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Hemispheric Asymmetry in Stress Processing in Rat Prefrontal Cortex and the Role of Mesocortical Dopamine

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The prefrontal cortex (PFC) is known to play an important role not only in the regulation of emotion, but in the integration of affective states with appropriate modulation of autonomic and neuroendocrine stress regulatory systems. The present review highlights findings in the rat which helps to elucidate the complex nature of prefrontal involvement in emotion and stress regulation. The medial PFC is particularly important in this regard and while dorsomedial regions appear to play a suppressive role in such regulation, the ventromedial (particularly infralimbic) region appears to activate behavioral, neuroendocrine and sympathetic autonomic systems in response to stressful situations. This may be especially true of spontaneous stress-related behavior or physiological responses to relatively acute stressors. The role of the medial PFC is somewhat more complex in conditions involving learned adjustments to stressful situations, such as the extinction of conditioned fear responses, but it is clear that the medial PFC is important in incorporating stressful experience for future adaptive behavior. It is also suggested that mesocortical dopamine plays an important adaptive role in this region by preventing excessive behavioral and physiological stress reactivity. The rat brain shows substantial hemispheric specialization in many respects, and while the right PFC is normally dominant in the activation of stress-related systems, the left may play a role in countering this activation through processes of interhemispheric inhibition. This proposed basic template for the lateralization of stress regulatory systems is suggested to be associated with efficient stress and emotional self-regulation, and also to be shaped by both early postnatal experience and gender differences.

Keywords: Autonomic; Cerebral laterality; Emotion; Early handling; Infralimbic; Neuroendocrine

INTRODUCTION

Cerebral hemispheric specialization in a number of domains is a well accepted phenomenon in our understanding of human brain function. The large majority of individuals exhibit significant cerebral dominance not only in terms of language control and motor functions (left brain bias), but also in the realms of affective or emotional processing and modulation of stress regulatory systems (predominantly right brain bias). Although generally less appreciated, a surprising number of examples of lateralized brain function have been well documented in the animal literature as well.

In species ranging from songbirds to rodents to nonhuman primates, it has long been noted that left hemisphere activation is associated with communicative functions, while the right hemisphere is more activated when spatial performance is required and when affective components in the environment lead to the production of emotional responses (for review, see Denenberg, 1981). Work in rodents found that early environmental stimulation significantly enhances the development of such lateralized brain function, and suggested that interhemispheric interactions (activation/inhibition) are especially important when emotional processing is involved (Denenberg, 1981; Denenberg *et al.*, 1986).

Since that time, relatively little attention has been paid to this important aspect of brain function in animal studies. However, a recent resurgence of interest in this topic seems to have taken place, owing in part to its potential clinical implications in the etiology of stress-related psychopathology. In particular, major depressive and anxiety disorders, involving varying degrees of emotional dysregulation and abnormal stress physiology, are commonly associated with lateralized disturbances of brain structure or function, most notably in prefrontal

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cortical areas or PFC (see Sullivan and Gratton, 2002a). This has raised many questions as to (i) the nature of PFC involvement in the regulation of emotional behavior and stress physiology and (ii) the extent to which the two hemispheres may contribute differentially to such regulation. The present paper reviews some recent findings in the rodent that address each of the above issues. As many of these PFC findings regarding both stress and cerebral laterality have been gleaned from studies of the mesocortical dopamine (DA) system, this discussion will have particular emphasis on the role of this important prefrontal modulatory system.

THE MEDIAL PFC AND STRESS PROCESSING

The medial PFC, namely the prelimbic (PL) and more ventral infralimbic (IL) cortex, is well recognized as an integral component in the stress circuitry of the rat. Neuronal and genomic activation of medial PFC neurons is markedly enhanced by exposure to a wide variety of stressors, as reflected in the pronounced release of the excitatory neurotransmitter glutamate in this area (Moghaddam, 1993) and the expression of the immediate early gene c-fos (e.g. Handa *et al.*, 1993; Beck and Fibiger, 1995; Morrow *et al.*, 2000). Afferent monoamine pathways modulate medial PFC activity in times of stress, most notably and selectively, the mesocortical DA system originating in the ventral tegmental area (VTA; e.g. Thierry *et al.*, 1976; Deutch and Roth, 1990; Finlay *et al.*, 1995; Yoshioka *et al.*, 1995; Sullivan and Gratton, 1998; Jedema *et al.*, 1999; Hayley *et al.*, 2001). While the responsivity of such systems has been described in great detail in response to numerous stressors, pharmacological challenges or other interventions, the role of the PFC *per se* in regulating the downstream physiological and behavioral responses to stress is less well understood.

Anatomically, the PFC is certainly well positioned to modulate stress and emotion regulation. The more ventrolateral orbital and insular regions, having many sensory and limbic inputs, integrate viscerosensory information with affective signals, which in turn project to the ventromedial PFC (PL and IL) regarded as visceromotor cortex (Cechetto and Saper, 1990; Price, 1999). The latter region also receives diverse afferent inputs from limbic regions like amygdala and ventral hippocampus/subiculum, and provides direct outputs to hypothalamic and numerous brainstem areas involved in emotion and stress regulation, such as periaqueductal gray, the nucleus of the solitary tract, the dorsal motor nucleus of the vagus, the parabrachial nucleus and nucleus ambiguus (Terreberry and Neafsey, 1987; Hurley *et al.*, 1991; Takagishi and Chiba, 1991; Jodo *et al.*, 1998; Sesack *et al.*, 1989; Bacon and Smith, 1993). The ventromedial system is thus in a pivotal position to regulate autonomic and neuroendocrine activity in conjunction with the appropriate emotional states, particularly in times of stress or high arousal.

