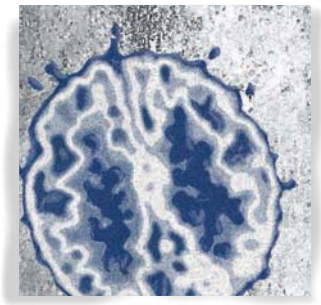
Behavioral control, the medial prefrontal cortex, and resilience

Steven F. Maier, PhD; Jose Amat, PhD; Michael V. Baratta, MA; Evan Paul, BA; Linda R. Watkins, PhD



The degree of control that an organism has over a stressor potently modulates the impact of the stressor, with uncontrollable stressors producing a constellation of outcomes that do not occur if the stressor is behaviorally controllable. It has generally been assumed that this occurs because uncontrollability actively potentiates the effects of stressors. Here it will be suggested that in addition, or instead, the presence of control actively inhibits the impact of stressors. At least in part, this occurs because (i) the presence of control is detected by regions of the ventral medial prefrontal cortex (mPFCv); and (ii) detection of control activates mPFCv output to stress-responsive brain stem and limbic structures that actively inhibit stress-induced activation of these structures. Furthermore, an initial experience with control over stress alters the mPFCv response to subsequent stressors so that mPFCv output is activated even if the subsequent stressor is uncontrollable, thereby making the organism resilient. The general implications of these results for understanding resilience in the face of adversity are discussed.

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The experience of traumatic life events is an important factor in the development of a number of clinical conditions, ranging from anxiety disorders such as post-traumatic stress disorder (PTSD) to drug addiction. However, not all individuals who encounter stressful life events develop these disorders, and so there is considerable interest in understanding what makes an individual vulnerable, and what makes an individual resilient to the deleterious effects of traumatic events.[1] Genetic factors doubtlessly play a role, but aspects of the stress experience and complex cognitive factors regarding how the individual appraises or views that experience have been argued to be key. In humans, most studies of resilience have included the individual's perceived self-efficacy,[2] perceived ability to cope,[3] or actual ability to exert control over the stressor[4] as key variables. Furthermore, other factors, such as religious faith[5] and sociopolitical effectiveness,[3] have been argued to produce resilience because they induce a sense of control.

It is difficult to study variables such as these in animals, yet it is in animals that detailed neurobiological mechanisms can be explored. The stressor controllability paradigm, however, is one of the few that allows isolation of this type of process. Here, animals that receive stressors that are physically identical are compared, with one group having behavioral control over an aspect of the stressor (its termination), and the other group having no control. In our version of this paradigm, rats are placed in small boxes with a wheel mounted on the front. The

Author affiliations: Department of Psychology and Center for Neuroscience, University of Colorado at Boulder, Colorado, USA

Address for correspondence: Steven F. Maier, University of Colorado, Department of Psychology, Campus Box 345, Boulder, CO 80309-0345, USA (e-mail: steven.maier@colorado.edu)

Selected abbreviations and acronyms

5-HT	*serotonin*
CE	*central nucleus of amygdala*
CS	*conditioned stimulus*
DRN	*dorsal raphe nucleus*
ES	*escapable shock*
IS	*inescapable shock*
LC	*locus coeruleus*
mPFCv	*medial prefrontal cortex*
mPFC	*ventral medial prefrontal cortex*
PTSD	*post-traumatic stress disorder*
US	*unconditioned stimulus*

rat's tail extends from the rear of the box so that electrodes can be directly fixed to the tail. For one group of rats ("escape") each of a series of tailshocks terminate when the rat turns the wheel with its paws. Thus, this group has behavioral control over the termination of each tailshock. Each member of a second group ("yoked") is paired with one of the escape group and simply receives tailshocks of the same durations as determined by its partner; turning the wheel has no consequence. There are other stressors whose sequelae may well be due to the uncontrollability of the stressor (eg, social defeat), but since controllability cannot be readily manipulated in these paradigms, this cannot be determined. Indeed, this is why shock is used in our studies. We know of no other aversive event whose controllability can readily be manipulated in such a way that the subjects with and without control experience identical physical events.

