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A Final Common Pathway for Depression? Progress Toward a General Conceptual Framework

Eric A. Stone, PhD, **Yan Lin, MD**, and **David Quartermain, PhD**
New York University School of Medicine, Department of Psychiatry, 550 First Ave, New York, NY 10016, USA

Abstract

Functional neuroimaging studies of depressed patients have converged with functional brain mapping studies of depressed animals in showing that depression is accompanied by a hypoactivity of brain regions involved in positively motivated behavior together with a hyperactivity in regions involved in stress responses. Both sets of changes are reversed by diverse antidepressant treatments. It has been proposed that this neural pattern underlies the symptoms common to most forms of the depression, which are the loss of positively motivated behavior and increased stress. The paper discusses how this framework can organize diverse findings ranging from effects of monoamine neurotransmitters, cytokines, corticosteroids and neurotrophins on depression. The hypothesis leads to new insights concerning the relationship between the prolonged inactivity of the positive motivational network during a depressive episode and the loss of neurotrophic support, the potential antidepressant action of corticosteroid treatment, and to the key question of whether antidepressants act by inhibiting the activity of the stress network or by enhancing the activity of the positive motivational system.

Keywords

depression; neuroimaging; fos; final common pathway; cytokines; corticosteroids; monoamines; neurotrophins; theory

The quest for a final common pathway has long been goal of research in depression. Famous candidates in this search have included dysregulated brain monoamines (Schildkraut, 1965; Siever and Davis, 1984; Nutt, 1997), beta adrenoceptors (Sulser, 1982; Frazer et al., 1985), α_2-adrenoceptors (Garcia-Sevilla et al., 1999; Neumeister et al., 2006), α_1-adrenoceptors (Stone et al., 2007c; Lipinski et al., 1987; Habib et al., 2001; Gold et al., 1988), dopaminergic systems (Brown and Gershon, 1993; Cabib and Puglisi-Allegra, 1996), corticotrophin releasing factor systems (Nemeroff, 2002), locus coeruleus activity (Weiss et al., 2005), HPA axis and corticosteroids (Asnis et al., 1985; Mueller and Holsboer, 2006), cytokines (Hayley et al., 2005; Leonard and Song, 1999), neurotrophins (Duman and Monteggia, 2006), neuronal atrophy (McEwen, 2005), and neurogenesis (Santarelli et al., 2003).

It is now generally recognized, however, that depression is a multifactorial disorder characterized by phenotypic heterogeneity and having complex genetic, experiential and

Mailing address: Dr. Eric A. Stone, Psychiatry MHL HN510, NYU Med Ctr, 550 First Ave, New York, NY 10016, USA, 212-263-5740, eric.stone@nyu.edu.

developmental causes. The illness is unlikely to be due to a single neural factor or change, and is most likely the result of alterations in distributed brain networks involving multiple neurotransmitters and pathways.

Despite its complexity, however, depression does have a common symptom which is the loss of interest or pleasure in virtually all activities (American Psychiatric Association, 2002). Most forms of the disorder are accompanied by a marked reduction in effortful and sustained positively motivated behavior, which is defined as behavior directed toward positive reinforcers. This is seen clinically as pervasive anhedonia (Willner, 1997), fatigue at minimal exertion (Demyttenaere et al., 2005), and a stark lack of participation in active forms of leisure (Merrick, 1992). The loss of positively motivated behavior occurs in both agitated and retarded types of depression.

Despite having multiple complex causes, this symptom may have a common underlying final neural state. With respect to the identification of this state, it is believed that the various cognitive, motivational and motor aspects of positively motivated behavior are mediated by a distributed network of brain structures which extends through the neuraxis and includes prefrontal motor, temporal and parietal cortical, limbic, lateral hypothalamic and thalamic areas that modulate basal ganglia, midbrain, brainstem and spinal motor control systems (Swanson, 2000). It is likely therefore that there is a widespread alteration in the function of this network during a depressive episode.

Recent developments in functional neuroimaging studies of depressed patients and in studies of c-fos expression of depressed animals have confirmed this suggestion. Neuroimaging studies of depressives have produced what is known as the Mayberg model in which there is a shift of neural activity away from dorsal cortical brain regions controlling executive function, attention, cognitive processes and motivated behavior toward regions of the ventral limbic system that are more involved in emotional expression, aversion, stress and negative affect. The dorsal or “positive motivational” regions include the dorsal frontal, premotor, orbital, parietal and temporal neocortex, dorsal anterior and posterior cingulate gyrus, and putamen while the ventral “stress” regions include the subgenual anterior cingulate gyrus (ACC), insula, central nucleus of the amygdala, ventral striatum, bed nucleus of the stria terminalis and paraventricular nucleus of the hypothalamus.

Mayberg and associates and other investigators (Mayberg et al., 1999; Depue and Iacono, 1989; Davidson, 1998; Weiss et al., 2005; Baxter, Jr. et al., 1989; Cabib and Puglisi-Allegra, 1996; Oathes and Ray, 2006; Drevets, 2001; Bremner et al., 2003) demonstrated that during depression or induced sadness, the neural activities of the positive motivational brain regions as measured by blood flow or glucose metabolism were decreased while those of the limbic stress/emotion regions were increased. Moreover these changes could be reversed by antidepressant drugs (Mayberg et al., 2000), cognitive behavioral therapy (Goldapple et al., 2004), or deep brain stimulation of the subgenual ACC, a node of interaction between the stress and positive networks (Mayberg et al., 2005). On the basis of these findings, the latter authors and others proposed that the above pattern of neural changes constitutes the final common pathway underlying depressive symptoms (Mayberg et al., 2000; 2005; Gold and Chrousos, 2002).

