

Neuroimaging resilience to trauma: convergent evidence and challenges for future research

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Resilience, or the phenomenon of successful adaptation following significant trauma exposure, is a complex, multidimensional, and dynamic process. To date, research on neural mechanisms involved in human resilience has comprised of two major research streams – involving individuals with childhood and adulthood trauma exposure, respectively. Although there are systematic differences in how both trauma and resilience have been defined across these two bodies of research, some striking regions of convergence emerge when considering the literature as a whole. Here, we review functional imaging studies from across these two research streams, alongside discussion of some of the methodological difficulties involved in quantifying both trauma and resilience in human participants. Due to the broad scope of this literature, we restrict the scope of our narrative to several key domains where studies from across these two bodies of work implicate common neural circuitry. These areas of convergence include brain networks implicated in emotion regulation, responses to rewards, and cognitive control. Further, we briefly review functional imaging evidence related to proposed mechanisms underlying resilient outcomes: namely active coping, cognitive reappraisal and successful fear extinction. Finally, we also touch upon several ongoing issues in neuroimaging study design and analysis that will need to be addressed in order 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.

1 | INTRODUCTION

1.1 | Defining resilience: a complex and dynamic process

Remarkably, only a subset of people go on to experience sustained psychological problems following experience of a traumatic event. Epidemiological estimates for clinically-significant post-traumatic stress symptoms range from 5-22% for adults exposed to natural disasters, life-threatening injuries, or physical assault. These estimates rise to 46-65% for individuals who experience sexual violence – although rates vary significantly according to social background, country of residence, and other demographic features (Shalev et al., 2017; Bromet et al., 2018; Watson, 2019). Similarly, whilst experience of childhood trauma (particularly physical, sexual, or emotional abuse) is a robust predictor of poorer future mental health, roughly 10-25% of individuals with a history of such maltreatment go on to function better than expected across behavioural, emotional, and educational domains (Walsh et al., 2010).

In the field of psychiatry, the phenomenon of better than expected psychosocial functioning following exposure to significant trauma or stress is known as resilience. Recently, a consortium of researchers involved in the study of stress-related disorders have proposed that resilience can best be defined as “*an outcome of good mental health following an adverse life event or a period of adversity*” (Kalisch et al., 2017). This represents a deliberately operational and atheoretical approach to defining resilience that is agnostic as to the mechanisms underlying this outcome. Importantly, from this perspective, resilience is not simply the inverse of vulnerability or risk for psychiatric disease (Yehuda and Flory, 2007), but rather describes a status it is only possible to confer after the fact of a traumatic event.

Resilience-promoting *factors* can be thought of as anything that modifies the risk of poor outcome following adverse circumstances in a positive direction. These can be drawn from biological, psychological, social or socio-economic spheres. 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). Indeed, much empirical research on resilience-promoting factors has emphasised that resilience is a dynamic process, involving active adaptation in response to adversity (Feder et al., 2009; Rutter, 2012; Kalisch et al., 2017; Scheffer et al., 2018; Ioannidis et al., 2020). According to this view, resilient outcomes result not so much from insensitivity to the damaging effects of trauma, as from the ability to harness compensatory mechanisms that counteract these effects. Critically, resilience-promoting and protective factors are not independently additive, but interact in complex ways (Luthar et al., 2006; Fritz et al., 2018a; 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.

Importantly, trauma exposure shows clear cumulative effects across the lifespan (Karam et al., 2014; Feder et al., 2016). This means that the expected level of emotional and social functioning following adversity should take into account the lifetime trauma burden of a given individual. Recently, researchers have proposed an approach to quantifying resilience whereby a composite psychosocial functioning score is first regressed against an appropriate measure of trauma exposure severity. Positive residuals from this model then represent better than expected (*‘resilient’*) and negative residuals worse than expected (*‘vulnerable’*) outcomes than would be predicted from the group as a whole (Amstadter et al., 2014, 2016; van Harmelen et al., 2017; Ioannidis et al., 2020). To complicate the picture further, there is also an important temporal dimension to resilience. Time to return to premorbid function, or trajectory of symptom changes over time, are critical variables in terms of both patient experience and overall psychological load (Bonanno and Diminich, 2013; Pietrzak et al., 2014; Ioannidis et al., 2020).

The necessity of considering multiple interacting factors, detailed lifetime trauma history, and how symptoms change over time (all ideally within the same participants) presents a considerable challenge to the experimental study of human resilience. However, we remain hopeful that the increasing availability of remote, minimally intrusive data-

gathering tools, in conjunction with modern analytic techniques for complex time-series data, hail the prospect of making considerable progress in resilience research: explicitly by embracing such complexity (Scheffer et al., 2018; Kalisch et al., 2019).

1.2 | Studies of human resilience: two major research streams

Research on factors that influence resilience to trauma can be described in terms of two major research streams: the first involving the study of children, adolescents, and adults who have history of childhood maltreatment (usually defined as physical, sexual, or emotional abuse or neglect), and the second examining the effects of adulthood trauma exposure (often in professionally-determined at-risk populations such as emergency service workers and military personnel, but also in individuals with experience of major disasters, traumatic accidents, or exposure to interpersonal and/or sexual violence).