Research conducted by numerous laboratories has revealed a constellation of behavioral changes that follow uncontrollable, but not controllable, shocks. Thus, rats exposed to uncontrollable shock later fail to learn to escape shock in a different situation (the so-called "learned helplessness" effect), are inactive in the face of aversive events (so-called "behavioral depression"), become less aggressive and show reduced social dominance, behave anxiously in tests of "anxiety" such as the social interaction test, are neophobic, develop ulcers, respond in exaggerated fashion to drugs of abuse, etc.[6] None of these outcomes follow if the organism is able to exert control over the stressor.

Prior research has focused on the neural mechanism(s) by which uncontrollable stress (inescapable shock, IS) leads to the above behavioral outcomes. Indeed, this can be said of most stress research in animals, since the stressors that are used (restraint, social defeat, cold water, etc) have almost always been uncontrollable. There has been very little work directed at understanding the mechanism(s) by which control confers protection from the effects of the stressor. Indeed, most experiments studying the neurobiology of stress do not even contain a group for whom the stressor is controllable—the typical comparison is between a group exposed to an uncontrollable stressor and a home cage control group. What is known is that uncontrollable stress produces sequelae that are not produced by physically identical controllable stress. It has been implicitly assumed that this difference occurs because the organism detects/learns/perceives that the uncontrollable stressor is uncontrollable, and that this sets in motion the neural cascade that mediates the behavioral outcomes. The unstated assumption has been that stress per se produces neural consequences that are then magnified by the detection/learning/perception of uncontrollability. That is, it has been assumed that uncontrollability is the "active ingredient." From this point of view, controllable stressors fail to produce outcomes such as exaggerated anxiety simply because they lack the active uncontrollability element. However, it is also possible that instead the *presence* of control is the "active ingredient." Here, the detection/learning/perception of control would *inhibit* neural responses to stressors. Of course, both could be true. As will become clear, this is not merely a semantic difference.

The purposes of the present paper are to review recent work suggesting that the presence of control does actively inhibit limbic and brain stem reactions to a stressor, and the mechanisms whereby this inhibition is achieved. It will be argued that the research that will be described provides insights into mechanisms that produce resilience in the face of adversity.

Serotonin and the dorsal raphe nucleus

As noted above, most of the research on stressor controllability has been directed at understanding how uncontrollable stress produces its behavioral outcomes, such as poor escape learning and exaggerated fear/anxiety. Different laboratories have focused on different brain regions and neurotransmitter systems. We have concentrated our efforts on the dorsal raphe nucleus (DRN). The DRN is the largest of the raphe nuclei and provides serotonergic (5-HT) innervation to much of the forebrain, as well as other structures. We originally stud-

ied the DRN as a potential critical mediator of the behavioral effects of IS because it projects to structures that are the proximate neural mediators of many of the behavioral sequelae of IS, and elevated 5-HT within these structures seemed to produce the appropriate behaviors. For example, the dorsal periaqueductal gray is a proximate mediator of escape behavior,[7] and it is innervated by the DRN. Moreover, stimulation of the DRN interferes with escape.[8] Analogous neural arrangements existed for many of the other behavioral consequences of IS, and so it seemed, a priori, as if the known behavioral consequences of IS would occur if IS were to differentially activate DRN 5-HT neurons. The DRN has proved to have a complex subnuclear organization, with different regions of the DRN receiving discrete sets of afferents and having different efferent projections.[9] Our work has implicated mid and caudal regions of the DRN as being critical to IS effects. All that needs to be noted here is that this work, as well as recent research from other laboratories,[10] has delineated a 5-HT system, projecting to a number of mesolimbic structures, that appears to be important in the mediation of anxiety-like behavior.[11] We[12] have argued that the changes produced by IS are much more related to anxiety than depression, and so the argument that what is involved is an exaggerated 5-HT response is not problematic.

The most relevant findings are the following: (i) IS produces a much greater activation of 5-HT neurons in the mid and caudal DRN than do exactly equal amounts and distributions of escapable tailshock (ES). This has been assessed both by an examination of Fos in 5-HT-labeled cells[13] as well as measurement of 5-HT efflux within the DRN[14] and projection regions of the DRN15 with in vivo microdialysis; (ii) This intense activation of 5-HT neurons leads to the accumulation of high extracellular levels of 5-HT within the DRN. This high concentration of 5-HT desensitizes/downregulates inhibitory somatodendritic 5-HT_{1A} receptors within the DRN for a number of days[16]; (iii) 5-HT_{1A} desensitization/downregulation within the DRN sensitizes DRN 5-HT neurons since this normal source of tonic inhibition is now reduced. Thus, for a number of days, stimuli that normally produce little or no 5-HT response now induce large 5-HT activation.[15] Behavioral testing conditions such as escape training, fear conditioning, etc, now lead to exaggerated 5-HT release in projection regions of the DRN, the proximate cause of the behavioral outcomes. It is known that DRN 5-HT activity is a cause of the behavioral outcomes of IS because lesion of the DRN[17] and selective pharmacological inhibition of 5-HT DRN neurons at the time of behavioral testing[18] completely block the behavioral effects of IS. In addition, pharmacological inhibition of DRN 5-HT activity at the time of IS prevents the usual behavioral outcomes of IS from occurring.[18] Finally, simply activating DRN 5-HT neurons, in the absence of any IS, produces the same behavioral outcomes as does IS.[19]