Analogous findings have been obtained by Stone and colleagues in depressed animals. These authors studied c-fos expression or the phosphorylation of ERK1/2, two measures of neural activity (Hoffman and Lyo, 2002; Pascoli et al., 2005), to a motivating stimulus in a number of mouse brain regions previously shown to be involved in positively motivated behavior or stress responses (Stone et al., 2006a; 2007a). The positive regions included the secondary motor cortex, anterior piriform cortex, posterior cingulate gyrus, and nucleus accumbens whereas the

stress areas included the paraventricular hypothalamus (PVH) and bed nucleus of the stria terminalis (BNST). The positive regions represent a subset of those known to be activated during several different forms of positively motivated behaviors in rodents (exploration of a novel home cage (Stone et al., 2006b), wheel running (Rhodes et al., 2003), and a water-reinforced approach task (Quartermain et al., 2007)) and are directly involved either in sequential motor movements (M2), sniffing behavior (APIR) (Kareken et al., 2004), motivation (NAC), or effort- and reward- related response decision making (CG, NAC) (Schweimer et al., 2005; Tabuchi et al., 2005). Moreover they also contain neuroexcitatory α_1-adrenoceptors which, when stimulated, produce both behavioral activation and c-fos expression (Stone et al., 2004; 2006b). The PVH and BNST, on the other hand, are known to be activated by various forms of stress and to be involved in HPA axis activation, autonomic arousal, anxiety, behavioral inhibition and aversion (Herman and Cullinan, 1997; Habib et al., 2001).

To study the effects of depression on the activation of these two networks, Stone et al subjected mice to one of five different models of the disorder: 1) repeated forced swimming, 2) chronic subordination stress, 3) immune system activation, 4) intracerebral administration of galanin, and 5) depletion of brain monoamines with reserpine. Each of these models had been shown to reduce motivated activities in rodents (Porsolt et al., 1978; Dantzer, 2006; Weiss et al., 2005; Avgustinovich et al., 2005). Moreover they sampled a diverse range of psychological and physiological stimuli that had only one thing in common, the suppression of positively motivated behavior. Once the animals were depressed, they were challenged with a motivating stimulus in the form of exposure to a novel (fresh) home cage or a forced swim and were then assayed for c-fos expression immunohistochemically in the above brain regions.

All 5 depression models were found to significantly reduce the c-fos response in virtually all the positive areas but either had no effect on or elevated the response of the stress regions. A similar result had been found in the lateral septum by others for the learned helplessness model in rats (Steciuk et al., 1999). The fos results were replicated in the CG by ERK1/2 phosphorylation in the immune activation model. The loss of the fos response to these stimuli was not the result of a decrease in baseline expression since in 2 of the models there was an increased baseline (undisturbed in home cage) expression. Furthermore, it was also not the result of habituation to repeated stimulation since the fos response of the PVH persisted unchanged or was increased.

The same authors then showed that pretreatment of mice with one of two effective antidepressant drugs, desmethylimipramine or tranylcypromine, attenuated the changes in both the positive and stress networks. Preliminary studies showed that these changes were also reversed by a serotonin-selective antidepressant, escitalopram (at high doses necessary for mice) and by environmental enrichment, a procedure that has features of antidepressant activity (Lehmann and Stone, 2006). These results indicated that the above effects were not simply the result of any form of chronic stimulation or nonspecific stress but were most likely related to the depressogenic aspects of the procedures.

The above shift in neural activity is consistent with the notion that the positive motivational and stress brain networks are mutually antagonistic. This concept had been advanced earlier in connection with the notion of a brain network underlying positively motivated behavior (Depue and Iacono, 1989; Davidson, 1998). Moreover it was consistent with the hypothesis advanced by Weiss et al (1998) of stress-induced inhibition of the NAC, and with the view advanced by Gold & Chrousos (2002) that stressful stimulation leads to a suppression of physiological activities that are not essential to immediate survival which include many positively motivated behaviors such as reproduction, feeding, exploration and growth. Neural pathways that are capable of mediating interactions between the stress and positive networks include cortical regions that have descending inhibitory projections to stress areas (Spencer

and Day, 2004; Amat et al., 2005; Barbas et al., 2003), and efferents from stress regions to aminergic activating nuclei in the brainstem and midbrain (Valdés et al., 2005; Reyes et al., 2005; Forray and Gysling, 2004; Van Bockstaele et al., 1999; 2001; Weiss et al., 2005).

A central question regarding the interpretation of these findings in both the human and animal studies is whether the reduced neural response in the positive areas is the cause or effect of the reduced behavioral activation produced by depression. Two findings in the animal studies argue that it is the cause. First, the fos response to novel cage exposure appears to occur in primary output (pyramidal) cells of the cerebral cortex (Ostrander et al., 2003; Staiger et al., 2000; Stone et al., 2006a). And second, stimulation or blockade of neuroexcitatory α_{1B}-adrenoceptors or 5HT2A receptors in several of the positive brain regions, in which the former are also predominantly located on pyramidal cortical cells (Papay et al., 2004; Xu and Pandey, 2000), leads to the stimulation or inhibition of exploratory behavior in the novel cage test (Stone et al., 2004; Millan et al., 2003). This suggests that the reduced neural activity in the positive brain areas during depression is the cause not result of the decrease in positively motivated behavior in these conditions.

A second question concerns how well the mouse findings model the human condition. First, while the mouse brain does not have the complexity of the human's, there is nevertheless considerable overlap between the general regions affected with dorsal cortical areas showing decreases and stress areas increases in neural activation. A possible exception to this finding is the ventral striatum which some studies have shown to be more active in depressed subjects than controls and which was found to be deactivated in the mouse models (Ketter et al., 2001). However, the NAC tended to be less deactivated than the other brain regions by these models which may be related to the fact that this region is known to be highly sensitive to both rewarding and aversive stimulation (Nestler and Carlezon, 2006; Di Chiara et al., 1999; Kalivas and Duffy, 1995).

