Functional neuroimaging of resilience to trauma: convergent evidence and challenges for future research

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Conflict of Interest

Dr Feder is named co-inventor on a patent application in the US, and several issued patents outside the US filed by the Icahn School of Medicine at Mount Sinai related to the use of ketamine for the treatment of PTSD. This intellectual property has not been licensed. Dr. Perez-Rodriguez has received research grant funding from Neurocrine Biosciences, Inc, Millennium Pharmaceuticals, Takeda, and AI Cure. She is a consultant for Neurocrine Biosciences, Inc. and Alkermes. She has served on an advisory board for Neurocrine Biosciences Inc. Drs. Norbury and Seeley have no relevant conflicts of interest to declare.

Abstract

Resilience is broadly defined as the ability to adapt successfully following stressful life events. Here, we review functional MRI studies that investigated key psychological factors that have been consistently linked to resilience to severe adversity and trauma exposure. These domains include emotion regulation (including cognitive reappraisal), reward responsivity, and cognitive control. Further, we briefly review functional imaging evidence related to emerging areas of study that may potentially facilitate resilience: namely social cognition, active coping, and successful fear extinction. Finally, we also touch upon ongoing issues in neuroimaging study design that will need to be addressed to enable us to harness insight from such studies to improve treatments for – or, ideally, guard against the development of – debilitating post-traumatic stress syndromes.

Introduction

Trauma exposure does not invariably result in adverse psychiatric outcomes. Epidemiological estimates for clinically significant posttraumatic stress symptoms range from 5-22% after exposure to natural disasters, severe injuries, or assault, to 46-65% after sexual violence (Shalev et al., 2017; Bromet et al., 2018; Watson, 2019). Similarly, 10-25% of those exposed to significant childhood maltreatment show better-than-expected functioning (Walsh et al., 2010).

Broadly, resilience is defined as successful adaptation following trauma, adversity, or stressful life events (Feder et al., 2019; Kalisch et al., 2017). Beyond vulnerability or risk for psychiatric disorders, resilience requires having experienced adversity or trauma (Yehuda & Flory, 2007) (**Box 1: Quantifying trauma**). Resilience research aims to identify mechanisms to improve prevention and treatment of posttraumatic stress and trauma-related disorders. In neuroimaging studies, resilience is typically defined as absence of psychopathology despite exposure to adversity or trauma, but in some studies *alternatively* as high scores on measures of trait resilience, e.g., the Connor-Davidson Resilience Scale (CD-RISC) (Connor & Davidson, 2003a) (**Box 2: Quantifying resilience**), notwithstanding significant variation in its operationalization and measurement (Denckla et al., 2020; Feder et al., 2019; Kalisch et al., 2017; Scheffer et al., 2018; Southwick et al., 2022).

Resilience-related psychological factors

Despite these definitional differences,, decades of research have identified psychological factors that promote resilience to trauma and severe adversity. Some widely replicated and potentially modifiable factors include effective emotion regulation, positive emotionality, cognitive flexibility and control, facing fears and active coping, and ability to harness social support (reviewed in (Seeley et al., in press; Southwick et al., 2023)). Effective emotion regulation is associated with higher executive control and supports adaptive coping. Facing fears, likely facilitated by successful extinction of conditioned fear coupled with cognitive flexibility, allows a person to critically appraise threats and actively cope by tackling stressors or problem solving. Positive emotions and related reward system function also promote resilience

by supporting positive reframing as well as ability to harness social support, which in turn serves as a safety net and facilitates stress recovery. The ability to harness social support draws in part on competent social cognition – the ability to accurately 'read' and respond to the intentions of others – making social cognition a potential factor in resilience.

The current review: neural correlates of psychological factors in resilience

Building on work identifying core psychological factors associated with resilience (Feder et al., 2019; Seeley et al., In press; Southwick et al., 2022) and previous neuroimaging resilience reviews in adults and/or youth (Méndez Leal & Silvers, 2021; Moreno-López et al., 2020; van der Werff et al., 2013), our narrative review covers human fMRI studies of neural circuitry underlying psychological factors associated with resilience to trauma and severe adversity. We organize fMRI studies around *emotion regulation*, *reward responsivity*, and *cognitive control*, e.g., (Dennison et al., 2016; Holz et al., 2020; Kaldewaij et al., 2021; van der Werff et al., 2013). As described above, *active coping*, *facing fears* (and related fear extinction) (Careaga et al., 2016), and the ability to harness *social support* (including competent *social cognition*) (Lepore & Kliewer, 2019; Stevens & Jovanovic, 2019) have also been linked to resilience, yet there have been fewer neuroimaging studies focusing on these as resilience-related psychological factors. Here, we include them under emerging areas for future investigation, as they might shed light on additional pathways to resilience and its underlying neural circuitry.

Cross-sectional fMRI studies of resilient individuals typically focus on *(1)* youth and adults who have experienced childhood maltreatment or *(2)* adults with a history of trauma exposure in adulthood such as severe accidents, assaults, or occupation-related incidents (e.g., first-responders, military). In this narrative review, we only discuss cross-sectional studies with a key comparison group of healthy, non-trauma-exposed participants (in addition to resilient and symptomatic groups), allowing researchers to disentangle effects of trauma exposure and psychopathology (see van der Werff et al., 2013). Also included are several studies of neural correlates of high trait resilience.

