Neurophysiological dynamics for psychological resilience: A view from the temporal axis

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ARTICLE INFO

Keywords:
- Stress
- Resilience
- Multi-temporal scale
- Rodents
- Humans
- Simultaneous MRI-EEG

ABSTRACT

When an individual is faced with adversity, the brain and body work cooperatively to adapt to it. This adaptive process is termed psychological resilience, and recent studies have identified several neurophysiological factors (“neurophysiological resilience”), such as monoamines, oscillatory brain activity, hemodynamics, autonomic activity, stress hormones, and immune systems. Each factor is activated in an interactive manner during specific time windows after exposure to stress. Thus, the differences in psychological resilience levels among individuals can be characterized by differences in the temporal dynamics of neurophysiological resilience. In this review, after briefly introducing the frequently used approaches in this research field and the well-known factors of neurophysiological resilience, we summarize the temporal dynamics of neurophysiological resilience. This viewpoint clarifies an important time window, the more-than-one-hour scale, but the neurophysiological dynamics during this window remain elusive. To address this issue, we propose exploring brain-wide oscillatory activities using concurrent functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG) techniques.

1. Introduction

1.1. Definition of psychological resilience

From daily rush-hour trains to a large earthquake, psychological and physical stressors require us to adapt to the environment. Failure to handle stressful situations can lead to psychiatric illnesses, such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). The ability to handle these stressors varies among individuals, and this is referred to as “psychological resilience,” which is usually assessed by the diagnosis of medical doctors/counselors or self-reported questionnaires. Although the definition of psychological resilience is partially different across researchers (Fletcher and Sarkar, 2013), in this paper, we follow the simple definition of psychological resilience by Feder et al. (Feder et al., 2009), which defined it as “a person’s ability to adapt successfully to acute stress, trauma, or more chronic forms of adversity.” This definition includes two essential components, ‘adversity’ and ‘positive adaptation’ (Fletcher and Sarkar, 2013).

To uncover the underlying neurophysiological factors of psychological resilience, we hereafter define them as “neurophysiological resilience.” It is important to capture the temporal adaptation dynamics of various biological signals driven by stressful events in resilient (RES) and susceptible (SUS) individuals. The dynamics can be observed as (1) neurophysiological representations prior to exposure to stress as a risk factor for future depression (stress vulnerability), (2) individual reaction variability to the faced stress, and (3) behavioral changes after the development of depressive symptoms (stress susceptibility). To the best of our knowledge, this is the first study to review recent findings of psychological resilience related to the temporal dynamics of biological signals.

1.2. Experimental approaches to investigate psychological resilience

The neurophysiological basis of psychological resilience has been intensively studied over the past two decades. Researchers have constructed several systematic approaches to investigate differences in individual sensitivity to stressors in both rodents (Table 1) and humans (Table 2). Rodent studies mainly aim to create animal models of MDD (Table 1). Recently, an increasing number of studies have focused on social stress via a frequently used protocol, the chronic social defeat...
neurophysiological factors in MDD and PTSD across species (see Cathomas et al., 2013). Psychological resilience. We focused on the resilience-related physiological responses and behavior (e.g., weight loss, anhedonia, and motor components). Chronic variable stress (cVS) (MDD model) A rodent experiences multiple unpredictable mild stress for several weeks. Stressors often include foot-shocks, tail-suspension, forced-swim, restraints, and sometimes social defeats. This method has an advantage as the rodent cannot predict and habituate to the stressors.

Chronic social defeat stress (cSDS) (MDD model) This method is developed to induce depression driven by social contexts. A rodent (C57BL/6.J mouse) is placed in the home cage of an aggressive larger animal (CD1 mouse) for 5–10 minutes. Subsequently, the rodent is placed on one side of the cage physically separated with a perforated divider for 24 h. The subject rodent is placed into novel CD1’s home cage every day and experiences defeats. This procedure usually continues for 10 days.

