REVIEW ARTICLE

Neuroimaging resilience to trauma

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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 work, some striking regions of convergence emerge when considering the literature as a whole. Here, we review neuroimaging studies of resilience in both trauma-exposed individuals and the general population, alongside discussion of some of the methodological difficulties involved in quantifying trauma and resilience in human participants. Results highlight the involvement of brain networks implicated in emotion regulation (medial prefrontal cortex and amygdala), responses to rewards (ventral striatum), and attentional control and cognitive flexibility (prefrontal cortex and hippocampus) in fostering positive outcomes following trauma. There is also emerging evidence for a role of neural circuitry subserving interoceptive awareness (in particular, the anterior insula cortex) in resilience. Further, we discuss 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.

KEYWORDS
resilience, trauma, functional imaging

1 | INTRODUCTION

1.1 | Defining resilience: a multidimensional 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 trauma – rising to 46-65% for 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 has generally been referred to 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) – a deliberately operational and atheoretical approach that is agnostic as to the mechanisms underlying this outcome across individuals. 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 - i.e., refers to the *outcome* itself, rather than any pre-existing collection of psychological resources which an individual may possess.

Resilience-promoting *factors* can be thought of as anything that modifies the risk of poor outcome following adverse circumstances in a positive direction – which can be drawn from biological, psychological, social or socioeconomic domains. These 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; Kalisch et al., 2017; Ioannidis et al., 2018; Scheffer et al., 2018). According to this view, resilient outcomes are thought to 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). It is therefore vital to study these factors not in isolation but in the context of each other – ideally within the same individuals.

Importantly, expected level of psychosocial functioning following adversity is relative to the overall trauma burden of a given individual, as trauma exposure shows clear cumulative effects across lifespan (Karam et al., 2014; Feder et al., 2016). Recently, researchers have proposed an approach to quantifying resilience whereby a composite psychosocial functioning score is regressed against an appropriate measure of trauma exposure severity – such that the residuals from this model represent better ('*resilient*') or worse ('*vulnerable*') outcomes than would be expected from considering the group as a whole (Amstadter et al., 2014, 2016; van Harmelen et al., 2017; Ioannidis et al., 2018). To complicate the picture further, there is also an important temporal dimension to resilience – as time to return to premorbid function, or trajectory of symptom change over time, is a critical variable in terms of patient experience and psychological load (Bonanno and Diminich, 2013; Pietrzak et al., 2014; Ioannidis et al., 2018). Although challenging, increases in the 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 by explicitly embracing such complexity (Scheffer et al., 2018; Ioannidis et al., 2018).

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

The ultimate aim of resilience research is to harness insight on protective or 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 a tool that may enhance our understanding of the brain mechanisms associated with different routes to resilient outcomes in humans. Although it is important to be clear about scope of inferences we can draw from existing data (see *Discussion*), the ambition is that neuroimaging studies of resilience might help generate human psychopathology-informed mechanistic hypotheses for further experimental testing in animal models, lead to better phenotyping of currently diagnosed patients or at-risk individuals, and perhaps even engender the development of directly imaging-informed interventions, such as targeted neurofeedback, brain stimulation, and cognitive-emotional training.

2 | APPROACHES TO STUDYING RESILIENCE IN HUMANS

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).

There are important conceptual and experimental considerations to bear in mind when studying these different cohorts (see **Box 1: Quantifying trauma**). 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. To complicate the picture further, there may be trauma-specific considerations it is important to take into account when interpreting data from different populations – 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 in a study of women who have experienced violence from a male partner (see Fonzo et al., 2017). Finally, 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**).

Nevertheless, when considering the literature from these two bodies of work in parallel, there are some striking regions of convergence. By highlighting these regions of convergence across cohorts, we hope to shed light on some of the general mechanisms underlying good outcomes following significant trauma exposure – whilst at the same time acknowledging the masking of complexity inherent in such an approach.

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, in the study of resilience, such a definition is somewhat circular, and what we really 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" (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. 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. Of note, a recent meta-analytic report has highlighted the 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 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, including exposure to human remains, sustaining an injury while on site, and working more than the median number of hours on site, 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 currently being taken in population cohort studies (where nature, severity, and chronicity of trauma exposure are all likely to vary significantly across individuals) 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., for different measures of childhood family experience; van Harmelen et al., 2017).

3 | EXISTING NEUROIMAGING STUDIES OF RESILIENCE

Here, we review existing neuroimaging studies of resilience in humans – in both significantly trauma-exposed individuals and the general population. Findings are divided into several broad domains based on previous concentrations of resilience-related imaging research – specifically, *emotion regulation*, *response to rewards*, *attentional control and cognitive flexibility*, *social cognition*, and other putative resilience-promoting factors (*'active coping style'* and *mindfulness/interoceptive awareness*). Further, we review relevant evidence from studies of potential resilience *mechanisms* – namely cognitive reappraisal and successful fear extinction.