We focus on literature published after the van der Werff and colleagues' 2013 review. Due to the emergence of recent large cohort studies and improved reporting standards for neuroimaging, this allows us to focus on better powered work. Within each section, we first cover

cross-sectional findings in resilient trauma survivors (children; adults) and high trait resilience (when available). Additionally, we discuss a growing number of longitudinal studies and a handful of available interventional studies that contribute new insights on the neural underpinnings of resilience. Although most studies reviewed here focus on task-based regional brain activity underlying specific resilience-related mechanisms, we also include relevant functional connectivity findings, including from resting state fMRI.

[Box 1 around here]

[Box 2 around here]

Functional neuroimaging of resilience mechanisms

Emotion regulation

Successful emotion regulation is key in resilience (Troy & Mauss, 2011). Resilient individuals downregulate neural responses to stress or threat via medial prefrontal cortex (mPFC) inhibition of emotional reactivity in a network of brain regions, including the amygdala and anterior cingulate cortex (ACC); conversely, absent or low resilience is associated with hyperreactivity to emotional stimuli, both trauma-related and -unrelated (Patel et al., 2012; Whittle et al., 2013). In an earlier review, resilient adults (exposed to trauma in childhood and/or adulthood) showed greater mPFC engagement, including rostral ACC, and lesser activity in the dorsal ACC and amygdala, compared to symptomatic trauma-exposed adults across several studies (van der Werff et al., 2013).

Cross-sectional studies in youth with a history of childhood maltreatment show increased frontolimbic connectivity in resilient youth (Demers et al., 2018; Moreno-López et al., 2020); for example greater down-regulation of amygdala activity during emotion regulation (Schweizer et al., 2016). Higher-trait resilience youth living in adverse environments spent more time than their lower-trait resilience peers in a dynamic resting state functional connectivity pattern of less salience network connectivity with both the central executive and default mode networks. This could suggest lesser influence of emotional reactivity during unconstrained thought (Iadipaolo et al., 2018).

Cross-sectional findings are bolstered by evidence from several recent longitudinal studies of early adversity. Among adopted children who experienced early institutional care, self-reported anxiety at three-year follow-up decreased more in children who showed reduced amygdala responses to images of their adoptive parents (versus strangers) at baseline (Callaghan et al., 2019). Similarly, previously-institutionalized youth showing stronger ventromedial (vm)PFC-hippocampal functional connectivity during an aversive learning task reported lower anxiety at two-year follow-up (Silvers et al., 2016). A longitudinal study of internalizing symptoms in older adolescents and youth with a childhood maltreatment history compared to propensity-matched controls found that greater baseline amygdala threat reactivity predicted later internalizing symptoms – independently of stressful life events and factors such as socioeconomic status, suggesting that lesser limbic reactivity may be a unique predictor of resilience to childhood maltreatment (Gerin et al., 2019).

Cross-sectional findings in adults are similar to those in youth. Healthy adults with a childhood maltreatment history demonstrated greater frontal inhibition of emotional distractors (Demers et al., 2021). In another study of resilient adults with a childhood maltreatment history, blunted amygdala response correlated with higher depression symptoms (Yamamoto et al., 2017). However, in Yamamoto and colleagues' sample of healthy individuals without clinically significant symptoms, it is notable that higher amygdala reactivity was accompanied by a compensatory increase in prefrontal functional connectivity, linked to top-down emotion regulation. Studies of adulthood trauma exposure similarly suggest lesser amygdala reactivity and greater mPFC regulation in resilient adults. Lower baseline amygdala reactivity to fearful faces at 2-3 weeks post-incident was associated with lower self-reported PTSD symptoms at one-year follow-up, in individuals recruited from a hospital emergency department (Stevens et al., 2017). Another study, using Granger causality analysis, revealed more resting state mPFC inhibition of the amygdala in resilient typhoon survivors, compared to both symptomatic survivors and non-trauma-exposed controls (Chen et al., 2018b).

Longitudinal work in adults links pre-exposure neural functioning to later outcomes. In a large prospective sample of trainee police officers, pre-exposure anterior PFC activity during an emotional action control task predicted lower PTSD symptoms at follow-up. Anterior PFC activity moderated the positive relationship between previous trauma load (a risk factor for PTSD) and PTSD symptom levels at follow-up, such that cumulative number of lifetime trauma exposures

was not linked to higher PTSD symptoms in trainees with higher anterior PFC activity (Kaldewaij et al., 2021). In another cohort of police trainees scanned pre- and post-trauma exposure, those with higher post-traumatic intrusion symptoms showed increased salience network resting state connectivity after stress induction (Zhang et al., 2022). Together, these studies provide evidence that prefrontal regulation of limbic reactivity to emotional threat cues may predict resilience to posttraumatic stress and anxiety symptoms. In Kaldewaij et al. (2021), amygdala reactivity appeared to be acquired, rather than a prospective marker of PTSD vulnerability. However, previous longitudinal studies linked stress vulnerability to higher baseline amygdala reactivity (Admon et al., 2009; Swartz et al., 2015). Longitudinal prospective cohort studies, such as the ongoing Advancing Understanding of Recovery After Trauma (AURORA) study (McLean et al., 2020), which follows patients scanned 2-3 weeks after visiting the emergency department post-trauma, hold promise for a more granular understanding of emotional responding in resilience. Notably, there may be multiple pathways to risk/resilience: cross-task cluster analysis in an AURORA cohort, replicated in a different cohort with a wider range of trauma exposures, identified two vulnerability-related "biotypes" characterized by heightened emotional reactivity to threat, but differential reactivity to reward, detailed in a later section (Stevens et al., 2021).

