy et al., 2015; Linehan, 1993; Storebø et al., 2020). An overview about the development, comparison, and empirical support base of the new DSM and ICD models can be found in Oltmanns and Widiger (2019), Reed et al. (2019), Tyrer et al. (2019), and Zimmermann et al. (2019). Preliminary data about the LPF severity dimension indicate acceptable interrater reliability, consistent latent structures (i.e., two correlated factors of self- and other functioning), convergence with other relevant measures, and some evidence for incremental validity (Zimmermann et al., 2019).

Our focus is on the biological validity of LPF. More specifically, we seek to identify biomarkers that co-vary with stress-related fluctuations in LPF in PD patients, which, down the line, we might use in clinical practice to predict a persistent decrease in LPF. Owing to

Key Practitioner Message

- New, dimensional models for the diagnosis of personality disorder (PD) dictate that the clinician first determines level of personality functioning (LPF).
- We propose that an adult's LPF shows fast and slow oscillations that relate to acute and chronic stress. We explain why a better understanding of these oscillations is pivotal if we want to move forward in the diagnosis, treatment, and prevention of PD.
- Longitudinal research about stress and LPF is in its infancy. We propose a theoretical framework to facilitate transdisciplinary research in this domain.

recent advances in smartphone-use and wearable technology, easy and non-invasive ways to measure physiology, behaviour, and context in daily life are readily available (Goodday & Friend, 2019; Myin-Germeys et al., 2018; Smets et al., 2018). A promising application is to use wearable technology to monitor parameters “passively” (i.e., without effort of the client), such as stress biomarkers (e.g., heart rate and electrodermal activity), and physical activity, sound pressure levels, high-risk locations, and so forth. Personalized algorithms could then recognize alarming shifts in these parameters and encourage clients to monitor their experiences and behaviours more closely with structured diary methods on their smartphone (Goodday & Friend, 2019; Myin-Germeys et al., 2018; Smets et al., 2018). Developing such an application requires a transdisciplinary approach. However, to date, there is no theoretical framework to guide research on the time-variant and stress-related fluctuations in LPF.

LPF shows clear conceptual overlap with social processes constructs delineated in the Research Domain Criteria (RDoC) matrix (Table 1). The RDoC matrix is the theoretical framework of the U.S. National Institute of Mental Health (NIH), developed to increase biological validity in research about mental health and illness. To pursue this aim, clinical problems are conceptualized dimensionally, across diagnostic categories, in terms of varying degrees of dysfunction in basic psychological/biological processes. RDoC acknowledges that these psychobiological processes change within an individual because of context and developmental stages (Kozak & Cuthbert, 2016; Lilienfeld & Treadway, 2016). However, RDoC does not tackle the issue of symptom-biomarker chronometry. Symptom-biomarker chronometry means that fluctuations in symptoms and biomarkers are meaningfully coupled (Treadway & Leonard, 2016). A trait-based model, dominant in all PD-related research, emphasizes temporal stability. Consequently, investigating the association with time-invariant biological factors such as genetic predisposition makes sense (White et al., 2020). Investigating the association between stable traits and volatile stress biomarkers does not. In this article, we provide a critical review to address this hiatus for LPF (Grant & Booth, 2009).

TABLE 1 Self and interpersonal functioning according to DSM-5 and ICD-11 compared with the RDoC social processes

	DSM-5	ICD-11	RDoC social processes
Self	<p>Identity: Experience oneself as unique, with boundaries between self and others. Stability of self-esteem and accuracy of self-appraisal. Stability for and capacity to regulate a range of emotional experiences</p> <p>Self-direction: Pursuit of coherent and meaningful short-term and life goals. Utilization of constructive and prosocial internal standards of behaviour. Ability to self-reflect productively.</p>	<p>Stability and coherence of one's sense of identity (e.g., extent to which identity or sense of self is variable and inconsistent or overly rigid and fixed). Ability to maintain an overall positive and stable sense of self-worth. Accuracy of one's view of one's characteristics, strengths, and limitations. Capacity for self-direction (ability to plan, choose, and implement appropriate goals).</p>	<p>Self-knowledge: The ability to make judgements about one's current cognitive or emotional internal states, traits, and/or abilities.</p>
Interpersonal	<p>Empathy: Comprehension and appreciation of other's experiences and motivations. Tolerance of differing perspectives. Understanding the effects of one's own behaviour on others</p> <p>Intimacy: Depth and duration of connection with others. Desire and capacity for closeness. Mutuality of regard, reflected in interpersonal behaviour.</p>	<p>Ability to understand and appreciate others' perspectives. Interest in engaging in relationships with others. Ability to develop and maintain close and mutually satisfying relationships. Ability to manage conflict in relationships.</p>	<p>Understanding of others: The ability to make judgements and/or attributions about the mental state of other animate entities that allows one to predict or interpret their behaviours. Mental state refers to intentions, beliefs, desires, and emotions.</p> <p>Affiliation and attachment: Affiliation is engagement in positive social interactions with other individuals. Attachment is selective affiliation as a consequence of the development of a social bond. Affiliation and attachment are moderated by social information processing and social motivation.</p>

Note: The DSM-5 differentiates five levels of impairment, ranging from no impairment to extreme impairment. If moderate or greater impairments are diagnosed, then PD might be present (APA, 2013). The ICD-11 determines whether a diagnosis of mild, moderate, or severe PD is appropriate based on (a) the disturbances in self-functioning, (b) the disturbances in interpersonal functioning, (c) the manifestations of the dysfunction, and (d) level of distress or psychosocial impairment (Reed et al., 2019; WHO, 2019).

Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders; ICD-11, International Classification of Diseases; RDoC, Research Domain Criteria.

In basic and translational neuroscience, *acute stress* is defined as the activation of neurophysiological stress responses that promote coping and adaption when an organism's survival or well-being is challenged and *chronic stress* as the sustained activation of these adaptive stress responses in adverse circumstances (de Kloet et al., 2005; McEwen, 1999, 2007; Sandi & Haller, 2015; Ulrich-Lai & Herman, 2009). We will depart from these definitions throughout this manuscript. We based our critical review on longitudinal data that might elucidate the nexus of stress and LPF fluctuations within individuals.

2 | ACUTE STRESS AND LPF

2.1 | Acute stress and social behaviour in basic neuroscience

Stress responses are characterized by continuous physiological changes. In safe conditions, the parasympathetic nervous system (PNS) is dominant, supporting rest-and-digest functions and

facilitating affiliative behaviours (Berntson et al., 2007; Sandi & Haller, 2015; Ulrich-Lai & Herman, 2009). When a potential threat is anticipated or identified, disinhibition of the sympathetic nerve system (SNS) increases circulating levels of adrenaline, as well as heart rate and energy. When such SNS activation occurs, social motivation decreases, whereas the tendency for antisocial behaviours increases (Sandi & Haller, 2015; Ulrich-Lai & Herman, 2009). Responses of the PNS and SNS wax and wane within seconds (Berntson et al., 2007; Sandi & Haller, 2015; Ulrich-Lai & Herman, 2009).

Activation of the hypothalamic–pituitary–adrenal (HPA) axis potentiates the sympathetically mediated effects by increasing the levels of circulating cortisol, a glucocorticoid. In the absence of stressors, the secretion of cortisol follows a circadian oscillation, with a daily peak around the habitual sleep–wake transition and minimal levels in the evening (McEwen et al., 2015; Oster et al., 2017). When confronted with an acute stressor, a cortisol peak promotes gluconeogenesis and inhibits insulin production, providing the body with an increase in energy. It also narrows the arteries while adrenaline increases heart rate, forcing blood to circulate faster (de Kloet et al., 2005; Gold, 2015; McEwen et al., 2015;

Russell & Lightman, 2019). Feedback loops targeting the pituitary, hypothalamus, and hippocampus ensure that these endocrine responses are shut down timely and stay within safe limits (Gold, 2015; Ulrich-Lai & Herman, 2009). Specialized brain circuits make sure that autonomic and neuroendocrine stress responses accord with the social situation (Sandi & Haller, 2015; Ulrich-Lai & Herman, 2009). Our focus is on the prefrontal cortex (PFC), amygdala, hippocampus, and dopaminergic (i.e., “reward”) circuit.

