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New tools for understanding coping and resilience

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Abstract

In humans, many of the factors determining vulnerability and resilience to the impact of an adverse event revolve around coping factors. This mini-review focuses on the neural mechanisms by which coping reduces the impact of adverse events, as studied in an animal model, and discusses some of the challenges of linking neural circuit activity with stressor outcome. We highlight several approaches for probing circuit function with cell-type and pathway-specificity that overcome some of the limitations of traditional neuroscience techniques and will likely yield a more detailed and comprehensive understanding of how the brain regulates stress-responsive structures when coping behaviors are engaged.

Keywords

stress; resilience; medial prefrontal cortex; serotonin; anxiety

It is often the case in neuroscience that new insights follow the development of new technologies. It is our charge to review, for investigators focused on human work on affect, the recent development of methods that allow for manipulations that are highly selective to discrete cell-types and pathways. At a global level, the use of these methodologies has made clear that a) behavioral/psychological processes are often mediated by discrete **circuits** of neurons located in multiple and different regions of the brain, rather than by global activation of a single anatomically defined region, b) neurons that participate in different circuits that perform different functions can be intermixed and literally next to each other, c) often circuits that perform important functions involve a very small number of neurons, and d) measures of global activation of a region or a structure can be misleading.

We believe that it is easier to appreciate the power of these methods by describing how they are able to answer questions within a particular context that could not even be approached by more traditional techniques. We will describe these new methodologies and their advantages

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within the context of research directed at understanding how it is that behavioral control over a stressor blunts the behavioral and neurochemical impact of the stressor being experienced, as well as the impact of future uncontrollable stressors.

The stressor controllability paradigm. In humans, many of the psychosocial factors associated with resilience involve processes that engage coping strategies [1,2], of which actual or perceived behavioral control over negative circumstances is a key element. Behavioral control is one of the few aspects of coping processes that can be studied/ modeled in animals where the underlying neural mechanisms can be explored. Control has been studied in a variety of species, but the rat has been most frequent. In our version of the paradigm, rats are placed in small boxes with a wheel mounted on the front wall that the rat can turn with its paws. Rats are run in triads, and a mild electric shock is periodically delivered to the tails of two of the subjects. For one of the subjects labeled escapable shock (ES), each of the tailshocks terminate when the subject turns the wheel. Thus, this subject has behavioral control over one element of the situation—the duration of each of the tailshocks. For the second subject labeled inescapable shock (IS), each shock terminates when the ES subject turns the wheel—for this subject turning the wheel has no consequence and this subject has no control over the durations of the tailshocks. The third subject does not receive tailshocks and serves as a control. Tailshock is used as a stressor in these studies because equality in stimulus exposure is required to allow for the isolation of the impact of controllability that is not confounded by differences in the physical stressor. In addition, the stimulus must be one that allows for the animals to readily learn an operant escape response. These criteria cannot be met with other animal stress paradigms such as restraint or social defeat.

Exposure to aversive events is well known to lead to behavioral and physiological changes that have been described as anxiety-like and depression-like, and as would be expected, IS does so. The important result is that none of these behavioral changes follow exposure to ES—that is, the experience of control, even over just the element of tailshock durations, completely blunts the impact of the stressor (see review by [3]). Moreover, this experience of control protects the organism against the anxiety and depression-like changes induced by future uncontrollable stressors occurring weeks later and in different environments, a phenomenon that has been called “behavioral immunization” [4].

Neural mediation of stressor controllability. It is necessary to understand how uncontrollable stressors (e.g., IS) produce anxiety and depression-like behavioral changes before it is possible to inquire as to how control blocks these effects. This is now understood in some detail (see [5,6] for review) and cannot be reviewed here. For present purposes the reader only needs to know that activation of serotonin (5-HT) neurons in the mid to caudal regions of the dorsal raphe nucleus (DRN) is critical to the production of the behavioral sequelae of IS and other stressors [7–9]. Thus, pharmacological blockade of DRN 5-HT activation during IS prevents the development of the behavioral consequences of IS [10] and merely activating DRN 5-HT neurons in the absence of any stressor produces them [11].

Clearly, stressors that are controllable should not activate 5-HT neurons in the DRN, and indeed, they do not [7,12]. So, how does control work? The most obvious possibility would

be that if stressors are controllable there is reduced excitatory input to the DRN. A series of studies identified the critical inputs to the DRN that lead to its intense stimulation during uncontrollable stressors, but ES produced as much activation of these inputs as did IS [13–15]. If IS does not lead to greater DRN 5-HT activation than does ES because it leads to greater excitatory input, then the remaining possibility is that the presence of behavioral control during a stressor actively inhibits the DRN.