From an interventional perspective, a pilot trial of fMRI-guided real-time neurofeedback training decreased amygdala activation and increased amygdala-vmPFC connectivity in combat veterans, but was not superior to sham in reducing PTSD symptoms (Zotev et al., 2018). However, training a pre-deployment military sample to downregulate EEG-derived amygdala signal successfully decreased amygdala BOLD signal and increased amygdala-mPFC functional connectivity at follow-up (Keynan et al., 2019). Active training improved experimental emotional regulation indices, but had no effect on self-reported anxiety (Keynan et al., 2019). Neurofeedback training represents a step towards developing new interventions for at-risk individuals. However, whether this approach will be effective in preventing or mitigating post-traumatic distress requires further study.

Cognitive reappraisal. Cognitive reappraisal is a deliberate form of emotion regulation shown to buffer risk for adverse outcomes following trauma exposure (Rodman et al., 2019). The ability to re-evaluate the meaning of experiences promotes adaptation after trauma, and

represents a core part of psychological interventions (Hofmann et al., 2013). For example, in an ecological momentary assessment study in individuals remitted from depression, positive appraisal (ability to "*focus on positive meaning*") and feelings of resilience were mutually reinforcing. Positive reappraisal was also associated with lower incidence of residual depressive symptoms (Hoorelbeke et al., 2019). Neuroimaging meta-analyses highlight ventrolateral (vl)PFC and dorsolateral (dl)PFC, dorsal ACC, and amygdala function in effortful emotional regulation in heathy individuals – and highlight functional differences in healthy vs. symptomatic participants (Zilverstand et al., 2017).

Laboratory studies of trauma-exposed individuals found inconsistent evidence for a link between neural activity during experimental cognitive reappraisal tasks (which instruct participants to deliberately modulate their emotional response to affective images using cognitive reframing) and psychological symptoms. A longitudinal study of maltreated youth found a relationship between prefrontal recruitment during effortful cognitive reappraisal (and associated downregulation of amygdala reactivity to negative stimuli) and subsequent risk for mood symptoms, but no relation to anxiety symptoms (Rodman et al., 2019). In a small sample of adolescent girls exposed to violent assault, participants who responded better to trauma-focused CBT demonstrated decreased functional connectivity between the amygdala and mid-posterior insula cortex during reappraisal of negative images following treatment (Cisler et al., 2016). However, in a larger sample of adults with PTSD, regional BOLD signal during a cognitive reappraisal task was not associated with exposure-based psychotherapy outcomes (Fonzo et al., 2017). Together, these data suggest that individual differences in ability to successfully engage active emotion regulation strategies like reappraisal may buffer against the deleterious effects of trauma exposure on mood, but are not necessarily related to changes in anxiety and PTSD symptom levels.

Reward responsivity

Responsivity to reward underlies key psychological factors linked to resilience such as optimism and positive emotionality (Feder et al., 2019). Resilient individuals show comparatively preserved ventral striatum response both when anticipating and receiving rewards, whereas PTSD and history of childhood maltreatment have been linked to anhedonia and blunted reward

responses – particularly to social reward cues (Dillon et al., 2009; Hanson et al., 2015, 2016; Sailer et al., 2008; Elman et al., 2009; Nawijn et al., 2015). In a cross-sectional community-based sample of adolescents (a substantial proportion of whom had a history of severe childhood maltreatment), greater pallidal activation in response to positive images was associated with lower depression symptoms, and higher putamen activation was associated with lesser increase in depression two years later (Dennison et al., 2016). Among a large sample of university students (*n* = 820) in the Duke Neurogenetics Study cohort, increased ventral striatal activation to both anticipatory and consummatory reward during a card guessing game significantly weakened the relationship between childhood trauma exposure and adult anhedonia – including when controlling for other depression symptoms and recent life stress (Corral-Frías et al., 2015).

In a cross-sectional study, trauma-exposed adults without PTSD had greater ventral striatal responses to happy faces compared to those with PTSD (Felmingham et al., 2014). Amongst individuals who felt negatively affected by the outcome of the 2016 US presidential election (and belonged to historically marginalized groups), higher nucleus accumbens BOLD signal and higher mPFC-accumbens connectivity during reward receipt attenuated the relationship between election-related distress and depression symptoms (Tashjian & Galván, 2018). In a longitudinal assessment of combat-exposed paramedics, decreased reward response in the nucleus accumbens post-, but not pre-exposure, was found to be related to self-reported PTSD symptoms – suggesting that preserved reward responses may be a marker of resilience, rather than a prospective indicator (Admon et al., 2013).