The Medial PFC and Stress-related Behavior

Behavioral studies examining the effects of medial PFC manipulations have yielded widely varying results, owing at least in part to differences in methodology and lesion extent as well as functional regional heterogeneity within the medial PFC. Lesions of PL and/or the more dorsal anterior cingulate cortex reportedly increase fear reactivity (Holson, 1986; Morgan and LeDoux, 1995). For example, classical conditioned fear paradigms have revealed that such dorsomedial PFC lesions increased freezing behavior (Morgan and LeDoux, 1995). In another lesion study which targeted the more ventral IL cortex, freezing behavior was dramatically reduced in response to the conditioned fear stimulus, as was the frequency of ultrasonic vocalizations which were a typical component of the conditioned fear response of control animals (Frysztak and Neafsey, 1991).

Studies using the elevated plus maze have also shown that ventromedial PFC lesions result in an anxiolytic profile. In cases where damage to IL cortex is substantial, if not complete, rats have been reported to spend significantly more time exploring the open arms of the plus maze (Lacroix *et al.*, 2000; Sullivan and Gratton, 2002b). Lesions restricted to prelimbic cortex have resulted in an intermediate effect, increasing activity generally, but not producing a selectively anxiolytic effect (Maaswinkel *et al.*, 1996). The essential role for IL cortex in anxious behavior was highlighted by two studies from the same lab. When excitotoxic lesions of medial PFC clearly destroyed the IL cortex, the anxiolytic profile was observed in the plus maze (Lacroix *et al.*, 2000), but in a study where the same type of lesions were slightly more dorsal and spared IL cortex, no such effect was found (Lacroix *et al.*, 1998). An additional lesion study in medial PFC (including IL cortex) and employing ibotenic acid to spare fibers of passage, also reported that lesions clearly resulted in selective anxiolytic effects in three well validated tests of anxiety, the elevated plus maze, social interaction and the shock probe burying test (Shah and Treit, 2003). The same authors then showed that benzodiazepine microinjection in (either dorsal or ventral) medial PFC produced the same fear-reducing effects in the two tests examined, elevated plus maze and shock probe burying (Shah and Treit, 2004). Transection of the medial PFC has also been shown to increase social interaction, suggesting an anxiolytic effect (Gonzalez *et al.*, 2000). IL cortex lesions also affect the expression of simple taste aversion. While rats with excitotoxic IL cortex lesions did not differ from controls in the consumption of a novel palatable food (sweetened condensed milk), they failed to show the usual decrease in consumption upon addition of bitter tasting quinine (Sullivan and Gratton, 2002b). It was concluded that IL-lesioned rats were either less sensitive to the aversive nature of the stimulus, or failed to produce the expected "emotional" response. It was also proposed that this region may normally guide behavior in an optimally cautious or adaptive manner in situations of

perceived threat or conflict. Taken together, the above findings strongly suggest that in spontaneous, anxiety-provoking situations, the ventromedial PFC mediates or facilitates the expression of anxiety or fearful behavior.

The role of this brain region in fear-related behavior however, has been shown to be more complicated (and seemingly contradictory to the above scenario) in more complex learning paradigms such as the extinction of conditioned fear. The medial PFC has been shown to be particularly important in the extinction of conditioned fear measured as freezing behavior to a tone previously paired with shock (e.g. Morgan *et al.*, 1993, 2003; Morgan and LeDoux, 1995; Herry *et al.*, 1999; Herry and Garcia, 2002; Milad and Quirk, 2002, although see Gerwitz *et al.*, 1997). Specifically, lesions of ventromedial PFC delay such extinction, which could be interpreted as increased rather than decreased fearfulness, or a preservation of fear. Indeed, in intact animals, potentiated neuronal activity within the IL and prelimbic cortex is associated specifically with extinction or reduced freezing during this period (Herry *et al.*, 1999; Herry and Garcia, 2002; Milad and Quirk, 2002).

Such apparent discrepancies in the role of medial PFC in fear-related behavior may reflect a more general phenomenon of stress processing and adaptation. For example, it is known that medial PFC/anterior cingulate lesions reduce stress-induced gastric ulcer formation in response to an acute restraint stress. If rats are subjected to the same stress repeatedly, control animals adapt to this by showing reduced stress ulcer pathology relative to acute controls. However, the same lesions which appeared protective in an acute situation, result in exaggerated stress pathology in the repeated stress condition, eliminating a normal process of adaptation (Sullivan and Henke, 1986). Simply, stress must be initially experienced and normally processed, before adaptation to that stressor can take place. Likewise, learning what is no longer a threat (extinction) requires the previous experience of what was a threat. It is noteworthy in this regard that if the ventromedial PFC is intact during the acquisition of fear conditioning (lesions made post-training), the lesions are much less effective in delaying subsequent extinction and the initial lesion effect is to reduce freezing to contextual stimuli. Re-acquisition of fear conditioning then reinstates the extinction deficit (Morgan *et al.*, 2003). It has also been suggested that the potentiation of transmission in medial PFC during (successful) extinction may at least in part, reflect the processing of additional cognitive information that the tone (CS) will no longer be followed by the shock (UCS), as extinction appears to involve the consolidation of new memory, not the erasing of fear conditioning (Herry *et al.*, 1999; Milad and Quirk, 2002).

The role of the medial PFC in the expression of fear-related behavior or anxiety is thus highly situation-specific (spontaneous behavior or initial exposures to a fearful situation vs. more complex learning/extinction paradigms). It is also a reflection of the animal's prior experience. The ventromedial PFC, in particular, is involved in facilitating the initial expression and experience of stress-related behavior. This initial incorporation of stressful experience is a necessary component in the animal's ability to adapt optimally to future stressful challenges relevant to that previous experience. Such longer term expressions of stress-related behaviors, most likely reflect the sum of experience-dependent plastic changes within the ventromedial PFC via pathways from mediodorsal thalamus, amygdala and hippocampus, visceral and other areas (Herry and Garcia, 2002; Morgan *et al.*, 2003).