In safe conditions, the PFC inhibits activation of the HPA axis and SNS via direct projections to the hypothalamus, providing emotional and cognitive restraint and facilitating understanding of self and others as well as affiliative behaviours (Adolphs, 2009; Gold, 2015; Sandi & Haller, 2015). When confronted with a stressor, inhibition of PFC decreases, and amygdala activity increases. The amygdala, in turn, further restricts activity of PFC sites and stimulates stress and fear responses, impeding affiliative behaviour (Adolphs, 2009; Sandi & Haller, 2015; Ulrich-Lai & Herman, 2009). The dopaminergic circuit is temporarily downregulated, reducing social motivation and susceptibility to pleasurable stimuli (Gold, 2015; Sandi & Haller, 2015; Ulrich-Lai & Herman, 2009). The hippocampus supports stress regulation, context evaluation, and learning (Christian et al., 2014; Gold, 2015; Sahay et al., 2011; Sandi & Haller, 2015; Squire, 1992; Ulrich-Lai & Herman, 2009).

Controllable stress can facilitate dendritic branching, synaptogenesis, and long-term potentiation, that is, the neurochemical foundations of learning. At a molecular level, glutamate (main excitatory neurotransmitter of the central nervous system [CNS]), brain-derived neurotrophic factor (BDNF) (protein that supports survival, growth, and differentiation of neurons), and epigenetic mechanisms (molecular changes to the genome that do not involve the nucleotide sequence) are assumed to play a key role in this transient increase of neuroplasticity (Autry & Monteggia, 2012; Christian et al., 2014; de Kloet et al., 2005; Gold, 2015; Huang & Reichardt, 2001; Nestler, 2012; Popoli et al., 2011; Sahay et al., 2011).

Stress modulation and social processes involve more than the circuits, cells, and molecules in the CNS. There is constant “cross-talk” between neuronal and non-neuronal cell types. Signalling molecules of immune cells reinforce stress responses and mediate neuroplasticity in the brain. The CNS, in turn, mediates immune cell activity via the stress response systems (a.o. via release of cortisol) (Gold, 2015; Pavlov et al., 2018; Steptoe et al., 2007). In addition, studies investigating the gut–brain axis demonstrated that the trillions of microorganisms that colonize our gastrointestinal tract also influence the social brain: directly, via neuroactive molecules and vagal nerve stimulation, and indirectly, via their impact on the immune system. Vice versa, HPA-axis activity changes microbiome composition, intestinal mobility, and immune regulation (Fung et al., 2017; Vuong et al., 2017). See Figure 1 for a conceptual model depicting the relationships between acute stress biological processes, RDoC social processes, and level of personality functioning.

2.2 | Longitudinal self-report data about momentary and daily fluctuations in LPF

We discuss the main findings from studies that utilized the experience sampling method (ESM). ESM is a structured diary method in which subjects report context, experiences, and behaviour in daily life (Myin-Germeys et al., 2018). Roche et al. performed two ESM studies to capture daily fluctuations of LPF in student samples. In both studies, participants were instructed to rate their daily LPF for 2 weeks in nightly diary records (Roche, 2018; Roche et al., 2016). The first study ($N = 248$) revealed a robust pattern of day-to-day oscillations for daily LPF (Roche et al., 2016). The second study ($N = 175$) confirmed within-person variance and provided evidence for incremental validity of daily LPF in predicting emotions, problem-solving abilities, awareness/regulation, relationships, and so forth, in daily life (Roche, 2018).

FIGURE 1 Conceptual model depicting the relationships between acute stress biological processes, psychobiological (RDoC) social processes, and level of personality functioning. Note. PFC = prefrontal cortex; HPA = hypothalamic–pituitary–adrenal; SNS = sympathetic nervous system. Full arrows represent direct relationships. Two-headed arrows represent covariation

To our knowledge, no ESM studies have yet assessed LPF fluctuations in clinical samples over minutes or hours. However, there is empirical evidence on ESM as it pertains to specific subdomains of LPF. Especially the capacity to regulate a range of emotional experiences, an aspect of self-functioning, is a well-studied topic in the ESM literature. A meta-analysis, incorporating 793 effect sizes from 79 articles ($N = 11,381$), identified relationships between patterns of momentary emotion changes and relatively stable indicators of psychological well-being and psychopathology. The patterns of interest were emotional variability (i.e., within-person standard deviation of emotions across all measurements), emotional instability (i.e., magnitude of emotional changes from one measurement to the next), and emotional inertia (i.e., autocorrelation of an emotion between two consecutive measurements). The authors concluded that having less variable, more stable, and less inert emotions indicates psychological well-being. Having more variable, unstable, or more inert emotions indicates overall psychological maladjustment. These findings were consistent across types of psychopathology and across research designs (Houben et al., 2015).

Various samples of individuals diagnosed with borderline, schizotypal, schizoid, and paranoid PD fit this profile of overall psychological maladjustment. As a rule, clinical PD samples report more emotional variability and instability than healthy controls (Chun et al., 2017; Ebner-Priemer et al., 2015; Santangelo, Bohus, & Ebner-Priemer, 2014; Santangelo, Reinhard, et al., 2014). In addition, people diagnosed with BPD have a negative emotional baseline (Ebner-Priemer et al., 2007). Last, BPD patients report several negative emotions at the same time more frequently, indicating impairments in the capacity to differentiate emotions (Ebner-Priemer et al., 2007; Tomko et al., 2015). Direct comparisons of BPD samples and samples with individuals diagnosed with post-traumatic stress disorder, bulimia nervosa, and depression show similar levels of emotional instability and undifferentiated negative affect across diagnostic categories (Ebner-Priemer et al., 2007; Houben et al., 2016; Köhling et al., 2016; Scheiderer et al., 2016; Tomko et al., 2015).

Data on microdynamics on LPF components other than emotion regulation are scarce and rely heavily on samples of individuals diagnosed with BPD. These data suggest that emotional instability co-occurs with instability in self-concept, self-esteem, and perceived attachment (Santangelo et al., 2017; Santangelo, Bohus, & Ebner-Priemer, 2014; Scala et al., 2018; Wright et al., 2015). ESM studies also suggest that daily fluctuations in interpersonal behaviours and affect are heavily impacted by stressful events (Gadassi et al., 2014; Hepp et al., 2018; Santangelo et al., 2017; Santangelo, Bohus, & Ebner-Priemer, 2014; Wright et al., 2015). For example, Wright et al. assessed daily shifts in interpersonal behaviour and affect over the course of 100 days in an ESM study among individuals ($N = 101$) previously diagnosed with any PD. Results indicated that approximately half of the variance in interpersonal behaviour and affect was due to daily fluctuations. These fluctuations were modestly related to dispositional measures of interpersonal problems and strongly related to daily stress (Wright et al., 2015). In addition, diary studies suggest that between-subject differences in stressor-symptom contingencies are

dimensional in nature, with PD severity being associated with more stressors, more symptoms, and stronger contingencies (Glaser et al., 2010; Herr et al., 2013; Miskewicz et al., 2015; Santangelo, Bohus, & Ebner-Priemer, 2014; Tomko et al., 2015).

In sum, ESM studies in student samples suggest that LPF shows daily fluctuations. ESM studies on clinical samples suggest that (a) emotion dysregulation is a transdiagnostic phenomenon that is clearly present in PDs; (b) that momentary and daily fluctuations in emotion dynamics are interrelated with fluctuations in self-esteem, self-concept, and capacity for closeness; and that (c) acute stressors predict momentary shifts.