While greater reactivity to rewarding social/environmental cues could promote resilience, the resilience-reward responsivity association may be more complex. The longitudinal AURORA biotypes study (Stevens et al., 2021) identified two clusters associated with resilience in adults scanned 2-3 weeks after seeking emergency department care for a serious injury or medical condition. One (a “high reward reactivity” cluster with low threat reactivity and low inhibitory control) did not replicate in the test cohort. The other, replicable, cluster had low reactivity to both threat and reward, with higher hippocampal and vmPFC engagement during the inhibitory control task, suggesting that resilience is associated with better inhibition of emotional reactivity broadly. The association between resilience and lower general reactivity echoes an earlier small cross-sectional study in Special Forces soldiers – considered highly resilient individuals –, who showed lower differential nucleus accumbens and subgenual PFC responses to monetary

reward versus no-reward, compared to non-trauma-exposed civilians (Vythilingam et al., 2009). These findings illustrate challenges for resilience research when trying to synthesize findings across different populations – e.g., repeated occupational trauma exposures may differ from a singular exposure, and certain occupations (like first responders) may select for traits like higher sensation-seeking and higher reactivity threshold. For example, a recent, rigorous attempt to replicate Stevens et al. (2021) AURORA biotypes identified threat- and reward-related clusters in their cohort, but these were not identical to those in AURORA and not related to PTSD vulnerability (Ben-Zion et al., 2023), potentially due to some differences in sample composition and methods.

Cognitive flexibility and cognitive control

Resilient individuals engage prefrontal and hippocampal regions during executive function tasks e.g., (Ben-Zion et al., 2018). Conversely, deficits in inhibition, working memory, attentional control, and cognitive flexibility are observed in both adults with a history of childhood maltreatment and individuals with a diagnosis of PTSD, not accounted for by comorbid psychopathology, substance use, or prior traumatic brain injury (Gould et al., 2012; Scott et al., 2015) (although the relationship between PTSD symptom severity and cognitive function may be bidirectional; Jacob et al., 2019). In an early study, both resilient and non-trauma-exposed healthy adults showed greater vlPFC, mPFC, and dlPFC activation during an inhibitory control task, compared to individuals with PTSD (Falconer et al., 2008). Resilient individuals have also shown greater dlPFC and superior frontal gyrus activation during an attentional control task with emotional distractors, compared to both individuals with PTSD and non-trauma-exposed controls (Blair et al., 2013). Recently, both resilient and non-trauma-exposed adults (but not adults with PTSD) exhibited significant decoupling between prefrontal regions and subcortical structures when attempting to suppress experimentally-induced memories (Mary et al., 2020): top-down prefrontal modulation of subcortical memory structures (hippocampus, parahippocampal gyrus, and precuneus) was associated with successful memory suppression, whereas the PTSD group showed bottom-up modulation of information flow. Indeed, greater whole-brain resting state hippocampal functional connectivity was a significant predictor of PTSD symptoms at six months in a prospective study in traumatically-injured adults recruited from the

emergency department (Fitzgerald et al., 2022). Optimal prefrontal-subcortical cognitive control network function may contribute to resilience.

A longitudinal study in the Duke Neurogenetics Study cohort (*n*=120) identified that greater neural responses to threat and reward predicted future increases in anxiety in university students with average or low but not *high* prefrontal activity during a working memory task, controlling for childhood maltreatment and stressful life events (Scult et al., 2019). These findings echo (Stevens et al., 2021) in suggesting that lower general reactivity and higher prefrontal inhibitory control could protect against adverse outcomes post-trauma exposure. Further, a longitudinal assessment of recently trauma-exposed adults found that increased inhibitory control-related hippocampal activation (at 1-2 months post-trauma) predicted decreased PTSD symptom severity at three and six months, and this finding was replicable (van Rooij et al., 2018). The hippocampus links cognition, memory and emotion (Speer & Delgado, 2017), and is thus likely relevant to resilience to PTSD symptoms like alterations in mood, cognitive function, and intrusive thoughts and memories.

Finally, NCANDA cohort (*n*=392) resting state fMRI showed that the association between childhood trauma severity and executive function difficulties in adolescents was mediated by lower functional connectivity between a network of the postcentral and precentral gyri, dorsal ACC, intraparietal sulcus, and anterior insula cortex – hub regions implicated in cognitive/behavioral control and sensorimotor integration. Preserved interconnectivity between the postcentral gyrus and dorsal ACC was related to lower reported executive dysfunction at baseline, and predicted lower likelihood of high-risk drinking 1-4 years later (Silveira et al., 2020). In addition to protecting against PTSD symptoms, preserved prefrontal function may reduce vulnerability to maladaptive coping strategies like substance use.

Emerging areas of interest for resilience neuroimaging research

Social support and social cognition. Social support is vital for resilience to trauma exposure occurring in childhood and/or adulthood (van Harmelen et al., 2016; van Harmelen et al., 2017; Fritz, de Graaff, et al., 2018; Yule et al., 2019). Conversely, non-supportive social contexts like discrimination and rejection impact emotion-responsive regions including the amygdala, insula, and ACC, even in the absence of (or after controlling for) associated psychological symptoms

(Akdeniz et al., 2014; Clark et al., 2018). Supportive social environments may converge with resilience-promoting traits to upregulate perigenual ACC and other PFC regions during acute social (and non-social) threats (Holz et al., 2020). Social support also has a protective effect against prolonged stressors. For example, supportive parenting during childhood attenuates the link between childhood adversity (e.g., maltreatment, poverty) and neural responses to negative emotional faces in childhood (Wymbs et al., 2020), and resting state functional connectivity by adulthood within executive and emotion regulation networks (Brody et al., 2019). However, a longitudinal study of adolescents found no association between childhood adversity resilience (no DSM Axis-1 disorder diagnosis following significant family discord) and neural responses to social rejection, although the authors suggest that the null finding might be due to the generally low frequency of abuse and higher socioeconomic status of the sample (Fritz et al., 2019).