3.1 | Emotion regulation

There is 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 regulation of the amygdala 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 amygdalar responses to emotionally salient stimuli.

Initial studies in small samples of adults provided evidence of lower amgydalar blood flow in response to trauma-script imagery in male combat veterans without PTSD (compared to non-trauma exposed healthy controls; Britton et al., 2005), and both lower amygdalar and higher medial prefrontal BOLD signal during cued traumatic memory retrieval in symptom-free trauma-exposed male police officers, compared to those with partial PTSD (Peres et al., 2011). 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). Importantly, the study design included a group of non trauma-exposed healthy individuals, as well as trauma-exposed individuals with and without a diagnosis of PTSD – which is necessary in order to parse out differential effects of current symptom experience and trauma exposure on neural activity (see van der Werff et al., 2013). 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 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). Similarly, 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) – providing evidence that decreased amygdala responses to fear-related social cues near time of trauma may predict lower future levels of post-traumatic stress.

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 had no effect on self-reported state anxiety; Keynan

Box 2a. Quantifying resilience in trauma-exposed individuals

In biological studies of adult participants, resilience has often been defined on the basis of the absence of an DSM Axis-1 disorder diagnosis following significant trauma exposure, as confirmed by in-depth clinical interview. These categorical case-control 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 heterogenous, 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. When assessing resilience in terms of 'good' psychosocial outcome, it is also important to bear in mind what patients themselves report as critical outcomes in terms of their quality of life, who often place more weight on factors such as ability to work or maintain a fulfilling social life than disorder-specific symptom measures (Zatzick et al., 2001; Coulter, 2017).

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 (academic, social, etc., – see McGloin and Widom, 2001; Cicchetti and Rogosch, 2012). 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 or adaptive functioning is *environment-dependent* – adaptive behaviour in violence-heavy, highly volatile, or resource-poor environments may not conform to normative accounts of behaviour in more stable or resource-rich environments. Later maladaptive functioning may result from a failure to update behavioural or cognitive strategies that were successful in the previous environment when conditions change (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).

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 is a promising step towards development of a feasible and scalable neurally-guided intervention for individuals at risk of significant trauma exposure – but it is yet to be demonstrated whether this approach will be effective in mitigating development of psychological symptoms post-deployment.

These functional findings are mirrored to some extent in structural imaging literature. Resilient functioning in individuals with a history of childhood maltreatment has been related to larger volumes in various medial prefrontal regions (Whittle et al., 2009; Morey et al., 2016; Ioannidis et al., 2018), suggesting that maintenance of mPFC volume may be either a protective factor or common consequence of other resilience-promoting mechanisms. However, meta-analyses suggest no evidence for differences in amygdala volumes between trauma-exposed adults with/without PTSD (Woon and Hedges, 2009), and no evidence of amygdala structural alterations in healthy individuals with a history of childhood maltreatment (Paquola et al., 2016; Calem et al., 2017). It has been suggested that this null finding may be a result of treating highly heterogeneous samples of individuals with post-traumatic stress syndrome as monolithic – with one recent study finding a selective moderating effect of amygdala volume between combat trauma exposure severity and experience of anxious-arousal symptoms, at least cross-sectionally (Pietrzak et al., 2015).

There may also be resilience-related effects on local neural architecture that are not detectable at the gross volumetric level. Recently, Ohashi and colleagues used network analysis of diffusion-weighted imaging data from 192 young adults with a history of childhood maltreatment to examine anatomical network architecture, and found that resilience (in terms of absence of clinically significant levels of anxiety/depression symptoms) was associated with sparser amygdalar networks. The authors suggest that a greater degree of amygdalar segregation from other brain areas (increased 'small-worldness' resulting from intact local modular architecture but lower connectivity between modules) may represent a resilience-promoting adaptation in these individuals (Ohashi et al., 2018). The general idea that greater functional segregation of emotion-responsive regions is associated with resilient outcomes is partially supported by preliminary observations of lower integration of the dorsal anterior cingulate cortex (ACC) into resting emotional processing networks in women with early life trauma resilient to depression (Cisler et al., 2013), and an association between greater trait resilience and lower resting regional homogeneity (a measure of synchronisation among neighbouring voxels) in the ACC and the anterior insula in a large sample of healthy volunteers (Kong et al., 2015). It will be of interest to observe whether future studies in trauma-exposed individuals provide support for this hypothesis.