Predator scent stress (PSS) (PTSD model) Freezing responses are induced by the exposure of cat or fox litter odor to rats. This stressor may be related to PTSD because a single exposure causes long-term depressive symptoms in rats.

| Protocol                        | Features                                                                 | Selected references                                                                 |
|---------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Chronic restraint stress (cRS)  | A rodent is put in a small hemicylindrical plastic tube for several minutes per day, for several weeks. This stress induction strategy has ultimately no social and motor components. | Bauer et al., 2001; Kim et al., 2013; Hodes et al., 2014; Tye et al., 2013 |
| (MDD model)                     |                                                                           |                                                                                     |
| Chronic variable stress (cVS)   | A rodent experiences multiple unpredictable mild stress for several weeks. Stressors often include foot-shocks, tail-suspension, forced-swim, restraints, and sometimes social defeats. This method has an advantage as the rodent cannot predict and habituate to the stressors. | Golden et al., 2011; Hodes et al., 2014; Krishnan et al., 2007; Warren et al., 2013 |
| (MDD model)                     |                                                                           |                                                                                     |
| Chronic social defeat stress    | This method is developed to induce depression driven by social contexts. A rodent (C57BL/6.J mouse) is placed in the home cage of an aggressive larger animal (CD1 mouse) for 5–10 minutes. Subsequently, the rodent is placed on one side of the cage physically separated with a perforated divider for 24 h. The subject rodent is placed into novel CD1’s home cage every day and experiences defeats. This procedure usually continues for 10 days. | Berton et al., 2006; Golden et al., 2011; Hodes et al., 2014; Krishnan et al., 2007; Warren et al., 2013 |
| (cSDS)                          |                                                                           |                                                                                     |
| Predator scent stress (PSS)     | Freezing responses are induced by the exposure of cat or fox litter odor to rats. This stressor may be related to PTSD because a single exposure causes long-term depressive symptoms in rats. | Cohen et al., 2006, 2008; Doppe et al., 2019 |
| (PTSD model)                    |                                                                           |                                                                                     |

Stress (cSDS: Golden et al., 2011). Notably, rodents that have experienced cSDS protocols have high constructive, face, and predictive validities as a model of MDD in humans (Golden et al., 2011). Regarding constructive validity, the cSDS protocol corresponds to social defeats, such as accepting a low social rank in humans (Huhman, 2006). Regarding face validity, this protocol develops strong depressive physiological responses and behavior (e.g., weight loss, anhedonia, and circadian rhythm changes) analogous to MDD symptoms (Huhman, 2006; Krishnan et al., 2007; Wells et al., 2017). Regarding predictive validity, human patients with MDD gradually but not acutely recover pro-social behaviors by antidepressant drugs. Such gradual recovery is observed in cSDS-experienced animals (Berton et al., 2006). While MDD models have been well-established, researchers are still developing a PTSD model in rodents to investigate the individual neurophysiological differences in psychological resilience against traumatic experiences (Verbitsky et al., 2020; Yehuda and LeDoux, 2007).

In contrast to the rodent models, the experimental scheme in most human studies is any one of (1) a comparison between clinical patients (MDD or PTSD) and non-patients, (2) a cohort survey of individuals in highly stressful environments, such as the army, and (3) personality traits related to stress resilience in healthy populations (Table 2). Using these schemes, researchers are trying to establish better behavioral and neurophysiological markers to evaluate individual differences in psychological resilience (Gruescow et al., 2021; Kaldewaij et al., 2021; Walker et al., 2017).

2. Neurophysiology of psychological resilience

In this chapter, we briefly introduce the neurophysiological factors of psychological resilience. We focused on the resilience-related physiological factors in MDD and PTSD across species (see Cathomas et al., 2019; Furuyashiki and Kitaoka, 2019 for detailed reviews on MDD models in rodents). This comparison revealed that the neurophysiological mechanisms of the resilience between PTSD and MDD are different, with some overlap in humans. However, this neurophysiological difference has not been sufficiently verified in rodents because of the lack of established protocols that mimic individual differences in the responses to traumatic experiences (Verbitsky et al., 2020; Yehuda and LeDoux, 2007).

2.1. Role of monoamines in the central nervous system

Accumulated findings indicate that monoamines such as dopamine (DA), serotonin (5HT), and noradrenaline (NA) are major neurophysiological factors that play a role in psychological resilience (Fig. 1, red circles). The following human research suggests that decreases and increases of DA and NA differ between MDD and PTSD patients.