DRN 5-HT neurons are under the inhibitory control of GABAergic interneurons, and glutamatergic pyramidal neurons from the prelimbic (PL) region of the ventral mPFC project to these cells [16]. Indeed, electrical stimulation of this region of the rat mPFC inhibits DRN 5-HT neuronal activity [17–19]. These anatomical facts led us to explore the role of the PL in mediating the impact of behavioral control. The tools available at the time allowed us to microinject drugs into the PL that would either inhibit or excite PL neuronal activity. Intriguingly, inhibition of PL activity during ES eliminated the protective effects of control, and now ES led to the same behavioral outcomes as did IS, even though the subjects turned the wheel and exerted control [20]. Correspondingly, activation of the PL during IS led to protection as if the stressor was controllable [21].

Parsing the separable features of behavioral control. Although these data clearly implicated the PL in the protective effects of control, they do not indicate what the PL is actually doing. At a logical level, control has to be detected or processed, and then the registration of control has to be used to inhibit the DRN and perhaps other stress-responsive limbic and brainstem structures. The PL could be involved in either or both of these processes. A variety of considerations that cannot be reviewed here suggest that control over aversive events might be detected by a circuit that involves connections from the PL to the dorsomedial striatum (DMS), then to the substantia nigra, on to the mediodorsal thalamic nucleus, and then back to the PL. We have theorized that the activation of this DETECT circuit by control leads to the activation of a PL-to-DRN pathway, the USE circuit, that inhibits the DRN activation produced by the stressor [22,23]. Furthermore, indirect evidence led us to suppose that perhaps immunization occurs because the experience of control induces plasticity in the PL-to-DRN pathway so that now even uncontrollable stressors activate this pathway, thereby inhibiting the DRN and producing future protection [24].

In an initial attempt to explore these possibilities and hypotheses we combined retrograde tracing with immediate early gene (IEG) expression to examine activation of DRN-projecting PL neurons [24], a minor projection representing 2–4% of layer V PL neurons in rat [25]. Surprisingly, overall IEG expression in the PL did not differ between ES and IS. However, behavioral control increased IEG expression in the PL-to-DRN pathway both the time of the initial experience of control and the time of the later uncontrollable stressor, highlighting the fact that global activation of a brain region alone is insufficient when interpreting data at a circuit level. We have also inquired as to whether the PL neurons that might be involved in DETECT and USE are the same PL neurons. Retrograde tracing with retrobeads tagged with different fluorescent markers were microinjected into the DMS and DRN. Intriguingly, they labeled completely different but intermingled populations of layer V PL neurons (unpublished results). That is, PL neurons that could participate in DETECT and USE were non-overlapping but neighboring. However, this is as far as traditional tools could

take us because any lesion, drug microinjection, etc., would impact both putative circuits. A variety of predictions could be made, but they all require selective inhibition or activation of PL neurons that project to the DMS and DRN, and as noted, they are intermingled.

Advances in several methodologies now enable experimental control over the inhibition (loss-of-function) or activation (gain-of-function) of select cell-types and pathways in order to investigate the causal role of a specific population of cells on behavior. With optogenetics, light-responsive proteins (“opto-”) encoded in DNA (“-genetic”), such as light-gated ion channels and pumps, are introduced into genetically defined cell populations in order to activate or silence neuronal circuit elements with light. The most commonly used prototypes for optical control are the light-gated cation channel channelrhodopsin-2 (ChR2) and the light-driven chloride pump halorhodopsin (NpHR) that enable neurons to be depolarized or hyperpolarized, respectively, in a rapid and reversible manner. Optogenetic effector proteins are expressed in brain using a variety of genetic strategies, such as viral-mediated gene delivery, *in utero* electroporation, and transgenic model organisms. Targeting a **cell type** of interest can be achieved with optogenetic transgene expression under the control of a cell-type specific promoter [26] or with technologies that induce site-directed recombination events in select cell types (e.g., Cre-lox, Flp-FRT) [27,28]. Such approaches are now widely used in neuroscience and have played a critical role in identifying the relevant mPFC circuits underlying emotional regulation [29–35].

As noted above, testing the hypothesized DETECT and USE circuits requires a method to selectively manipulate projection-defined PL neurons independently. Along these lines, Warden et al. [30] optically controlled mPFC neurons that project to either the lateral habenula (LH) or DRN in order to determine how these pathways impact motivated behavior during adversity. During a forced swim test (FST), the authors demonstrated in rat that general ChR2 activation of mPFC cell bodies had no effect on active (kicking) or passive (floating) responding. Interestingly, when light delivery was restricted to ChR2-expressing mPFC axon terminals in the DRN, animals rapidly transitioned from an immobile to mobile state, and the increase in effortful behavior was coupled to light onset and offset. As is the case with behavioral control, a general role of mPFC-to-DRN pathway activation may be to promote active coping. A third experiment revealed that photoactivation of mPFC axons that project to the LH produced had the opposite effect of escape behavior in the FST – mobility was decreased. Thus, optogenetic excitation of three separate mPFC ensembles (mPFC-to-DRN, mPFC-to-LH, or mPFC principal neurons independent of connectivity) led to three separate behavioral outcomes, a finding that is unattainable with traditional methodologies. Remarkably, behavior was only impacted when manipulations were made to projection-defined mPFC neuronal subsets (mPFC-to-DRN and mPFC-to-LH), even though these pathways represent relatively sparse projections of the rat mPFC (layers V and VI, respectively) [25,36,37]. These experiments, along with other optogenetic studies, highlight the fact that the activity of different ensembles of neurons intermingled in the same brain area can produce divergent patterns of behavior [38–41].