The PFC and Autonomic Function

The effects of stimulation or lesioning of prefrontal sites across a number of species on autonomic function (primarily cardiovascular and respiratory) have been reviewed in detail elsewhere (e.g. Cechetto and Saper, 1990; Van Eden and Buijs, 2000). As with the expression of emotional behavior, the effects on autonomic activity appear to exhibit a similar dorsal/ventral dissociation. Electrical stimulation of more dorsal zones (prelimbic/anterior cingulate or areas 32 and 24, respectively), results in parasympathetic profiles, while stimulation of the ventral zone (IL cortex or area 25) elicits typically sympathetic responses (Powell *et al.*, 1994).

In studies employing classically conditioned emotional responses (CERs), it was found that when the CER normally involves a bradycardic or parasympathetic response (typically where the animal is restrained), lesions of area 32 but not 25 greatly reduce the conditioned cardiac adjustment (Powell *et al.*, 1994). In contrast, when the CER involves a tachycardic response (typically in freely-moving rats), area 25 lesions greatly decrease this sympathetic adjustment, often converting it to a bradycardic profile. As well, respiratory changes normally associated with CERs were significantly altered by the same IL cortex lesions (Frysztak and Neafsey, 1991, 1994). These authors concluded that the ventromedial PFC is necessary for the full sympathetic activation of cardiovascular responses to both, mild and severe stressful stimuli. Similarly, ibotenate lesions of medial PFC which include IL cortex, greatly reduce gastric stress ulcer formation, an autonomically mediated form of stress pathology (Sullivan and Gratton, 1999).

Interestingly, human patients with damage specifically in ventromedial PFC, fail to respond autonomically to emotionally charged stimuli, and exhibit greatly impaired emotional and social functioning, decision-making and risk assessment (Damasio *et al.*, 1990; Damasio, 1994). Moreover, brain imaging studies have shown that in response to procedures designed to alter blood pressure and/or heart rate, neuronal activity was particularly increased in medial orbital/medial prefrontal regions, confirming the importance of these areas in

regulating autonomic adjustments in response to challenge (King *et al.*, 1999; Harper *et al.*, 2000).

The PFC and Stress-related Neuroendocrine Activation

The optimal activation (and termination) of the hypothalamic–pituitary–adrenal (HPA) axis is one of the most fundamental aspects of the individual's ability to respond to stress and adjust appropriately to repeated stressful experience. While the extra-hypothalamic regulation of HPA axis function has focused on the hippocampus (e.g. Sapolsky *et al.*, 1984), it is now clear that prefrontal areas are also very important in this regard. The medial PFC of the rat contains high levels of glucocorticoid receptors (Meaney and Aitken, 1985; McEwen *et al.*, 1986; Cintra *et al.*, 1994) and this area acts as a negative feedback site whereby high levels of circulating glucocorticoids (as in times of stress) suppress the continued activation of the HPA axis (Diorio *et al.*, 1993; Akana *et al.*, 2001).

Electrolytic lesions of medial PFC/anterior cingulate result in exaggerated plasma stress hormone release following restraint stress, consistent with removal of a negative feedback site (Diorio *et al.*, 1993). Brake *et al.* (2000a) reported the same effect in response to restraint stress, in rats which received dorsomedial PFC lesions as neonates. However, HPA activity has been reported to be suppressed by medial PFC lesions, which include the IL cortex (Sullivan and Gratton, 1999), suggesting an activational role for ventromedial PFC on HPA function. For other types of stress however, HPA activity has been reported to be either unaffected (noise stress as well as ether exposure) or even increased (systemic interleukin-1beta treatment) following IL cortex lesions (Diorio *et al.*, 1993; Crane *et al.*, 2003).

An excitatory role of ventromedial PFC on at least certain types of HPA activation is consistent with the increase in plasma corticosterone observed, following electrical stimulation of this area in the rat (Feldman and Conforti, 1985), and with early human data reporting that ventral frontal (but not cingulate) stimulation selectively increased plasma adrenocorticotrophic hormone or ACTH (Frankel and Jenkins, 1975).

In summary, it appears that the medial PFC plays a major role in directing both behavioral and physiological adjustments in response to stressful situations. An overall pattern is emerging that dorsomedial prefrontal regions tend to be normally involved in dampening behavioral reactivity, enhancing parasympathetic system activity and reducing HPA activation. In contrast, ventromedial prefrontal activity primarily stimulates anxious (or perhaps cautious/defensive) behavior, sympathetic system activation and HPA function. It is proposed that the ventromedial region may be the more prominent of the two in terms of determining the net functional output of prefrontal contribution to stress-related behaviors and physiological adjustments. For example, in cases where both dorsal and ventral structures are affected (by lesions), the typically ventral effects appear to predominate. Such a scenario may reflect the anatomical reality that the IL cortex is a visceromotor cortical output center, with the more direct projections to the relevant subcortical control centers. In fact, more dorsomedial sites may exert their effects in part via modulatory inputs to the IL cortex (Cechetto and Saper, 1990).

Superimposed on the above scenario is the additional factor of hemispheric specialization. It will be proposed that not only the predominant role of the medial PFC outputs is an activational one in times of stress, but that the right PFC is primarily responsible for this activation, and the mesocortical DA system plays an important role in keeping this activation "in check" or within optimal limits.

HEMISPHERIC ASYMMETRY IN STRESS AND EMOTION REGULATION

A wide variety of evidence from human studies in recent decades has suggested that the right hemisphere in general plays a prominent role in processes related to emotional perception and expression, particularly negative emotional states (e.g. Wittling and Roschmann, 1993; Davidson, 1998; Simpson *et al.*, 2001). Early studies suggested a preferential role for the right brain in both the facial expression and perception of emotion as well as affective components of speech (Sackeim *et al.*, 1978; Ross and Mesulam, 1979; Levine and Levy, 1986; Lane *et al.*, 1995). Patients with strokes in the left frontal lobe showed a disproportionate incidence of depression or catastrophic reaction (possibly reflecting the increased emotional expression of the relatively "unrestrained" right hemisphere), while comparable damage to the right frontal lobe often produced indifference, inappropriate cheerfulness or mania (e.g. Robinson *et al.*, 1984). Particularly relevant in the present context, is a recent functional imaging study reporting that the region most closely correlated with negative affect is the ventromedial PFC of the right hemisphere (Zald *et al.*, 2002).

