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What the rodent prefrontal cortex can teach us about attention-deficit/hyperactivity disorder: The critical role of early developmental events on prefrontal function.

Ron M. Sullivan[1] and Wayne G. Brake[2]

[1]Centre de Recherche Fernand-Seguin
Dept. of Psychiatry
University of Montreal

[2]Laboratory for Neurodevelopment
Dept. of Psychology and Neuroscience Research Institute
University of California, Santa Barbara

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Corresponding Author:

Wayne G. Brake, Ph.D.
Department of Psychology
University of California Santa Barbara
Santa Barbara, CA, 93101-9660
Phone: (805) 893-5006
FAX: (805) 893-4303
E-mail: brake@psych.ucsb.edu

Full address of all authors:

Ron M. Sullivan

Dept. of Psychiatry
University of Montreal
Centre de Recherche Fernand-Seguin
7331 rue Hochelaga
Phone: (514) 251-4015 Ext. 3553
FAX: (514) 251-2617
E-mail: rsullivan@crfs.umontreal.ca

Wayne G. Brake

Department of Psychology
University of California, Santa Barbara
Santa Barbara, CA, 93101-9660
Phone: (805) 893-5006
FAX: (805) 893-4303
E-mail: brake@psych.ucsb.edu

Abstract The present review surveys a broad range of findings on the functions of the rodent prefrontal cortex (PFC) in the context of the known pathophysiology of attention-deficit/hyperactivity disorder (ADHD). An overview of clinical findings concludes that dysfunction of the right PFC plays a critical role in ADHD and that a number of early developmental factors conspire to increase the risk of the disorder. Rodent studies are described which go far in explaining how the core processes which are deficient in ADHD are mediated by the PFC and that the mesocortical dopamine (DA) system plays a central role in modulating these functions. These studies also demonstrate a surprising degree of cerebral lateralization of prefrontal function in the rat. Importantly, the PFC is highly vulnerable to a wide variety of early developmental insults, which parallel the known risk factors for ADHD. It is suggested that the regulation of physiological and behavioral arousal is a fundamental role of the PFC, upon which many "higher" prefrontal functions are dependent or at least influenced. These right hemispheric arousal systems, of which the mesocortical DA system is a component, are greatly affected by early adverse events, both peri- and post-natally. Abnormal development, particularly of the right PFC and its DAergic afferents, is suggested to contribute directly to the core deficits of ADHD through dysregulation of the right frontostriatal system.

Keywords:

arousal	executive function	stress	emotional regulation
dopamine	maternal separation	anoxia	asymmetry

1. **Introduction**

The neurodevelopmental disorder known as attention-deficit/hyperactivity disorder or ADHD, is the most prominent childhood psychiatric condition and its features or core deficits frequently persist well into adulthood. It is increasingly appreciated that functional deficits in frontostriatal circuitry contribute substantially to the pathophysiology of ADHD and that the right prefrontal cortex (PFC) is especially important in this regard. While genetics play a very important role in this condition, intra-uterine, perinatal and postnatal factors have all been significantly linked with the development of ADHD.

Studies in the rodent have revealed that the PFC is intimately involved in mediating numerous neural functions of central relevance to ADHD, not only behavioral inhibition, attentional processes and working memory, but also less appreciated aspects of this condition such as arousal level, physiological stress responsiveness and emotional self-regulation. Not surprisingly, the maturation of these prefrontal circuits is significantly affected by a wide variety of early developmental events, both adverse and advantageous. The present review examines many of these animal findings and describes the important modulatory role of mesocortical dopamine (DA) on PFC function, as well as the extent to which this system may be particularly vulnerable to early developmental insults. Many of these findings also highlight the important role of cerebral laterality in mediating the above processes, even at the level of the rodent.

The first section of the paper thus provides a brief overview of the pathophysiology of ADHD with particular reference to PFC dysfunction and the proposed nature of altered DA function in this condition. The following sections review the rodent literature in terms of how the PFC modulates the various processes deemed central to ADHD symptomology. The final sections discuss first the evidence that early adverse events contribute to the development of ADHD, and secondly, that in rodents numerous early manipulations modeled upon these types of events lead to long-lasting impairments in prefrontal function. It is proposed that early adverse events impact negatively on the maturation of prefrontal circuits particularly in the right hemisphere, and that deficits in mesocortical DA function in this region contribute significantly to ADHD symptomology.