3.2 | Reward responsivity

There is also 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 (Dillon et al., 2009; Hanson et al., 2015, 2016; Sailer et al., 2008; Elman et al., 2009; 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 a 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). In a longitudinal study, decreased response to rewards in the nucleus accumbens post-, but not pre-exposure, was related to self-reported PTSD symptoms in combat-exposed paramedics – suggesting that preserved reward responses are a marker of resilience to PTSD (Admon et al., 2013). An 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 *nb* this is a relatively high-functioning and low maltreatment-exposure population; Corral-Frías et al., 2015). A 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 during viewing of positive images was associated with lower increases in depression scores at 2 year follow-up – suggesting that greater reactivity to rewarding social/environmental cues may represent a resilience-promoting factor against the development of depression symptoms in these children (Dennison et al., 2016).

Box 2b. Quantifying resilience in the general population

Contrary to the operational definition of resilience described by Kalisch and colleagues (Kalisch et al., 2017), some researchers have 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 resilience 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' that may not translate well to other 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 focus on putative *resilience-promoting traits* such as cognitive re-appraisal, mindfulness, and active coping – however the evidence for a relationship between these individual differences and resilient outcomes is still somewhat lacking in many cases. Finally, other studies have attempted 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.

3.3 | Attentional control and cognitive flexibility

Deficits in neurocognitive function, including working memory, attention, and cognitive flexibility, have been observed in groups of individuals with PTSD – which 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 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 greater BOLD signal in the dorsolateral PFC and superior frontal gyrus during incongruent trials on a Stroop task in healthy trauma-exposed group, compared to both individuals with PTSD and trauma-free controls (Blair et al., 2013). A study using data from N=1870 adolescents from the IMAGEN consortium showed that grey matter volumes in the right middle and superior frontal gyri were larger in adolescents who had experienced past adversity but were currently well-functioning – with results robust across different domains of resilient functioning, including social skills/relationships, academic performance, and experience of anxiety and depression (Burt et al., 2016). Although it is not clear how exactly greater cortical volume might relate to function, it is possible that larger grey matter volumes and increased executive control-related BOLD signal in these regions may be a common consequence of lower stress-related neurotoxicity in resilient individuals (see Discussion). Importantly, in a recent study of 120 university students that measured multiple domains of neural function within the same individuals, moderation analysis revealed that higher amygdala response to threat and lower ventral striatum activity to reward predicted increases in anxiety in those with average or low but not *high* prefrontal activity during an executive function task – suggesting that preserved prefrontal executive control may 'rescue' risk for anxiety in these individuals (Scult et al., 2019).

Increased hippocampal BOLD signal during inhibitory control on a Go-noGo task, measured 1-2 months following Category A trauma exposure, has also been shown to predict decreased PTSD symptom severity at 3 and 6 months post-trauma in an initial discovery and replication sample (van Rooij et al., 2018). Several previous studies have reported smaller hippocampal volumes in individuals with a diagnosis of PTSD compared to trauma-exposed controls – although it is somewhat unclear if this represents a vulnerability factor for or consequence of posttraumatic stress symptoms (van der Werff et al., 2013). 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.

3.4 | Social cognition

Behavioural and epidemiologic studies have identified social support as a vital factor in fostering resilient outcomes (van Harmelen et al., 2016, 2017; Fritz et al., 2018b; Yule et al., 2019). Further, higher levels of social cognitive function may predict better outcomes following trauma exposure, by conferring ability to recruit and maintain these important social support structures (Stevens and Jovanovic, 2019; Lepore and Kliewer, 2019). A recent mega-analysis (N=3872) from the ENIGMA consortium found that childhood maltreatment affects brain structure in regions implicated in social cognition on the basis of functional imaging studies (Tozzi et al., 2019). However, to our knowledge, only one study to date has probed neuroimaging correlates of social cognition in resilience. This study found 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 this 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.

3.5 | Other putative resilience-promoting factors

Active Coping Studies of individual differences in coping styles have implicated variation in medial prefrontal function in adaptive responses to prolonged (versus acute) stressors. For example, a cross-sectional association was identified between self-reported 'positive coping style' (tendency to endorse statements such as "*I tell myself that everything will turn our all right*" and "*I tell myself I can cope with it*"), lower levels of anxiety and depression symptoms, and increased rostral ACC volume in a sample of healthy young adults (Holz et al., 2016). Further, 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' ("*I take additional actions to get rid of the problem*", "*I concentrate my effort on doing something about it*") 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 coper', or *vice versa*.

'Mindfulness' and interoceptive awareness Although the role of mindfulness in promoting resilience following trauma exposure is still a somewhat open question (Boyd et al., 2018), several preliminary studies have identified a relationship between self-reported mindfulness, interoceptive awareness, insula cortex BOLD, and trait resilience scores. Higher trait mindfulness (defined as "*tendency to notice thoughts and emotions without getting engrossed in them, and without reacting automatically*") has been associated with lower insula BOLD during negative emotion trials on a response inhibition task (Paul et al., 2013) and with lower prefrontal and right insular BOLD when expecting negative images (Lutz et al., 2014). Lower BOLD signal in the middle insula and thalamus has also been identified during an aversive interoceptive awareness task (involving probabilistic impedance of inward breathing) in higher compared to lower trait resilient individuals – which the authors interpreted as being indicative of lower processing of aversive bodily perturbation in the higher resilience group (Haase et al., 2016).