2.3 | Longitudinal physiological data about momentary and daily fluctuations in LPF

Longitudinal data of stress responses in individuals diagnosed with a PD are scarce. One 24-h ambulatory monitoring study showed that, in comparison with healthy controls, nonmedicated BPD patients exhibit higher levels of additional heart rate (that part of a heart rate increase that does not directly result from metabolic activity and is used as an indicator of emotional reactivity), indicating an overall increased activation of the SNS (Ebner-Priemer et al., 2007). Additional heart rate also co-occurred with reports of undifferentiated affect. Co-occurrences between biological stress responses and fluctuations in LPF are not unique to people diagnosed with a PD (Treadway & Leonard, 2016; Trull & Ebner-Priemer, 2013). For example, a 2-day ambulatory assessment study in remitted depressed patients showed that mean daily ruminative self-focus was associated with higher daily cortisol levels (Huffziger et al., 2013). In a 24-h monitoring study, participants with high emotional variability showed greater increases in blood pressure and heart rate during negative emotions. These “emotionally responsive” individuals also reported less satisfaction with social support and higher levels of daily stress, anxiety, and depressive symptoms (Carels et al., 2000). Another 24-h monitoring study in people diagnosed with panic disorder showed that fluctuations in heart and breathing rate and increased electro-dermal activity precede overwhelming feelings of disabling anxiety (Meuret et al., 2011).

In short, it appears plausible that LPF correlates negatively with acute stress, but the scarcity of data precludes conclusions.

3 | CHRONIC STRESS AND LPF

3.1 | Chronic stress and social behaviour in basic neuroscience

A robust finding in basic neuroscience is that persistent, uncontrollable stress in adulthood leads to structural alterations in the social brain. Neurons in the medial PFC and hippocampus show reduced length and branching of dendrites, as well as a decrease in number of synaptic contacts (Autry & Monteggia, 2012; de Kloet et al., 2005; McEwen, 1999, 2007; McEwen et al., 2015). These structural changes

are clinically relevant. Atrophy in the PFC is associated with impulsivity, emotion dysregulation, and poor executive functioning, in turn, impairing all RDoC social processes (Adolphs, 2009; McEwen et al., 2012; Wager et al., 2008). Atrophy in the hippocampus hampers stress regulation, context evaluation and learning, and is associated with low self-esteem (Christian et al., 2014; McEwen, 1999; McEwen et al., 2012; Sahay et al., 2011; Sandi & Haller, 2015; Shors, 2006; Ulrich-Lai & Herman, 2009). Mutual reinforcement can occur between an overactive amygdala and a suppressed PFC, increasing vulnerability for aggression, anxiety, and social impairments (Adolphs, 2009; McEwen, 1999, 2007; McEwen et al., 2012).

At a molecular level, loss of neuroplasticity is attributed primarily to glutamate, BDNF, and glucocorticoids. Uncontrollable, prolonged stress can lead to a decrease of BDNF in PFC and hippocampus as well as to neurotoxic levels of glutamate (Autry & Monteggia, 2012; de Kloet et al., 2005; Gold, 2015; McEwen, 2007; McEwen et al., 2015; Popoli et al., 2011). Glucocorticoids contribute to the depletion of BDNF and to the adverse effects of glutamate (Autry & Monteggia, 2012; Duman et al., 2019). Glucocorticoids also have direct effects on neuroplasticity by altering gene transcription and epigenetic factors (de Kloet et al., 2005; McEwen, 1999; McEwen et al., 2015; Oster et al., 2017; Ulrich-Lai & Herman, 2009). The dopaminergic circuit becomes chronically downregulated, impeding the motivation to engage in affiliative behaviours (Adolphs, 2009; de Kloet et al., 2005; McEwen, 1999; Sandi & Haller, 2015; Shors, 2006; Ulrich-Lai & Herman, 2009). Just as “healthy” stress modulation in the adult social brain involves more than the CNS, the effects of chronic stress transcend the CNS and HPA axis. Chronic stress also increases someone's susceptibility for immune-mediated inflammatory diseases, as well as metabolic disorders and cardiovascular diseases (Cohen et al., 2007; Gold, 2015; Russell & Lightman, 2019; Tost et al., 2015). Of note, periods of heightened biological vulnerability occur in

adulthood. Women, for example, are significantly more vulnerable during and within 2 years after pregnancy (Hoekzema et al., 2016). See Figure 2 for a conceptual model depicting the relationships between chronic stress biological processes, psychobiological (RDoC) social processes, and level of personality functioning.

3.2 | Longitudinal self-report data about persistent fluctuations in LPF

Do between-subject differences in the temporal dynamics of LPF represent a stable characteristic of an individual or does it refer to a condition that changes periodically? This is an intriguing question that resonates with an ongoing debate on whether personality pathology is time-invariant (i.e., a trait) or time-variant (i.e., a state) (Conway et al., 2018; Morey & Hopwood, 2013; Wright et al., 2016).

Roche et al. (2016) had students rate their current overall level of impairment and presence of pathological traits with respectively an adapted version of the DSM-5 LPF scale and the Personality Inventory for DSM-5 (PID-5; Krueger et al., 2012). After this baseline survey, they completed 14 nightly diary records. The authors found that the LPFS and PID-5 only predicted, respectively, between 13% and 23%, and 14% and 37%, of between-subject variance in daily LPF. These numbers could be interpreted as evidence that daily fluctuations of LPF are not manifestations of stable individual differences. However, we need prospective cohort studies that assess people's baseline LPF and LPF oscillations repeatedly for years to verify this hypothesis. In addition, both the survey and the diary tap into recollected LPF, be it within different timeframes. Data on momentary LPF are lacking.

Two high-quality studies assessed the course of PDs: the McLean Study of Adult Development (MSAD) and the Collaborative

FIGURE 2 Conceptual model depicting the relationships between chronic stress biological processes, psychobiological (RDoC) social processes, and level of personality functioning. Note. PFC = prefrontal cortex; HPA = hypothalamic–pituitary–adrenal; SNS = sympathetic nervous system. Full arrows represent direct relationships. Two-headed arrows represent correlations

Longitudinal Personality Disorders Study (CLPS). Both studies started decades before LPF became the agreed definition of PD severity. At the time, the DSM-III-R was used as a framework (3rd ed., rev.; DSM-III-R; APA, 1987). The still ongoing MSAD recruited patients from inpatient units at McLean Hospital in 1992. The sample consists of 290 patients with BPD and a comparison group of 72 patients, who met diagnostic criteria for at least one PD other than BPD. Raters, blind to previous diagnoses, reassessed patients every 2 years (Zanarini et al., 2005). The CLPS began in 1996. The samples consisted of individuals diagnosed with BPD ($n = 175$), avoidant and obsessive-compulsive PD ($n = 312$), and major depressive disorder without PD (MDD; $n = 95$). Patients were assessed annually for 10 years (Gunderson et al., 2000). The studies converged on three conclusions about the course of PDs:

- a. *High remission rates.* In 16 years of prospective follow-up, 99% of the MSAD BPD sample reported a 2-year remission, 95% a 4-year remission, 90% a 6-year remission, and 78% an 8-year remission. In people diagnosed with another PD, these remission rates were even higher: 99% for 2-year remission and 97% for 4-, 6-, and 8-year remission (Zanarini et al., 2012). In the CLPDS samples, over 85% of PD patients achieved remission of at least 12 months. This rate approximated the MDD sample (about 90%) (Gunderson et al., 2011).
- b. *Symptoms reoccur in a minority of remitted patients.* In the MSAD, cumulative rates of recurrence of symptoms in BPD patients ranged from 10% after an 8-year remission to 36% after a 2-year remission. The comparable figures for people diagnosed with other PDs were 4% and 7%, respectively (Zanarini et al., 2012). In the CLPS, 1 year of symptomatic recurrence after 1 year of remission occurred in 11% of remitted BPD patients and in 25% of cluster C PDs. Two consecutive months of symptomatic recurrence after

2 months of remission occurred in 21% of remitted BPD patients and in 67% of patients with MDD (Gunderson et al., 2011).

- c. *Good social and occupational functioning is more difficult to attain than remission.* Both studies assessed recovery by means of the Global Assessment of Functioning (GAF) (APA, 1987). A GAF score of 61 or higher indicated “good recovery,” defined as “having some mild symptoms or some difficulty in social, occupational, or school functioning, but generally functioning pretty well, has some meaningful interpersonal relationships.” A GAF score of 71 or higher indicated “excellent recovery,” defined as “if symptoms are present, they are transient and expectable reactions to psychosocial stressors; no more than slight impairment in social, occupational, or school functioning” (Zanarini et al., 2016). Zanarini et al. (2018) found that over half of the patients in the heterogeneous PD sample achieved at least good recovery after 2 years. This cumulative percentage increased to 84% after 10 years and 92% after 20 years. In the sample diagnosed with BPD, only 14% of the patients achieved good recovery after 2 years, which increased to 47% after 10 years and 59% after 20 years (Zanarini et al., 2018). The same trend held when the higher threshold (i.e., >71) of excellent recovery was used but with lower cumulative percentages: 12% (2 years), 62% (10 years), and 73% (20 years) in the heterogeneous PD sample and 2%, 24%, and 39% in the BPD sample, respectively. The CLPS results were similar: By 10 years, 21% of the BPD sample achieved excellent recovery. This was 48% in the cluster C sample and 61% in the MDD sample (Gunderson et al., 2011).