2. Prefrontal Involvement in ADHD Pathophysiology and the Possible Role of DA

Numerous reviews have elucidated the behavioral and cognitive characteristics of ADHD in great detail, as well as describing the known neuropathological correlates of this condition (eg. Barkley, 1997, 1998; Castellanos, 1997; Castellanos and Tannock, 2002; Spencer *et al*., 2002; Swanson *et al.*, 1998). The present paper focuses on the pivotal role that the PFC appears to play in mediating the spectrum of ADHD symptomology.

Heilman *et al*. (1991) proposed that the pathophysiology of ADHD derives from right-sided frontal-striatal dysfunction in combination with an impairment of the mesocortical DA system. Since this time, brain imaging studies have done much to support this view. Numerous structural imaging studies have reported significantly reduced volume of the right frontal (particularly prefrontal) cortex in ADHD subjects (Castellanos *et al.*, 1996b; Filipek *et al.*, 1997; Casey *et al*., 1997; Pueyo *et al*., 2000; Mostofsky *et al*., 2002) in conjunction with right caudate abnormalities. Casey *et al*. (1997) reported that such right frontal volume reductions are significantly correlated with impaired performance in response inhibition tasks. Neuropsychological and other studies have support the view that ADHD is a disorder of right hemispheric function, primarily right-sided attentional and arousal systems (Voeller and

Heilman , 1988; Carter *et al*., 1995; Malone *et al*., 1988; Campbell *et al.*, 1996; Stefanatos and Wasserstein, 2001). For example, Silberstein *et al*. (1998) employed an electrical brain mapping technique during a continuous performance task to demonstrate that normal boys show an increased speed of processing during critical periods of the task, specific to right prefrontal sites. However, this task-related change in processing ability was not evident in ADHD boys. Moreover, functional imaging studies have shown that a normal right prefrontal increase in metabolism during response inhibition tasks, is markedly reduced in ADHD subjects (Langleben *et al*., 2001; Rubia *et al*., 1999; 2001).

Abnormalities in DAergic transmission are well accepted as predisposing factors in ADHD, yet the nature of DAergic dysfunction is not well understood. Given the strong genetic component in the incidence of ADHD, it is notable that at least four DA-related gene loci have been implicated in this condition, including that of the DA transporter or DAT (Cook *et al*., 1995; Gill *et al*., 1997; Kirley *et al*., 2002; Hawi *et al*., 2003). While no single gene abnormality reliably predicts the occurrence of ADHD, it is quite possible that one or more DA-related gene variants contribute to the abnormal development and functioning of certain DA circuits, thus predisposing to the development of the disorder.

The most common treatment for ADHD is methylphenidate or Ritalin, which blocks DA reuptake into the cell by the DAT. The resulting elevations in synaptic DA levels are presumed to be related to its therapeutic benefits at some level, but the most critical site(s) of action for these effects is the subject of debate. Perhaps the most parsimonious theory accounting for DA involvement in ADHD was put forward by Castellanos (1997), who proposed that a mesocortical DA deficit (related to attentional and executive deficits) coexists with a striatal *hyper*DAergic state (related to behavioral hyperactivity, Castellanos *et al*., 1996a). As such, enhancing prefrontal DA activity would have the greater therapeutic benefit. This theory also proposed (based on regional differences in DA autoregulation) that continued treatment with methylphenidate would result in a constant facilitation of PFC DA function, but would lead to a downregulation of striatal DA function. Recent findings by Ernst *et al*., (1998) suggest prefrontal DAergic deficits in ADHD. In a PET study measuring the uptake of $[F^{18}]$fluorodopa to assess DOPA decarboxylase activity (and thus DA synthesis), it was found that $[F^{18}]$-DOPA uptake ratios in medial PFC were reduced by approximately half in ADHD subjects compared to controls, with no such effect seen in striatum.