This focus on the DRN is not meant to suggest that other structures are not involved. For example, the work of J. Weiss (eg, ref 20) clearly implicates the locus coeruleus (LC). However, the behavioral effects of IS and other uncontrollable stressors must be mediated by a complex neural circuit, and the DRN is likely but one, albeit critical, part of the circuit. We believe that the DRN is a key integrative site on the efferent end of the circuit and receives inputs from multiple key structures. The LC can be viewed as one of these inputs.[21]

The medial prefrontal cortex

Although the work summarized above clearly implicates the DRN as a key site in the mediation of the behavioral effects of uncontrollable stress, the concept that it must be part of a more extended circuit naturally suggests the question of whether the DRN (or LC) could be the structure that detects/learns/perceives whether a stressor is, or is not, under behavioral control. The DRN is a small brain stem structure consisting of perhaps 30 000 neurons in the rat. Moreover, the DRN does not receive direct somatosensory input. Thus, it would appear to have neither the inputs required, nor the "processing power," to compute whether a stressor is controllable or uncontrollable. The circuitry that performs this analysis must have available to it information concerning exactly when motor responses occur and when the stressor begins and ends. Further, it must be able to compute the correlation between the two. We thus determined inputs to the DRN that mediate the effects of uncontrollable stress, and uncovered several (locus coeruleus, lateral habenula, and likely the bed nucleus of the stria terminalis [BNST]). However, none were themselves sensitive to stressor controllability—they simply provided excitatory drive to the DRN whenever a stressor was present, controllable or uncontrollable.[22]

In any case, the detection/computation of degree of control would seem likely to be a cortical function, and so

it is of interest to inquire into which regions of cortex provide monosynaptic inputs to the DRN. Interestingly, the DRN receives all, or virtually all, of its cortical inputs from infralimbic (IL) and prelimbic (PL) regions of the medial prefrontal cortex (mPFC).[23] The mPFC is involved with mediating "executive functions"[24]; functions that are consistent with behavioral control detection. Furthermore, the mPFC has been shown to be a key site in "contingency learning" as opposed to habit formation,[25] a process very close to control learning.

IL and PL regions, which comprise the ventral mPFC (mPFCv) send excitatory glutamatergic projections to the DRN.[26] However, within the DRN these pyramidal glutamatergic projections synapse preferentially onto γ-aminobutyric acid (GABA)-ergic interneurons that inhibit the 5-HT cells.[26] As would be expected from this anatomy, electrical stimulation of regions of the mPFCv that contain output neurons to the DRN leads to *inhibition* of 5-HT activity within the DRN.[27,28]

The fact that activation of mPFCv output to the DRN actively inhibits DRN 5-HT activity immediately suggests that if the mPFCv is indeed involved in control/lack of control detection, then perhaps it is really control that is the active ingredient, leading to mPFCv-mediated active inhibition of the DRN when it is present. Here the idea is that aversive stimulation per se drives the DRN, and when the presence of behavioral control is detected by the mPFCv, the DRN, and perhaps other stress-responsive limbic and brain stem structures (see below) are actively inhibited.