Importantly, higher levels of social cognitive function (ability to infer the thoughts of others and navigate the social world) may help foster adaptive outcomes following trauma, by conferring the ability to recruit and maintain social ties (Stevens & Jovanovic, 2019; Lepore & Kliewer, 2019). Hudson et al. (2018) administered a theory-of-mind task to women with childhood maltreatment exposure and unexposed controls. Women with history of childhood maltreatment without sub-clinical or clinical PTSD symptoms in adulthood showed greater functional connectivity between dorsomedial (dm)PFC and right temporoparietal junction (TPJ) during implicit theory of mind, whereas unexposed controls vs. women with PTSD symptoms showed similar dmPFC-right TPJ functional connectivity. Those with PTSD symptoms also demonstrated right TPJ *hypo*activation during theory of mind, relative to unexposed controls. The TPJ and dmPFC represent nodes in the default network dorsomedial subsystem, involved in mentalizing and social processing (Spreng & Andrews-Hanna, 2015). In summary, we need further research on the proximal neural mechanisms underlying social support and social cognitive functioning in resilience. Considering the broader social environment would improve our understanding of mechanisms underlying resilience (**Box 2**; Biglan et al., 2012).

Active coping. Active coping focuses on approach-oriented behaviors for managing stressors. Active or problem-focused coping (such as "*I take additional actions to get rid of the problem*" or "*I concentrate my effort on doing something about it*") is associated with lower cross-sectional PTSD symptoms (e.g., Stratta et al., 2015; Bistricky et al., 2019; Getnet et al., 2019). Further, there is preliminary evidence that a switch toward active coping accompanies response to

cognitive-behavioral therapy for PTSD (Bourdon et al., 2019). mPFC function in resilience to prolonged stressors is implicated in individual differences in coping styles: healthy men with high early life stress but low trait rumination decreased amygdala and increased vmPFC perfusion during a mental arithmetic stress task, whereas men with high early life stress and high trait rumination showed the opposite (Wang et al., 2013). Healthy volunteers undergoing an acute stress paradigm exhibited initial vmPFC deactivation during early task runs of the task. vmPFC signal recovery later in the task was correlated with self-reported active coping and anticorrelated with maladaptive coping behaviors (Sinha et al., 2016), consistent with preclinical evidence that downregulating prefrontal function during *acute* stress is adaptive, but should be modified when stress is prolonged (Maier & Watkins, 2010; Sinha et al., 2016). However, a single laboratory study session represents a very different timescale than naturalistic prolonged human stress, and directionality of the relationship between mPFC recovery during chronic stress and coping style is unclear. Gender roles and social norms can also differentially reinforce active versus avoidant coping styles (McLean and Anderson, 2009; Street and Dardis, 2018; **Box 2**); interrelationships between these factors may warrant attention.

Fear extinction. It is important to update fear memories when transitioning from threat to safety, in order to respond appropriately to context (Lissek & van Meurs, 2015). vmPFC and hippocampus are key in fear extinction maintenance, in both human and animal studies (Milad et al., 2007; Fullana et al., 2018). Enhanced extinction learning is associated with surprise-related learning signals in the vmPFC, and amygdala connectivity with a ventral mPFC subregion (Dunsmoor et al., 2019); the same circuitry might be critical for extinction learning as an interventional mechanism (Fullana et al., 2020). Indeed, greater success of prolonged exposure therapy for PTSD – which promotes extinction learning – is linked to pre-treatment neural responses to emotion, including higher vmPFC signal during emotional regulation, greater magnitude of PFC responses during viewing of fearful faces, and greater inhibition of the amygdala by lateral PFC transcranial magnetic stimulation (Fonzo et al., 2017). Further, vmPFC activity has been demonstrated to be central to the success of *imagined* fear extinction, which may be particularly relevant to the psychotherapeutic context, as in-vivo exposure is not always feasible (Reddan et al., 2018). Together, these studies suggest that vmPFC recruitment during emotional contexts may be important to later success of exposure-based treatment strategies – and may play a role in successful maintenance of extinction learning broadly.

Resting state findings support the relevance of vmPFC recruitment. Occupational trauma-exposed firefighters with greater insula-vmPFC functional connectivity had fewer PTSD symptoms, although firefighters had greater insula functional connectivity with other fear circuitry regions compared to healthy non-firefighter adults, regardless of PTSD symptoms (Jeong et al., 2019). Similarly, typhoon survivors with PTSD showed greater vmPFC connectivity with the basolateral amygdala, relative to trauma-exposed controls. The basolateral amygdala has a central role in fear learning and emotional responding. This latter study illustrates the difficulty in inferring a directional relationship between brain regions from most functional neuroimaging studies. However, a resting state study in typhoon survivors and unexposed healthy adults using Granger causality identified that both individuals with PTSD and trauma-exposed controls exhibited greater amygdala-to-mPFC effective connectivity vs. unexposed controls, but inhibitory mPFC-to-amygdala connectivity was only observed in trauma-exposed controls. (Chen et al., 2018a).