It should be recognized, however, that, at the present time there are two primary difficulties in comparing the human and animal studies: 1) there is presently no evidence on how well CNS fos expression and MAPK phosphorylation in animal studies are correlated with the blood flow and glucose metabolic measures of neural activity used in depressed patients and this question remains to be investigated in future research, and 2) the human and animal subjects are in vastly different behavioral states with the animals free to engage in active locomotor behavior while the humans are lying largely motionless in scanners. With regard to the latter point, it should be noted that when the animals were at rest and presumably asleep, there were increases rather than reductions in the basal fos activity of portions of the positive network. As the waking state is known to produce high fos expression in the rodent brain (Basheer et al., 1997; Cirelli et al., 1995), these results suggest that the "depressed" mice were not as deeply asleep as the control animals. Since disrupted sleep is characteristic of (typical) human depression (Farina et al., 2003) and of animal models of the disorder (Papale et al., 2005), this effect may represent a further analogy between the mouse models and human disorders. But it also confirms that there are dramatic differences in the mobilization of these brain regions during different behavioral states and that future measurement of regional neural activity in the brains of actively behaving depressed humans might reveal the more marked or widespread impairment in regional CNS activation to motivational stimuli that occurs in depressed mice.

Despite these caveats, the strength of conceptualizing depression as a shift of neural activity from the positive to the stress network is that it can serve as a heuristic framework with which to organize the various factors implicated in depression etiology and can help elucidate key research questions and directions. This framework attributes key behavioral functions to CNS regions or networks as opposed to neurochemical/neurotransmitter systems which have dominated previous conceptions of depressive illness. These points are briefly discussed in the

following sections which are not meant to serve as comprehensive reviews but only to illustrate the utility of the present framework for ordering a highly complex field.

1) Positive motivational network

According to the present framework, a positive motivational brain network that integrates the various cognitive and motor aspects of goal directed approach behavior can be distinguished from a stress-related network. It should be emphasized at the outset that while these two networks are separable based on their predominant functions, the dichotomy is not absolute and under certain conditions low level activity of the stress network appears necessary for the function of the positive network (see below). It is generally assumed that the positive system is a distributed hierarchical network comprising a central behavioral control column in the ventromedial upper brainstem that includes the medial preoptic area, anterior hypothalamus, ventromedial and premamillary nucleus, the mamillary body and finally the substantia nigra and ventral tegmental area (reviewed by Swanson (2000)). This column outputs to motor pattern generators in the midbrain, brainstem and spinal cord and is itself under the control of excitatory cortical, inhibitory striatal and disinhibitory pallidal systems (Grillner et al., 2005). The various aspects of positively motivated behavior that are mediated by different parts of this network include working memory, representation of goal states, evaluation of rewards, incentives and response costs, translation of goals into action plans in anticipation of reinforcement, the organization and planning of behavioral strategies and the sequential ordering of motor responses.

The gross neural function of the positive motivational network can be examined using regional c-fos expression in animals engaged in various positively motivated active behaviors. Using this method Rhodes et al (2003) has shown that mice engaged in wheel running, a form of positively motivated behavior in this species, have extensive labeling in various cortical regions (visual, prefrontal, motor, piriform, sensory and entorhinal), the CA2/3 regions of the hippocampus, some thalamic structures (paraventricular nucleus of the thalamus and superior colliculus), hypothalamic areas (suprachiasmatic nucleus) and brainstem structures (pontine nucleus, dorsal raphe, periaqueductal grey). Very little labeling, however, is seen in structures associated with stress such as the PVH, BNST and central nucleus of the amygdala (CeA). A similar pattern of fos expression was found by the present authors in the brains of mice that were engaged in exploration of a novel (fresh) home cage (Stone et al., 2006b) or a water-reinforced approach task (Quartermain et al., 2007), two additional forms of positively motivated behaviors. Again, there was extensive labeling of a variety of cortical, thalamic, hippocampal, and anterior hypothalamic areas with little labeling of stress regions. In contrast, preliminary studies in our laboratory have shown that if animals are subjected to repeated stressors in the form of either passive avoidance training or repeated daily restraint, there is extensive labeling in the PVH and less in the above “positive” areas (Quartermain et al., 2007).

The positive network is subserved by a number of different neurotransmitter systems including monoamines, excitatory amino acids, opioid peptides and other peptide neurotransmitters and hormones. The aminergic neurotransmitters have been most closely associated with depression etiology and treatments. These include NE, DA, 5HT and histamine and mediate various aspects of positively motivated behavior via a group of neuroexcitatory receptors including the α_{1B}- (Stone et al., 2001) and β1- (Zhang et al., 2001; Berridge et al., 2003) adrenoceptors, D1 (Schweimer and Hauber, 2006), 5HT2A (Esposito, 2006) and H1 receptors (Lamberti et al., 1998). Pharmacological blockade of these receptors abolishes many of the above fos responses as well as the positively motivated behaviors in the above conditions (Stone et al., 2006b; Bing et al., 1991; O'Neill et al., 1998; Kauffman et al., 2005). Activation of the α_{1B}-adrenoceptor in a wide range of positive network locations induces vigorous exploratory behavior of mice

in familiar environments and may also enhance reward processes (Lin et al., 2007a; Stone et al., 2004; Drouin et al., 2002). Brain sites from which exploratory behavior have been elicited by α_1-receptor stimulation include the secondary motor and piriform cortex, NAC, POA, LC and vermis cerebellum, DR. The 5HT2A receptor appears to be a principal regulator of the mesolimbic and mesocortical dopaminergic components of the positive network and to facilitate behavioral activation by enhancing the release of DA on output neurons in these sites (Esposito, 2006). It is also involved in cortical pyramidal cell excitation (Jakab and Goldman-Rakic, 2000). Excitatory D1 dopaminergic receptors operating synergistically with D2 receptors in the mesolimbic system are well-established mediators of exploratory behavior and reward processes while these receptors in the prefrontal cortex may be involved in behavioral flexibility (Lanser et al., 2001; Floresco et al., 2006) and working memory (Vijayraghavan et al., 2007). Excitatory H1 histamine receptors are also widely distributed throughout the positive network and may also be involved in behavioral activation (Shigemoto et al., 2004).

The present hypothesis assumes that the above neuroexcitatory aminergic receptors increase the excitatory neural output of the positive areas to motor control systems in the midbrain, brainstem and spinal cord. In support, these receptors appear to be localized primarily on overlapping populations of output cells (pyramids and medium spiny neurons) in the neocortex (Papay et al., 2004; Jakab and Goldman-Rakic, 1998; Xu and Pandey, 2000; Willins et al., 1997; Goldman-Rakic et al., 1990) and mesolimbic system, respectively (Surmeier et al., 1996; Grillner et al., 2005). Studies by Bertini et al. (2002) and preliminary experiments in our laboratory have shown a population of cortical pyramidal cells to have marked c-fos expression during exploration of a novel home cage in mice. The subtypes of these cell populations have not as yet been established and although it is assumed that they include neurons that project to the direct striatopallidal pathway (Grillner et al., 2005).