In our first attempt to test the role of the mPFCv, we inactivated the mPFCv during exposure to IS and ES by microinjecting muscimol into the region.[29] Muscimol is a GABA agonist, and so inhibits the activity of cells that express GABA receptors, such as the pyramidal output neurons. Inactivating the mPFCv did indeed eliminate the differential effects of controllability—that is, IS and ES now produced the same outcomes. However, mPFCv inactivation eliminated the IS-ES in a particular way. The presence of control was no longer protective, and now ES as well as IS produced later escape learning failure and exaggerated fear conditioning. Furthermore, ES now activated the DRN to the same degree as did IS. Inactivating the mPFCv did not make IS better or worse; it acted only in ES subjects to eliminate the protective effect of control. It is important to note that muscimol microinjection did not retard the learning of the wheel-turn escape response during ES by the ES subjects. That is, the ES subjects turned the wheel and terminated the tailshocks, but did not benefit from the experience. This is in keeping with data indicating that the mPFC is not involved in the learning of habits or motor responses, but rather in more complex cognitive aspects of behavior. Thus, when the mPFCv was inactivated the animals learned to turn the wheel, but this now did not lead to inhibition of the DRN. The DRN acted as if the stressor was uncontrollable, even though the rats turned the wheel and escaped normally!

The foregoing suggests that what is important is whether the mPFCv is activated during a stressor, not whether the stressor is actually controllable or not. To further test this idea, we directly activated the mPFCv during IS and ES. The mPFCv was activated by microinjection of the GABA antagonist picrotoxin, a procedure that has been shown to activate mPFCv output.[30] *Figure 1* shows the results of shuttlebox escape testing administered 24 hours after the ES and IS sessions, or home cage control treatment. Escape trials terminated automatically after 30 sec if the subject failed to escape on that trial, and so group means near 30 seconds indicate that most of the rats in the group completely failed to escape. In vehicle-injected subjects, IS interfered with later shuttlebox escape and ES did not, as is typical. Dramatically, IS produced no interference with escape at all if the mPFCv was activated during the IS with picrotoxin. These animals did not have a means to control shock during the initial stress

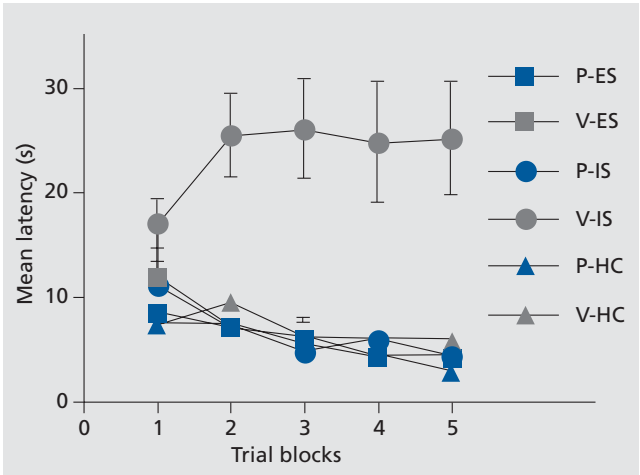

Figure 1. Mean latency to escape across blocks of five shuttlebox trials 24 h after experimental treatment. Experimental treatments were escapable shock (ES), yoked inescapable (IS), or home cage control (HC). P, picrotoxin before experimental treatment; V, vehicle

experience, but simply activating the mPFC during the stressor protected them. Importantly, the DRN was now not activated—it responded as if the shock was controllable (these data are not shown).

Behavioral immunization, resilience, and the mPFCv

In both humans and animals, an individual's early or initial experiences with stressors can determine how that individual reacts to subsequent stressful life experiences.[31] Many years ago, it was reported that an initial experience with controllable shock blocks the typical behavioral effects of a later exposure to uncontrollable shock, even if the two experiences occur in very different environments.[32,33] That is, an initial experience with control seemed to "immunize" the rat subjects.

This immunization phenomenon is very different than the usual effects of control that have been studied. In the typical experiment, the presence of control blunts the impact of the stressor that is occurring at that time. However, in the immunization paradigm, an initial experience with control blunts the impact of an uncontrollable stressor occurring at a later period of time.

This immunization phenomenon has not been studied at the neurobiological level. Clearly, the initial exposure to controllable stress would activate the mPFCv. It is our hypothesis that there is plasticity in this system so that mPFCv activity becomes associated with or "tied" to the stressor or some aspect of the stress experience such as fear/anxiety (see below). If this were so, then the mPFCv would become activated during the later uncontrollable stressor, thereby inhibiting the DRN and protecting the organism from outcomes that depend on DRN activation.