In short, data on remission and relapse in people diagnosed with a PD disprove the proposition that severity of personality pathology is a stable phenomenon. On the other hand, the majority of this body of evidence pertains to PD patients that were in psychotherapy and/or

FIGURE 3 Illustration of time-variant and stress-related dimensions in level of personality functioning in two hypothetical persons with and without a personality disorder. Note. The X-axis indicates time, expressed in respectively hours (a), to illustrate the impact of acute stress, and years (b) to illustrate the impact of chronic stress. The Y-axis represents level of personality functioning, ranging from healthy (0) to some (−1), moderate (−2), severe (−3), and extreme (−4) impairments. Round dot black line = a hypothetical person diagnosed with a personality disorder (PD). Solid black line = a hypothetical person who is considered healthy

taking psychotropic medications (Bender et al., 2006; Zanarini et al., 2015). It is unclear to what extent these results generalize to patients who are not in treatment. Furthermore, longitudinal GAF scores seem to support the notion that PD severity is stable. However, we are reluctant to use GAF as a proxy for PD severity (Widiger & Trull, 2007). Primarily because reliability and validity issues have been widely documented, leading up to the decision to abandon the GAF in the DSM-5 (Aas, 2010; APA, 2013). Also, given the stigma associated with PDs, we caution against using undesirable social outcomes as an indicator of pathology severity. With regard to the relationship between PD severity and sustained stress in adulthood, we only found secondary analyses on data of the CLPS sample. Those analyses showed that negative life events, especially interpersonal events, predicted decreased functioning (Pagano et al., 2004).

Taken together, we conclude that it is premature to interpret between-subject differences in PD severity as a stable characteristic that originated before adulthood. We need more prospective cohort data to reject the hypothesis that PD represents an episodic, stress-related condition that can improve within 2 years, much like other forms of psychopathology.

3.3 | Longitudinal neurophysiological data about persistent fluctuations in LPF

Despite the mounting neuroscientific evidence that chronic stress in adulthood increases an individual's vulnerability for disturbed social

TABLE 2 Operationalizations for research questions concerning acute stress and LPF

Electrophysiology	Self-report	Behaviour
Continuous measurement of heart rate, electrodermal activity, heart rate variability. Analyses in ± 5 -min windows for at least 2 days and nights.	Rate momentary impairments in self- and other functioning multiple times a day for at least 2 days.	Systematic behavioural observations of overt behaviours indicative of impairments in LPF (e.g., nonsuicidal self-injury, suicide attempts, abuse of alcohol or drugs, binge eating, violence, social withdrawal), or of healthy functioning (e.g., engaging in affiliative behaviour). Passively monitors voice volumes, time spent among other people or in high risk locations, etc.

Abbreviation: LPF, level of personality functioning.

TABLE 3 Operationalizations for research questions concerning chronic stress and LPF

Electrophysiology	Self-report	Behaviour
Protocols for acute stress (see Table 2) multiple times a year; OR passively monitors ANS activity during the entire period of interest and uses machine learning techniques to detect significant changes; OR repeated measurements in a laboratory setting.	ESM protocols for acute stress and LPF (see Table 2) multiple times a year; OR validated questionnaires/interviews for LPF at least twice a year, for at least 2 years; OR validated instruments that demonstrated convergent validity with LPF and/or elements of LPF.	Systematic behavioural observations of overt behaviours indicative of impairments in LPF (e.g., nonsuicidal self-injury, suicide attempts, abuse of alcohol or drugs, binge eating, violence, and social withdrawal) or of healthy functioning (e.g., engaging in affiliative behaviour). Passively monitors voice volumes, time spent among other people or in high risk locations, etc.

Abbreviations: ANS, autonomic nervous system; ESM, experience sampling method; LPF, level of personality functioning.

functioning, as well as stress-related mental and physical disorders, we found no reports on prospective cohort studies that collected information on the relationship between persistent decrease in LPF and chronic stress biomarkers in adulthood. As a result, it is impossible to determine whether the biological correlates of personality pathology severity in adulthood reflect the impact of chronic stress in adulthood, the impact of adversity during earlier developmental stages, genetic vulnerabilities, or an interaction of these factors. The only longitudinal data we found were repeated neuroimaging measurements during clinical trials suggesting that changes in the function and structure of—among others—the amygdala and prefrontal areas mediate improvement during specialized psychological treatment (Davidson & McEwen, 2012; Marceau et al., 2018). The hypothesis that effects of chronic stress drive persistent decline in LPF in adulthood at a biological level is plausible, but longitudinal data to support this are lacking.

4 | CONCLUSION AND AGENDA FOR FUTURE RESEARCH

We provided a critical review about the associations between stress and LPF. Our aim was to propose a theoretical framework to guide research on stress-related fluctuations in LPF that showed a good fit with the RDoC model and accounted for the issue of symptom-biomarker chronometry. More specifically, we wanted to identify electrophysiological biomarkers that co-vary with stress-related fluctuations, which we might use in clinical practice to predict

a decrease in LPF. We based our review on high quality and impactful research from basic neuroscience, psychology, and psychiatry. Our goal was to foster conceptual innovation and to derive new hypotheses, not to provide answers on a specific research question (Grant & Booth, 2009).

A key finding was the importance of distinguishing between acute stress (i.e., activation of stress responses that promote adaption when an organism's survival or well-being is challenged) and chronic stress (i.e., sustained activation of these acute stress responses in adverse circumstances) (Figure 3). This definition modifies the conceptual model and, consequently, the hypotheses that need testing (Figures 1 and 2).

Research questions about the impact of acute stress (e.g., social conflicts, traffic jams, deadlines, acute pain) require measuring stress biomarkers multiple times a day, for at least 2 days. Repeating the ESM protocol is necessary to make sure that the data are accurate, especially because stress response systems follow a circadian rhythm (see "Acute stress and social behaviour in basic neuroscience"). Within this time dimension, we hypothesize that momentary impairments in LPF are directly related to biomarkers of the SNS stress response, such as heart rate and electrodermal activity, and inversely related to biomarkers of PNS activity, such as heart rate variability (Table 2). Wearable technology to perform ambulatory monitoring of electrical activity of the heart and changes in skin conductance, as well as a reliable and valid ESM protocol that measures momentary fluctuations in LPF, is pivotal for such investigations. Clinical applications of ESM protocols for acute stress and LPF include case conceptualization, biofeedback during specialized therapy, and prevention of high-risk behaviours in people diagnosed with severe levels of PD (see, e.g., de Looft et al., 2019). If research questions concern the impact of enduring challenges to health or well-being (e.g., abuse, stigmatization, chronic pain, social isolation, incarceration), then assessments should be repeated multiple times within months to years. The exact frequency, time window, and number of repetitions within that window depend on the stressors and biomarkers of interest, as well as the measurement conditions (i.e., in the lab versus in daily life) and confounders (Table 3). If we limit ourselves to electrophysiological stress biomarkers that co-vary with chronic stress-related fluctuations in LPF, then we would expect to see changes in *patterns* of autonomic stress responses. More specifically, we would expect a gradual decline in PNS activity, indicated by a decrease in baseline heart rate variability. Analogous to the field of emotion dynamics (see Houben et al., 2015), we would assume an increase in variability, instability, and inertia of SNS biomarkers as the activation of acute stress responses is sustained over time. To put our theoretical framework about chronic stress and LPF (Figure 2) to the test, we would also have to include other biomarkers of chronic stress (i.e., PFC and hippocampus atrophy, amygdala hyperactivity, chronic dopamine downregulation, inflammatory diseases). Clinical applications of ESM protocols for chronic stress and LPF could improve existing procedures for continuous monitoring of LPF during specialized therapy (see Linehan, 1993, 2015, for an example of structured diary methods in clinical practice). It could also lead to innovations in relapse prevention after treatment,

as already delineated in the introduction (Goodday & Friend, 2019; Myin-Germeys et al., 2018; Smets et al., 2018).