[Figure 1 around here]

Discussion

Here, we summarized task-based and resting state fMRI studies of resilience to childhood and adulthood trauma, focusing on psychological factors widely linked to resilient responses to severe adversity and trauma: effective emotion regulation, reward responsiveness, and cognitive control. We also reviewed findings related to social cognition, fear extinction, and active coping, as emerging areas of interest in resilience research **(Figure 1)**. Across studies, we found robust evidence for preserved mPFC function in downregulation of limbic responses to emotional stimuli in resilient individuals. This is consistent with evidence from animal and human experimental models implicating mPFC engagement in adaptive coping with prolonged stress (Maier & Watkins, 2010). Chronic social defeat stress-susceptible mice showing social impairment exhibit selective reductions in vmPFC spike frequencies – suggesting a potential role of preserved vmPFC function in mediating adaptive *social* behaviour following chronic stress (Abe et al., 2019), in line with emerging human evidence for perigenual cingulate and prefrontal function as mediators of social support's positive effects on responses to stress and pain (Holz et al., 2020). However, we lack knowledge of neural correlates of social functioning and social cognition *in resilient humans* despite their role in fostering positive outcomes (Stevens &

Jovanovic, 2019). Considering the broader social environment is also critical for understanding the brain-environment interactions underlying resilience **(Box 2).**

Preserved reward signal processing in the ventral striatum has been linked to resilience to anhedonia and depression symptoms. One possibility is that preserved reward system function promotes participation in social and other rewarding experiences, thereby buffering the impacts of stress. Intact reward circuitry could also contribute to positive prospection – e.g., a hippocampal-midbrain-vmPFC circuit has recently been implicated in imagined future positive outcomes (Iigaya et al., 2019). However, reward system findings have been mixed; resilient people may be less reactive both to reward and threat. Lesser reactivity might allow for greater stability in the face of a changing environment, for example via lower emotional lability or greater ability to remain focused on goals by inhibiting salient yet distracting cues (e.g., Stevens et al., 2021).

Cognitive control-related brain activation predicts positive outcomes following trauma, specifically frontal (dlPFC) and hippocampal. Adult hippocampal neurogenesis is shown to play an important role in cognitive flexibility, which may enable individuals to disengage from trauma-related memories and thoughts, decreasing cardinal PTSD symptoms such as intrusive thoughts and flashbacks (Aupperle et al., 2012; Anacker & Hen, 2017). Prefrontal-subcortical connectivity (including hippocampal) in cognitive control appears important for suppressing unwanted memories (Mary et al., 2020). Although perhaps not specific to PTSD, activity in this circuit may represent an important factor in vulnerability to PTSD and maladaptive coping mechanisms (e.g., substance use problems) following trauma (Ersche, 2020). Recent work in this area highlights the importance of considering within-person interactions between resilience-relevant factors – specifically, how higher levels of prefrontally-mediated executive function may ‘rescue’ risk for anxiety in individuals who are more reactive to threat and less responsive to rewards (Scult et al., 2019). We note that the brain regions highlighted across the resilience-linked psychological factors also broadly correspond to those described in recent models of psychological *vulnerability* to trauma (e.g., Pitman et al., 2012; Patel et al., 2012; Yehuda et al., 2015).

Longitudinal findings

Given that resilience inherently involves a temporal relationship between stressor and response, large longitudinal studies are better able to answer key questions – for example, are

the differences between resilient people and those who develop a psychiatric disorder already present prior to the stressor, or do the differences emerge afterward in a compensatory manner? Can we identify people at greater risk of negative consequences at the time of the event or soon after, and intervene early to prevent PTSD and related disorders? Several of the studies reviewed here illustrate the potential of longitudinal, cohort-based neuroimaging research. Though their samples differ in terms of trauma exposure type and developmental stage, the work by Scult et al. (2019) in the Duke Neurogenetics cohort, Silveira et al. (2020) in the NCANDA cohort, and Stevens et al. (2021) in the AURORA cohort suggest that greater general bottom-up neural reactivity to emotional stimuli – both positive and negative – is linked to poorer outcomes unless accompanied by the capacity for inhibitory hippocampal and prefrontal engagement.

Limitations

It is important to clarify the scope of inference we can draw from the current data. There are too few studies to differentiate results by developmental stage at the time of the traumatic event and/or the study. In addition to differences in brain development, another difference between studies of adults and youth is that the measures used in adult studies typically focus on symptoms (psychopathology), whereas youth studies tend to operationalize resilience more broadly (**Box 2**). Many studies are retrospective and cross-sectional. Only longitudinal studies can tease out whether differences seen in resilient individuals represent pre-existing vulnerabilities or adaptations. There are also methodological weaknesses, including small sample sizes and low power (Szucs & Ioannidis, 2020). Many older studies used liberal multiple comparison corrections, which increases risk for type 1 errors (Eklund et al., 2016; Cox et al., 2017). However, some key findings replicate in well-powered samples (e.g., (Corral-Frías et al., 2015; McLean et al., 2020; Silveira et al., 2020) – with the caveat that these findings may not necessarily be robust to cohort and methodological differences between studies (Ben-Zion et al., 2023). Finally, identifying robust neuroimaging biomarkers requires establishing intrapersonal reliability of fMRI measures (Nord et al., 2017; Elliott et al., 2019, 2020). Multivariate approaches exploiting the high dimensionality of neuroimaging data may be more appropriate (Dubois & Adolphs, 2016; Finn et al., 2020).