During the past year we have begun to test this admittedly speculative hypothesis. *Figure 2* shows the results of an experiment in which rats received either ES, IS, or HC treatment on Day 1, and IS in a different environment 7 days later. Shuttlebox escape testing occurred 24 hours after the Day 8 IS. Either intra-mPFCv muscimol or vehicle microinjection preceded the Day 1 treatment. As is evident, the experience of ES 7 days before IS completely blocked the behavioral effect of IS. That is, behavioral immunization occurred. However, mPFCv inactivation during ES blocked the ability of ES to produce immunization. In a separate experiment, the mPFCv was inactivated at the time of the Day 8 IS rather than during ES on Day 1. This manipulation also blocked immunization (data not shown in the *Figure*). Thus, mPFCv activity is necessary for immunization, both at the time of the initial experience with control and the later exposure to the uncontrollable stressor for protection to occur.

The hypothesis being considered suggests that, as above, it is not control per se that is critical, but rather whether the mPFCv is activated during the initial experience with the aversive event. Thus, we conducted an identical experiment to the one just described, but activated the mPFCv with picrotoxin during the Day 1 stress session. *Figure 3* shows the shuttlebox escape latencies. ES, of course, produced immunization. Activating the mPFCv by itself, without the presence of a stressor (P-HC/IS) did not confer protection against the effects of IS. However, the combination of picrotoxin and IS produced immunization. That is, the experience of uncontrollable stress actually protected the organism if the mPFCv was activated during the experience.

Finally, if it is true that after an initial experience with control now even IS would activate the mPFCv, then the DRN should be inhibited during IS. *Figure 4* shows extracellular levels of 5-HT within the DRN during IS in animals that had received either IS, ES, or HC 7 days earlier. IS produced a large increase in 5-HT as usual, but this effect was virtually eliminated by prior ES. Here, the DRN acted as if the stressor were controllable. This result is analogous to an "illusion of control" at the neuro-

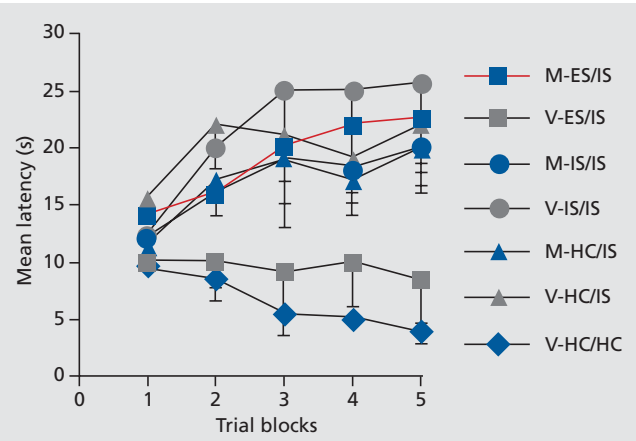

Figure 2. Mean latency to escape across blocks of five shuttlebox trials. Day 1 treatments were escapable shock (ES), yoked inescapable (IS), or home cage control (HC). All animals received inescapable shiock (IS) on Day 8. Escape testing occurred on Day 9. M, muscimol before day 1 treatment; V, vehicle

chemical level. Clearly, an initial experience with control promotes resilience in the face of later aversive stimulation, and does so by activating the mPFCv.

Fear conditioning and the amygdala

To this point we have focused on the interaction between the mPFCv and the DRN, with control leading to protection against the effects of aversive events by increasing mPFCv inhibition of the DRN. However, the mPFCv projects to other stress-responsive structures as well. The amygdala is of special interest in this regard. The amygdala is a key site in the mediation of fear and anxiety. Its role in fear conditioning is well known, and fear conditioning has been argued to be a key process in the development of a number of anxiety disorders.[34] The work of numerous investigators has suggested the following scenario (see ref 35 for a review). Inputs from neutral stimuli (the conditioned stimulus [CS], eg, a tone) and aversive stimulation (the unconditioned stimulus [US], eg, a footshock) converge in the lateral amygdala (LA) where the association between the CS and US is formed by an *N*-methyl-D-aspartate (NMDA)/long-term potentiation (LTP)-dependent process. Expression of conditioned fear involves CS transmission to the LA, connections from the LA to the central nucleus of the amygdala (CE) either directly or indirectly via the basal nucleus, and then output connections from the CE to regions of the brain that are the proximate mediators of the specific aspects of fear responses (autonomic, endocrine, and behavioral). This is an oversimplified scheme (eg, 36, 37), but it nevertheless captures a large amount of data.