Our review also demonstrated that research about time-varying and stress-related dimensions of LPF is at its infancy. We found only preliminary evidence for momentary, stress-related fluctuations of LPF. However, questions about the stability of these individual differences in LPF and the role of chronic stress in personality pathology could not be answered at this point. We argued that the lack of a coherent theoretical framework for transdisciplinary research about stress and LPF is part of the problem. Notwithstanding the limitations of our approach, we hope that our effort will prove useful in guiding future research in this understudied domain.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Roland Sinnaeve <https://orcid.org/0000-0002-2410-4598>

Inez Myin-Germeys <https://orcid.org/0000-0002-3731-4930>

REFERENCES

- Aas, I. H. (2010). Global assessment of functioning (GAF): Properties and frontier of current knowledge. *Annals of General Psychiatry*, 9, 20. <https://doi.org/10.1186/1744-859X-9-20>
- Adolphs, R. (2009). The social brain: Neural basis of social knowledge. *Annual Review of Psychology*, 60(1), 693–716. <https://doi.org/10.1146/annurev.psych.60.110707.163514>
- American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., revised ed.). American Psychiatric Association.
- American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). American Psychiatric Association. <https://doi.org/10.1176/appi.books.9780890425596>
- Autry, A. E., & Monteggia, L. M. (2012). Brain-derived neurotrophic factor and neuropsychiatric disorders. *Pharmacological Reviews*, 64(2), 238–258. <https://doi.org/10.1124/pr.111.005108>
- Bateman, A. W., Gunderson, J., & Mulder, R. (2015). Treatment of personality disorder. *The Lancet*, 385(9969), 735–743. [https://doi.org/10.1016/S0140-6736\(14\)61394-5](https://doi.org/10.1016/S0140-6736(14)61394-5)
- Bender, D. S., Skodol, A. E., Pagano, M. E., Dyck, I. R., Grilo, C. M., Shea, M. T., Sanislow, C. A., Zanarini, M. C., Yen, S., McGlashan, T. H., & Gunderson, J. G. (2006). Prospective assessment of treatment use by patients with personality disorders. *Psychiatric services*, 57(2), 254–257. <https://doi.org/10.1176/appi.ps.57.2.254>
- Berntson, G., Cacioppo, J. T., & Tassinary, L. G. (2007). *Handbook of Psychophysiology* (3rd ed.). Cambridge: Cambridge university press.
- Björkenstam, C., Ekselius, L., Berlin, M., Gerdin, B., & Björkenstam, E. (2016). Suicide risk and suicide method in patients with personality Disorders. *Journal of Psychiatric Research*, 83, 29–36. <https://doi.org/10.1016/j.jpsychires.2016.08.008>
- Carels, R. A., Blumenthal, J. A., & Sherwood, A. (2000). Emotional responsiveness during daily life: Relationship to psychosocial functioning

- and ambulatory blood pressure. *International Journal of Psychophysiology*, 36(1), 25–33. [https://doi.org/10.1016/S0167-8760\(99\)00101-4](https://doi.org/10.1016/S0167-8760(99)00101-4)
- Christian, K. M., Song, H., & Ming, G. (2014). Functions and dysfunctions of adult hippocampal neurogenesis. *Annual Review of Neuroscience*, 37(1), 243–262. <https://doi.org/10.1146/annurev-neuro-071013-014134>
- Chun, C. A., Barrantes-Vidal, N., Sheinbaum, T., & Kwapil, T. R. (2017). Expression of schizophrenia-spectrum personality traits in daily life. *Personality Disorders: Theory, Research, and Treatment*, 8(1), 64–74. <https://doi.org/10.1037/per0000141>
- Clarkin, J. F., Yeomans, F., & Kernberg, O. F. (2006). *Psychotherapy for Borderline Personality: Focusing on Object Relations*. Washington, DC: American Psychiatric Publishing.
- Cohen, S., Janicki-Deverts, D., & Miller, G. E. (2007). Psychological stress and disease. *JAMA*, 298(14), 1685–1687. <https://doi.org/10.1001/jama.298.14.1685>
- Conway, C. C., Hopwood, C. J., Morey, L. C., & Skodol, A. E. (2018). Borderline personality disorder is equally trait-like and state-like over ten years in adult psychiatric patients. *Journal of Abnormal Psychology*, 127(6), 590–601. <https://doi.org/10.1037/abn0000364>
- Davidson, R. J., & McEwen, B. S. (2012). Social influences on neuroplasticity: Stress and interventions to promote well-being. *Nature Neuroscience*, 15(5), 689–695. <https://doi.org/10.1038/nn.3093>
- de Kloet, E. R., Joels, M., & Holsboer, F. (2005). Stress and the brain: From adaption to disease. *Nature Reviews Neuroscience*, 6(6), 463–475. <https://doi.org/10.1038/nrn1683>
- de Looft, P., Noordzij, M. L., Moerbeek, M., Nijman, H., Didden, R., & Embregts, P. (2019). Changes in heart rate and skin conductance in the 30 min preceding aggressive behavior. *Psychophysiology*, 56(10), e13420. <https://doi.org/10.1111/psyp.13420>
- Dixon-Gordon, K. L., Whalen, D. J., Layden, B. K., & Chapman, A. L. (2015). A systematic review of personality disorders and health outcomes. *Canadian Psychology/Psychologie Canadienne*, 56(2), 168–190. <https://doi.org/10.1037/cap0000024>
- Duman, R. S., Sanacora, G., & Krystal, J. H. (2019). Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. *Neuron*, 102(1), 75–90. <https://doi.org/10.1016/j.neuron.2019.03.013>
- Ebner-Priemer, U. W., Houben, M., Santangelo, P., Kleindienst, N., Tuerlinckx, F., Oravecz, Z., Verleysen, G., van Deun, K., Bohus, M., & Kuppens, P. (2015). Unraveling affective dysregulation in borderline personality disorder: A theoretical model and empirical evidence. *Journal of Abnormal Psychology*, 124(1), 186–198. <https://doi.org/10.1037/abn0000021>
- Ebner-Priemer, U. W., Welch, S. S., Grossman, P., Reisch, T., Linehan, M. M., & Bohus, M. (2007). Psychophysiological ambulatory assessment of affective dysregulation in borderline personality disorder. *Psychiatry Research*, 150(3), 265–275. <https://doi.org/10.1016/j.psychres.2006.04.014>
- First, M. B., Bell, C. C., Cuthbert, B., Krystal, J. H., Malison, R., Offord, D. R., Reiss, D., Shea, M. T., Widiger, T. A., & Wisner, K. L. (2002). Personality disorders and relational disorders: A research agenda for addressing crucial gaps in DSM. In D. J. Kupfer, M. B. First, & D. A. Regier (Eds.), *A Research Agenda for DSM-V* (pp. 123–199). Washington, DC: American Psychiatric Association.
- Fok, M. L., Hayes, R. D., Chang, C. K., Stewart, R., Callard, F. J., & Moran, P. (2012). Life expectancy at birth and all-cause mortality among people with personality disorder. *Journal of Psychosomatic Research*, 73(2), 104–107. <https://doi.org/10.1016/j.jpsychores.2012.05.001>
- Fonagy, P., Luyten, P., & Allison, E. (2015). Epistemic petrification and the restoration of epistemic trust: A new conceptualization of borderline personality disorder and its psychosocial treatment. *Journal of Personality Disorders*, 29(5), 575–609. <https://doi.org/10.1521/pedi.2015.29.5.575>
- Frances, A. J. (1993). Dimensional diagnosis of personality—Not whether, but when and which. *Psychological Inquiry*, 4, 110–111. https://doi.org/10.1207/s15327965pli0402_7
- Fung, T. C., Olson, C. A., & Hsiao, E. Y. (2017). Interactions between the microbiota, immune and nervous systems in health and disease. *Nature Neuroscience*, 20(2), 145–155. <https://doi.org/10.1038/nn.4476>
- Gadassi, R., Snir, A., Berenson, K., Downey, G., & Rafaeli, E. (2014). Out of the frying pan, into the fire: Mixed affective reactions to social proximity in borderline and avoidant personality disorders in daily life. *Journal of Abnormal Psychology*, 123(3), 613–622. <https://doi.org/10.1037/a0036929>
- Glaser, J. P., van Os, J., Thewissen, V., & Myin-Germeys, I. (2010). Psychotic reactivity in borderline personality disorder. *Acta Psychiatrica Scandinavica*, 121(2), 125–134. <https://doi.org/10.1111/j.1600-0447.2009.01427.x>
- Gold, P. W. (2015). The organization of the stress system and its dysregulation in depressive illness. *Molecular Psychiatry*, 20(1), 32–47. <https://doi.org/10.1038/mp.2014.163>
- Goodday, S. M., & Friend, S. (2019). Unlocking stress and forecasting its consequences with digital technology. *NPJ Digital Medicine*, 2(1), 75. <https://doi.org/10.1038/s41746-019-0151-8>
- Grant, M. J., & Booth, A. (2009). A typology of reviews: An analysis of 14 review types and associated methodologies. *Health Information & Libraries Journal*, 26(2), 91–108. <https://doi.org/10.1111/j.1471-1842.2009.00848.x>
- Gunderson, J. G., Shea, M. T., Skodol, A. E., McGlashan, T. H., Morey, L. C., Stout, R. L., Zanarini, M. C., Grilo, C. M., Oldmand, J. M., & Keller, M. (2000). The collaborative longitudinal personality disorders study: Development, aims, design, and sample characteristics. *Journal of Personality Disorders*, 14(4), 300–315. <https://doi.org/10.1521/pedi.2000.14.4.300>
- Gunderson, J. G., Stout, R. L., McGlashan, T. H., Shea, M. T., Morey, L. C., Grilo, C. M., Zanarini, M. C., Yen, S., Markowitz, J. C., Sanislow, C., Ansell, E., Pinto, A., & Skodol, A. E. (2011). Ten-year course of borderline personality disorder psychopathology and function from the collaborative longitudinal personality disorders study. *Archives of General Psychiatry*, 68(8), 827–837. <https://doi.org/10.1001/archgenpsychiatry.2011.37>
- Hepp, J., Lane, S. P., Wycoff, A. M., Carpenter, R. W., & Trull, T. J. (2018). Interpersonal stressors and negative affect in individuals with borderline personality disorder and community adults in daily life: A replication and extension. *Journal of Abnormal Psychology*, 127(2), 183–189. <https://doi.org/10.1037/abn0000318>
- Herr, N. R., Keenan-Miller, D., Rosenthal, M. Z., & Feldblum, J. (2013). Negative interpersonal events mediate the relation between borderline features and aggressive behavior: Findings from a nonclinical sample of undergraduate women. *Personality Disorders: Theory, Research, and Treatment*, 4(3), 254–260. <https://doi.org/10.1037/a0032212>
- Hoekzema, E., Barba-Müller, E., Pozzobon, C., Picado, M., Lucco, F., García-García, D., Soliva, J. C., Tobeña, A., Desco, M., Crone, E. A., Ballesteros, O., Carmona, S., & Vilarroya, O. (2016). Pregnancy leads to long-lasting changes in human brain structure. *Nature Neuroscience*, 20(2), 287–296. <https://doi.org/10.1038/nn.4458>
- Houben, M., Bohus, M., Santangelo, P. S., Ebner-Priemer, U., Trull, T. J., & Kuppens, P. (2016). The specificity of emotional switching in borderline personality disorder in comparison to other clinical groups. *Personality Disorders: Theory, Research, and Treatment*, 7(2), 198–204. <https://doi.org/10.1037/per0000172>
- Houben, M., van den Noortgate, W., & Kuppens, P. (2015). The relation between short-term emotion dynamics and psychological well-being: A meta-analysis. *Psychological Bulletin*, 141(4), 901–930. <https://doi.org/10.1037/a0038822>
- Huang, E. J., & Reichardt, L. F. (2001). Neurotrophins: Roles in neuronal development and function. *Annual Review of Neuroscience*, 24, 677–736. <https://doi.org/10.1146/annurev.neuro.24.1.677>
- Huang, Y., Kotov, R., de Girolamo, G., Preti, A., Angermeyer, M., Benjet, C., Demyttenaere, K., de Graaf, R., Gureje, O., Karam, A. N., Lee, S., Lépine, J. P., Matschinger, H., Posada-Villa, J., Suliman, S.,