2.1.1. Dopamine

Several studies in rodents have reported that the firing of DA neurons in the ventral tegmental area (VTA) increases in SUS but not RES mice after cSDS exposure (Cao et al., 2010; Chaudhury et al., 2013; Krishnan et al., 2007). Human studies with patients with PTSD or MDD partially support these findings but provide more complex insights. DA transporter (DAT) density, an index of DA abundance, increases in the

| Table 2 | Experimental approaches for human resilience studies. |
|---------|-------------------------------------------------------|
| Approach                                      | Features                                                                 | Selected references                                                                 |
| Evaluation of PTSD or MDD patients            | One of the most fundamental approaches is to compare individuals who showed PTSD or MDD symptoms and those who did not show these symptoms in spite of facing similar traumatic experiences or being under stressful environments. The advantage of this approach is that researchers can discriminate resilient (RES) and susceptible (SUS) individuals using robust and stable criteria, whereas the disadvantage is that it is impossible to compare between pre-trauma and post-trauma data within an individual. | Drysdale et al., 2017; Harnett et al., 2021; Mary et al., 2020 |
| Longitudinal study under highly stressful environments | This approach targets newcomers in stressful workplaces, such as the army, police, or intensive care unit. The advantages of this method are that it is possible to compare pre-stressed data with post-stressed data within an individual and that it allows predictive analyses; however, it takes time and effort for data collection. | Admon et al., 2009; Gruescow et al., 2021; Kaldewaij et al., 2021 |
| Questionnaire survey                          | This approach enables researchers to understand individual differences in psychological resilience among healthy populations, as well as psychiatric patients. This approach possibly has the highest reliability and reproducibility as long as people honestly answer the questions. The advantages of this approach is its simplicity and ease of collecting big samples; however, this approach itself cannot evaluate the temporal dynamics of neurophysiological resilience. | Connor and Davidson, 2003; Friborg et al., 2005; Kong et al., 2015; Smith et al., 2008 |
| Behavioral indicators                         | Despite various attempts, researchers have not successfully invented behavioral paradigms that predict individual resilience. Recent approaches are related to emotional conflict regulations, such as emotional Stroop task or emotional approach-avoidance task. | Gruescow et al., 2021; Kaldewaij et al., 2021; Keynan et al., 2019; Mary et al., 2020 |
striatum of patients with PTSD (Hoexter et al., 2012). In contrast, DAT density decreases in patients with MDD in the striatum and VTA (Meyer et al., 2001; Pizzagalli et al., 2019). The effectiveness of monoamines is also influenced by the projected regions and their receptor types. DA receptor type 1 (D1R) decreases in SUS mice with cSDS in the nucleus accumbens (NAC) (Francis et al., 2015) and medial prefrontal cortex (MPFC) (Shinohara et al., 2016), but DA receptor type 2 (D2R) increases in RES mice in the MPFC (Shinohara et al., 2018).

2.1.2. Serotonin

As shown by the fact that serotonin reuptake inhibitors are a major treatment option for MDD, the dysfunction of 5HT transmission is strongly associated with stress susceptibility. A reduction in 5HT levels in the dorsal raphe nucleus (DRN) has been observed in both rodents (Challis et al., 2013; Zou et al., 2020) and humans (Stockmeier, 2003; Sullivan et al., 2013) studies. For example, in humans, 5HT receptor type 1A (5HT1A), an auto-receptor that suppresses 5HT release, was highly expressed in DRN in patients with MDD (Stockmeier, 2003 for more details). A similar 5HT1A increase in the DRN was also reported in patients with PTSD (Sullivan et al., 2013 for more details).