In the present context, it is interesting to note that the mPFCv projects to the amygdala,[38] and stimulation of the mPFCv has been reported to inhibit the increase in electrical activity in the LA produced by an already conditioned fear stimulus, as well as the fear response to that stimulus, and to prevent the association between CS and US when they are paired.[39] Similarly, Quirk et al[40] found that mPFCv stimulation reduces output from the CE in response to electrical stimulation of input pathways to the CE, and Milad et al[41] found mPFCv stimulation to reduce fear responses produced by a fear CS. Although the exact projections of the mPFCv to the amygdala responsible for the inhibition of fear conditioning and fear responses resulting from mPFCv stimulation are unclear, the mPFCv does project to the intercalated cell mass (ITM) within the amygdala. These cells are almost all GABAergic, and project to the CE, providing an obvious pathway by which mPFCv activation could inhibit the CE.[42] Indeed, Berretta et al[30] found that stimulation of the mPFCv with picrotoxin increases Fos expression in the GABAergic cells of the ITM.

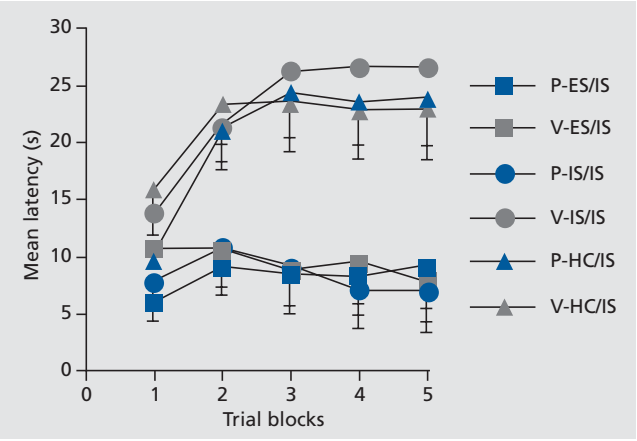

Figure 3. Mean latency to escape across blocks of five shuttlebox trials. Day 1 treatment s were escapable shock (ES), yoked inescapable (IS), or home cage control (HC). All animals received inescapable shock (IS) on Day 8. Escape testing occurred on Day 9. P, picrotoxin before experimental treatment; V, vehicle

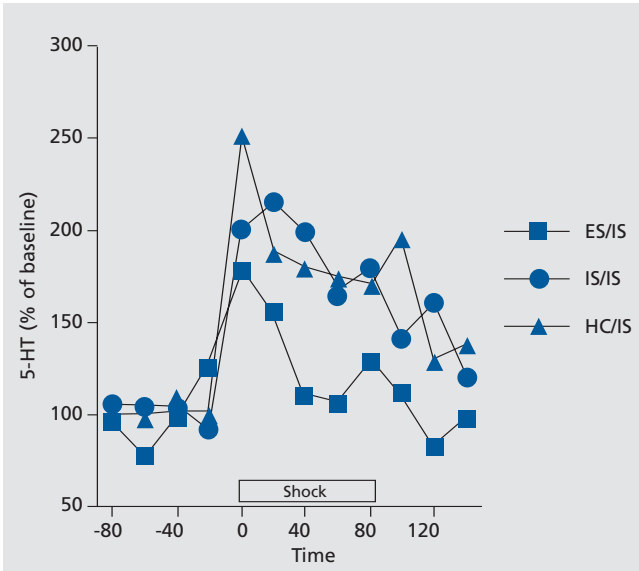

Figure 4. Extracellular levels of serotonin (5-HT) within the dorsal raphe nucleus (DRN), as a percentage of baseline, before, during, and after inescapable shock (IS). Separate groups received either escapable shock (ES), yoked inescapable (IS), or home cage control (HC) 7 days earlier.

The foregoing suggests that any factor that increases mPFCv output to the amygdala should reduce fear. We have reviewed research that suggests that behavioral control increases mPFCv output to the DRN, thereby reducing DRN-driven behavioral changes. Perhaps this phenomenon is more general, and control also increases mPFCv output to the amygdala, thereby inhibiting CE function and fear. Consistent with this possibility, it is already known that ES leads to the conditioning of less fear to cues that are present than does IS. However, the possibility being considered here makes an even stronger prediction. Recall that an initial experience with ES protected the organism against the effects of subsequent IS, the argument having been that the original experience led the later IS to now activate the mPFCv. The idea was that the initial ES experience "tied" mPFCv activation to shock, or to something associated with or produced by shock. What if that "something" is fear? If this were so, then an initial experience with ES should actually interfere with fear conditioning conducted some time later in a different environment.