- Vilagut, G., & Kessler, R. (2009). DSM-IV personality disorders in the WHO world mental health surveys. *The British Journal of Psychiatry: The Journal of Mental Science*, 195(1), 46–53. <https://doi.org/10.1192/bjp.bp.108.058552>
- Huffziger, S., Ebner-Priemer, U., Zamoscik, V., Reinhard, I., Kirsch, P., & Kuehner, C. (2013). Effects of mood and rumination on cortisol levels in daily life: An ambulatory assessment study in remitted depressed patients and healthy controls. *Psychoneuroendocrinology*, 38(10), 2258–2267. <https://doi.org/10.1016/j.psyneuen.2013.04.014>
- Köhling, J., Moessner, M., Ehrenthal, J. C., Bauer, S., Cierpka, M., Kämmerer, A., & Dinger, U. (2016). Affective instability and reactivity in depressed patients with and without borderline pathology. *Journal of Personality Disorders*, 30(6), 776–795. <https://doi.org/10.1521/pedi.2015.29.230>
- Kozak, M. J., & Cuthbert, B. N. (2016). The NIMH research domain criteria initiative: Background, issues, and pragmatics. *Psychophysiology*, 53(3), 286–297. <https://doi.org/10.1111/psyp.12518>
- Krueger, R. F., Derringer, J., Markon, K. E., Watson, D., & Skodol, A. E. (2012). Initial construction of a maladaptive personality trait model and inventory for DSM-5. *Psychological Medicine*, 42(9), 1879–1890. <https://doi.org/10.1017/S0033291711002674>
- Krueger, R. F., Skodol, A. E., Livesley, W. J., Shrout, P. E., & Huang, Y. (2008). Synthesizing dimensional and categorical approaches to personality disorders: refining the research agenda for DSM-IV Axis II. In J. E. Helzer, H. C. Kraemer, R. F. Krueger, H. U. Wittchen, P. J. Sirovatka, & D. A. Regier (Eds.), *Dimensional Approaches to Diagnostic Classification. Refining the Research Agenda for DSM-V* (pp. 85–100). Washington, DC: American Psychiatric Association.
- Lilienfeld, S. O., & Treadway, M. T. (2016). Clashing diagnostic approaches: DSM-ICD versus RDoC. *Annual Review of Clinical Psychology*, 12(1), 435–463. <https://doi.org/10.1146/annurev-clinpsy-021815-093122>
- Linehan, M. M. (1993). *Cognitive-Behavioral Treatment of Borderline Personality Disorder*. New York, NY: Guilford Press.
- Linehan, M. M. (2015). *DBT Skills Training Manual* (2nd ed.). New York, NY: Guilford Press.
- Ma, G., Fan, H., Shen, C., & Wang, W. (2016). Genetic and neuroimaging features of personality disorders: State of the art. *Neuroscience Bulletin*, 32(3), 286–306. <https://doi.org/10.1007/s12264-016-0027-8>
- Marceau, E. M., Meuldijk, D., Townsend, M. L., Solowij, N., & Grenyer, B. F. S. (2018). Biomarker correlates of psychotherapy outcomes in borderline personality disorder: A systematic review. *Neuroscience and Biobehavioral Reviews*, 94, 166–178. <https://doi.org/10.1016/j.neubiorev.2018.09.001>
- McEwen, B. S. (1999). Stress and hippocampal plasticity. *Annual Review of Neuroscience*, 22, 105–122. <https://doi.org/10.1146/annurev.neuro.22.1.105>
- McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews*, 87(3), 873–904. <https://doi.org/10.1152/physrev.00041.2006>
- McEwen, B. S., Bowles, N. P., Gray, J. D., Hill, M. N., Hunter, R. G., Karatsoreos, I. N., & Nasca, C. (2015). Mechanisms of stress in the brain. *Nature Neuroscience*, 18(10), 1353–1363. <https://doi.org/10.1038/nn.4086>
- McEwen, B. S., Eiland, L., Hunter, R. G., & Miller, M. M. (2012). Stress and anxiety: Structural plasticity and epigenetic regulation as a consequence of stress. *Neuropharmacology*, 62(1), 3–12. <https://doi.org/10.1016/j.neuropharm.2011.07.014>
- Meuret, A. E., Rosenfield, D., Wilhelm, F. H., Zhou, E., Conrad, A., Ritz, T., & Roth, W. T. (2011). Do unexpected panic attacks occur spontaneously? *Biological Psychiatry*, 70(10), 985–991. <https://doi.org/10.1016/j.biopsych.2011.05.027>
- Miskewicz, K., Fleeson, W., Arnold, E. M., Law, M. K., Mneimne, M., & Furr, R. M. (2015). A contingency-oriented approach to understanding borderline personality disorder: Situational triggers and symptoms. *Journal of Personality Disorders*, 29(4), 486–502. <https://doi.org/10.1521/pedi.2015.29.4.486>
- Moran, P., Romaniuk, H., Coffey, C., Chanen, A., Degenhardt, L., Borschmann, R., & Patton, G. (2016). The influence of personality disorder on the future mental health and social adjustment of young adults: A population-based, longitudinal cohort study. *The Lancet Psychiatry*, 3(7), 636–645. [https://doi.org/10.1016/S2215-0366\(16\)30029-3](https://doi.org/10.1016/S2215-0366(16)30029-3)
- Morey, L. C., & Hopwood, C. J. (2013). Stability and change in personality disorders. *Annual Review of Clinical Psychology*, 9(1), 499–528. <https://doi.org/10.1146/annurev-clinpsy-050212-185637>
- Myin-Germeys, I., Kasanova, Z., Vaessen, T., Vachon, H., Kirtley, O., Viechtbauer, W., & Reininghaus, U. (2018). Experience sampling methodology in mental health research: New insights and technical developments. *World Psychiatry*, 17(2), 123–132. <https://doi.org/10.1002/wps.20513>
- Nestler, E. J. (2012). Epigenetics: Stress makes its molecular mark. *Nature*, 490(7419), 171–172. <https://doi.org/10.1038/490171a>
- Oltmanns, J. R., & Widiger, T. A. (2019). Evaluating the assessment of the ICD-11 personality disorder diagnostic system. *Psychological Assessment*, 31(5), 674–684. <https://doi.org/10.1037/pas0000693>
- Oster, H., Challet, E., Ott, V., Arvat, E., de Kloet, E. R., Dijk, D. J., Lightman, S., Vgontzas, A., & van Cauter, E. (2017). The functional and clinical significance of the 24-hour rhythm of circulating glucocorticoids. *Endocrine Reviews*, 38(1), 3–45. <https://doi.org/10.1210/er.2015-1080>
- Pagano, M., Skodol, A., Stout, R., Shea, M., Yen, S., Grilo, C., Sanislow, C. A., Bender, D. S., McGlashan, T. H., Zanarini, M. C., & Gunderson, J. (2004). Stressful life events as predictors of functioning: Findings from the collaborative longitudinal personality disorders study. *Acta Psychiatrica Scandinavica*, 110(6), 421–429. <https://doi.org/10.1111/j.1600-0447.2004.00398.x>
- Pavlov, V. A., Chavan, S. S., & Tracey, K. J. (2018). Molecular and functional neuroscience in immunity. *Annual Review of Immunology*, 36(1), 783–812. <https://doi.org/10.1146/annurev-immunol-042617-053158>
- Popoli, M., Yan, Z., McEwen, B. S., & Sanacora, G. (2011). The stressed synapse: The impact of stress and glucocorticoids on glutamate transmission. *Nature Reviews Neuroscience*, 13(1), 22–37. <https://doi.org/10.1038/nrn3138>
- Reed, G. M., First, M. B., Kogan, C. S., Hyman, S. E., Gaebel, W., Maj, M., Stein, D. J., Maercker, A., Tyer, P., Claudino, A., Garralda, E., Salvador-Carulla, L., Ray, R., Saunders, J. B., Dua, T., Poznyak, V., Medina-Mora, M. E., Pike, K. M., Ayuso-Mateos, J. L., ... Saxena, S. (2019). Innovations and changes in the ICD-11 classification of mental, behavioural and neurodevelopmental disorders. *World Psychiatry*, 18(1), 3–19. <https://doi.org/10.1002/wps.20611>
- Roche, M. J. (2018). Examining the alternative model for personality disorder in daily life: Evidence for incremental validity. *Personality Disorders: Theory, Research, and Treatment*, 9(6), 574–583. <https://doi.org/10.1037/per0000295>
- Roche, M. J., Jacobson, N. C., & Pincus, A. L. (2016). Using repeated daily assessments to uncover oscillating patterns and temporally-dynamic triggers in structures of psychopathology: Applications to the DSM-5 alternative model of personality disorders. *Journal of Abnormal Psychology*, 125(8), 1090–1102. <https://doi.org/10.1037/abn0000177>
- Russell, G., & Lightman, S. (2019). The human stress response. *Nature Reviews Endocrinology*, 15(9), 525–534. <https://doi.org/10.1038/s41574-019-0228-0>
- Sahay, A., Scobie, K. N., Hill, A. S., O'Carroll, C. M., Kheirbek, M. A., Burghardt, N. S., Fenton, A. A., Dranovsky, A., & Hen, R. (2011). Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature*, 472(7344), 466–470. <https://doi.org/10.1038/nature09817>