However, in general, recent brain imaging studies have revealed a much more complex picture than a simple lateralization of emotion. A recent meta-analysis of imaging studies assessing a wide variety of emotional states found no evidence of an overall right lateralization of emotion, but numerous examples of regional and emotion-specific asymmetries in brain activation (both left and right), as well as significant gender effects (Wager *et al.*, 2003). Although differences in the degree of physiological arousal induced by the various techniques for eliciting emotion could not be controlled for across studies, this analysis highlights the need for generating specific hypotheses of the brain's role in emotion. Others have concluded that there is still a good case for believing that the right hemisphere is more involved in the perception and processing of emotion than the left, which may be particularly important in positive, approach-related

emotions. Yet to speak of the right hemisphere as the one specialized for emotion, oversimplifies what we know about hemispheric asymmetry, as well as what we call emotion (Springer and Deutch, 1998).

In human studies, which have assessed hemispheric asymmetry in the context of physiological arousal, neuroendocrine or autonomic activity, a more consistent picture of right brain dominance emerges. Elevations in plasma cortisol levels are most pronounced when emotional stimuli are presented selectively to the right hemisphere (Henry, 1997; Wittling, 1997; Wittling and Pfluger, 1990). While reversals of this asymmetry in the control of cortisol secretion are certainly common, they may be associated with increased risk for a variety of pathologies (Wittling and Schweiger, 1993). Similarly, the right hemisphere is dominant in the sympathetic component of cardiovascular control (Yoon *et al.*, 1997; Wittling *et al.*, 1998; Hilz *et al.*, 2001). As well, autonomic and emotional deficits resulting from selective ventromedial PFC damage are due predominantly to right hemispheric damage (Tranel *et al.*, 2002). Studies in monkeys employing frontal EEG measures report that strong right-biased asymmetries in frontal activity are significantly associated with very high levels of plasma cortisol, as well as highly fearful and defensive behavior (Kalin *et al.*, 1998, 2000).

In the rat, similar patterns are emerging in studies which examine the possibility of hemispheric differences in emotion and stress regulation. Early studies employing large unilateral cortical lesions revealed that in animals handled in infancy, the (intact) right cerebral cortex preferentially mediates emotional behaviors such as open field exploration, mouse killing (muricide) and taste aversion (Denenberg, 1981; Denenberg *et al.*, 1986).

In studies focused on the ventromedial PFC, it was recently reported that unilateral right-sided lesions result in significantly more open arm exploration in the elevated plus maze than either controls or left-lesioned rats. This right lesion effect was at least as pronounced as the effect of bilateral lesions (Sullivan and Gratton, 2002b). The identical pattern was observed for taste aversion, as right lesions alone were effective in reducing this behavior. A similar pattern was suggested in terms of unilateral ventromedial PFC lesion effects on stress-induced neuroendocrine activation. While left, right or bilateral lesions produced a downward shift in baseline corticosterone levels, there was a strong trend for right lesions alone to maintain reduced levels during restraint stress (relative to shams), with left lesioned rats mounting a stress response indistinguishable from shams (Sullivan and Gratton, 1999). The same study reported that the dramatic reduction in cold restraint-induced gastric stress ulcer formation following bilateral lesions, was entirely accounted for by unilateral right-sided damage. In a similar study on the cortical regulation of stress ulcer formation, DA-depleting lesions were produced in the medial PFC (including IL cortex) with 6-OHDA. In this case, lesions exacerbated gastric stress pathology and the most significant increase was produced by right-sided depletion alone, presumably due to a net disinhibition of the cortical output neurons of this area (Sullivan and Szechtman, 1995). Taken together, these findings suggest that in terms of ventromedial PFC function, the right-sided structure may be both necessary and sufficient for the expression of "normal" emotional behavior, the full activation of the HPA axis in times of stress, and the activation of autonomic circuits associated with highly arousing or stressful situations. Activation of these arousal systems, of course, is a perfectly normal part of coping effectively with stress. The DA depletion findings however, suggest that excessive activity of right ventromedial PFC may impair coping ability, heighten stress sensitivity and lead to increased vulnerability to the pathological effects of stress exposure.

Other areas with close functional anatomical links with medial PFC also demonstrate asymmetrical regulation of emotion and stress-related processes. For example, it has been shown that the contribution of the right amygdala to the expression of memory for aversively motivated training is significantly greater than that of the left amygdala (Coleman-Mesches and McGaugh, 1995a,b,c). As well, increases in anxiety-like defensive behaviors induced by various methods are reportedly dependent upon increased long-term potentiation in the pathway from the right amygdala to the periaqueductal gray area (Adamec, 1999, 2000). Additionally, the nucleus ambiguous, which receives direct projections from IL cortex, regulates adjustments in heart rate and vocalization frequencies in response to stress, and the right-sided structure is critical for these functions (Porges, 1995).

The Role of Mesocortical DA in Stress and Emotional Behavior

Given the above examples of the intrinsic functional differences between the left and right medial PFCs, it may not be surprising that one of this regions' most significant modulatory input should also be functionally asymmetric in nature. But before focusing specifically on asymmetries in the mesocortical DA system, it is important to address the more general question, "What exactly is the role or purpose of mesocortical DA release during stress?" In other words, "Does DA contribute to the perception/experience of stress, activating associated stress circuits?" or "Does DA represent a compensatory, adaptive coping system to dampen excessive stress reactivity?"