To begin to explore these ideas, we first gave rats ES or yoked IS in wheel turn boxes, or HC treatment. Seven days later the rats received fear conditioning in a standard gridbox chamber. A tone was paired with gridshock, and the level of conditioning to the tone and to the environmental context was measured 2 days later. Freezing to the context was used as the measure of conditioning to the context. The rats were simply placed in the fear conditioning chamber for 5 min and freezing assessed. To assess fear conditioned to the tone, the rats were placed in a novel chamber and freezing measured for 3 min. The tone was then sounded for 3 min. *Figure 5* shows the results. First, it should be stated that there was virtually no freezing at all on the conditioning day before the first footshock. Thus, the freezing observed on the test day was the result of conditioning, not some aftereffect of the earlier IS or ES. The results for fear conditioned to the context are on the left. IS 7 days before fear conditioning exaggerated fear conditioning, a result that was already known.[43] In contrast, prior ES *retarded* fear conditioning. The results for conditioning to the tone, shown on the right, were similar. These results are dramatic, as ES is itself quite "stressful" and is not somehow "negative stress." Indeed, the ES conditions used here produce a hypothalamo-pituitary-adrenal response that is as large as that produced by IS.[44,45] We know of no other position that would predict, or even explain, how exposure to a highly stressful event could retard the later development of fear.

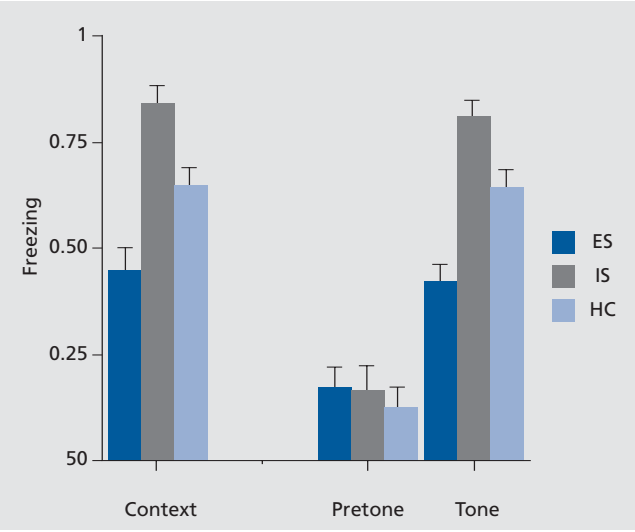

Figure 5. Percentage of the observation intervals on which freezing occurred during testing for fear conditioning. Testing was 24 h after conditioning. Groups received either escapable shock (ES), yoked inescapable (IS), or home cage control (HC) 7 days before fear conditioning. Data on the left shows freezing in the context in which conditioning had occurred. Data on the right shows freezing before and during the tone that had been paired with shock, with testing occurring in a novel context.

Clearly, much more work is needed, but it may be that experiences of control produce resilience in the face of circumstances that induce fear. The amygdala is importantly involved in fear-related processes that go beyond the conditioning of fear to anxiety more generally. It thus may be that experiences of control, and other circumstances that might activate the mPFCv, confer resistance to the development of anxiety.

Conclusions and clinical implications

The general conclusion to be reached is that control is not detected or computed by brain stem structures such as the DRN, but rather by circuitry within the mPFCv. Stress or aversive stimulation per se would seem to activate structures such as the DRN, with this activation then being inhibited by input from the mPFCv if behavioral control is present. This arrangement might make good evolutionary sense. Primitive organisms possess only a limited behavioral capacity to deal with threats, and in such species adaptations and responses to threats are largely physiological in nature. For these types of species

behavioral control and other methods of psychological coping are largely irrelevant, and so it may make sense that more primitive parts of the brain that are involved in responding to threats are themselves insensitive to dimensions such as behavioral controllability. As organisms became more complex, behavioral methods of coping became possible. Under circumstances in which a threat can be dealt with behaviorally, it would be adaptive to inhibit or reduce the more physiological adaptive mechanisms since they can be costly in various ways.[46] Of course, more recently evolved "higher" regions of the brain such as the mPFC would have taken this function. It is also possible that a lack of control might weaken the inhibitory control exerted by the mPFC. The experiments discussed above were not well suited to detecting effects in this direction given possible "ceiling effects." Indeed, we have some evidence that uncontrollability might exert this sort of effect, but it is too preliminary to present.