Different subtypes of excitatory receptors may be located on different populations of cells, however. α_{1A}-adrenergic (Papay et al., 2006) and 5HT2C (Pasqualetti et al., 1999) receptors (in contrast to α_{1B}- and 5HT2A receptors) appear to be located on interneurones rather than output cells in the cortex and mesolimbic system. This differential localization can produce different functional effects with interneuron excitation acting to decrease and pyramidal cell excitation to increase neural output. As will be discussed in the following section, selective activation of the pyramidal and interneuron receptors by different aminergic afferents can form the basis for differential modulation of the output of the positive network under differing affective conditions.

An important aspect of positive network function in the present hypothesis concerns the level of output cell activation that is optimal for behavioral performance. Arnsten and colleagues have shown that there is an inverted U shaped relationship between D1 and α_1-adrenoceptor activation in the PFC and performance on spatial working memory tasks (Vijayraghavan et al., 2007; Arnsten et al., 1999). The high levels of activity of these systems during stress may block their neural output resulting in more automatic survival-related behaviors at the expense of more complex cortical based behavioral processing.

Inhibitory aminergic receptors (α_2-adrenergic, 5HT1A, D2) are also present throughout the positive network and are also located on pyramidal cells (Palchaudhuri and Flügge, 2005; MacDonald and Scheinin, 1995; Boyson et al., 1986; Camps et al., 1989). These receptors serve to reduce the neural output from these structures except perhaps, under conditions of high stress when there is excessive activation of excitatory receptors. Another key inhibitory receptor in the neocortex is the delta opioid, which appears to be selectively activated during aversive conditions (Nieto et al., 2005) and may play an important role in aversion and dysphoria. If and how the inhibitory and excitatory aminergic receptors are differentially activated and how they function under different psychological and physiological conditions

are long standing, unresolved questions. It has been proposed, at least for the α_2- receptor of the noradrenergic system, that a different ligand (agmatine) than NE is involved (Gonzalez et al., 1996). In view of the beneficial behavioral effects on performance during stressful conditions of agonists of some of the inhibitory receptors such as the α_2-adrenergic (Arnsten and Cai, 1993) and 5HT1A (Groenink et al., 2003), it would be of informative to determine their effects on pyramidal cell fos expression during positively motivated behavioral tasks performed under stress.

The positive network is subject not only to acute regulation but also to long term modifications that affect its activity and output. Chronic stress and antidepressant treatment, which produce opposite changes in positively motivated behavior, have been shown also to produce a series of opposing changes in receptor and neuronal function in this system. These effects which include alterations in α_1-adrenergic (Maj and Rogóz, 1999), 5HT1 (Ossowska et al., 2001; Srinivas et al., 2001), 5HT2A (Ossowska et al., 2001; Esposito, 2006), D1(Ossowska et al., 2001; Huzarska et al., 2006), D2 (D'Aquila et al., 2000), GR and MR (Holsboer, 2001; Schule, 2007) as well as in neurotrophin release (Duman and Monteggia, 2006) and neuronal morphology (Fuchs et al., 2004; McEwen, 2003). These multiple correlated effects appear to be the results of a combination of factors including altered neurotransmitter, cytokine, corticosteroid and neurotrophin release (Duman and Monteggia, 2006; Bisagno et al., 2000; McEwen, 2000). Whether they result from correlated changes in gene activation across the positive network is not known but is now being actively studied by various laboratories (Alfonso et al., 2004; de Kloet et al., 2005b). While the functional consequence of each of these changes is still under investigation, it is likely that those occurring with chronic stress contribute to long-term diminutions of neural output of the positive network while those produced by antidepressants result in long-term enhancements. However, it has not been established whether these changes are restricted to the positive network or occur in the stress circuit as well.

Stress area activation

According to the above framework and to current conceptions of stress physiology (Gold and Chrousos, 2002), a key factor causing the reduced neural output of positive motivational brain regions during a depressive episode is excessive stress. As noted above, the PVH (Arborelius et al., 1999; Shumake et al., 2001), CeA (Siegle et al., 2007), BNST (Greenwood et al., 2005; Marvel et al., 2004; Stout et al., 2000), LC (Grant and Weiss, 2001), DR (Maier and Watkins, 2005) and periaqueductal gray (PAG) (Kollack-Walker et al., 1997; Miczek et al., 1999; Kroes et al., In press), which are regions of the brain associated with stress, are known to be excessively activated in human and/or animal depression. Stress regions can be activated either by systemic (“bottom-up”) or by processive (“top-down”) stressors (Herman and Cullinan, 1997). Systemic stresses that induce sickness behavior such as hemorrhage, ether and immune system activation produce a so-called “bottom-up” activation of stress regions in which there is little initial involvement of cortical structures. Marvel et al (2004) showed that the immune stimulant, lipopolysaccharide (LPS) produced intense neural activity of the dorsal vagal motor complex (DVMC), LC, PVH, BNS and CeA, which could be blocked (and sickness behavior alleviated) by local anesthesia of the DVMC. On the other hand “processive” stresses, such as restraint, footshock or social stress, which require cognitive processing and interpretation, activate limbic and thence lower stress centers by way of a “top-down” mechanism. Mayberg et al (2005) have argued that the subgenual ACC represents a key node for a top-down influence of stress on limbic and hypothalamic stress center activity. These authors have shown that high frequency electrical stimulation blockade of this area in depressives attenuates limbic stress region activity, while it restores neural activity in the dorsal cortex and elevates mood. Of particular interest is the fact that mood can be elevated almost immediately at the start of stimulation suggesting that long term changes in the positive network

are not absolutely essential for the relief of depression although they are required for a full remission.

