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State-of-Science Review: E7
The Neural Basis of Resilience

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Summary

Resilience can be characterised as adaptive responding to stressful or traumatic circumstances or events. Stress and trauma are major precipitants of mental health problems in vulnerable individuals and therefore understanding why resilient people are protected from these effects is important for mental health research. Resilience has been studied in psychosocial research for some time. However, the neurobiology of resilience is a more recent and less developed research area. Important reviews have emphasised the importance of multiple interacting factors, with clear roles for both biological and environmental influences. This review considers briefly how specific biological factors impact on resilience, with reference to post-traumatic stress disorder (PTSD) and depression. We consider cognitive factors, particularly the coping strategies that resilient individuals employ. Neurochemical factors are also important, and we discuss evidence implicating neuropeptide Y and dehydroepiandrosterone in the mediation of stress and resilience. Brain imaging provides a tool for assessing *in vivo* brain structure and function, with several studies suggesting that regions of the extended limbic system are likely to play key roles in determining resilience. Finally, genetic research is showing how genetic markers underpin personality traits including resilience to stress and trauma. These biological factors interact with each another as well as environmental triggers to determine how an individual responds to stressful or traumatic events. Understanding these interactions may offer clues to help us strengthen resilience in individuals vulnerable to stress-induced mental health problems.

1. Introduction

Although the concept of resilience has been of interest for thousands of years, empirical study of human resilience has only developed in the last few decades. Resilience can be defined as an individual's successful adaptation and functioning in the face of stress or trauma. Psychological resilience is a relatively stable feature of personality that allows an individual to bounce back from stress or adversity. Much of the initial empirical research on resilience was psychosocial. However, a seminal review by Curtis and Cicchetti (2003) emphasised the biological aspects of resilience, and the concept is now attracting increasing interest among neuroscientists.

Cicchetti and Blender (2006) recently presented a perspective on resilience research that stressed the need for multiple levels of analysis. Although there is clear evidence for biological factors (neuroendocrine markers, genetic factors and neuroimaging indices of brain structure and function), these occur in the context of environmental influences. Key questions concern how environmental factors produce the biological influences that underpin resilience.

An important concept for research is plasticity in neural development. Experiences affect neural structure and function, and plasticity relates to the brain's ability to respond and recover. There are at least two distinct mechanisms for the brain basis of resilience. One possibility is that resilient individuals have a particularly enhanced ability to recover from adversity or trauma (a type of 'super-plasticity'). Alternatively, individuals may have a better-than-average resistance to environmental impact. That is, stress or trauma produce less significant detrimental effects on neural function. Both mechanisms may contribute to resilience, and modern neuroscience techniques are allowing these possibilities to be explored.

The neuroscience of resilience has largely been studied in three contexts. The first is developmental psychology/psychopathology: specifically studying why childhood adversity leads to maladjustment in some children but not others. The second is post-traumatic stress disorder (PTSD) and why some individuals develop PTSD in response to trauma while others do not. Finally, the third is depression. Environmental stressors and adverse life events are important triggers for depression in vulnerable individuals, but others are resilient in the face of life stress.

Understanding mechanisms of vulnerability is a typical focus for studying the aetiology of mental health problems. However, understanding resilience provides a valuable counterpoint. This review briefly explores the role of four neuroscience factors in resilience: cognitive psychology; neurochemistry; brain structure and function; and genetic factors, with examples from research on post-traumatic stress disorder and depression.

2. Psychological factors

A number of psychological characteristics have been associated with resilience. Studies of children raised in a variety of adverse situations have consistently revealed that successful adaptation is predicted by factors including high levels of intellectual functioning, strong attachment behaviour, optimism, altruism and active coping styles (Masten and Coatsworth, 1998; Bell, 2001). In adults employed in stressful professions (military forces, fire-fighting, police), resilience to stress is associated with group bonding, altruism and effective performance under stress.

Other important psychological constructs related to resilient responses to stress and trauma include positive affectivity or optimism, cognitive reserve, cognitive flexibility and the development of coping strategies (Yehuda et al., 2006; Barnett et al., 2006).

2.1. *Positive affectivity*

Positive affectivity has been explored in studies of patients with depression and mania. Elliott et al. (1998) studied how patients with depression and healthy controls responded to performance feedback on cognitive tasks. The feedback was 'rigged' such that, in some conditions, feedback was positive regardless of performance. In others, it was negative, while in a control condition, no feedback was provided. Both patients and controls performed better when the feedback was positive compared to when it was negative. In the absence of feedback, controls performed as though receiving positive feedback, while patients performed as though receiving negative feedback. This suggests that, unlike depressed patients, controls assume they are performing well in the absence of information to the contrary; they have a form of positive affectivity that may confer resilience to depression.