Although our evidence is limited, it further suggests that initial experiences with stressors can bias the system such that the mPFCv responds to later stressors as it did to earlier stressors. If this plasticity proves to be real, then this would constitute a mechanism of resilience. The fear conditioning data presented above suggests that this mechanism may generalize broadly, with control over tailshock generalizing to fear conditioning. Thus, experiences with control may be broadly protective. Of course, there is no reason to believe that behavioral control is unique, and there are likely other aspects of experience that would activate mPFCv inhibition of stress-responsive limbic and brain stem structures.

The research and theorizing presented here articulates well with the recent clinical literature. Abnormalities in mPFC function have been detected in disorders ranging from depression[47] to PTSD.[48] Imaging studies of PTSD are especially illuminating in the present context, since they typically measure both amygdala and mPFC function. Not surprisingly, PTSD patients show substantial amygdala activation to stimuli related to the events that caused the disorder. Thus, combat veterans with PTSD show exaggerated amygdala activation to war scenes, relative to non-PTSD controls.[48] Interestingly, they also show exaggerated amygdala activity to fear stimuli unrelated to combat, such as fearful faces.[49] However, PTSD patients have *reduced* mPFC activity in response to these stimuli,[48-50] and this often correlates with the degree of disorder. It is possible that there is exaggerated amygdala activation in PTSD because there has been a loss of mPFC inhibition of the amygdala. Many of the events that induce PTSD are ones over which the individual has little behavioral control. Not all of the individuals who experience these events develop PTSD, and it may be that earlier experiences with control or other forms of coping protect against the development of the disorder by biasing the mPFC to respond actively, thereby maintaining inhibition of the amygdala, and perhaps other stress-responsive structures. ❑

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Control comportamental, corteza prefrontal medial y resiliencia

El grado de control que ejerce un organismo sobre un factor estresante modula poderosamente la repercusión de éste; los elementos incontrolables generadores de estrés determinan una constelación de resultados que no se daría si esos factores pudieran controlarse comportamentalmente. En general, se ha admitido que esto ocurre porque la falta de control potencia de una manera activa los efectos de los elementos estresantes. Aquí se propone como tesis complementaria o alternativa que la presencia del control inhibe activamente la repercusión de estos elementos. Esto sucede, al menos en parte, porque i) las regiones de la corteza prefrontal ventromedial detectan el control e ii) la detección del control activa las eferencias de la corteza prefrontal ventromedial hacia el tronco encefálico y las estructuras límbicas, que responden al estrés lo que inhibe fuertamente la activación de estas estructuras inducida por el estrés. Es más, la experiencia inicial de control del estrés modifica la respuesta de la corteza prefrontal ventromedial a los factores estresantes subsiguientes, de manera que las eferencias de la corteza prefrontal ventromedial se activan, aun cuando el elemento estresante posterior resulte incontrolable, con lo que el organismo adquiere resiliencia. Se comentan las implicaciones generales de estos resultados para entender la resiliencia frente a la adversidad.

Contrôle comportemental, cortex médian préfrontal et résilience

Le degré de contrôle qu'un organisme exerce sur un facteur de stress module fortement l'impact de ce dernier. Les facteurs de stress incontrôlables engendrent un cortège de comportements qui ne se produiraient pas si le facteur de stress pouvait être maîtrisé. L'absence de contrôle est connue pour potentialiser fortement les effets des facteurs de stress. A contrario, ainsi qu'il l'est suggéré dans cet article, la présence d'un contrôle inhibe de manière active l'impact des facteurs de stress. Ceci survient au moins du fait de deux facteurs 1) la présence du contrôle est détectée au niveau des régions du cortex préfrontal médioventral (mPFCv) ; et 2) cette détection active les efférences du mPFCv vers le tronc cérébral et les structures limbiques sensibles au stress inhibant fortement leur activation due au stress. De plus, une première expérience de stress contrôlé modifie la réponse du mPFCv face aux agressions ultérieures, si bien que l'efférence du mPFCv est activée même si le facteur de stress suivant reste incontrôlable, rendant de ce fait l'organisme résilient. Les implications générales de ces résultats pour comprendre la résilience face aux agressions vont être examinées dans cet article.

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