Since Thierry *et al.* (1976) described the selective activation of this system in response to stress, countless studies have elaborated on the characteristics or determinants of this response in many contexts. Neurochemical studies of post mortem tissue, as well as *in vivo* microdialysis and voltammetric recording studies of changes in extracellular DA levels, have all revealed that the mesocortical DA system is especially sensitive to stress (Abercrombie *et al.*, 1989; Deutch and Roth, 1990; Sorg and Kalivas, 1993; Feenstra *et al.*, 1995; Doherty and Gratton, 1996; Feenstra, 2000). Even brief handling, exposure to novelty or a mild two-minute tail pinch stress

is sufficient to induce a significant and long-lasting increase in extracellular DA levels in medial PFC (Feenstra *et al.*, 1995, Sullivan and Gratton, 1998). In addition to the direct activation of the mesocortical DA system by a wide variety of stressors, this system also shows considerable conditioned activation, when the animal is exposed to stimuli paired with stressors (e.g. Feenstra *et al.*, 2001).

There remains however, a considerable lack of consensus as to what this activation represents. It is significant that the DAergic innervation of the PFC by the mesocortical system (originating in the VTA) is most dense in the IL cortex and ventral PL cortex (Van Eden *et al.*, 1987), the very regions suggested to be responsible for the activation of behavioral and physiological responses to stress. This alone however, does not suggest the nature of DA's role here, only that it is likely to be a significant one. To assume the role of DA in this region to be either inhibitory or excitatory is almost surely too simplistic, and while the net effect of DA's actions are likely to be one or the other, this may even vary depending on arousal state of the animal and/or the activational state of the intrinsic prefrontal neurons.

The fact that treatments which have anti-anxiety and antidepressant effects (such as benzodiazepines or chronic antidepressant regimens) also reduce mesocortical DA activation by stress, can be used to support the notion that this DAergic activation is in fact anxiogenic, or the equivalent of stress itself (e.g. Dazzi *et al.*, 2001a,b; Deutch and Roth, 1990). It was suggested that it is the reduction in mesocortical DA release which actually contributes to the anti-anxiety and antidepressant effects of such drugs (Dazzi *et al.*, 2001a,b). An equally plausible explanation however, is that such treatments act at many brain sites to reduce activity within central stress circuits, including the PFC itself, to result in a general reduction in stress perception/experience and hence reduced need for compensatory DAergic modulation. Other studies using behavioral paradigms have also suggested a specifically anxiogenic action of DA within the ventromedial PFC (Broersen *et al.*, 1995, 2000). A possible confound to such studies is that they have involved a major learning component, and DA within the medial PFC and is known to be intricately involved in various aspects of attention, learning and memory, such that too little or too much DA is detrimental to performance (Williams and Goldman-Rakic, 1995; Morrow *et al.*, 1999; Granon *et al.*, 2000; Robbins, 2000). As such, it is difficult to ascribe the observed effects to being purely anxiogenic/anxiolytic in nature, given the interdependence of affective, attentional, arousal and motivational processes within the PFC (see Berridge *et al.*, 2003).

In studies, which have examined the effects of direct manipulations of the DAergic system within the medial PFC in spontaneous behavioral situations or on physiological indices of acute stress, a different picture emerges. If DA is depleted within the medial PFC with 6-OHDA, rats tested in the elevated plus maze show enhanced anxiety profiles relative to controls (Espejo, 1999). The same treatment has also been reported to result in reduced levels of social interaction, also indicating heightened anxiety (Fernandez Espejo, 2003). It was suggested that DAergic activation was necessary for coping with an anxiogenic challenge, allowing for adaptive exploratory responses in a fear-inducing environment. Still other behavioral studies have concluded that the role of mesocortical DA is to maintain the animal's response adaptability with regard to stress-related changes in the external environment (Morrow *et al.*, 1999). These interpretations are consistent with the increased susceptibility to stress ulcer formation following medial PFC DA depletion, particularly in the right brain (Sullivan and Szechtman, 1995), insofar as DA is playing an adaptive or protective role in times of stress.

Mesocortical DA also plays an adaptive role in the extinction of conditioned fear behavior. As previously noted, the ventromedial PFC is particularly important in this process. Studies of DA depletion in this area have shown that lesioned animals still acquire normal fear conditioning, but are substantially impaired in extinction of learned fear associations (Morrow *et al.*, 1999; Fernandez Espejo, 2003). In other words, suppressing fearful responses, especially when they are no longer adaptive, is dependent upon mesocortical DA activity. Pezze *et al.* (2003) have also shown that DA in the medial PFC is important in the retrieval/expression of conditioned fear behaviors. Interestingly, they reported that either facilitating (with local amphetamine microinjection) or blocking (with cis-flupenthixol) mesocortical DA function, reduced freezing to the conditioned stimulus, suggesting that an optimal level or window of DAergic activity is essential for the normal expression or experience of conditioned fear. As stated earlier, such stress-related experience is the prerequisite for subsequent adaptive processes like extinction, also shown to be dependent upon DA activity in the ventromedial PFC (Morrow *et al.*, 1999; Fernandez Espejo, 2003). Such findings of an optimal window of DAergic activity in the medial PFC parallel findings noted earlier in a number of attentional and learning/memory paradigms, where too much or too little DA activity impairs the performance of prefrontally-mediated functions (Williams and Goldman-Rakic, 1995; Granon *et al.*, 2000; Robbins, 2000).

Regarding the relationship between stress-induced mesocortical DA activity and stress-induced HPA activation, *in vivo* studies have shown that these two important indices of stress are indeed positively correlated, such that rats with the highest plasma corticosterone elevations also show the greatest increase in extracellular DA in IL cortex. In response to the psychological stress of predator odor, this relationship was markedly asymmetrical as the highest corticosterone responders had strongly right-biased DA responses in IL cortex. This positive correlation was not asymmetrical however for the DAergic response to the more physical stress of tail-pinch (Sullivan and Gratton, 1998).