In another study of depression, Erickson et al. (2005) used an affective 'Go/No-go' task. Subjects were presented with blocks of emotional words, some happy and some sad. In some blocks, subjects had to respond to the happy words and ignore the sad, while in others the reverse pattern of responding was required. Depressed patients responded more slowly and made more errors for happy words. Healthy subjects were slower and less accurate for sad words, suggesting a positive affective bias that may be associated with resilience. The functional neural basis of these effects has also been studied (see below).

Interestingly, it is possible that there is an optimum level of positive affectivity for psychological resilience. Individuals who are vulnerable to mania may experience excess positive affect. Farmer et al. (2006) performed a study in which they induced positive mood in stable subjects with bipolar depression and controls. Positive mood was induced in both groups but was more sustained in the subjects with mania, suggesting that extremes of positive affectivity may be maladaptive.

2.2. *Cognitive flexibility*

The salient aspect of cognitive flexibility is the ability to reinterpret an adverse event to find meaning or opportunity. In studies of combat veterans, PTSD is less prevalent in those who have this characteristic (Baldwin et al., 1994). Cognitive flexibility may be correlated with general cognitive functioning. There is evidence that patients with PTSD have impaired cognitive function on various measures (e.g. Golier et al., 2002), and Kanagaratnam and Asbjornsen (2006) have suggested there may be some specificity of impairment on laboratory measures of cognitive flexibility. However, it is not clear whether this is a vulnerability factor or a consequence of developing PTSD.

In a recent study (Kremen et al., 2007), a large sample of Vietnam veterans were considered. Cognitive ability scores had been obtained at the onset of military service (i.e. prior to trauma exposure) and higher levels of cognitive ability were associated with lower risk of PTSD after stress exposure, which may reflect resilience. Similarly Barnett et al. (2006) have suggested that superior cognitive function, or cognitive reserve, may be a resilience factor in schizophrenia (and other psychiatric disorders).

2.3. *Coping strategies*

Active coping strategies involve adopting a problem-solving approach to a stressful situation, and this type of strategy (as opposed to passive approaches like denial) has been associated with resilience in a number of contexts. This strategic approach may confer a mastery over the situation which prevents a sense of 'learned helplessness' (see, for example, Amat et al., 2005; Robbins, 2005). For example, Gulf War veterans who employ active coping strategies show lower levels of stress-related symptoms (Sharkansy et al., 2000). More recently, studies have shown that individuals affected by the 9/11 terrorist attacks in New York reported lower levels of distress and PTSD six months after the attacks if they used active coping strategies (Silver et al., 2002).

Other important aspects related to coping strategies are religious coping and social support. Various studies have suggested that people with strong religious affiliation are more resilient (Hill and Pargament, 2003), although it is unclear whether this is due to religious faith *per se* or the social support offered by religious communities. It is certainly clear that strong social support networks of various forms promote resilience in the face of stress or trauma (Cohen et al., 2000).

3. Neurochemical factors

A variety of neurochemical compounds have been suggested to influence resilience. For example, a review by Charney (2004) identified 11 compounds involved in mediating psychobiological responses to stress and thus may contribute to resilience. A detailed account of stress neurochemistry is beyond the scope of this review. However, two key neurochemicals that have been empirically associated with resilience will be discussed briefly below.

3.1. *Neuropeptide Y (NPY)*

NPY is a peptide that influences the function of the hippocampus and may act as an anxiolytic (Heilig, 2004). Patients with PTSD show reduced baseline levels of NPY (Morgan et al., 2003) and, conversely, individuals with high levels of NPY show enhanced performance under stressful conditions (Morgan et al., 2000).

Findings in combat veterans also support the idea that high levels of NPY serve as a biological marker for resilience to, or recovery from, stress and trauma (Yehuda et al., 2006b).

3.2. *Dehydroepiandrosterone (DHEA)*

DHEA and cortisol are adrenal steroids released in response to stress. Both DHEA levels and DHEA/cortisol ratios have been suggested as biological markers of resilience. Morgan et al. (2004) reported positive correlations between DHEA levels (and DHEA/cortisol ratios) and the performance of military recruits under stressful conditions.

Rasmusson et al. (2004) found a negative correlation between DHEA reactivity to stress and PTSD symptom severity, which may suggest that high levels of DHEA protect against the adverse effects of stress and trauma. Negative associations have also been reported between DHEA levels and depressive symptoms in adolescents, again implicating a role for elevated DHEA levels in psychological resilience (Goodyer et al., 2001).