This division can be explained by the different conceptual and experimental considerations involved in studying these cohorts. For example, the developmental stage (age or pubertal status) of individuals at onset may be critical in studies of childhood trauma, but less so in adulthood (*cf* 'sensitive period' hypotheses; Harpur et al., 2015; Dunn et al., 2019). Similarly, the temporal nature (chronicity) of trauma exposure may be an important differentiating factor between childhood neglect or abuse, and some more punctate adulthood traumas, such as being involved in an accident or disaster (see **Box 1: Quantifying trauma**). In consequence, there are some systematic differences in how both trauma and resilience have been defined and quantified in experimental studies of childhood maltreatment and adulthood trauma-exposure (see **Box 2: Quantifying resilience**). For example, studies of the biological consequences of adult trauma exposure have tended to use absence of DSM axis-1 disorder diagnosis as evidence of resilient status, whilst studies of the effects of childhood adversity have tended to take a more holistic approach, including assessing resilience across various psychosocial outcome domains.

Nevertheless, when considering the literature from these two bodies of work in parallel, there are some striking regions of convergence. By highlighting these regions, we hope to shed light on some of the general mechanisms underlying adaptive outcomes after trauma. We fully acknowledge that such an approach inevitably results in the masking of important complexities, such as those touched on above. For a fuller discussion, we direct the reader towards excellent recent reviews encompassing the developmental complexities involved in the study of childhood maltreatment (Ioannidis et al., 2020; Moreno-López et al., 2020).

1.3 | What value can neuroimaging bring to the understanding of resilience?

The ultimate aim of resilience research is to harness insight into protective and compensatory mechanisms to improve treatments for – or, ideally, prevent the development of – posttraumatic stress symptoms (Kalisch et al., 2017). If we accept that the brain is the final effector in the pathway from environment to psychological experience, it should be possible to locate the effects of even distal resilience-related factors on psychosocial outcomes here. Given appropriate power and sensitivity, neuroimaging is therefore a tool that may enhance our understanding of the mechanisms associated with different routes to resilient outcomes in humans.

It is important to be clear about the scope of inferences we can draw from the existing data. Most existing imaging studies of resilience have yet to incorporate the important nuances described above – in particular, investigating multiple potential resilience-promoting factors within the same individuals, and including multiple measurements in the same individuals over time. If these issues can be addressed, neuroimaging studies of resilience may progress our understanding of differential responses to trauma by helping generate psychopathology-informed hypotheses

for experimental testing in animal models, developing tools to better phenotype currently diagnosed patients or at-risk individuals, and perhaps even enabling the development of imaging-informed interventions: such as targeted neurofeedback, brain stimulation, or cognitive-emotional training.

2 | FUNCTIONAL IMAGING OF RESILIENCE: AREAS OF CONVERGENCE

Here, we review functional neuroimaging studies of resilience in humans from across the childhood and adulthood trauma exposure literatures. We build on previous work providing thorough assessments of the literature on neural mechanisms implicated in resilience to stress (van der Werff et al., 2013), and studies of adults resilient to childhood maltreatment (Moreno-López et al., 2020). As in these works, we focus on studies that included trauma-exposed asymptomatic ('resilient'), trauma-exposed symptomatic ('vulnerable'), and non-trauma exposed healthy participants, which is necessary to tease apart effects of trauma exposure and current symptom experience on neural activity. In order to advance on previous scholarship, we also primarily discuss post-2013 research. Due to the relatively recent emergence of larger cohort studies, and progress in analytic and reporting standards across the field of neuroimaging, this also has the advantage of allowing us to devote greater weight to better powered work with more rigorous analytic approaches (see **Discussion**). Where possible, we follow discussion of cross-sectional study designs with evidence from longitudinal cohorts and interventional studies, which provide more insight into direction of effects and causality.

In order to highlight regions of convergence across the literature, our discussion is informed by concentrations of previous resilience research, with the bulk of results restricted to areas of significant overlap between the two bodies of work described above. Specifically, these domains describe functional imaging findings related to *emotion regulation*, *responses to rewards*, *cognitive control and cognitive flexibility*, and *social cognition*. Further, we briefly review relevant evidence from studies of potential mechanisms underlying resilient outcomes – namely *active coping*, *cognitive reappraisal* and *fear extinction*. The brain regions highlighted across these domains broadly correspond to those described in recent models of psychological vulnerability to trauma, full details of which are beyond the scope of the current paper, but which can be found elsewhere (Pitman et al., 2012; Yehuda et al., 2015; Akiki et al., 2017).

2.1 | Emotion regulation

Imaging studies have consistently identified several core brain regions as being involved in human emotional responses including the medial prefrontal and cingulate cortex, ventral striatum, amygdala, and hippocampus (Dalglish, 2004). There is also substantial evidence of heightened amygdala responsivity to emotional and threat-related stimuli in individuals with both child and adulthood trauma exposure, which has been linked to decreased down-regulation of amygdala responses by the medial prefrontal cortex (mPFC) (for reviews see Patel et al., 2012; Whittle et al., 2013). Conversely, convergent evidence in resilient individuals suggests increased ability to downregulate neural responses to stress or threat, involving medial prefrontal-mediated inhibition of responses to emotionally salient stimuli in a network of brain regions that includes the amygdala and anterior cingulate cortex.