An 8-week trial of a mindfulness-based intervention emphasizing interoceptive awareness in a small military sample found significant attenuation of anterior insula and dorsal ACC BOLD response to emotional faces at follow-up in the active intervention group, with individuals who exhibited greater reductions in insula BOLD reporting greater improvements on the Response to Stressful Experiences Scale (Johnson et al., 2014). Interestingly, a recent simulation study used a hierarchical generative model incorporating both cardiac data and an agent's awareness of its own internal state to demonstrate that 'lesions' of interoceptive awareness can lead to higher baseline tendency to expect fear-provoking events in the environment – such that intact interoceptive precision may play an important role in fostering resilience to disorders involving inappropriately high levels of fear expectancy (Allen et al., 2019).

3.6 | Studies of putative resilience mechanisms

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 et al., 2013). 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 heathy individuals – with differences in function in these regions identified between healthy control subjects and various patient samples (Zilverstand et al., 2017).

Regional BOLD signal measured during performance of a cognitive reappraisal task was not found to be associated with clinical response following exposure-based psychotherapy in individuals with PTSD – suggesting that this task may not be a good measure of individual capacity to engage in psychological processes associated with success of this particular form of therapy (Fonzo et al., 2017). Further, some commentaries have highlighted that cognitive reappraisal may not be a strategy available to all individuals, and may be particularly hard to implement during high intensity or stressful situations (Ford and Troy, 2019). However, one recent 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 a longitudinal study of maltreated youth (Rodman et al., 2019) – suggesting 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.

Successful fear memory 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 (Phelps et al., 2004), and greater retention of extinction memory during a lab-based fear conditioning test has been associated with increased ventromedial prefrontal cortical thickness (Milad et al., 2005). 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.

4 | DISCUSSION

The brain areas highlighted in neuroimaging studies of *resilience* to trauma so far overlap largely with those implicated in *vulnerability* for stress-related disorders – including the medial prefrontal and insula cortex, amygdala, and hippocampus. It is unclear if this an artefact of region-of-interest analyses derived from the psychopathology literature, or whether these 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-supressing effects of these molecules during chronic stress may be an important pathway towards resilience (McEwen and Morrison, 2013; Anacker and Hen, 2017).

Evidence for a role of preserved medial prefrontal function, in particular in downregulation of limbic responses to emotional stimuli, in fostering resilience outcomes 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). Despite a clear role in fostering positive outcomes following trauma exposure (Stevens and Jovanovic, 2019), there is currently almost no literature on the neural correlates of social functioning and social cognitive ability in resilient humans.

There is also evidence for an association between preserved reward signal processing in the ventral striatum and resilience to anhedonia and other depressive 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). 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). Recent work in this area has 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). Interestingly, individual differences in hippocampal function have also been related to positive autobiographical memory specificity, which has recently been identified as a predictor of resilience to depression following early life stress (McCrory et al., 2017; Askelund et al., 2019).

Studies of both trauma-exposed individuals and questionnaire measures of trait resilience in the general population have identified an association between variation in insula cortex function, interoceptive awareness and ability to modulate autonomic reactivity to salient stimuli, and resilience. The insula has been identified as a core hub of interoceptive processing (Gu et al., 2013), and recent perspectives highlight a role for the insula in both coordinating externally-oriented and internally-oriented attention and integrating context and expectations into response to aversive experience (Menon and Uddin, 2010; Wang et al., 2019; Atlas, 2019). It is possible that increased ability to shift attention away from salient signals in the environment, and instead focus on internal loci may help protect against PTSD hypervigilance symptoms (the 'mindfulness' approach), and/or that intact interoceptive accuracy may play a role in maintaining low threat expectations based on physiological feedback in the absence of explicit threat signals (Allen et al., 2019) – although this is yet to be empirically demonstrated.

There are some methodological weaknesses in the studies reviewed here. Much of the extant literature is based on small sample sizes, and many older studies have also made use of overly-liberal multiple comparison correction methods, so may be subject to inflated type 1 error rates (see Eklund et al., 2016; Cox et al., 2017). However, larger cohort-based imaging studies of resilience are starting to emerge, and some key findings have now been replicated in well-powered samples (e.g., Corral-Frías et al., 2015). The vast majority of the studies reviewed here 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. Finally, the identification of robust neuroimaging biomarkers (e.g. for prognosis of outcomes 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., 2019b,a; Wall, 2019). 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., 2019b; Finn et al., 2019).

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 remediative 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.

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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 (for example race/ethnicity, gender identity, and perceived social support).
- 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 resilience 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 mechanisms.

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