- Sandi, C., & Haller, J. (2015). Stress and the social brain: Behavioural effects and neurobiological mechanisms. *Nature Reviews Neuroscience*, 16(5), 290–304. <https://doi.org/10.1038/nrn3918>
- Santangelo, P., Reinhard, I., Mussgay, L., Steil, R., Sawitzki, G., Klein, C., Trull, T. J., Bohus, M., & Ebner-Priemer, U. W. (2014). Specificity of affective instability in patients with borderline personality disorder compared to posttraumatic stress disorder, bulimia nervosa, and healthy controls. *Journal of Abnormal Psychology*, 123(1), 258–272. <https://doi.org/10.1037/a0035619>
- Santangelo, P. S., Bohus, M., & Ebner-Priemer, U. W. (2014). Ecological momentary assessment in borderline personality disorder: A review of recent findings and methodological challenges. *Journal of Personality Disorders*, 28(4), 555–576. https://doi.org/10.1521/pedi_2012_26_067
- Santangelo, P. S., Reinhard, I., Koudela-Hamila, S., Bohus, M., Holtmann, J., Eid, M., & Ebner-Priemer, U. (2017). The temporal interplay of self-esteem instability and affective instability in borderline personality disorder Patients' everyday lives. *Journal of Abnormal Psychology*, 126(8), 1057–1065. <https://doi.org/10.1037/abn0000288>
- Scala, J. W., Levy, K. N., Johnson, B. N., Kivity, Y., Ellison, W. D., Pincus, A. L., Wilson, S. J., & Newman, M. G. (2018). The role of negative affect and self-concept clarity in predicting self-injurious urges in borderline personality disorder using ecological momentary assessment. *Journal of Personality Disorders*, 32(SS), 36–57. <https://doi.org/10.1521/pedi.2018.32.sup.36>
- Scheiderer, E. M., Wang, T., Tomko, R. L., Wood, P. K., & Trull, T. J. (2016). Negative affect instability among individuals with comorbid borderline personality disorder and posttraumatic stress disorder. *Clinical Psychological Science*, 4(1), 67–81. <https://doi.org/10.1177/2167702615573214>
- Schulze, L., Schmahl, C., & Niedtfeld, I. (2016). Neural correlates of disturbed emotion processing in borderline personality disorder: A multimodal meta-analysis. *Biological Psychiatry*, 79(2), 97–106. <https://doi.org/10.1016/j.biopsych.2015.03.027>
- Sheehan, L., Nieweglowski, K., & Corrigan, P. (2016). The stigma of personality disorders. *Current Psychiatry Reports*, 18(1), 1–7. <https://doi.org/10.1007/s11920-015-0654-1>
- Shors, T. J. (2006). Stressful experience and learning across the lifespan. *Annual Review of Psychology*, 57, 55–85. <https://doi.org/10.1146/annurev.psych.57.102904.190205>
- Smets, E., Rios Velazquez, E. R., Schiavone, G., Chakroun, I., D'Hondt, E., Raedt, D., Cornelis, J., Janssens, O., van Hoecke, S., Claes, S., van Diest, I., & van Hoof, C. (2018). Large-scale wearable data reveal digital phenotypes for daily-life stress detection. *NPJ Digital Medicine*, 1(1), 67. <https://doi.org/10.1038/s41746-018-0074-9>
- Soeteman, D. I., Hakkaart-van Roijen, L., Verheul, R., & Busschbach, J. J. (2008). The economic burden of personality disorders in mental health care. *The Journal of Clinical Psychiatry*, 69(2), 259–265. <https://doi.org/10.4088/jcp.v69n0212>
- Squire, L. R. (1992). Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychological Review*, 99(2), 195–231. <https://doi.org/10.1037/0033-295x.99.2.195>
- Steptoe, A., Hamer, M., & Chida, Y. (2007). The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain Behavior and Immunity*, 21(7), 901–912. <https://doi.org/10.1016/j.bbi.2007.03.011>
- Storebø, O. J., Stoffers-Winterling, J. M., Völlm, B. A., Kongerslev, M. T., Mattivi, J. T., Jørgensen, M. S., Faltinsen, E., Todorovac, A., Sales, C. P., Callesen, H. E., Lieb, K., & Simonsen, E. (2020). Psychological therapies for people with borderline personality disorder. *Cochrane Database of Systematic Reviews*, 2020(5). <https://doi.org/10.1002/14651858.CD012955.pub2>
- Tomko, R. L., Lane, S. P., Pronove, L. M., Treloar, H. R., Brown, W. C., Solhan, M. B., Wood, P. K., & Trull, T. J. (2015). Undifferentiated negative affect and impulsivity in borderline personality and depressive disorders: A momentary perspective. *Journal of Abnormal Psychology*, 124(3), 740–753. <https://doi.org/10.1037/abn0000064>
- Tost, H., Champagne, F. A., & Meyer-Lindenberg, A. (2015). Environmental influence in the brain, human welfare and mental health. *Nature Neuroscience*, 18(1), 1421–1431. <https://doi.org/10.1038/nn.4108>
- Treadway, M. T., & Leonard, C. V. (2016). Isolating biomarkers for symptomatic states: Considering symptom-substrate chronometry. *Molecular Psychiatry*, 21(9), 1180–1187. <https://doi.org/10.1038/mp.2016.83>
- Trull, T. J., & Ebner-Priemer, U. (2013). Ambulatory assessment. *Annual Review of Clinical Psychology*, 9(1), 151–176. <https://doi.org/10.1146/annurev-clinpsy-050212-185510>
- Tyrer, P., Mulder, R., Kim, Y.-R., & Crawford, M. J. (2019). The development of the ICD-11 classification of personality disorders: An amalgam of science, pragmatism, and politics. *Annual Review of Clinical Psychology*, 15, 481–502. <https://doi.org/10.1146/annurev-clinpsy-050718-095736>
- Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews Neuroscience*, 10(6), 397–409. <https://doi.org/10.1038/nrn2647>
- Volkert, J., Gablonski, T. C., & Rabung, S. (2018). Prevalence of personality disorders in the general adult population in Western countries: Systematic review and meta-analysis. *British Journal of Psychiatry*, 213(6), 709–715. <https://doi.org/10.1192/bjp.2018.202>
- Vuong, H. E., Yano, J. M., Fung, T. C., & Hsiao, E. Y. (2017). The microbiome and host behavior. *Annual Review of Neuroscience*, 40, 21–49. <https://doi.org/10.1146/annurev-neuro-072116-031347>
- Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. A., & Ochsner, K. N. (2008). Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron*, 59(6), 1037–1050. <https://doi.org/10.1016/j.neuron.2008.09.006>
- White, C. N., Conway, C. C., & Oltmanns, T. F. (2020). Stress and personality disorders. In K. L. Harkness & E. P. Hayden (Eds.), *The Oxford Handbook of Stress and Mental Health* (eBook ed.). New York, NY: Oxford University Press. <https://doi.org/10.1093/oxfordhb/9780190681777.013.8>
- Widiger, T., & Trull, T. (2007). Plate tectonics in the classification of personality disorder. *American Psychologist*, 62(2), 71–83. <https://doi.org/10.1037/0003-066X.62.2.71>
- Witt, S. H., Streit, F., Jungkunz, M., Frank, J., Awasthi, S., Reinbold, C. S., Treutlein, J., Degenhardt, F., Forstner, A. J., Heilmann-Heimbach, S., Dietl, L., Schwarze, C. E., Schendel, D., Strohmaier, J., Abdellaoui, A., Adolfsson, R., Air, T. M., Akil, H., Alda, M., ... Rietschel, M. (2017). Genome-wide association study of borderline personality disorder reveals genetic overlap with bipolar disorder, major depression and schizophrenia. *Translational Psychiatry*, 7(6), E1155. <https://doi.org/10.1038/tp.2017.115>
- World Health Organization. (1992). *International Classification of Diseases and Related Health Problems* (10th rev., ICD-10). World Health Organization.
- World Health Organization. (2019). *International Statistical Classification of Diseases and Related Health Problems* (11th ed.). World Health Organization. <https://icd.who.int/>
- Wright, A. G., Hopwood, C. J., & Simms, L. J. (2015). Daily interpersonal and affective dynamics in personality disorder. *Journal of Personality Disorders*, 29(4), 503–525. <https://doi.org/10.1521/pedi.2015.29.4.503>
- Wright, A. G., Hopwood, C. J., Skodol, A. E., & Morey, L. C. (2016). Longitudinal validation of general and specific structural features of personality pathology. *Journal of Abnormal Psychology*, 125(8), 1120–1134. <https://doi.org/10.1037/abn0000165>
- Zanarini, M. C., Frankenburg, F. R., Hennen, J., Reich, D. B., & Silk, K. R. (2005). The McLean study of adult development (MSAD): Overview and implications of the first six years of prospective follow-up. *Journal*