Early studies across a variety of functional imaging modalities identified increased activity in the mPFC (including rostral anterior cingulate regions), and decreased activity in emotion-responsive regions such as the dorsal anterior cingulate and amygdala, in resilient compared to symptomatic trauma-exposed adults (van der Werff et al., 2013). These differences were identified both at rest, and during tasks designed to actively engage emotion-regulation mechanisms (challenge with unpleasant images, sounds, or trauma scripts). A recent review of individuals with a history of childhood maltreatment found evidence for increased frontolimbic connectivity during emotion-processing tasks

Box 1. Quantifying trauma

If resilience is an outcome that is expected to relate to the degree of trauma to which a particular individual has been exposed, then we need a way to objectively assess the severity of trauma experienced by different individuals. This is not a trivial task: to some extent the degree to which any event is 'traumatic' is defined in subjective terms involving the psychological impact on a given individual. However, when studying resilience, such a definition is somewhat circular, so what we require is a way to examine individual differences in response to similarly adverse events.

Traumas sufficient to fulfil 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" (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" (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. the Clinician-Administered PTSD Scale; Weathers et al., 1993).

Experience of childhood trauma in younger research participants may be assessed using developmentally sensitive interviews with a child's primary caregiver, such as the Cambridge Early Experience Interview (Goodyer et al., 2010), which probes the occurrence of sexual, physical, emotional abuse and family discord (conflict, incidental violence, and/or lack of communication and engagement within the family that had a significant impact on daily life). In studies involving adult participants, experience of childhood trauma is often assessed using retrospective questionnaire measures, such as the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994), which records the frequency and severity of physical, emotional and sexual abuse and neglect. 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. This is likely to have relevance for studies that assess resilience to childhood trauma based on relatively contemporary records (e.g., in developmental cohort studies), versus those that rely on retrospective reporting in adults.

Further, although both intensity and chronicity are considered to be 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, allowing the use of event-specific criteria for trauma severity (e.g. for studies of the World Trade Center rescue and recovery worker cohort, a standard set of criteria has been developed to assess high severity exposure, Pietrzak et al., 2014; similarly, standardised instruments exist for measuring exposure to combat-related traumas; Keane et al., 1989). However, even in such samples, there is likely to be additional relevant trauma exposure in many participants (particularly in studies of older adults). 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 or stress exposure severity (e.g., van Harmelen et al., 2017). It is important to bear in mind when synthesizing data in such a way that there may also be trauma-specific considerations to take into account during analysis – for example differences in psychophysiological reaction evoked by male versus female faces is usually not considered in studies of emotion perception or regulation, but is likely to be important when participants include participants who have experienced violence from a male partner (Fonzo et al., 2010).

Box 2. Quantifying resilience

In trauma-exposed populations. In biological studies of adult participants, resilience has often been defined on the basis of the absence of a DSM Axis-1 disorder diagnosis following significant trauma exposure. Such categorical analyses may be complemented by dimensional approaches that relate various predictors to current symptom severity scores (usually total scores on measures of PTSD, depression, or anxiety symptoms). However, it is increasingly being acknowledged that total symptom scores for specific diagnoses are not the only key outcome variable in studies of resilience. Indeed, trauma-related psychopathology is highly heterogeneous, and different symptom dimensions may differentially relate to overall burden of disability (e.g. Greene et al., 2018) – suggesting more nuanced approaches may be warranted. 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 acknowledgement of the importance of assessing functioning across multiple domains (e.g. academic and social; McGloin and Widom, 2001; Cicchetti and Rogosch, 2012). This is significant, as research participants often report outcomes such as ability to work or maintain a fulfilling social life as being more important than disorder-specific symptom measures in terms of contribution to their overall quality of life (Zatzick et al., 2001; Coulter, 2017). Recent examples of this more integrated approach include testing resilience across different functional outcome categories in children (Burt et al., 2016), analysing outcomes in terms of functional disability in work/social/family life as well as 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 (van Harmelen et al., 2017).

Importantly, 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 (Brondolo, 2015; Portnoy et al., 2018). For example, Portnoy et al. found that differences in resilience between male and female veterans could be explained by differences in trauma type exposure across genders (women reported greater exposure to sexual abuse and military sexual trauma, whereas men reported greater exposure to accidents and combat trauma; Portnoy et al., 2018), and both female gender among police and Hispanic ethnicity in general have been associated with poorer PTSD symptom trajectory in World Trade Center first responders (Pietrzak et al., 2014; Feder et al., 2016). Racism is an additional source of trauma in minoritized people that may be under-recognized by current clinical assessments (Williams et al., 2018).