Additional approaches for viral targeting of effector proteins to mPFC neurons with defined connectivity include the use of an intersectional genetic strategy that leverages a recombination system such as Cre-lox. Here, a retrograde virus such as canine adenovirus

type 2 that expresses Cre recombinase (CAV2-Cre) and a recombinase-dependent virus that encodes an effector protein are injected into a downstream and upstream region, respectively. Following delivery of retrograde CAV2-Cre virus to a downstream brain site (Region B), CAV2 efficiently infects axon terminals and is retrogradely transported towards cell bodies and expresses Cre recombinase. A second virus that encodes for a Cre-dependent inverted sequence of an optogenetic actuator, which is reoriented only in the presence of Cre, is delivered to the site where the Cre-expressing cell bodies are located (Region A). Therefore, opsin expression is restricted to Region A neurons that project to Region B, providing optical control over a defined neural pathway during behavioral testing.

Although this dual viral strategy can be used with optogenetics, chemogenetic technologies, such as DREADD (designer receptors exclusively activated by designer drugs), can also be employed for remote manipulation of neural activity during behavior. DREADDs are engineered G protein-coupled receptors (GPCRs) that can be selectively activated by otherwise biologically inert compounds. Similar to endogenous GPCRs, DREADDs are coupled to inhibitory (Gi) or excitatory (Gq, Gs) signaling cascades [42,43]. To date, the prototypical ligand for DREADD activation is the inactive clozapine metabolite, clozapine *N*-oxide (CNO). It should be noted that careful consideration of experimental control groups along with dose is critical as recent data suggests that systemic CNO can be metabolized via back-transformation to clozapine, which then serves as the ligand for DREADD activation [44]. Other non-CNO chemical actuators have been developed that can serve as alternatives to CNO in which back metabolism of CNO to clozapine is an issue [45,46].

Both optogenetic and chemogenetic methods are particularly well suited for stressor controllability studies since they allow for independent inactivation (necessity) and activation (sufficiency) of intermixed PL subpopulations hypothesized to participate in separable DETECT and USE circuits. If PL regulation of the DRN is a consequence of PL-DMS detection of behavioral control, then several predictions can be made. Optogenetic (NpHR) or chemogenetic (Gi-DREADD) silencing of the PL-to-DMS pathway during controllable shock (ES) should now produce the same behavioral outcomes and exaggerated DRN response as produced by IS. Furthermore, ES should also now fail to activate the PL-to-DRN pathway as the hypothesis is that activation of the DETECT pathway **leads** to the activation of the USE pathway. Genetic strategies that target and inactivate the USE (PL-to-DRN) system during ES should also eliminate protection afforded by behavioral control. However, the PL-to-DMS pathway should still be engaged by control given that the process of DETECT is independent of whether or not control-related information is utilized.

Concluding remarks. The recent development of circuit-targeting strategies represent an unprecedented opportunity to study how controllability information is routed through adjacent PL circuits involved in its initial detection to those involved in its subsequent use. To maximize the insights provided by projection-based optogenetics and chemogenetics, they should be combined with complementary read-out measures that exhibit similar temporal and/or spatial resolution (e.g. *in vivo* calcium imaging). Furthermore, several techniques allow for effector proteins to be expressed in an activity-dependent manner (see [47] for review), which is ideal for behavioral immunization experiments. For instance, PL ensembles recruited by behavioral control could be selectively tagged with optogenetic and

DREADD effector proteins so that those cells can be manipulated during a later challenge in order to determine their necessity in mediating the stress-buffering effects of control. The opportunities discussed above provide unprecedented experimental control over circuit function and represent critical steps in testing proposed mechanisms and theories of how coping processes inculcate resilience/resistance.

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Highlights

- Behavioral control that an organism has over a stressor potently modulates the impact of that stressor.
- Hypothesized circuits that detect and utilize information about the controllability of the stressor are intermixed with the prelimbic region of the medial prefrontal cortex.
- Viral-based genetic strategies provide an opportunity to independently address the hypothesized function of these circuits in processing controllability information.

Fig. 1.
 (A) Schematic diagram of the PL circuits involved in stressor controllability phenomena. First, behavioral control is detected by PL neurons that participate in the corticostriatal system (DETECT). After detection, a separate population of PL neurons project to the DRN (USE) and inhibit DRN 5-HT activation, thereby preventing the impact of the stressor. Communication between these two circuits is unknown. PL, prelimbic cortex; DMS, dorsomedial striatum; SN, substantia nigra; MD, mediodorsal thalamus; DRN, dorsal raphe nucleus; 5-HT, serotonin. (B) Confocal image of retrogradely labeled (retrobeads) PL neurons projecting to the DMS (red) or DRN (green) that are intermixed within PL layer V. Scale bar represents 50 μ m.