To further investigate a causal relationship between mesocortical DA function and neuroendocrine activity, a study was conducted whereby the DA (D1/D2) antagonist alpha-flupenthixol was injected directly into the IL cortex just prior to a 20 min restraint stress, to determine how prevention of stress-induced mesocortical DA action would affect HPA activity. This treatment resulted in significantly increased levels of plasma ACTH and corticosterone induced by restraint, suggesting that mesocortical DA release during the experience of stress actively dampens otherwise excessive reactivity of this stress regulatory system (Sullivan and Dufresne, 2002). Taken together with the positive *in vivo* correlations noted above, these findings suggest that in animals predisposed to particularly heightened levels of HPA function (either by genetic or early environmental factors), the corresponding elevations in mesocortical DA release represent a high level feedback or coping mechanism to contain physiological stress reactivity within manageable limits. The magnitude of the mesocortical DA stress response can still be seen as proportional to the "stressfulness" of the experience, but rather than contributing to the latter, the magnitude of the response reflects the need for its modulatory actions.

Such a compensatory role for DAergic activation is in general agreement with a series of findings by Rots *et al.* (1996) in Wistar rat lines genetically selected for differences in the sensitivity of central DAergic systems. These rat lines also differ in many aspects of HPA axis function, however, it was shown that the early developmental divergence of HPA function in these rat lines precedes that of divergence in DAergic system activity. Thus, the functional nature of DAergic systems was in response to differences in HPA axis function. The studies cited above also suggest that this type of relationship can occur in a more dynamic manner (i.e. during the experience of an acute stressor).

Stress-related Asymmetries in Mesocortical DA Activation

Considering the role of mesocortical DA as an adaptive one, may help to interpret some of the findings of stress-related hemispheric asymmetries within this system. Using the example of gastric stress ulcers, it was shown that across groups of animals, the levels of the DA metabolite DOPAC in the right, but not left, medial PFC were significantly correlated with reduced levels of stress pathology (Sullivan and Szechtman, 1995). Thiel and Schwarting (2001) have reported that DA turnover (DOPAC/DA ratio) selectively in the right medial PFC is strongly correlated with reduced anxiety or greater open arm exploration in the elevated plus maze. However, one study reported that DA content in the right medial PFC was strongly correlated with anxiety in the same test (Andersen and Teicher, 1999). It is possible however, that higher levels of post mortem tissue DA (rather than measures of turnover) may have reflected poor DA utilization in this area. Carlson *et al.* (1993) have demonstrated that poor DA utilization in the right medial PFC is associated with compromised coping behavior. Employing a learned helplessness (footshock) paradigm, they showed that DA activity in the right medial PFC was positively correlated with subsequent successful escape behavior, following exposure to uncontrollable footshock stress. In other words, across normal (unlesioned) animals in the face of stressful challenge, right medial PFC DA utilization appears to be associated with enhanced behavioral adaptability, reduced anxiety and reduced vulnerability to the pathological consequences of stress.

It has also been reported that rats or mice placed in a brightly lit novel environment show an increase in medial PFC DA metabolism lateralized to the right hemisphere (Berridge *et al.*, 1999, 2003). Interestingly, when the animals were given the opportunity to engage in a non-escape displacement or coping behavior, namely chewing on inedible objects, the DAergic activation was selectively suppressed in the right medial PFC, despite other indices of neurochemical activation (e.g. PFC serotonin and subcortical DA) being unchanged. That chewing of objects is indeed a coping behavior, is reflected in the fact that such behavior reduces stress-induced HPA activation. In the present framework, it could be said that the reduction in right medial PFC DA activity follows from a reduced perception of stressfulness afforded by this coping behavior. While the mechanism(s) of this effect are unclear, an involvement of the amygdala was suggested (Berridge *et al.*, 1999, 2003). The amygdala is not only a critical component in the circuitry of stress and emotional regulation, but is directly involved in the control of jaw (chewing) movements (Ohta, 1984; Henke *et al.*, 1991). Amygdala manipulations also significantly affect the mesocortical DA stress response (e.g. Davis *et al.*, 1994), which in at least one example was lateralized to the right medial PFC (Stevenson *et al.*, 2003).

As suggested from the above example of a coping behavior, the aspect of controllability is central to the nature of stress-induced mesocortical DA activation. Carlson *et al.* (1993) showed that rats receiving footshock and having control over termination of the stressor, exhibited bilateral increases in mesocortical DA metabolism. In contrast, paired yoked controls receiving identical shock but having no control over it, had significantly greater DA turnover in the right medial PFC than in the left. Such findings suggest that the right medial PFC is especially activated in situations where control is perceived as minimal, as in the brightly lit novel environment with no escape or coping options (Berridge *et al.*, 1999), or when the stress is most severe. This may also be relevant in terms of how the two hemispheres interact in the processing of stress-related inputs.

Interhemispheric Interactions in Stress and Emotion Regulation

While the discussion to this point has emphasized the particularly direct role of right prefrontal systems in stress

and emotion regulation, it should not mean that the contribution of left-sided structures is insignificant. From the early Denenberg studies with unilateral cortical ablations, it was clear that not only was the right cortex dominant in mediating emotional behaviors, but the left cortex actively inhibited the emotional expression of the right. As such, left-lesioned rats (uninhibited right hemisphere), exhibited emotional behaviors to an extent beyond that of controls. It was shown that this left to right form of interhemispheric inhibition was mediated by the corpus callosum (Denenberg, 1981; Denenberg *et al.*, 1986). In another example of this type of finding, it was reported that during restraint stress, defecation (considered a physiological index of emotional reactivity) was significantly greater in rats with left medial PFC lesions than either controls or right-lesioned rats (Sullivan and Gratton, 1999).

In humans, the same type of pattern has been observed. Using various measures of autonomic function, it has been observed that patients with left hemispheric brain damage show significantly greater autonomic reactivity than controls, while in right-damaged patients such measures are significantly reduced (Meadows and Kaplan, 1994; Crucian *et al.*, 2000).