Conclusions and future directions

Real-world settings have started to translate neuroscientific findings to interventions (Greenberg, 2006; Waugh & Koster, 2015; Keynan et al., 2019). Examining neural correlates of treatment response may illuminate neural resilience mechanisms 'activated' by successful treatment. Ongoing and future longitudinal cohort studies with a peritraumatic baseline, such as AURORA (McLean et al., 2020), along with additional consideration of interindividual sociodemographic differences **(Box 3**), will contribute to further understanding resilience to severe adversity and trauma.

[Box 3 around here]

Box 1: Quantifying trauma

Assessing the severity of different traumatic experiences is not a trivial task. Indeed, to a large extent, the degree to which any event is traumatic is determined by the psychological impact on the person or people involved (Green, 1990). However, such a definition poses some difficulties for studies of resilience, which aim to investigate individual differences in response to similarly adverse events. Studying trauma-exposed samples optimally involves several considerations, including severity of trauma exposure and chronicity, and in the case of childhood maltreatment, developmental stage at the time of trauma exposure (Harpur et al., 2015; Dunn et al., 2019; Gee, 2020).

Events sufficient to fulfill criteria for a diagnosis of post-traumatic stress disorder (PTSD) have been codified within the American Psychiatric Association's Diagnostic and Statistical Manual (DSM) as 'Category A' events – specifically, in DSM-5, as being "exposed to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence" (American Psychiatric Association, 2013). In the World Health Organization's International Classification of Diseases (ICD-10), the requirement is simply that a person has experienced an event or situation "of exceptionally threatening or catastrophic nature, which would be likely to cause pervasive distress in almost anyone" (World Health Organization, 1993). Under either scheme, presence of such an event in an individual's history is usually probed using a structured clinical interview (e.g., Weathers et al., 2013).

Experience of childhood trauma in younger research participants may be assessed using developmentally sensitive interviews with a child's primary caregiver (e.g., Goodyer et al., 2010). In comparison, in studies involving adult participants, experience of childhood trauma is often assessed using retrospective questionnaires, such as the Childhood Trauma Questionnaire (Bernstein et al., 1994). Notably, a recent meta-analysis reported poor agreement between prospective and retrospective measures of childhood maltreatment (Baldwin et al., 2019). Although both prospective and retrospective measures identify groups of at-risk individuals, they appear to highlight largely non-overlapping sets of people – meaning that it may not be valid to assume the same risk mechanisms apply to individuals identified using different methods.

Further, although both intensity and chronicity are important dimensions of trauma, it is not always clear how to combine these different aspects of adverse event exposure in a standardized way. Some studies have addressed this issue by restricting recruitment to individuals exposed to a specific precipitating event, for example in volunteers from the World Trade Center rescue and recovery worker cohort (Pietrzak, Feder, et al., 2014), or individuals with combat trauma (Keane et al., 1989). However, even in such samples, there is likely to be additional lifetime trauma exposure in many participants. One approach to this problem is to use a data reduction technique such as principal components analysis (PCA) to combine several different continuous measures into a single index of trauma exposure severity (e.g., to combine different aspects of childhood family experience; van Harmelen et al., 2017). It important to bear in mind when synthesizing data in this way that there may also be trauma-specific considerations to take into account during analysis – for example when considering responses to differently gendered angry faces in people exposed to intimate partner violence (Fonzo et al., 2010).

Box 2: Quantifying resilience

In trauma-exposed populations. In neurobiological studies with adult participants, resilience has often been defined based on the absence of a DSM Axis-1 disorder diagnosis following significant trauma exposure. Such categorical analyses may be complemented by dimensional approaches that relate measures to current severity scores for PTSD, depression, or anxiety symptoms. However, it is increasingly acknowledged that symptom sum scores for specific diagnoses are not the only key outcome variable in studies of resilience. Indeed, trauma-related psychopathology is highly heterogenous, and different symptom dimensions may differentially relate to overall burden of disability (e.g., Pietrzak, el-Gabalawy, et al., 2014) – suggesting more nuanced approaches may be warranted. Conversely, studies of the effects of childhood maltreatment have tended to take a more holistic approach towards assessing resilience, including a greater focus on psychosocial outcomes, and examining functioning across multiple domains (McGloin & Widom, 2001; Cicchetti & Rogosch, 2012). Recent examples of this approach across the literature include examining resilience across different functional outcome categories in

children (Burt et al., 2016), analysing disruption to work, social, and family life in addition to PTSD symptomatology in trauma-exposed adults (Horn et al., 2016), and the use of PCA-derived cross-domain psychosocial functioning scores in an adolescent cohort (A. L. van Harmelen et al., 2017).

The notion of good functioning invoked by definitions of resilience is *environment-dependent:* adaptive behaviour in violent, volatile, or resource-poor environments may not conform to normative accounts of behaviour in more stable or resource-rich environments (Luthar et al., 2006). Further, psychosocial environments may differ across individuals within a shared wider context – e.g. for individuals who identify as different genders and/or belong to different racial or ethnic groups (Tolin & Foa, 2008; Portnoy et al., 2018; Street & Dardis, 2018; Brondolo, 2015). For example, differences in resilience between men and women have been found to be explained by differences in trauma type exposure across genders (particularly sexual violence; Tolin & Foa, 2008; Portnoy et al., 2018), and socialized gender norms may further contribute to differences in chronic environmental stress exposure and propensity to engage in less adaptive coping strategies (Street & Dardis, 2018). In particular, racism is an additional source of trauma in minoritized people that may be under-recognized by current clinical assessments (Carter, 2007; Williams et al., 2018). For example, previous experiences of racial discrimination has recently be shown to add significant risk for PTSD symptom development following traumatic injury (Bird et al., 2021).