Stress may also impair positive network activity by acting on inhibitory processes or systems intrinsic to this network. In this regard, it should be noted that the original catecholamine hypothesis assumed that depression was due to a deficiency of these neurotransmitters in positive networks. Two such inhibitory factors are adenosine and α_2-adrenoceptors. It has been demonstrated that adenosine, which can inhibit all forms of excitatory neurotransmission via the A2A receptor, builds up in neurons of the frontal cortex and other brain regions in a glutamate-dependent fashion during repeated energy consuming unsuccessful coping attempts (Minor et al., 1994). The A2A receptor forms a complex with dopaminergic and glutamate receptors that inhibits neurotransmission via the latter receptors (Svenningsson et al., 1998; Fuxe et al., 2003). Increases in the density and functional activity of inhibitory α_2-adrenoceptors in cortical structures occur during depression (Garcia-Sevilla et al., 1999) and chronic stress (Flügge et al., 2001). Furthermore there is evidence that tissue necrosis factor α (Reynolds et al., 2005), which is elevated in depression, can enhance the ability of α_2-adrenergic receptors to inhibit NE release from the hippocampus, an action that is reversible by antidepressant therapy. Other work has shown that corticosterone can reduce noradrenergic excitation of hippocampal neurons in a brain slice preparation (Joels and DeKloet, 1989). Thus, positive network activity may be inhibited during adverse conditions because of intrinsic factors that appear independent of stress area activation.

With regard to stress area activation, it is likely that this is an important factor in the specific negative affects and feelings of depression. Some data suggest that the excessive activity of the PVH is associated with autonomic and sympathetic system hyperactivity (Dayas et al., 2004; Perrin et al., 2003; Kenney et al., 2001), which underlie the somatic distress of the disorder. Activation of the BNST, CeA and dorsolateral PAG may be associated with aversion (Delfs et al., 2000), anxiety (Davis et al., 1997), and defeat (Kroes et al., In press) respectively. Recent findings on the role of the anterior insula on the representation of internal bodily states and emotion suggest a principal role for this structure in the negative affects of depression (Craig, 2004).

The principal neurotransmitter for the stress network is CRF, which exerts neuroexcitatory effects via the CRFR1 receptor (Bale and Vale, 2004; Berns and Nemeroff, 2003). This compound plays a major role in stress-induced activation of the BNST (Stout et al., 2000), CeA (Sajdyk and Gehlert, 2000), LC (Van Bockstaele et al., 2001) and DR (Hammack et al., 2002). High doses of CRF infused into the PVH and BNST produce behavioral inhibition, freezing, aversion and autonomic arousal (Monnikes et al., 1992). There is extensive evidence for enhanced CNS CRF release and action in depression (Berns and Nemeroff, 2003), preclinical studies have shown CRFR1 antagonists to have antidepressant potential (Jutkiewicz et al., 2005; Overstreet et al., 2004). According to the present framework, it would be predicted that CRFR1 antagonists in models of depression would attenuate the fos response of the stress network and restore that of the positive network to a motivational stimulus.

Recent work by Kroes et al (In press) has suggested a key role for cholinergic neurotransmission in the PAG in stress responses related to depression confirming the earlier hypothesis of Janowsky et al. (1974).

A possible mechanism by which stress region hyperactivity can blunt the output of positive regions involves CRF projections to the LC and DR from the PVH, CeA and BNST (Reyes et al., 2005; Van Bockstaele et al., 2001), which in turn activate selective adrenergic, serotonergic and gallanergic receptors in the positive areas that may inhibit these (Arnsten and Li, 2005; Weiss et al., 2005). Weiss' group showed in seminal studies that inhibition of LC activity with

the α_2-agonist, clonidine, blocked the effects of prior footshock stress on immobility in the forced swim test in rats (Simson et al., 1986). These authors subsequently demonstrated that galanin, presumably released from LC efferents to the NAC during stress, inhibits this major activational region (20625). Maier and associates have shown that blockade of CRF neurotransmission in the DR alleviates some of the behavioral inhibitory effects of severe stress in rats (Maier and Watkins, 2005).

However, a difficulty with this view is that it conflicts with the role of the noradrenergic and serotonergic systems in stimulating the neural output of the positive network. It may be, however, that the degree of LC and DR activation is a critical variable with moderate levels of activity supporting increased positive network activity while high levels, produced during stress, suppressing output. As noted above, this conflicts with the view that the dichotomy between positive motivational and stress regions is absolute. In support of this qualification, it should be noted that the neural activity of the stress regions is not monotonically related to behavioral inhibition and distress. Low level activation of the PVH, CeA and BNST with CRF leads to increased exploratory behavior in rats in a familiar environment whereas high level activation produces freezing, defecation and distress in this same environment (Heinrichs and Koob, 2004). Also CRF stimulates motor behavior from the ventral tegmental area (Kalivas et al., 1987). This raises the question of what role the peptide plays in the positive network and how its action in the latter system is differentially regulated from that in the stress network. If CRF does function in the positive system, one would predict that CRFR1 antagonists may under some conditions have behaviorally depressing effects. Furthermore, while the LC and DR are activated by stress, LC activation has also been shown to be involved in the rewarding effects of lateral hypothalamic self stimulation (Lin et al., 2007a), and DR activation in voluntary wheel running in mice (Rhodes et al., 2003), both forms of positively motivated behavior. Therefore, it may be that low to moderate activity in stress regions is necessary for the activation of positively motivated behavior and that an inhibitory effect only becomes apparent at high levels of activation. While this represents a post-hoc explanation, it can be directly tested experimentally by measuring fos expression in positive motivational brain regions during low and high level activation of the PVH with CRF.