The notion of a balance of activity between the hemispheres is evident in a number of realms. In terms of cardiovascular control, the right hemisphere predominantly controls sympathetic activation and the left controls parasympathetic activation (Yoon *et al.*, 1997; Wittling *et al.*, 1998; Hilz *et al.*, 2001). Rodent studies have shown that immune function is differentially regulated by the two hemispheres, with a general pattern of immunopotentiation by the left hemisphere, and immunosuppression by the right, with the prefrontal cortex (PFC) playing a particularly important role in some of these effects (Barneoud *et al.*, 1988; Neveu, 1993; Vlajkovic *et al.*, 1994). Similarly in humans, subjects with right frontal biases in EEG activity show decreased killer cell activity, while those with left frontal biases increase killer cell activity in response to emotional situations (Davidson *et al.*, 1999). Given that the same measure of frontal asymmetry is strongly linked to differences in affective style and emotional regulation (Davidson, 1998), and the importance of the PFC in stress regulation (Figs. 1 and 2), such findings generally have significant implications for the relationship between stress and disease.

In the rat, the mesocortical DA system also seems to demonstrate reciprocal hemispheric influences. For example, in regard to the role of this system in cocaine and ethanol self-administration, it has been shown that the left and right medial PFC DA systems do not merely modulate these processes to different extents, but actually in different directions (Glick *et al.*, 1994; Nielsen *et al.*, 1999).

Specifically in the present context of stress-induced activation, functional hemispheric differences in this system are related to temporal factors as well as aspects of

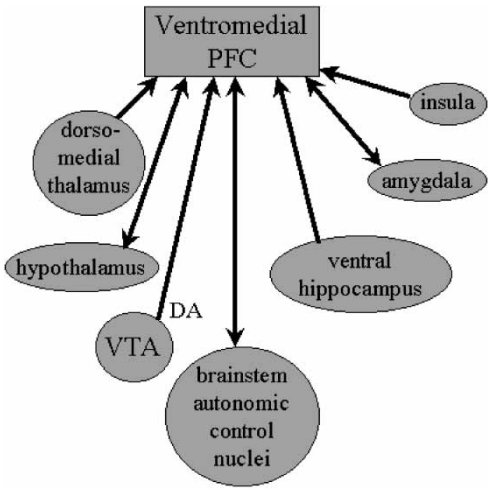

FIGURE 1 Simplified schematic of some of the key structures involved in cortical stress regulation. The ventromedial PFC (infralimbic and ventral prelimbic) is a region of visceromotor cortex proposed to predominantly activate behavioral and physiological responses to stressful situations. Numerous regions relay stress- and affect-related information to this region, where it is integrated for the expression of appropriate stress responses via subcortical limbic, hypothalamic and brainstem control centers. Mesocortical DA inputs originating in the ventral tegmental area (VTA) are proposed to prevent excessive cortical activation and maintain optimally adaptive responses to stress.

controllability and severity of the stress. In the case of a relatively mild stress like 24 h food deprivation, mesocortical DA metabolism is significantly greater in the left medial PFC than the right (Carlson *et al.*, 1988). With differing durations of restraint stress, a clear left to right shift is seen in mesocortical DA activation, as left-sided DA turnover is greatest at 15 min, but right-sided metabolism is greater at 60 min (Carlson *et al.*, 1991). In situations where stress is more severe as with uncontrollable footshock or even exposure to a stressful novel environment with no

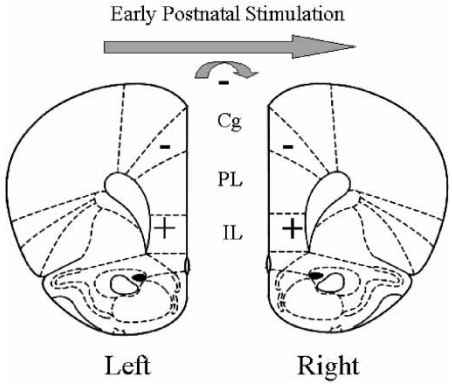

FIGURE 2 Basic template of proposed asymmetrical stress regulation by the medial PFC. The negative signs indicate that dorsomedial regions of PFC tend to suppress behavioral and physiological responses to stress, while positive signs in ventromedial regions reflect the activation of such responses as noted earlier. In the lateralized rat brain, which requires a necessary amount of early postnatal stimulation (e.g. handling), the control of such stress and emotional regulation is suggested to shift predominantly to the right brain. In concert with this (right) lateralized regulation, the left brain appears to functionally inhibit right-sided stress-related and emotional expression, by processes of interhemispheric inhibition as described by Denenberg (1981).

opportunity for escape or displacement behavior, right-sided activation is predominant and more immediate (Carlson *et al.*, 1993; Berridge *et al.*, 1999).

In conceptual or theoretical terms, an initial left-biased prefrontal activation in the face of a mildly stressful challenge may represent initial coping attempts by the more analytical, less emotional and motor dominant left hemisphere. Given that the majority of life's stressors are in fact manageable and not life-threatening, such left prefrontal dominance should successfully deal with mildly challenging situations, without the need of recruiting right prefrontal mechanisms with their more negative emotional attachment and physiological activation of stress regulatory systems. Essentially, the left PFC may help prevent small stressors from becoming big stressors. Such a role of the left PFC could help account for the functional inhibition of right cortical emotional expression by the left cortex, as described by Denenberg (1981). However, where coping attempts are perceived as having failed or are not possible (as in prolonged or uncontrollable stress), activity in the stress-sensitive right PFC would predominate. The associated rightward shift in DA activity would then represent, in essence, a control mechanism to restrain excessive right PFC activity and prevent pathological outcomes associated with the stress. Thus both left and right mesocortical DA activation may be viewed as adaptive, although each may be preferentially associated with distinct stages or strategies of coping with stressful experience, based on the intrinsic specializations of the left and right PFC.