Importantly, the expected level of psychosocial functioning for a given individual should take into account their lifetime trauma burden (Karam et al., 2014; Feder et al., 2016). Various researchers have therefore proposed that resilience can best be quantified by regressing metrics of psychosocial functioning against an appropriate measure of trauma exposure severity: such that positive residuals from this model represent better than expected ('resilient') outcomes, and negative residuals represent worse than expected ('vulnerable') outcomes – compared to what would be predicted based on the group as a whole (Amstadter et al., 2014, 2016; A. L. van Harmelen et al., 2017; Ioannidis et al., 2020). Resilience-promoting factors can then be described as any resource (biological, psychological, social/socioeconomic) that decreases the risk of poor outcomes following adverse circumstances. Resilience-promoting factors may include both protective factors that help buffer the impact of stress, and resources that are able to foster positive compensatory changes following trauma exposure (Luthar et al., 2006; Schultze-Lutter et al., 2016). Critically, resilience-promoting factors are not independently additive, but interact in complex ways (Luthar et al., 2006; Fritz, Fried et al., 2018; Liebenberg, 2020). It is therefore vital not to study such factors in isolation, but rather in the context of each other – ideally within the same individuals.

In the general population. Some researchers have also examined population variation in self-reported trait resilience. For example, the Connor-Davidson Resilience Scale (CD-RISC) probes how likely individuals are to endorse statements such as "*I am able to adapt to change*" and "*I tend to bounce back after illness or hardship"* (Connor & Davidson, 2003b). There is somewhat equivocal evidence regarding the relationship between trait resilience and outcomes following trauma exposure (Daniels et al., 2012; Powers et al., 2014). Interestingly, a recent study of emergency department attendees found that a negative association between CD-RISC score close to admission and PTSD symptoms six months in the future was mediated by lower social withdrawal in higher trait resilience individuals – suggesting that the impacts of trait resilience on functional outcome may be via increased ability to maintain or recruit social support (N. J. Thompson et al., 2018). Further, most questionnaire measures of resilience relate to a specific conceptualisation of resilience that focuses on individual 'grit' or 'hardiness' and that may not translate well to non-Western cultural settings – particularly those that emphasise the role of communities rather than individuals in fostering resilience (Meili & Maercker, 2019; Mendenhall & Kim, 2019). An alternative approach for studies of resilience in the general population is to study the *mechanisms* underlying resilience based on experimental intervention data – for example as reflected in lower self-reported fear or physiological reactivity during stress induction paradigms.

Box 3: Considerations for future work

Studying multiple potential resilience-promoting factors within the same individual is necessary to tease apart how putative neurobiological resilience factors interact both with each other and with other sociodemographic factors known to affect resilience to trauma-related psychopathology. We would encourage greater consideration of an individual's social, cultural, and socioeconomic environment in future studies of neural mechanisms related to resilience.

The trade-off for high power in large cohort studies is often the selective pressure on study measures (for inclusion, brevity, and ease of administration). However, accurate assessment of both resilience and the sociodemographic factors described above requires in-depth clinical phenotyping and trauma history screening, often by clinical interview with appropriately trained study personnel. To build our understanding of the neural correlates of resilience, future work should aim to hit a sweet spot in this trade-off between appropriate power and depth of individual phenotyping.

An important next step will be to integrate neuroimaging metrics related to resilience with other biological measurements relevant to both individual differences in neural function and environmental exposure. Novel analytic approaches such as the calculation of polygenic risk scores, or quantification of gene co-expression modules may yield sufficient power in (single site) achievable imaging sample sizes to link neural correlates of psychological constructs to underlying biology (Dima & Breen, 2015; Bogdan et al., 2017). Greater integration of neuroimaging data into such pathways should improve our ability to interpret existing findings in terms of underlying molecular mechanisms. The cost of well-powered samples in neuroimaging genetics is typically prohibitively expensive for a single researcher or work group, but large-scale multi-site efforts e.g., the international ENIGMA [Enhancing NeuroImaging Genetics through Meta Analysis] Consortium have been extremely successful in facilitating robust and reproducible research, and will continue to be a tremendous resource (Thompson et al., 2020).

Figure Caption

Figure 1. Brain regions most commonly associated with higher resilience to trauma, organized by psychological factor (including emerging areas of interest) and underlying neural circuitry, based on review of fMRI BOLD activation literature.
Note. All figures use parcellations from the Desikan-Killiany Cortical Atlas parcellation or Freesurfer's automatic subcortical segmentation, implemented with ggseg() and ggsegExtra() packages for R (Mowinckel & Vidal-Piñeiro, n.d., 2019), except for the subcortical Reward Responsivity plot (approximate location of the nucleus accumbens drawn by hand) and the cortical Social Support & Cognition plot (which uses the AAL2 parcellation). ACC = anterior cingulate, PFC = prefrontal cortex, d = dorsal, dl = dorsolateral, m = medial, l = lateral, r = rostral, v = ventral, vm = ventromedial. Upward arrows indicate regions of greater activation resilient individuals vs. others; downward arrows indicate regions of lower activation in resilient individuals vs. others; and both arrows together indicate mixed findings.

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