Another complicating factor in the above scheme is the fact that excitatory aminergic neurotransmission, which is essential for the activity of the positive network, is also involved in the neural activation of portions of the stress network. Thus increased activity of noradrenergic α_1-adrenergic system of the PVH is associated with elevated ACTH secretion (Kiss and Aguilera, 2000) and in the CeA and BNST with increased anxiety and increased HPA axis activity (Cecchi et al., 2002a;b). Elevated serotonergic 5HT2 and D1 receptor activity in the basolateral amygdala has been associated with increased anxiety, aversion and behavioral inhibition (Macedo et al., 2007). Furthermore, since stress regions can stimulate neural activity in the LC and DR, which, in turn, can increase activity in the stress regions, this makes for a positive feedback loop that may serve to maintain activity in the stress network for prolonged periods (Heinrichs and Koob, 2004). However, stress regions also contain dense concentrations of inhibitory aminergic receptors such as the α_2-(MacDonald and Scheinin, 1995), 5HT1A (Zifa and Fillion, 1992) and D2 (Boyson et al., 1986) which are present in the PVH, LC, DR, BNST and CeA which may function to terminate such positive feedback effects. This property could be an important factor in therapeutic interventions and might underlie the potentiation of antidepressant action seen with agonists of these receptors (Nyberg et al., 2006; Gershon et al., 2007; Blier and Ward, 2003).

Since the positive and stress networks contain the same aminergic neurotransmitters, the question arises as to how the aminergic activity in the two networks is differentially regulated under differing emotional conditions. One possible mechanism involves separate afferents. It was postulated in early work that the noradrenergic innervation of the positive network is

achieved via the dorsal noradrenergic bundle (DNB) originating in the LC which enhances behavioral activation whereas the noradrenergic innervation of stress areas proceeds via the ventral noradrenergic bundle (VNB) and emanates from the tegmental nuclei, A1 and A2, and functions to produce behavioral inhibition (Kostowski, 1979). However, recent experiments have shown that the effects of antidepressant drugs on behavioral activation in the forced swim test are more dependent on the functional integrity of the VNB whereas immobility in this test is more related to integrity of the DNB (Cryan et al., 2002). Also, as noted above, studies of inhibition LC activity also support a role of the DNB in the loss of positively motivated behavior. It is not known whether a similar divergence of inputs to these structures occurs in the raphe system (Hollis et al., 2006). It may be possible, however, to resolve this question now that a clear demarcation between the fos responses of the two systems to stress and positively motivating stimuli has been established.

A new approach to this question involves the possibility that DA, in addition to or instead of NE, innervates α_{1B}-adrenoceptors in certain regions of the positive network. While it has traditionally been assumed that the endogenous agonist for this receptor is NE, recent work by Wisor and Eriksson (2005) and by Cornil et al (2002) has suggested involvement of brain DA. Preliminary data from our laboratory indicates that DA in the pons is involved in the activation of α_1-receptors in the LC that are involved in exploratory behavior in the novel cage test (Stone et al., 2007b). We have found that the D2 agonist, quinpirole, which inhibits DA release, produces immobility and catalepsy in mice when microinjected near the LC and that this effect can be abolished in an α_1-receptor dependent manner by coinfusion of DA. Furthermore, systemic quinpirole, which induces inactivity in mice, also appears to inhibit the fos response of the mouse motor cortex to novel cage exposure, a response that we have previously shown to be mediated in large part by α_1-receptors (Stone et al., 2006b). If DA stimulation of the α_{1B}-receptor in fact occurs, and if the interneuron-localized α_{1A}-adrenoceptor, which is assumed to have an opposing behavioral function, is preferentially activated by high concentrations of NE from the LC during stress, then this would make for a mechanism by which the positive network can be selectively modulated by different aminergic afferents under differing emotional conditions. In this regard, it should be noted that two of the most reliable neurochemical changes that occur during depression are a reduction in the availability of brain DA (Brown and Gershon, 1993; Nestler and Carlezon, 2006) and an increased availability of NE (Nemeroff, 2002). It is of further interest that Arnsten et al (1999) have found that injection of the PFC with urapidil, an α_1-antagonist that has high affinity for the α_{1A}-receptor (Hancock, 1996), facilitates behavioral performance in a working memory task under stress.

The present framework assumes that the positive motivational regions can inhibit stress area activity. This is consistent with the known inhibitory connections of the PFC and hippocampus to the PVH, CeA and BNST (Herman and Mueller, 2006; Amat et al., 2005). It is also supported by the findings of intense activation of stress regions after whole brain blockade of α_1-adrenoceptors, key activating receptors of the positive network (Stone et al., 2006b). Furthermore, in pilot experiments we have found a similar intense activation of the mouse PVH after inhibition of brain DA release with the D2 agonist, quinpirole (Stone et al., 2007b). It should be possible to utilize this strategy to further delineate the positive regions in which these receptors produce inhibition of stress area activity.

The view that the loss of motivated behavior during depression results from an altered balance between the positive and stress networks can also help illuminate differences underlying the different subtypes of affective disorders. For example, in atypical depression in which neurovegetative symptoms are the reverse of those of typical depression (i.e, hypersomnolence and hyperphagia versus insomnia and hypophagia) it would be predicted that there would be hypoactivity of the stress as well as the positive network. Gold and Chrousos (2002) have provided strong evidence for a reduction in stress system activity in this depression subtype.

In bipolar illness on the other hand, one would expect a greater activation of the positive network occurring possibly in connection with increased activity of the stress circuit. Several studies have suggested a pattern of subcortical hyperactivity occurring with either increased or decreased activation in cortical regions in manic bipolar patients (Chang et al., 2004; Blumberg et al., 2003)

The above analysis may also be applicable to other areas of affective disorder research. For example, most animal models of depression deal with a melancholia-like syndrome in which behavioral output is reduced. It would be of interest to examine the above regional CNS activity changes in other depressive states, e.g., agitated depression and in anxiety disorders which are also amenable to antidepressant treatment. Presently there are no proven animal models of agitated depression however a case could be made for using olfactory bulbectomy, which induces an antidepressant-sensitive increased behavioral activity in novel environments (Possidente et al., 2000; Song and Leonard, 2005) and in the forced swim test (Mucignat-Caretta et al., 2006), as one. Also, depending on how behavior is measured, some chronic stressors lead to a sensitization of active behavior (Nikulina et al., 2004; Herman et al., 1984; Strekalova et al., 2005) and to a sensitization of systems involved in drug self administration (Piazza et al., 1990).