Additional neuropharmacological evidence reinforces the importance of the PFC in providing therapeutic benefits in ADHD. The selective norepinephrine uptake inhibitor atomoxetine, has been shown in clinical trials to be at least as effective as methylphenidate in the treatment of ADHD (Kratochvil *et al.*, 2002). In the rat, elevations of norepinephrine in PFC following atomoxetine, independently increase local DA levels as well (Gresch *et al*., 1995). While methylphenidate increases extracellular levels of DA 3-fold in both PFC and striatum, atomoxetine also increases DA levels 3-fold in PFC, but has no effects in striatum (Bymaster *et al.*, 2002). Such findings strongly support the notion that the PFC is the more crucial site in the amelioration of ADHD symptoms. Moreover, facilitating PFC DA activity, and possibly that of norepinephrine as well, may contribute in large part to the therapeutic effects of such drugs.

3. Rodent Studies of PFC Function of Relevance to ADHD

3.1 Prefrontal regulation of subcortical DA systems

It is well known that the frontal cortex projects massively to basal ganglia as part of a series of feedback loops, to regulate a broad spectrum of functions from executive to motor to affective (Alexander *et al*., 1986). It is thus not surprising that frontostriatal circuits are implicated in a number of forms of psychopathology. In the case of ADHD, as stated above, a prefrontal DA deficit is suggested to coexist with excessive striatal DAergic function. There are numerous findings in the rodent literature, which not only suggest that these two conditions can coexist, but that a PFC DA deficit can directly *induce* an upregulation of striatal DA activity.

Depletion of medial prefrontal DA with 6-hydroxydopamine (6-OHDA) has been shown to increase DA turnover in basal ganglia structures (Pycock *et al*., 1980). It has also been reported that DA depletion of the right PFC alone, but not the left, results in bilateral increases in striatal DA turnover ratios, at least following exposure to stress (Sullivan and Szechtman, 1995). Other studies report that increased DA activity in dorsal or ventral striatum following prefrontal DA depletion or receptor blockade, is particularly evident after pharmacological challenge, exposure to mild stress or exposure to positively reinforcing stimuli (Deutch *et al*., 1990; Mitchell and Gratton, 1992; Rosin *et al*., 1992; Banks and Gratton, 1995; Doherty and Gratton, 1996). The reciprocal relationship between prefrontal and subcortical DA systems is also shown by the fact that injection of the DA agonist apomorphine into medial PFC *reduces* DA metabolism in the caudate nucleus (Jaskiw *et al*., 1991). This reciprocal relationship between DA systems is also reflected behaviorally in the expression of locomotor activity.

3.2 Regulation of motor activity by prefrontal cortex

Rodent studies have demonstrated a specific role for mesocortical DA in motor inhibition. While the systemic or subcortical administration of DAergic agonists or DA-releasing agents can greatly increase motor activity, the intracortical administration of such drugs counteracts this activation. For example, amphetamine injected directly into the medial PFC, blocks the locomotor-activating effects of amphetamine injected into the ventral striatum (Vezina *et al.*, 1991). Conversely, the same study reported that intracortical injection of DA D1 receptor antagonists *enhances* the activating effects of subcortical amphetamine, while drugs more selective for other DA receptor subtypes or noradrenergic and serotonergic receptors were ineffective in altering motor behavior. In another study, the DA agonist quinpirole, when injected into the medial PFC, completely blocked the motor activating effects of acute, peripherally administered cocaine (Beyer and Steketee, 2000). In contrast, DA depletion of the medial PFC with 6-OHDA increases both the locomotor activating effects and the subcortical DA release, induced by the peripheral administration of either amphetamine or cocaine (Banks and Gratton, 1995; Beyer and Steketee, 1999).

Rodent studies have also shown that the right frontal cortex is especially important in motor inhibition. A variety of lesion techniques including 6-OHDA lesions, of right but not left frontal cortex, results in pronounced behavioral hyperactivity and altered subcortical catecholamine function (Robinson, 1979; Robinson and Stitt, 1981; Pearlson and Robinson, 1981; Kubos *et al*., 1982). Such findings are also in keeping with recent human imaging data.

For instance, when subjects were required to withhold a learned motor response, structures which were strongly activated included middle and inferior frontal gyri and frontal limbic cortex. Moreover, this activation was strongly lateralized to the right hemisphere (Garavan *et al.*, 1999).

It thus appears that right frontal systems play a key role in motor inhibition and that mesocortical DA is an important part of this regulation. Any conditions involving compromised development or functioning of this system would therefore be expected to exhibit varying degrees of behavioral hyperactivity.