2.1.3. Noradrenaline

Both rodent and human studies have shown that NA derived from the locus coeruleus (LC) is also related to psychological resilience. Isingrini et al. found that the NA levels around the VTA increased only in RES mice after cSDS and that these increases resulted in the suppression of DA neuron firing (Isingrini et al., 2016). Consistently, in patients with MDD, postmortem analyses revealed decreased expression levels of NA transporters in the LC (Klimek et al., 1997). Patients with MDD showed that the expression of NA α2 adrenergic receptor (α2AR), which suppresses NA release, increases in the LC (Ordway et al., 2003). However, in patients with PTSD, chronic NA density increases in the cerebrospinal fluid (Geracioti et al., 2001), and medical treatments with NA inhibitors are effective in reducing hyperactivity symptoms (Strawn and Geracioti, 2008). These studies suggest that, compared with healthy individuals, patients with MDD have lower levels of NA in the LC, whereas the opposite is true for those with PTSD.

2.2. Brain rhythms

The relationship between oscillatory neural activity (Buzsáki et al., 2012) and stressors has been investigated in rodent and human studies. In summary, the current state of knowledge does not provide an integrated understanding of the brain rhythms underlying psychological resilience, but oscillatory activity around beta frequency bands would play a key role (Fig. 1, sky blue circles).

Hultman et al. reported that stress vulnerability (future depression risk) in mice is represented in beta synchronization across the MPFC/NAC–amygdala (AMY)/VTA–ventral hippocampus (HIP) pathway, while stress susceptibility (depression phenotype) is represented in both delta/beta synchronization across the NAC–ventral HIP/VTA pathway and in delta synchronization across the MPFC/NAC–AMY pathway (Hultman et al., 2018). A human magnetoencephalography (MEG) study also reported patients with MDD have increased beta synchronization between the insula and AMY (Nugent et al., 2015). Another MEG study, including patients with PTSD, showed that the individual psychological resilience measured by CD-RISC (Connor-Davidson resilience scale: Connor and Davidson, 2003) was negatively correlated with beta synchronization of the MPFC with the dorsal anterior cingulate (ACC), insula, and precuneus (Brunetti et al., 2017). However, the roles of oscillations in other frequency bands are still under debate (e.g., Dunkley et al., 2014; Jiang et al., 2019).

2.3. Hemodynamics

Functional magnetic resonance imaging (fMRI) is frequently used to identify psychological resilience-related brain regions in humans. Interestingly, some identified regions, such as the insula, ventromedial PFC (VMPFC), and lateral PFC (LPFC), have not been well studied in rodents (Fig. 1, dark green circles).

2.3.1. Insula

An early study reported that the hemodynamics in the anterior insula increase in low-resilient participants when presented with visually stressful stimuli (unpleasant pictures) (Waugh et al., 2008). Resting-state fMRI (rsfMRI) studies also reported that resilience questionnaire scores are negatively correlated with spontaneous activity in...
the insula and dorsal ACC (Kong et al., 2015).

2.3.2. VMPFC

Sinha et al. reported that VMPFC activity gradually increased during the six-minute stress exposure (Sinha et al., 2016). This increase was positively correlated with the individual active coping level, which is one of the traits of psychological resilience.

2.3.3. LPFC

This region contributes to the suppression of memory and emotion regulation. Mary et al. identified that the suppression signal from the right anterior dorsolateral PFC (DLPFC) to HIP and precuneus decreases in patients with PTSD during the intentional memory suppression task (Mary et al., 2020). Kaldewaij et al. reported that left ventrolateral PFC (VLPFC) activity during the emotional conflict regulation task buffers developments of PTSD against traumatic experiences among police rookies (Kaldewaij et al., 2021).

Interestingly, abnormal resting-state functional connectivity across the insula, VMPFC, VLPFC, and multiple subcortex areas was also detected as a biomarker of MDD (Drysdale et al., 2017). Whereas in patients with PTSD, abnormalities in subgenual ACC, parahippocampal cortex (PHC), and AMY were detected (Koch et al., 2016).

2.4. Peripheral nervous system

The central and peripheral nervous systems influence each other, resulting in autonomic, hormonal, and immune reactions to adapt to environmental stress. The dysregulation of this brain-body loop may cause stress vulnerability and susceptibility. We herein list several markers of the peripheral nervous system for resilience (orange circles and arrows in Fig. 1).