2. Extension to Cytokines

The complex relationship between cytokine action and depression has recently been extensively reviewed and will not be recounted here (Dantzer, 2006; De La Garza, II, 2005; Anisman et al., 2002). Two key actions of cytokines that may lead to depression and are relevant to the present framework are the sensitization of stress circuits and potential direct impairment of positive network activity. With respect to the former, cytokines are known to trigger and sensitize neural activity in the stress circuits of the brain. The mechanism of this effect has been recently reviewed by Dantzer (2006) and Hayley et al (2005). In brief, IL1β acts via activation of the vagus nerve which then stimulates primary and secondary projection areas including the dorsal motor complex, PVH, BNST and CeA. It also acts by stimulating macrophage-like cells in the circumventricular organs and endothelial cells of the CNS resulting in local production of cytokines and prostaglandin E2 (PGE2). The latter compound then diffuses into the brain parenchyma and activates catecholaminergic and serotonergic brainstem nuclei that innervate the PVH, BNST and CeA. Cytokines appear to trigger two behavioral processes involved in depression: the first occurs rapidly and involves sickness behavior, malaise and fatigue, the second is delayed and involves depressed mood (Dantzer, 2006). Whether these two processes differentially involve stress and positive circuits is not known. An important unresolved question regarding cytokine involvement in depression is what is the mechanism of their mobilization during psychological stress.

With regard to the second action, whether cytokines have a direct and possibly long-term impairing action on neurotransmission in the positive motivational network is not yet clear but represents a key question in the mechanism of their behavioral action. These compounds may impair dopaminergic and possibly serotonergic neurotransmission (Anisman et al., 2002; Lestage et al., 2002) and may also adversely affect α_1-receptor function (Bucher et al., 2003) but it is not clear whether these effects occur in both the stress and positive networks and whether they are primary effects or are secondary to activation of stress circuits.

5. Extension to Corticosteroids

As with cytokines, the involvement of corticosteroids in depressive etiology and/or therapy has been extensively reviewed elsewhere (Mueller and Holsboer, 2006; Gold and Chrousos, 2002; de Kloet et al., 2005a). Two opposing actions of these hormones that can be interpreted according to the present framework are a facilitation of behavioral activation and a potential

antidepressant effect, occurring at low doses and possibly as a result of suppression of stress circuit activity, and an opposing exacerbation of depression, which occurs at higher doses and with chronic exposure.

With regard to the first action, corticosteroids are known to block CRF release in the PVH possibly by inhibiting cytokine and prostaglandin synthesis (Pezeshki et al., 1996; Johnson et al., 1996) and by stimulating inhibitory membranal (Coddington et al., 2007) and GR receptors located on stress network neurons. They also activate brain areas (PFC, hippocampus), which have inhibitory connections with the PVH (Herman and Mueller, 2006). Based on these actions, the present framework would predict corticosteroids at some dosages to have antidepressant effects. This has been confirmed in a number of clinical studies (Dinan et al., 1997; DeBattista et al., 2000; Arana et al., 1995). We have also confirmed this in a study showing that corticosterone addition to the drinking water markedly reduces immobility in the mouse forced swim test (Stone and Lin, 2007; Lin et al., 2007b). The corticosterone-treated animals also showed a suppression of evoked fos expression in the PVH and a disinhibition of fos expression in the piriform cortex, a brain region involved in positively motivated behavior. These results confirm findings with genetically modified mice that have implicated corticosteroid action in antidepressant effects (Mueller and Holsboer, 2006) and are consistent with several reports of behaviorally activating (Deroche et al., 1992; Sandi et al., 1996; Tenk et al., 2006), anti-stress (Schelling et al., 2001; Johnson et al., 1996; Stone et al., 2002), mood-elevating effects of corticosteroids (Het and Wolf, 2007). It is also of interest that diurnal corticosterone increases appear to be essential for increases in neurogenesis elicited by serotonin selective antidepressants (Huang and Herbert, 2006), an effect that appears necessary for antidepressant action.

In support of the above antidepressant effect, there is some evidence for reduced corticosterone action in depression in that mice subjected to chronic subordination stress show adrenal insufficiency (Reber et al., 2007) and from findings of hypocortisolemia in atypical and nonhypercortisolemic depression (Gold and Chrousos, 2002; Carroll et al., 2007). Adrenal insufficiency is known to produce many of the somatic signs of depression including lethargy, depressed mood and psychomotor slowing (Arlt and Allolio, 2003).

Corticosteroids, however, are more traditionally thought to precipitate or exacerbate depression (Gregus et al., 2005; Brown and Suppes, 1998; Buchman, 2001; Sonino et al., 1998). At high dosages these hormones can cause neurodegeneration of hippocampal neurons that inhibit parvocellular PVH CRF- containing neurons (McEwen, 2005). This action would serve to disinhibit stress circuit activity. High doses of corticosterone also enhance the expression of CRF in the CeA (Makino et al., 1994) and in a PVH pathway projecting to the LC (Gold and Chrousos, 2002) and can result in the suppression of the expression of neurotrophins that are necessary for adaptation and neural plasticity (Schaaf et al., 1997).

Corticosteroids also have been shown to affect central dopaminergic (Cyr et al., 2001), serotonergic (Gur et al., 2001) and noradrenergic neurotransmission (Gannon and McEwen, 1990; Stone et al., 1987) and may be responsible for long-term modifications in these systems but whether these effects are selective to positive or stress circuits has not been established.

Therefore corticosteroids have dual effects producing antidepressant actions under certain conditions and depressant actions under others. The conditions under which these opposite effects occur, however, have not been adequately defined and the potentially differential actions of these hormones on the positive and stress CNS networks have not yet been fully clarified.

6) Neurotrophins and neurogenesis

Stress and depression both have been extensively documented to produce widespread CNS reductions of neurotophin expression, hippocampal neurogenesis and neuron survival as well as atrophy and apoptosis (Duman and Monteggia, 2006). The reduction in BDNF after defeat stress in the hamster has been shown to occur widely throughout the positive motivational network (neocortex, piriform cortex, hippocampus, hypothalamus) (Pizarro et al., 2004). The functional consequences of down-regulation of neurotrophic support are atrophy, degeneration, loss of excitatory neurotransmitter release (Jovanovic et al., 2000), and down-regulation of certain excitatory aminergic receptors (5HT2A (Rios et al., 2006) and D1 (Do et al., 2007)).