In the general population.. Contrary to the operational definition of resilience described here (Kalisch et al., 2017), some researchers have also examined correlates of population variation in questionnaire measures of trait resilience. For example, the Connor-Davidson Resilience Scale (CD-RISC; Connor and Davidson, 2003) 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*”. There is somewhat equivocal evidence regarding the relationship between trait resilience and outcomes following trauma exposure. In a sample of $N=70$ acutely traumatised subjects recruited at the emergency department, CD-RISC scores predicted PTSD symptom severity at both 6 weeks and 3 months post-trauma (Daniels et al., 2012) – however, a subsequent study of $N=227$ Trauma Center visitors found that baseline resilience score did not predict whether an individual met diagnostic criteria for PTSD 3 months later (Powers et al., 2014). Interestingly, a recent study of 164 emergency department attendees with Category A trauma exposure found that a negative association between CD-RISC score at 1-month post-trauma and PTSD symptoms 6 months later was mediated by lower social withdrawal in higher trait resilience individuals – suggesting that the impacts of trait resilience scores on functional outcome may be indirect, e.g. via relation to increased ability to maintain or recruit relevant social support resources (Thompson et al., 2018). However, 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 many cultural settings – particularly those that emphasise the role of communities rather than individuals in fostering resilience (Meili and Maercker, 2019; Mendenhall and Kim, 2019). An alternative approach for studies in the general population is to attempt to study the *mechanisms* underlying resilience on the basis of experimental intervention data – for example as reflected in lower self-reported fear or physiological reactivity during stress induction paradigms.

in resilient compared to healthy adults (Moreno-López et al., 2020), including greater down-regulation of amygdala activity during negative emotion regulation in healthy children with a history of moderate childhood maltreatment, compared to controls (Schweizer et al., 2016). In a recent study of survivors of a natural disaster, task-free intrinsic connectivity data were evaluated using Granger causality analysis in order to investigate temporal relationships between signal in the amygdala and rest of the brain (Chen et al., 2018). The authors observed increased inhibition of the amygdala by the mPFC in trauma-exposed individuals without PTSD compared to both individuals with a diagnosis of PTSD and non trauma-exposed healthy controls – suggesting that increased resting inhibition of the amygdala by medial prefrontal regions may reflect a resilience-promoting adaptation following trauma.

In a longitudinal study of amygdala responses to social stimuli, Callaghan and colleagues studied BOLD responses to parent versus stranger faces in children who had experienced early adversity (institutional care prior to adoption), and found that previously institutionalised children who showed reduced amygdala responses to images of their parents, compared to strangers, at the time of initial testing showed greater reductions in self-reported anxiety three years later (Callaghan et al., 2019). An earlier study in this population showed that previously institutionalized youth showed both stronger recruitment of the hippocampus, and increased prefrontal-hippocampal connectivity, during an aversive learning task that also robustly activated the amygdala (Silvers et al., 2016). Significantly, previously institutionalised individuals with stronger ventromedial prefrontal-hippocampal connectivity estimates had reduced anxiety scores at two-year follow-up. In the adult literature, lower amygdala reactivity to fearful faces, measured a few weeks following Category A trauma exposure in individuals recruited from a hospital emergency department, has been found to be associated with lower self-reported PTSD scores at 1 year follow-up (Stevens et al., 2017). Together, these studies provide evidence that decreased amygdala responses to fear-related cues near time of trauma (possibly via the additional recruitment of prefrontal and hippocampal circuitry) may predict resilience to post-traumatic stress and anxiety.

From an interventional perspective, a recent trial of electro-encephalography (EEG)-guided neurofeedback in individuals recruited from a pre-deployment military training program (N=180, all male), found that amygdala electrical fingerprint-guided neurofeedback training (i.e., training to volitionally downregulate EEG-derived amygdala signal), but not non-amygdala targeted training, improved 'emotional regulation' performance as measured by response times on an emotional Stroop task and alexithymia questionnaire (but did not affect self-reported state anxiety; Keynan et al., 2019). Post-intervention fMRI neurofeedback sessions confirmed this improvement was related to ability to volitionally downregulate amygdala BOLD signal, and that the active treatment was associated with greater amygdala-mPFC functional connectivity estimates than control conditions. This represents a promising step towards development of a feasible and scalable neurally-guided intervention for individuals at risk of significant trauma exposure – however it is yet to be demonstrated whether this approach will be effective in mitigating development of psychological symptoms following real-world trauma.

2.2 | Reward responsivity

There is a strong body of evidence for blunted ventral striatal responses to rewards in adults with a history of childhood maltreatment and adults with a diagnosis of PTSD – particularly in response to social reward cues (Hanson et al., 2015, 2016; Nawijn et al., 2015). Preserved ventral striatal reward responses during both anticipation and receipt of rewards have, on the other hand, been identified in resilient trauma-exposed individuals.