2.4.1. Heart

The cardiac rhythm is controlled by the sympathetic-adrenal-medullary (SAM) axis (Schommer et al., 2003). Several human studies have reported greater heart rate changes to acute stressors and higher heart rate variability (HRV) at rest in high-resilient individuals (Là et al., 2016; Souza et al., 2007, 2013). Similarly, one rat study reported lower resting heart rates and higher resting HRV in RES rats after cSDS (Moraïs-Silva et al., 2019).

2.4.2. Pupil

The SAM axis also affects the iris muscles, which control the size of the pupil. Pupil size is highly correlated with firing rates in the LC (Joshi et al., 2016). Gruesserow et al. attempted to predict the future anxiety and depression levels of new workers in the ICU and found that pupil size or LC activity alone did not predict future anxiety levels, but their combination did (Gruesserow et al., 2021).

2.4.3. Glucocorticoid (CORT)

Cortisol in humans or corticosterone in rodents is a stress hormone that regulates the activity of the hypothalamic-pituitary-adrenal (HPA) axis (Sapolsky et al., 2000). Some studies have reported that the CORT response to stress was more robust in RES individuals than in SUS individuals in both rodents and humans (Galatzer-Levy et al., 2014; Kim et al., 2013). Our unpublished data in humans also showed that individual CORT levels in response to acute stress were positively correlated with CD-RISC scores (but see also García-León et al., 2019).

2.4.4. Immune response

Chronic increases in cytokine concentrations have been observed in patients with MDD (Dowlati et al., 2010; Ménard et al., 2017) and those with PTSD (Baker et al., 2012; Gill et al., 2009). Hodes et al. revealed that higher peripheral circulating leukocyte and interleukin (IL)-6 levels prior to cSDS exposure predict future depression symptoms in mice, indicating stress vulnerability (Hodes et al., 2014). Their group also reported that peripheral IL-6 could promote depression by infiltrating the blood-brain-barrier (BBB) around the NAC (Menard et al., 2017; Dudek et al., 2020). Microglia also influence resilience. Nie et al. reported increased IL-1α and tumor necrosis factor (TNF)-α release from the microglia in the MPFC in SUS mice’s brain after cSDS (Nie et al., 2018).

3. Temporal dynamics of neurophysiological resilience

As introduced in Chapter 1, psychological resilience is a process of adaptation to a given environmental stress. This feature in psychological resilience raises several possibilities of how neurophysiological resilience is underpinned in temporal dynamics. The first possibility is that each resilience-related neurophysiological factor differs in amplitude between RES and SUS individuals. The second possibility is that each factor differs over time. Although the actual temporal dynamics of each factor can be represented as a combination of these two possibilities, to the best of our knowledge, there is no systematic understanding of the temporal dynamics of physiological resilience introduced in Chapter 2. A major reason for this was the limited number of sampling points in each study. In this chapter, we systematically review the findings of the temporal dynamics of physiological resilience by comparing them across studies (Fig. 2).

3.1. Stress vulnerability as a risk factor for future depression

Growing evidence shows that future risks of depression (stress vulnerability) are related to several neural and physiological factors (Naïve column in Fig. 2). For example, Hultman et al. identified that, with the ten-day cSDS paradigm, beta-band activity synchronization across the MPFC/NAC-AMY/VTA–ventral HIP pathway increased in future SUS individuals (Hultman et al., 2018). Human longitudinal studies also revealed that individual AMY activity predicted PTSD symptoms 18 months later (Admon et al., 2009). Moreover, both higher brain activity in the LC and higher functional connectivity between the LC and AMY predict anxiety and depression levels several (3 and 6) months later (Gruesserow et al., 2021). Both longitudinal studies indicate the involvement of the AMY in stress vulnerability. Another longitudinal study indicated that greater activation in the left VLPFC before trauma could buffer the future development of PTSD symptoms (Kaldewaij et al., 2021). These findings suggest the involvement of the neural mechanisms of emotion regulation as suppressive control of AMY activity through the PFC (Ochsner and Gross, 2008; Watanabe et al., 2019a, 2019b). Indeed, both MDD and PTSD symptoms are characterized by difficulties in regulating negative emotions (Ehring and Quack, 2010; Joormann and Stanton, 2016).