4. Brain structure and function

Neuroimaging techniques, particularly functional magnetic resonance imaging (fMRI), can be used to examine how individual differences in brain structure and function may relate to resilience. This kind of research is very much in its infancy. However, there are two established lines of imaging evidence that are relevant to resilience.

The first is research examining normal responses to anxiogenic and other emotional stimuli, and the second is research in depressed patients and patients with PTSD. Both these avenues are important in establishing likely functional mechanisms of resilience, which can then be explored in more explicit studies.

4.1. *Neuroimaging of emotional stimuli*

Imaging studies of responses to various emotional stimuli have identified the amygdala and regions of the medial prefrontal cortex (mPFC) as particularly important. LaBar et al. (1998) reported amygdala activation during a fear conditioning task, suggesting that this region is an important mediator of acquired anxiety. Chua et al. (1999) reported areas including the anterior cingulate (part of the mPFC) associated with anticipatory anxiety.

Differences between anticipatory responses to aversive stimuli and responses to the stimuli themselves have been reported in prefrontal regions (Nitschke et al., 2006). However, this study also found common amygdala and mPFC response to both anticipation and actual exposure. Kalisch et al. (2006) suggested that anticipatory responses in mPFC/anterior cingulate may reflect higher-level cognitive appraisal of emotional material.

These findings have clear implications for resilience research. If normal responses to aversive or anxiogenic stimuli involve the amygdala and mPFC, it is reasonable to hypothesise that the trait of resilience may be associated with significant modulation of these responses. Some evidence for this comes from Kalisch et al. (2005; 2006b) who have shown that using strategies to reduce anxiety during anticipatory anxiety paradigms is associated with altered function in prefrontal regions, including mPFC.

Evidence for a role of mPFC in resilience also comes from studies of paradigms described in the section on positive affectivity above. Behaviourally, control subjects show a bias towards positive material in an affective

Go/No-go task. This bias is reflected in the functional response of the anterior cingulate which shows enhanced activity when subjects are responding to happy targets and decreased activity when responding to sad targets (Elliott et al., 2000).

This positive bias in healthy volunteers has been shown to be diminished or abolished by acutely reducing brain serotonin through dietary means (Murphy et al., 2002; Rosier et al., unpublished data). Responses to negative performance feedback have also been studied, with control subjects showing decreased amygdala response and enhanced prefrontal (including mPFC) response (Taylor-Tavares et al., unpublished findings). The amygydala decrease predicted the extent to which subjects suppressed any tendency to inappropriately change behaviour in response to negative feedback information. This suggests that amygdala function may be related to adaptive responses to potentially stressful environmental information.

In the last few years, neuroimaging research has increasingly entered the realms of social neuroscience, with studies examining the neural basis of social behaviours. Given the clear importance of social factors in adaptive and resilient behaviours, much of this research may prove relevant to the neuroscience of resilience. For example, Rilling et al. (2002) showed that regions including ventral mPFC were more responsive during mutual co-operation in an interactive game. Conversely, Eisenberger et al. (2003), using a paradigm that modelled social exclusion, found that the anterior cingulate was more responsive during exclusion then inclusion, and this increased response correlated with self-reported distress. Both social cooperation and inclusion/exclusion may be relevant to understanding how social support networks modulate resilience.

4.2. *Neuroimaging in patients*

Imaging studies of patients with PTSD have identified brain regions associated with a pathological response to stress and trauma, which may also be regions associated with resilience.

Typically, structural imaging studies of PTSD have implicated the hippocampus as a potentially important site of pathology (Rauch et al., 2006 for review). This structure is involved in the normal consolidation of emotional memories (LaBar and Phelps, 2005) and interacts closely with the amygdala and mPFC. Neurochemical imaging studies with magnetic resonance spectroscopy (MRS) have also suggested hippocampal abnormalities in PTSD, while functional MRI studies have reported abnormalities within amygdala/hippocampus/mPFC circuitry (Rauch et al., 2006).

However, the imaging results in PTSD are not always consistent. Three recent studies have found no evidence of structural or neurochemical abnormalities in the hippocampus of three distinct, elderly populations with PTSD: Holocaust survivors, combat veterans and former prisoners of war (Golier et al., 2005; Freeman et al., 2005; Yehuda et al, 2006). In all three studies, subjects with PTSD were compared to those who had experienced comparable trauma but were not symptomatic for PTSD. Yehuda et al. suggest that the effects of normal ageing on hippocampal structure may have obscured any effects of PTSD. Freeman et al. suggest an alternative hypothesis.