In an initial cross-sectional study, greater magnitude ventral striatal BOLD responses to happy faces were observed in Category A trauma-exposed individuals who did not meet criteria for PTSD, compared to those with a PTSD diagnosis (Felmingham et al., 2014). A later analysis of N=820 university students drawn from the Duke Neurogenetics

Study cohort found that increased ventral striatal BOLD responses during reward anticipation/receipt in a card guessing game significantly weakened the relationship between childhood trauma exposure and adult anhedonia symptoms – including when controlling for other depression symptoms and recent life stress (although this was a relatively high-functioning and low maltreatment-exposure population; Corral-Frías et al., 2015). A further cross-sectional study carried out in the aftermath of the 2016 US presidential election found that amongst individuals who felt negatively affected by the result (and who also belonged to historically marginalized groups in terms of ethnicity and/or sexual orientation), ventral striatal responses to rewards moderated the relationship between election-related distress and self-reported depression (Tashjian and Galván, 2018). Specifically, individuals with higher nucleus accumbens BOLD signal, and higher mPFC-accumbens connectivity during reward receipt showed attenuated relationships between distress and depression symptoms.

In a longitudinal assessment of combat-exposed paramedics, decreased responses to rewards in the nucleus accumbens post-, but not pre-exposure, were found to be related to self-reported PTSD symptoms – suggesting that preserved reward responses may be a marker of resilience to PTSD (Admon et al., 2013). A recent study of a community-based sample of adolescents, a substantial proportion of whom had a history of severe childhood maltreatment (physical and/or sexual abuse), showed that greater left pallidal BOLD to positive images was associated with lower depression symptoms in maltreated youth, and that higher BOLD in the left putamen to positive images was associated with lower increases in depression scores at 2 year follow-up (Dennison et al., 2016). Convergent evidence therefore suggests that greater reactivity to rewarding social and environmental cues may represent a resilience-promoting factor against the development of anhedonia and depression symptoms.

2.3 | Cognitive flexibility and cognitive control

Deficits in neurocognitive function, including working memory, attention, and cognitive flexibility, have been observed in both adults with a history of childhood maltreatment and adults with a diagnosis of PTSD (Gould et al., 2012; Scott et al., 2015). These impairments cannot be accounted for by comorbid depression, substance use disorders, or history of traumatic brain injury (Scott et al., 2015). Further, greater cognitive flexibility, as measured using a behavioural attention-switching task 1-2 weeks following traumatic injury, has been shown in one recent study to be a significant predictor of lower PTSD symptoms measured one month post-trauma (Ben-Zion et al., 2018) – although there is also evidence that the relationship between experience of PTSD symptoms and cognitive function integrity may be bidirectional (Jacob et al., 2019). Differences in function in prefrontal and hippocampal regions during performance of tasks that require attentional control and cognitive flexibility, have also been observed in resilient, compared to symptomatic, individuals.

An early functional imaging study found that both resilient trauma-exposed and non trauma-exposed healthy control groups showed significantly greater BOLD in the ventrolateral, medial, and dorsolateral PFC during an inhibitory control (Go-noGo) task, compared to individuals with a diagnosis of PTSD (Falconer et al., 2008). Similarly, Blair and colleagues found evidence for greater BOLD signal in the dorsolateral PFC and superior frontal gyrus during incongruent Stroop trials in a healthy trauma-exposed group, compared to both individuals with PTSD and trauma-free controls (Blair et al., 2013). In a notable recent study, Mary and colleagues demonstrated that trauma-unexposed and resilient, but not vulnerable (PTSD) adults, exhibited significant decoupling between prefrontal regions and subcortical structures implicated in memory during a conscious suppression of an experimentally-generated intrusive memory (Mary et al., 2020). Further analysis revealed that in healthy and resilient individuals, top-down modulation of subcortical memory structures (hippocampus, parahippocampal gyrus, and precuneus) by prefrontal regions was associated with successful intrusive memory suppression, but that this effect was absent in the PTSD group (who showed a re-

versed pattern of information flow). Together, these studies suggest that preserved function in prefrontal-subcortical cognitive control networks may be necessary for resistance to development of clinical levels of PTSD symptoms.

Interestingly, in a recent analysis of longitudinal data from 120 university students that included multiple domains of neural function within the same individuals, higher amygdala response to threat and lower ventral striatum activity to reward predicted future increases in anxiety in students with average or low but not high prefrontal activity during a working memory task (Scult et al., 2019). This suggests that preserved prefrontal executive control may 'rescue' risk for anxiety in these individuals. Although this was a relatively high-functioning and low maltreatment-exposed sample (see Corral-Frías et al., 2015), results were robust to inclusion of childhood trauma and recent life stress measures in analysis models. Further, a longitudinal assessment of Category A trauma-exposed adults found that increased hippocampal BOLD signal during inhibitory control (Go-noGo) task measured 1-2 months post-trauma predicted decreased PTSD symptom severity at 3 and 6 month follow-up in both an initial discovery and replication sample (van Rooij et al., 2018). As the hippocampus has been identified as a crucial structure involved in linking cognition, memory and mood (Speer and Delgado, 2017), it is likely to have high relevance for resilience to post-traumatic stress syndromes, that are characterised by alterations in mood, cognitive function, and intrusive thoughts and memories.