Stress vulnerability also affects the peripheral physiological systems. An important finding is that the circulating leukocyte concentration and IL-6 releasing ability of leukocytes are significantly higher in future SUS mice compared to RES mice before cSDS (Hodes et al., 2014). Studies on human patients support the finding that the genetic variants controlling IL-6 expression accelerate depressive symptoms and are increased in patients with MDD (Tarter et al., 2015; Udina et al., 2013).

3.2. Minutes-to-hour scale factors for stress susceptibility and resilience

Immediately after exposure to the stressor, multiple peripheral physiological systems are quickly driven to adapt to the environment (Minute and Hour columns in Fig. 2). The first response is driven by catecholamines (adrenaline and noradrenaline). It is activated within a minute and subsequently decreases to baseline levels within 10 min (Sapolsky et al., 2000). Cardiac dynamics are affected by this system. Indeed, the increase in heart rate driven by acute stress was larger in high-resilient human individuals than in low-resilient individuals (Lü et al., 2016; Souza et al., 2007, 2013). Although their results also imply that the heart rate decreases rapidly after stress, they have not tested this...
The second response is glucocorticoids (CORT), which are activated several minutes after exposure to stress, peak at 25 min, and return to baseline levels approximately one hour after exposure (Goodman et al., 2017; Schwabe and Schachinger, 2018). Some studies have reported that the peripheral CORT response to stress is more robust in high-resilient than low-resilient individuals among both rodents and humans (Galatzer-Levy et al., 2014; Kim et al., 2013). Furthermore, CORT still works in the brain for more than two hours and modulates neural dynamics in several regions, such as the HIP, AMY, and hypothalamus (Joels et al., 2007). This slow modulation regulates neuron firing in each brain region (Karst et al., 2005, 2010) and potentially affects various cognitive functions, such as memory consolidation (Schwabe, 2017). The dysfunction of this modulation may reduce the capacity to adapt to stressful environments (Joels, 2018). Although some studies quantified the CORT responses every 20 min (e.g., Galatzer-Levy et al., 2014; Kim et al., 2013), more detailed observations focusing on both amplitude and timing with better temporal resolutions are warranted to understand the temporal dynamics of individual resilience.

The third response is the immune system. The concentrations of different cytokines, such as IL-1β, IL-6, and TNF-α, are increased in the body and brain. Although these increases occurred immediately after exposure to stress (Sapolsky et al., 2000), some cytokine responses persisted, peaked at 40-90 min, and possibly continued for more than one day in humans (Marsland et al., 2017). While the relationship between psychological resilience and immune responses has not been systematically investigated in humans, one study in mice under the cSDS paradigm reported that IL-6 strongly increased within 20 min after an acute stressor in SUS mice compared with RES mice (Hodes et al., 2014). IL-6 also directly affects the brain dynamics around the NAC through infiltration from the blood-brain-barrier (BBB: Menard et al., 2017). Additional studies are required to confirm the role of immune reactions in individual stress resilience, especially in humans.

It is also known that monoamines (DA, SHT, and NA) are strongly elevated immediately after acute stress (Sapolsky et al., 2000), some cytokine responses persisted, peaked at 40–90 min, and possibly continued for more than one day in humans (Marsland et al., 2017). While the relationship between psychological resilience and immune responses has not been systematically investigated in humans, one study in mice under the cSDS paradigm reported that IL-6 strongly increased within 20 min after an acute stressor in SUS mice compared with RES mice (Hodes et al., 2014). IL-6 also directly affects the brain dynamics around the NAC through infiltration from the blood-brain-barrier (BBB: Menard et al., 2017). Additional studies are required to confirm the role of immune reactions in individual stress resilience, especially in humans.
3.3. Days-to-month scale factors for stress susceptibility and resilience