In their study of former POWs, they noted that the subjects in their elderly cohort were both longer-lived than average and extremely fit and healthy for their age. Those with PTSD showed unusually low levels of psychiatric co-morbidity and much lower symptom severity levels than a younger group of combat veterans with PTSD. They therefore argued that even those of the cohort with PTSD actually represented a rather resilient sample who had survived to advanced old age. Extreme combat stress is associated with elevated mortality rates (Guest and Venn., 1992; Johnson et al., 2004), so those who survive well into old age may reflect a resilient population, even those individuals experiencing symptoms of PTSD.

Freeman et al. (2005) thus imply that normal hippocampal volumes in the face of severe stress and chronic PTSD symptomatology may be a marker for resilience.

Imaging studies of depression have also provided clues about resilience, particularly those using cognitive/emotional challenges. As discussed above, normal subjects show enhanced ventral anterior cingulate responses to happy words in an affective Go/No-go task but reduced responses to sad words. Depressed patients show exactly the opposite pattern (Elliott et al., 2002). This suggests that the ventral cingulate mediates affective biases. A bias towards sad information may influence vulnerability to, and persistence of, depression; while a bias towards happy information, as seen in control subjects, may confer resilience.

Performance feedback is another form of affective information that has been studied with fMRI. Elliott et al. (1998) reported reduced medial frontal responses to feedback in depression. More specifically, Taylor-Tavares et al. (unpublished findings) have observed an absence of the normal amygdala and prefrontal responses to negative feedback in depressed patients, suggesting that the normal responses in these regions may be associated with resilience.

In a more explicit imaging investigation of resilience to depression, Kruger et al. (2006) performed a PET study of bipolar disorder. As well as bipolar patients and healthy controls, they studied patients' siblings. This was a group who were healthy but considered at-risk. In response to a negative mood induction procedure, patients showed various neuronal abnormalities including decreased medial prefrontal response. The at-risk siblings showed a number of common abnormalities. However, response in the medial prefrontal region was *increased* in this group. Kruger at al. suggest that this increased medial frontal activity may reflect 'a compensatory effect and a capacity for resilience in the siblings'.

Overall, the neuroimaging studies related to resilience suggest that a number of brain regions may mediate these effects, with the amygdala and medial prefrontal cortex prominent among these.

5. Genetic markers

In recent years, genetic influences related to resilience have been studied. Caspi et al. (2002) investigated the influence of genetic factors on the propensity of abused children to develop antisocial personality disorders. A functional polymorphism in the gene encoding the enzyme monoamine oxidase A (MAOA) was found to be important. The gene for high MAOA was associated with a greatly reduced risk of antisocial behaviour, suggesting that this gene may confer a degree of resilience.

Caspi et al. (2003) also studied genetic influences on the development of depression in response to stressful life events. They found that a functional polymorphism in the serotonin transporter gene (5-HTT) modulated the interaction between life events and depression. The gene has two alleles: a long and a short form. Individuals with either one or two short alleles were more vulnerable to depression in the face of stressful life events. Individuals with two long alleles, by contrast, were resilient in response to life stresses, and much less likely to develop depressive symptoms.

It is important to note that these genetic studies were considering interactions between genes and environmental factors. In both studies, a particular genetic polymorphism was associated with a more resilient response to stressful or traumatic life events.

6. Conclusions

Although the neuroscience of human resilience is a relatively new research area, important clues are emerging.

Psychological factors, neurochemical balances, structural and functional brain markers and genetic influences have all been associated with potential mechanisms of resilience to stress and trauma.

Patient studies of PTSD and depression have also provided important leads, identifying factors that may confer vulnerability, and thus suggesting possible mediators of resilience in individuals who do not develop psychiatric symptoms in response to comparable levels of trauma.

We emphasise, however, that the various factors described here should not be considered in isolation; rather they interact with each other, and with environmental and psychosocial influences, in determining levels of resilience. For example, key genetic polymorphisms are likely to dictate neurochemical balances, while differences in brain function in response to emotional challenges may underpin crucial psychological strategies.

Psychological constructs such as cognitive reserve, cognitive flexibility and coping strategies may depend on top-down control of amygdala function by prefrontal cortical regions. It may, therefore, be possible to strengthen resilience through pharmacological and non-pharmacological means, including cognitive behavioural or other psychological therapies and education.

Recent reviews of resilience highlight the importance of maintaining an interactive perspective in future research (Yehuda et al., 2006; Cicchetti and Blender, 2006).

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