Finally, Silveira and colleagues recently used task-free imaging data from the NCANDA cohort ($N=392$) to show that an association between childhood trauma severity and executive function difficulties was mediated by lower functional connectivity between a network of hub regions implicated in cognitive/behavioural control and sensorimotor integration (specifically, the postcentral and precentral gyri, dorsal anterior cingulate cortex, intraparietal sulcus, and anterior insula cortex). Preserved interconnectivity between these frontal regions (particularly the postcentral gyrus and dorsal anterior cingulate) was related to lower reported executive dysfunction and baseline, and predicted lower likelihood of high-risk drinking behaviour at 1-4 year follow-up (Silveira et al., 2020). This suggests that in addition to protecting against post-traumatic stress symptoms, preserved prefrontal function may be an important path towards resilience to problematic coping behaviours that may also emerge following trauma, such as substance abuse.

2.4 | Social support and social cognition

Behavioural and epidemiologic studies have identified social support as a vital factor in promoting resilience in the face of both childhood and adulthood trauma (van Harmelen et al., 2016, 2017; Fritz et al., 2018b; Yule et al., 2019). Social discrimination has been demonstrated to impact function in emotion-responsive neural circuitry including the amygdala, insula, and anterior cingulate cortex, even in the absence of (or after controlling for) associated psychological symptoms (Akdeniz et al., 2014; Clark et al., 2018). Conversely, a recent review describing the protective effects of social support on brain responses to social stress and experimentally-induced aversive events (electric shock or heat pain) concluded that the effect of supportive social environments may converge with other resilience-promoting traits in positively modulating function in the perigenual anterior cingulate and other prefrontal cortical regions (Holz et al., 2020). One further study found evidence that greater maternal support attenuated the relationship between childhood adversity and neural responses to fearful emotional faces in the anterior cingulate cortex, insula, nucleus accumbens, and frontal pole (Wymbs et al., 2020). 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 these important social support structures (Stevens and Jovanovic, 2019; Lepore and Kliewer, 2019). However, to date, very few studies have examined role of neural activity related to social cognition in resilience following trauma exposure.

In a cross-sectional study of young adults with a history of emotional maltreatment, no evidence was found for differences in neural responses to social exclusion between a group of healthy individuals (with low to moderate

history of maltreatment) and DSM Axis-1 disorder diagnosed patients (who had moderate to high maltreatment scores) (van Harmelen et al., 2014). There was also no evidence of a relationship between resilience to childhood adversity (defined as the absence of any recent DSM Axis-1 disorder diagnosis following significant family discord) and neural responses to social rejection in a longitudinal study of adolescents aged 14-18 (Fritz et al., 2019) – although the authors report that this null finding may be related to a relatively low frequency of emotional/physical abuse and higher socioeconomic status of individuals in the study sample. Further research is therefore needed on the proximal neural mechanisms underlying the role of social support and high social cognitive functioning in resilience.

2.5 | Studies of potential resilience mechanisms

Active Coping Greater tendency to engage in active or problem-focused coping strategies in the face of stress (as reflected in endorsement of statements such as “*I take additional actions to get rid of the problem*” or “*I concentrate my effort on doing something about it*”) has been associated with lower PTSD symptom levels in cross-sectional assessments carried out in the aftermath of trauma (e.g., Stratta et al., 2015; Bistricky et al., 2019; Getnet et al., 2019). Further, there is preliminary evidence that switches towards endorsing active coping strategies accompany response to cognitive-behavioural therapy for PTSD (Bourdon et al., 2019).

Experimental studies of individual differences in coping styles have implicated variation in medial prefrontal function in adaptive responses to prolonged (versus acute) stressors. A study in a small group of healthy men found that individuals with high levels of early life stress but low trait rumination scores decreased amygdala and increased vmPFC perfusion during performance of a mental arithmetic stress task, whereas men with early life stress but high trait rumination showed the opposite effect (Wang et al., 2013). Sinha and colleagues tested healthy volunteers on an acute stress paradigm (successive exposure to highly aversive images), and found that whilst the ventromedial PFC exhibited significant deactivation during early task runs of the task, degree of recovery of function (BOLD signal increase) in this region later in the task was positively related to self-reported active coping and negatively related to frequency of engagement in maladaptive coping behaviours (emotional eating, alcohol consumption, and interpersonal arguments/fights; Sinha et al., 2016). This is consistent with observations from the preclinical literature that whilst it may be adaptive to downregulate prefrontal function (resulting in upregulated function in emotion-responsive brain regions) during acute stress, this response should be modified as the stressor becomes prolonged (Maier and Watkins, 2010; Sinha et al., 2016). However, it should be noted that temporal effects measured during a single laboratory study session represent a very different timescale to naturalistic prolonged human stress – which is more likely to be measured in years than minutes. Further, the directionality of the relationship between mPFC recovery during chronic stress and coping style is currently not clear – i.e., whether increased prefrontal capacity to regulate emotional responses may result in increased likelihood of self-identifying as an ‘active copier’, or *vice versa*.