There is some evidence that the loss of trophic support occurs primarily or exclusively in the positive motivational network and in the hippocampus and PFC, which have inhibitory connections with stress nuclei. In contrast, the stress nuclei of the PVH (Bruijnzeel et al., 2001), amygdala (Frodl et al., 2002), and BNST (Stout et al., 2000) show enhanced size and/or neural activity with chronic stress and depression possibly as a result of sensitization. Such effects may be the result of enhanced neurotrophic activity. The NAC, which is involved not only in positive but also negative affective regulation (Green et al., 2006; Di Chiara et al., 1999), shows an increased expression of BDNF with repeated stress and one that is involved in aversive conditioning (Berton et al., 2006).

The present framework provides a new insight into the stress- and depression-induced atrophy of positive network areas and one that has been overlooked in previous discussions of this effect. This concerns the prolonged hypoactivity of the positive system during a depressive episode which may induce disuse atrophy. Neurotrophin release is activity-dependent (Dechant and Neumann, 2002) and therefore the decreased neural activity of the positive network is likely to be a major factor in the down-regulation of neurotrophin activity. In peripheral organs, such as skeletal muscle, prolonged metabolic and physiologic inactivity produces atrophic changes that result from the loss of trophic support. Interestingly, the amount of skeletal muscle atrophy during inactivity is greatly magnified by high levels of circulating corticosteroids (Paddon-Jones et al., 2006) possibly as a result of interference with neurotrophin release or synthesis. Conceivably a similar corticosteroid-induced potentiation of atrophic changes in the inactive positive regions may occur in the CNS during stress and depression.

The loss of neurotrophic support and neurogenesis in the positive brain regions during stress and depression is also consistent with findings that aminergic systems are important regulators of these processes in these brain areas. Dopaminergic (Juric et al., 2006), noradrenergic (Rizk et al., 2004; Garcia et al., 2003; Lesselyong et al., 2005) and serotonergic (Kuhn et al., 2005) systems have each been found to regulate neurotrophin expression and neurogenesis and /or neuronal survival under a variety of conditions. Altered aminergic neurotransmission in the positive network during these disorders may therefore be a mediating factor in the reduced neurotrophic activity. It is of interest that while numerous studies have examined the effects of stress and depression-inducing stimuli on brain monoamine release in various CNS regions, no studies have been conducted on the effects of these conditions on monoamine turnover in response to a positive motivational stimulus in the positive network. The present framework would suggest a major decline in such responses during depression which would support original monoaminergic hypotheses of the disorder. Recent evidence for an increase in monoamine oxidase A in the brains of depressive supports this view (Meyer et al., 2006). Moreover, such a prolonged decrease may result in receptor sensitization which would be consistent with the observation that depressives have a greater euphoric response to pharmacological release of monoamines (Tremblay et al., 2005).

The above analysis has significant implications for therapy in that it assumes that agents that stimulate activity in the inactive positive regions would gradually restore their trophic support and hence functionality. Antidepressant drugs, exercise and environmental enrichment would all fall under this category and have all been shown to gradually reverse depression.

Mechanism of action of antidepressants

Whether antidepressants act on either or both the positive and stress networks to achieve their behavioral and psychological effects is not yet established and represents a significant question raised by the present analysis. For example, it is possible that these agents act primarily on excitatory aminergic function in the positive network to enhance its output and suppress the activity of the stress network. Conversely, they may act on inhibitory aminergic function in the stress regions to suppress these and disinhibit the positive network. In either case the process of full recovery and restoration of positive motivation would be gradual and require neurotrophic action and neurogenesis to overcome atrophic effects and cell loss caused by the prolonged inactivity of the positive system. It would also entail a correspondingly gradual recession of trophic effects and sensitization in the overactive stress system to diminish anxiety and aversions. There is evidence supporting a primary action of antidepressants on both systems. For the first are the findings that enhancement of aminergic neurotransmission by blockade of inhibitory α_2- (Zebrowska-Lupina, 1980; Nyberg et al., 2006) and 5HT1A (Ballesteros and Callado, 2004) receptors can hasten and enhance antidepressant action in both animal models and people. Furthermore, physiological stimulation of the positive network by exercise and environmental enrichment are known to have therapeutic effects in depression (Harris et al., 2006; Koh et al., 2007). In support of the second are the findings that a) localized deep brain stimulation blockade of the subgenual anterior cingulate stress-node produces immediate relief and long term recovery from depression Mayberg et al (2005); b) antidepressants increase expression of GR and MR in the hippocampus, which would have the effect of dampening stress circuit activation (Het and Wolf, 2007); c) antidepressants infused into the CeA have been shown to reverse the immobility in the repeated forced swim test (Duncan et al., 1986); and finally, d) suppression of stress circuit activity by clonidine infusion in the LC and systemic corticosterone produce rapid antidepressant effects. It may be that both mechanisms are operative and vary with the type of antidepressant agent. This problem can be investigated experimentally by examining the time course of changes in neural activity in the stress and positive networks starting with the inception of antidepressant therapy in an animal model of depression. Another approach would be to determine the therapeutic effects of localized infusion of antidepressants into positive versus stress brain regions.

Conclusions and future directions

The present review indicates that conceptualizing depression as the result of a pattern of high stress-low positive motivational neural circuit activities can help to order the multiple complex factors involved in this illness and can suggest new research directions and novel therapeutic strategies. Long term changes in the activities of the stress and positive networks are under genetic and epigenetic controls. Studies are now beginning to map out changes in gene expression (Kroes et al., 2006) and histone regulation (Tsankova et al., 2006) in various regions of the CNS of depressed animals and patients although clear demarcations between positive and stress areas has not yet been established. A critical area for future research will be to determine how these substrates are differentially modulated in the two networks by monoamines, hormones and cytokines and what kinds of correlated patterns of cell signaling and neurotrophic changes emerge in these areas.

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