Abnormal imbalances in prefrontal activity have far-reaching implications for stress-related psychopathology and there is much evidence to support the view that both anxiety and depressive disorders are associated with a relative excess of right prefrontal activity (for review, see Sullivan and Gratton, 2002a). While many neurochemical systems are likely to be involved in optimizing the functional balances in prefrontal activity which seem to be so important in stress and emotional regulation, the mesocortical DA system certainly appears to be a key player. It is also noteworthy that mesocortical DA inputs are known to synapse on PFC pyramidal neurons projecting to contralateral PFC, thus positioning them ideally to modulate interhemispheric information flow in this region (Carr and Sesack, 2000). Clearly, many questions remain unanswered regarding the neural basis of hemispheric specialization and interaction, such as whether certain anatomical regions (e.g. ventral vs. dorsal medial PFC) show relatively greater degrees of functional asymmetry than other regions, and whether certain regional asymmetries can be modified more easily than others. What seems clear, is that early environmental factors as well as gender, are important determinants of the patterns of cerebral asymmetry observed throughout life.

The Importance of Early Environment and Gender on the Development of Cerebral Asymmetry

As noted earlier, the (right) lateralized regulation of emotional behaviors was observed only in rats handled in infancy and not in nonhandled controls (Denenberg, 1981). In relation to nonhandling, infantile stimulation or handling, stimulates maternal behaviors upon reunion of the mother and her pups, and more closely mimics natural species conditions where mothers frequently leave the nest to forage (Levine, 1975; Smotherman, 1983; Liu *et al.*, 1997). While early handling stimulation is known to facilitate cerebral lateralization of emotion, it should be noted that virtually all the examples of hemispheric asymmetries of stress/emotion regulation in rodents presently reviewed, were from male rats reared under standard laboratory conditions, which typically involve a level of early stimulation/disruption (e.g. cage maintenance) intermediate between nonhandling and handling protocols.

In comparing handled and nonhandled rats to better study the expression and implications of brain asymmetry, we have found that early handling induces a rightward shift in benzodiazepine receptor binding in IL cortex, insula and hippocampus, the extent of which was correlated with reductions in anxiety-related behaviors and HPA activation (Sullivan and Gratton, 2003). It was suggested that handling enhanced the inhibitory tone in key right brain cortical and limbic regions, better equipping individuals to prevent excessive emotional and stress reactivity. Using a similar neonatal handling protocol, it was reported that early handling (or novelty exposure) increased hippocampal volume selectively on the right (Verstynen *et al.*, 2001). It was also recently reported that the ability of unilateral DA blockade in IL cortex to exaggerate stress-induced HPA activation, is not lateralized in nonhandled rats, but is lateralized to the right IL cortex in handled rats (Sullivan and Dufresne, 2002). Moreover, examining post mortem measures of mesocortical DA turnover, we have found that handled rats significantly increase DA turnover in the right IL cortex following repeated mild stress, while nonhandled rats do not, perhaps contributing to the superior stress adaptation shown by handled rats (manuscript in preparation).

Early handling is well documented to result in highly efficient HPA axis regulation, enhanced feedback regulation by increased hippocampal and frontal cortical glucocorticoid receptor expression, and behavioral profiles characterized by low anxiety and high exploratory activity (Meaney *et al.*, 1985, 1996; Plotsky and Meaney, 1993; Caldji *et al.*, 1998).

Taken together, early handling stimulation appears to trigger a number of associated changes. First, it stimulates the development of "normal" (right) brain lateralization for stress and emotional regulation, while simultaneously enhancing interhemispheric interactions, namely the ability of the left brain to modulate the activity of the right. Secondly, it enhances the capacity for self-regulation within the right hemisphere itself. Thirdly, it optimizes the efficient regulation of HPA activity while resulting in a general reduction in emotional reactivity.

It therefore seems reasonable to speculate that optimal stress and emotional regulation may not only be associated

with the development of lateralized control of these processes, but may actually be dependent upon it. Moreover, the medial PFC appears to be a critical region in this lateralized regulation. If the development of normal functional lateralization in this region is even in part responsible for such optimal regulation, then any perturbations in the normally lateralized development of these prefrontal systems may be expected to result in detrimental outcomes, not only in terms of stress-related psychopathologies, but for somatic manifestations as well, consequent to chronic neuroendocrine and/or autonomic dysfunction. It is known for example, that adverse early events such as perinatal anoxia can dramatically compromise the function of the mesocortical DA system selectively in the right medial PFC (Brake *et al.*, 2000b), and that a variety of early insults cause long-lasting abnormalities in prefrontal function (for review, see Sullivan and Brake, 2003).

An additional important factor in the expression of hemispheric asymmetry is gender. While there have been very few studies specifically examining sex differences and prefrontal asymmetries in the context of stress or emotionality, there have been well documented sex differences in rats regarding patterns of asymmetry generally (e.g. Drew *et al.*, 1986; Zimmerberg and Reuter, 1989; Diamond, 1991). Sex steroid hormones play a role in the development of cortical laterality, morphology and ultimately behavior, and in the neonatal period males and females exhibit an asymmetrical distribution of cortical estrogen receptors, which is opposite in direction (Diamond, 1991). Human brain imaging studies have shown significant sex by region interactions in brain activation to specific emotions, and generally a reduced degree of lateralized activation in females compared to males (Wager *et al.*, 2003). There have also been data suggesting that a family history of psychopathology in females is associated with reduced right prefrontal volume, while the same history in males is associated with increased right prefrontal volume (Sharma *et al.*, 2003). Given the substantial sex differences in the incidence or presentation of a variety of stress-related psychopathologies, it will be very important for future studies to elucidate the different functional nature of hemispheric asymmetries in prefrontal function in both males and females, and their implications for both normal and abnormal stress-related behavior and physiology.

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