Ten-day scale factors have been well investigated by the cSDS paradigm in rodents. One noticeable factor during this time window was changes in balance among monoamines (Fig. 2, red circles between Day and Month columns). After ten-day cSDS, SUS mice showed an increase in DA in the VTA (Cao et al., 2010; Krishnan et al., 2007) and a decrease in 5HT in the DRN (Challis et al., 2013; Zou et al., 2020) compared with RES mice or non-stressed controls. In contrast, RES mice after cSDS exposure showed an increase in NA release from the LC to the VTA compared with SUS mice with non-stressed controls (Isingrini et al., 2016). These monoamine dynamics can affect the ensemble neural activity in the brain. In fact, after ten-day cSDS exposure, the delta and beta synchronization across the NAC, HIP, and VTA, as well as the delta synchronization across the MPFC, NAC, and AMY increased in SUS mice compared with those in RES mice (Hultman et al., 2018) (Fig. 2, light blue circles). Neurogenesis during this time window may also be essential to prevent the development of depression. Anacker et al. showed that enhancing newborn granule cells in the ventral dentate gyrus prevented depression after ten-day cSDS exposure (Anacker et al., 2018), while after four weeks from the end of cSDS, the survival rate of newborn granule cells was higher in SUS mice than in RES mice (Lagace et al., 2010) (Fig. 2, purple circles). Ten-day scale physiological changes in RES individuals showed lower resting heart rates with higher resting HRV and sustained increases in resting CORT levels (10 days: Morais-Silva et al., 2019; 38 days: Krishnan et al., 2007).

Almost all cSDS studies investigating days-to-month scale factors compared the pre-cSDS baseline levels of neurophysiological resilience with those at the endpoint of cSDS. Thus, the day-by-day temporal dynamics of these factors during cSDS remain unclear. Future studies are required to unravel how the balance of monoamines or neurogenesis gradually changes during the ten-day chronic stressor experience.

3.4. Months-to-years scale factors for stress susceptibility and resilience

Longer temporal dynamics from months to years have mainly been investigated in human studies using MRI or MEG (Fig. 2, dark green and light green circles between Month and More than a year columns). Although there is still no integrated view of the findings, it is likely that the default mode network (DMN) and salience network (SaN) are involved in the temporal dynamics of this timescale (Menon, 2011; van Oort et al., 2017). For example, after 18 months of engagement in the army, increases in PTSD symptoms were positively correlated with AMY (in SaN) and HIP (in DMN) activation and negatively correlated with HIP-VMPFC (within DMN) functional coupling (Admon et al., 2009). Another study also reported that, after 16 months of work as police officers, increases in traumatic episodes were associated with decreased ACC and MPFC (in DMN) activation and increased AMY (in SaN) activation (Kalidewaj et al., 2021). A meta-analysis of rsfMRI data of patients with PTSD confirmed these observations and the involvement of the subgenual ACC and PHC (in DMN) and AMY (in SaN), as compared with healthy controls (Koch et al., 2016). Moreover, the CD-RISC score, including those from patients with PTSD, was negatively correlated with MEG beta synchronization in the precuneus in DMN and dorsal ACC and insula in SaN (Brunetti et al., 2017). The involvement of PCC, PHC, and VMPC (in DMN), insula, and AMY (in SaN) has also been demonstrated in patients with MDD along with rsfMRI (Drysdale et al., 2017). Partially consistent with this finding in patients with MDD, another MEG study reported an increase in insula and AMY (within SaN) synchronization in the beta-band in patients with MDD (Nugent et al., 2015). Although it is still challenging to reach consistent conclusions, briefly, decreased DMN relative to increased SaN might enhance stress susceptibility in the months-to-years scale.

3.5. The unexplored time window (more-than-one-hour scale)

As described above, we have re-organized previous findings related to neurophysiological resilience based on the temporal axis (Fig. 2). This figure notices the important fact that knowledge on the more-than-one-hour scale remains elusive. Although the glucocorticoid, immune, and dopaminergic systems activated by stress exposure are still active during this time window, the relationship between these systems and individual differences of psychological resilience has not been clarified. Other reviews have also predicted the importance of this time window from the viewpoint of slow CORT dynamics (Hermans et al., 2014; Joëls, 2018).