Cognitive re-appraisal The ability to re-evaluate experiences and their meaning has been identified as playing an important role in adaptive responses to trauma, as well forming a core part of many psychological therapies for post-traumatic stress disorders (Hofmann, 2008). Cognitive reappraisal has been described as an ‘effortful emotion regulation strategy’ that individuals may employ in order to buffer risk for adverse outcomes following trauma exposure (Rodman et al., 2019). In a recent ecological momentary assessment study carried out in currently-remitted individuals with a history of depression, individual differences in ‘positive appraisal’ (ability to “*focus on positive meaning*”) were found to be mutually reinforcing of self-reported feelings of resilience and associated with lower occurrence of residual depressive symptoms (Hoorelbeke et al., 2019). Meta-analyses have highlighted the involvement of ventrolateral and dorsolateral prefrontal cortices, the dorsal ACC, and the amygdala in effortful emotional regulation in healthy indi-

viduals – with differences in function in these regions identified between healthy control subjects and various patient samples (Zilverstand et al., 2017).

There is mixed evidence for an association between neural function during laboratory tests of ‘cognitive reappraisal’ (which instruct participants to try and consciously modulate their emotional response to affective images) and psychological symptoms in trauma-exposed individuals. A study in small group of adolescent girls exposed to violent assault found that participants who responded better to trauma-focused cognitive-behavioural therapy for PTSD demonstrated decreased functional connectivity between the amygdala and mid-posterior insula cortex during re-appraisal of negative images following treatment (Cisler et al., 2016). However, regional BOLD signal measured during performance of a cognitive reappraisal task in larger sample of adults with PTSD was not found to be associated with clinical response to exposure-based psychotherapy (Fonzo et al., 2017). This suggests classic cognitive reappraisal tasks may not be a good measure of individual capacity to engage in psychological processes associated with success of this form of therapy. One longitudinal study found a relationship between prefrontal recruitment during effortful cognitive reappraisal (and associated downregulation of amygdala reactivity during perception of negative stimuli) and subsequent risk for depression – but not anxiety – symptoms in maltreated youth (Rodman et al., 2019). Together, these data suggest that individual differences in ability to successfully engage this kind of active emotion regulation strategy may help buffer against the deleterious effects of trauma exposure on mood, but are not necessarily related to changes in anxiety and post-traumatic stress symptom levels.

Successful fear extinction Successful updating of fear memories is likely to be a prerequisite for adaptive functioning when transitioning from dangerous to safe contexts (Lissek and van Meurs, 2015). The ventromedial prefrontal cortex (vmPFC) has been identified as a core brain structure for the successful maintenance of fear extinction learning in both human and animal studies (Phelps et al., 2004). Retention of extinction learning during recall testing is associated with BOLD signal in the vmPFC and hippocampus, with greater signal in both regions relating to greater extinction retention (Milad et al., 2007; Fullana et al., 2018). A recent study demonstrated that enhancement of lab-based extinction learning (via inclusion of a novel neutral outcome in place of the omitted aversive stimulus) was associated with representation of surprise-related learning signals in the vmPFC and a distinct pattern of vmPFC-amygdala connectivity (Dunsmoor et al., 2019). This implies that this circuitry might be critical to attempts to augment extinction learning in a clinical context (Fullana et al., 2020). Indeed, greater success of a psychological therapy aimed at promoting extinction learning (prolonged exposure therapy) has been linked to a variety of baseline brain responses during emotion-related tasks – including higher vmPFC signal during emotional regulation, greater magnitude prefrontal 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 (Reddan et al., 2018). Together, these studies suggest that ability to recruit prefrontal structures during emotional experience may be important to the success of exposure-based treatment strategies – and likely may play a role in successful maintenance of extinction learning more generally.

3 | DISCUSSION

Here, we summarised functional imaging studies of resilience to both childhood and adult-aged trauma. We identified three major areas of convergence across the literature: implicating networks of brain regions involved in emotion regulation, responses to rewards, and cognitive control in better outcomes. Although taking a high-level approach

necessarily involved omission of many interesting complexities, we believe that such an overview may be useful in highlighting commonalities across the field. Further, we attempt to draw attention to parallels between findings from studies in trauma-exposed individuals, and findings from studies of proposed resilience *mechanisms* (both lab-based and as activated by treatments for post-traumatic stress). This may be particularly important is identifying resilience mechanisms that are amenable to augmentation in high-risk populations or already vulnerable trauma-exposed individuals.

Notably, the brain areas highlighted in functional imaging studies of *resilience* to trauma so far overlap largely with those implicated in *vulnerability* for stress-related disorders – including the prefrontal, medial, and anterior cingulate cortices, amygdala, and hippocampus. It is unclear if this an artefact of region-of-interest analyses derived from the psychopathology literature, or whether these highly interconnected regions simply represent a key circuit in mediating both responses to stressors and emotional experiences more generally. Notably, many of these brain regions have been implicated in regulating stress responses via the hypothalamic-pituitary-adrenal axis and contain a high density of glucocorticoid receptors – suggesting that resistance to the neurotoxic and neurogenesis-suppressing effects of these molecules during chronic stress may be an important pathway towards resilience (McEwen and Morrison, 2013; Anacker and Hen, 2017).