- of *Personality Disorders*, 19(5), 505–523. <https://doi.org/10.1521/pedi.2005.19.5.505>
- Zanarini, M. C., Frankenburg, F. R., Reich, D. B., Conkey, L. C., & Fitzmaurice, G. M. (2015). Treatment rates for patients with borderline personality disorder and other personality disorders: A 16-year study. *Psychiatric Services*, 66(1), 15–20. <https://doi.org/10.1176/appi.ps.201400055>
- Zanarini, M. C., Frankenburg, F. R., Reich, D. B., & Fitzmaurice, G. M. (2012). Attainment and stability, of sustained symptomatic remission and recovery among patients with borderline personality disorder and axis II comparison subjects: A 16-year prospective follow-up study. *American Journal of Psychiatry*, 169(5), 476–483. <https://doi.org/10.1176/appi.ajp.2011.11101550>
- Zanarini, M. C., Frankenburg, F. R., Reich, D. B., & Fitzmaurice, G. M. (2016). Fluidity of the subsyndromal phenomenology of borderline personality disorder over 16 years of prospective follow-up. *American Journal of Psychiatry*, 173(7), 688–694. <https://doi.org/10.1176/appi.ajp.2015.15081045>
- Zanarini, M. C., Temes, C. M., Frankenburg, F. R., Reich, D. B., & Fitzmaurice, G. M. (2018). Description and prediction of time-to-attainment of excellent recovery for borderline patients followed prospectively for 20 years. *Psychiatry Research*, 262, 40–45. <https://doi.org/10.1016/j.psychres.2018.01.034>
- Zimmermann, J., Kerber, A., Rek, K., Hopwood, C. J., & Krueger, R. F. (2019). A brief but comprehensive review of research on the alternative DSM-5 model for personality disorders. *Current Psychiatry Reports*, 21(9), 92. <https://doi.org/10.1007/s11920-019-1079-z>

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