As shown above, each resilience-related factor is activated in different time windows, thus supporting a “difference-in-time” possibility. However, it is notable that these factors do not work independently. Instead, they are reciprocally affected in a complex manner. For example, catecholamines, CORT, and immune reactions mutually influence each other (Marsland et al., 2017; Sapolsky et al., 2000). In addition, DA, 5HT, and NA interact in the brain (Isingrini et al., 2016; Zou et al., 2020). Therefore, it is not sufficient to track the temporal dynamics of a single factor to understand the temporal resilience dynamics. Rather, it is necessary to clarify the interaction between factors in the time domain to fully understand resilience dynamics.

4. Future insights for human resilience studies

We have discussed the importance of tracking the temporal dynamics of neurophysiological factors to fully understand psychological resilience. However, most previous studies have not addressed this matter. For example, previous human resting-state neuroimaging studies in which questionnaires were used to assess psychological resilience did not apply any stress perturbations during experiments. Such studies may be insufficient to capture resilience-related neural activity because they did not study temporal dynamics after actual stress exposure.

Although the resilience-related more-than-one-hour dynamics after acute stress have not been assessed in previous studies, some rsfMRI studies have suggested that acute stress drives large-scale functional connectivity (Maron-Katz et al., 2016; Zhang et al., 2019). Moreover, stress-driven connectivity did not return to pre-stress levels within an hour but continuously changed following one hour (Quaedflieg et al., 2015; Vaisvler et al., 2013). Thus, a new experimental paradigm, which investigates whether the temporal dynamics of acute stress-induced brain-wide functional connectivity is different between high- and low-resilient participants, is warranted to elucidate the neurophysiological underpinnings of psychological resilience.

Additionally, a study comprising MDD model mice by Dzirasa laboratory revealed the importance of the brain’s rhythms on stress resilience (Hultman et al., 2016, 2018; Kumar et al., 2014) and suggested that depression-like behavior is characterized by differences in temporal oscillatory patterns of neural activity within the functional network. Although similar neural implementation may also exist in the human brain, conventional measurements by using neither fMRI nor electroencephalography (EEG) (or MEG) alone can detect similar dynamics because of low temporal or low spatial resolutions. To overcome these limitations, several techniques, such as “simultaneous fMRI/EEG recording” and “fMRI/EEG fusion,” are gaining attention (Huster et al., 2012; Philiaastides et al., 2021). These experimental approaches allow us to investigate neural oscillatory synchronization at the whole-brain scale with sufficient spatiotemporal resolution. Additionally, considering that both EEG and LFP originate from extracellular biophysical processes (Buzsáki et al., 2012), EEG findings can be directly compared with those of previous LFP studies in rodents. Moreover, these techniques are suitable for examining the human-specific characteristics of resilience. Human psychological resilience is considered to include several high cognitive functions, such as positive reappraisal of the stress event, persistence/tenacity, and a sense of self-efficacy (Carlson et al., 2012; Connor and Davidson, 2003), which are quite difficult to...
investigate in rodents.

We herein propose the use of combined fMRI/EEG measurements to investigate the neurophysiological underpinning of psychological resilience. With this data collection technique, we can approach the resilience dynamics during the unexplored more-than-one-hour time window. The findings obtained in this window will help fill the gaps of knowledge between rodent and human studies and provide new insights into both fields.

Funding sources

This work was supported by Grant-in-Aid for Scientific Research on Innovative Areas, “Constructive understanding of multi-scale dynamism of neuropsychiatric disorders.” for Japan Society for the Promotion of Science Receiver: Noriya Watanabe [grant number: 21H00211], Grant-in-Aid for Scientific Research (C) for Japan Society for the Promotion of Science Receiver: Noriya Watanabe [grant number: 21K07262], Research Grant for Public Health Science (2020–2021) Public Health Research Foundation Receiver: Noriya Watanabe, Grant-in-Aid for Scientific Research (A), Japan Society for the Promotion of Science Receiver: Masaki Takeda [grant number: 20H00521], Grant-in-Aid for Challenging Research (Exploratory) for Japan Society for the Promotion of Science [grant number: 21K18267], and Research Grant for Life Innovative Areas, [grant number: 21K18267].

Acknowledgments

We are grateful to the members of the Research Center for Brain Communication for their helpful discussions. We also thank Wanquin Ma (M.S.) for providing illustrations for the figures.

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