We found robust evidence for a role of preserved medial prefrontal function, in particular in downregulation of limbic responses to emotional stimuli, in fostering resilience outcomes. This is consistent with evidence from animal and human experimental stress-induction paradigms, which have reliably implicated the re-emergence of mPFC activity levels with adaptive coping as stress exposure becomes prolonged (Maier and Watkins, 2010). Intriguingly, it has recently been shown that chronic social defeat stress-susceptible mice (who show impairments in social interaction) exhibit selective reductions in ventromedial prefrontal spike frequencies – suggesting a potential role of preserved vmPFC function in mediating adaptive social behaviour following chronic stress (Abe et al., 2019). This finding is line with emerging experimental evidence from human studies, that implicate perigenual and prefrontal function in mediating positive effects of social support on responses to stress and pain (Holz et al., 2020). Despite a clear role in fostering positive outcomes following trauma exposure (Stevens and Jovanovic, 2019), there is currently very little literature on the neural correlates of social functioning and social cognitive ability in resilient humans.

There is also convergent evidence for an association between preserved reward signal processing in the ventral striatum and resilience to anhedonia and depression symptoms. One possibility is that preserved reward system function fosters resilient outcomes by allowing individuals to continue to engage in rewarding experiences (including socially-derived rewards), buffering the impacts of stress by diminishing control of attention and behaviour by negative stimuli. It is also possible that intact reward circuitry plays an important role in anticipation of future positive experiences – for example a hippocampal-midbrain-vmPFC has recently been implicated in imagination of future positive outcomes in humans (Iigaya et al., 2019).

Finally, there is increasing acknowledgement of the brain regions implicated in executive function and cognitive control in predicting positive outcomes following trauma, specifically networks including frontal and dorsolateral cortex, and the hippocampus. The hippocampus has been identified as an important region for the interplay between memory and mood: adult hippocampal neurogenesis has been shown to play an important role in cognitive flexibility, which may enable individuals to disengage from trauma-related memories and cognition, decreasing distress from cardinal PTSD symptoms such as intrusive thoughts and reminder-prompted flashbacks (Aupperle et al., 2012; Anacker and Hen, 2017). A notable recent study demonstrated the importance of connectivity between prefrontal and subcortical (including hippocampal) regions in cognitive control in terms of suppressing unwanted memory retrieval: with intact function in this network apparent in resilient but not vulnerable traumatised individuals (Mary et al., 2020). Although this signature may not be specific to PTSD, it may represent an important vulnerability factor for the devel-

opment of post-traumatic stress and other maladaptive coping mechanisms (e.g. substance use problems) following trauma (Ersche, 2020). Recent work in this area has also highlighted the importance of considering how multiple resilience-relevant factors may interact within the same individuals – specifically, how higher levels of prefrontally-mediated executive function may ‘rescue’ risk for anxiety in individuals with high neural responses to threat and low responses to rewards (Scult et al., 2019).

For understandable reasons, much of the work discussed here is unable to speak to the raft of complexities identified as being important in understanding resilience. The majority of the studies to date are both retrospective and cross-sectional in design, and few (particularly in the adult literature) have tested the same participants at multiple timepoints. This is significant, as only longitudinal studies can really tease out whether differences observed in resilient individuals represent pre-existing traits or active adaptations in the face of trauma. There are also some methodological weaknesses in some of the studies reviewed here. Much of the extant literature is based on small sample sizes, which are likely to be underpowered (Szucs and Ioannidis, 2020), and many older studies have also made use of overly-liberal multiple comparison correction methods, which may be subject to inflated type 1 error rates (Eklund et al., 2016; Cox et al., 2017). However, larger cohort-based functional imaging studies of resilience are starting to emerge, and some key findings have now been replicated in well-powered samples (e.g., Corral-Frias et al., 2015; Silveira et al., 2020). Finally, the identification of robust neuroimaging biomarkers (e.g. for prognosis in populations at high risk of trauma exposure) will likely require greater attention to the within-subject reliability of these measures – particularly given recent observations that this reliability may be low for both mean regional BOLD signal during emotional response/regulation tasks and canonical resting state networks (Nord et al., 2017; Elliott et al., 2019; Wall, 2019; Elliott et al., 2020). Multivariate approaches that exploit the high dimensionality of imaging data – perhaps in conjunction with naturalistic stimulus sets – may be more appropriate for this purpose (Dubois and Adolphs, 2016; Elliott et al., 2020; Finn et al., 2020).

Despite these challenges, interventions derived from neuroscientific studies of resilience are starting to be implemented in real-world settings (Greenberg, 2006; Waugh and Koster, 2015; Keynan et al., 2019). A complementary research stream examining the neural correlates of treatment response to existing therapies may give further insight into neural resilience mechanisms that may be ‘activated’ by successful engagement with treatment (e.g., increased ability to assimilate or reappraise trauma memories following psychotherapy). Together, it is hoped that these approaches may help resilience researchers achieve the aim of improving preventative and remedial interventions for stress-related disorders.

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Conflict of Interest

AF 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. AN and MPR have no relevant conflicts of interest to declare.

Box 3: Recommendations for future studies

- Studying multiple potential resilience-promoting factors *within the same individual* is necessary in order 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. In particular, 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. In order 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 and 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.

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