3.3 Regulation of executive functions by prefrontal cortex

Perhaps the best known role of the prefrontal cortex concerns the realm of “executive” functioning, namely the intimately associated processes involved in decision-making, attentional control and working memory. Indeed, deficits in these areas are a defining feature of ADHD, whether hyperactivity is present or not (eg. Barkley, 1997; 1998; Schweitzer *et al*., 2000).

An integral aspect of attentional control and working memory (which allows for optimal decision-making), is the ability to hold relevant information “on line” for brief periods. Much of our knowledge of prefrontal regulation of executive function comes from the excellent work in primates employing delayed response tasks, where electrophysiological studies have demonstrated that classes of PFC neurons fire specifically during the delay period between presentation of a task-relevant stimulus and performance of the required response. Importantly, the activity of such neurons is precisely regulated by mesocortical DA, as either too much or too little DA D1 receptor stimulation alters the firing pattern of these neurons and impairs task performance (Sawaguchi and Goldman-Rakic, 1991; Williams and Goldman, 1995; Murphy *et al.*, 1996; Sawaguchi, 2001).

In the rodent, possibly the best means of studying attentional control over performance, involves a behavioral paradigm known as the 5-choice serial reaction time task (or 5CSRTT), which can measure aspects of sustained attention, or selective and divided attention (for review, see Robbins, 2002). With this task, low doses of methylphenidate have been shown to reduce premature or impulsive responding and also tend to improve accuracy of responding in poorly performing animals (Puumala *et al*., 1996). When DAergic drugs are injected directly into the medial PFC, task performance is significantly affected in a manner dependent on individual differences in baseline task performance. Intracortical D1 agonists significantly enhance performance accuracy in rats with low baseline performance, but not in rats already performing at a high or optimal level (Granon *et al*., 2000). Conversely, local D1 receptor blockade impairs choice accuracy, but only in rats already performing at a high level. Intra-PFC administration of D1 agonists has also been shown to improve memory retrieval in a delayed version of the radial maze task, but only after long delays (Floresco and Phillips, 2001).

Rodent studies employing the 5CSRTT have even reported hemispheric differences in the regulation of task performance. For example, *post mortem* measures of DA turnover ratios (DOPAC/DA) in the right but not left PFC, showed significant positive correlations with choice accuracy, while serotonin turnover in the right PFC was related to premature or impulsive responding (Puumala and Sirvio, 1998).

In general, the role of mesocortical DA in attentional processes has thus been described as making the animal focus more effectively on the stimuli currently controlling performance, reflected in performance improvements seen following D1 stimulation in the 5CSRTT requiring divided and shifting attention (Robbins, 2000). It is noteworthy that ADHD children are particularly impaired in the ability to relocate their attention focus, and to *disengage* attention rapidly from one spatial location to another, due to compromised right hemisphere attention systems (McDonald *et al*., 1999). Such executive functions are known to be improved in humans by DA receptor agonists (Muller *et al.*, 1998), and methylphenidate induces similar effects in both normal adults (Mehta *et al.*, 2000) and in children with ADHD (Kempton *et al.*, 1999).

Taken together, the animal studies demonstrate a very important role for mesocortical DA in the modulation of executive functions and suggest that a critical window of DA activity is necessary for optimal cognitive functioning. Indeed, it is reminiscent of the classic inverted U relationship, or Yerkes-Dodsen Law, between arousal and performance, as too much or too little cortical DA is detrimental to performance. A major factor in determining the amount of cortical DA activity is stress, either acutely or chronically, as the mesocortical DA system is especially responsive to even acute, mild stressors. Chronic stress in rats has been shown to reduce PFC DA transmission in association with impairments in working memory; impairments which are ameliorated by intra-PFC infusion of D1 receptor agonists (Mizoguchi *et al*., 2000). It is therefore likely that individual differences in physiological arousal and the ability to respond to stress, could account in significant part for variations in executive functions mediated by the PFC.

3.4 Regulation of physiological arousal, stress responsivity and emotional behavior

In humans, the right hemisphere is believed to contribute to the arousal dimension of attention, and ADHD, by virtue of right hemispheric dysfunction, has been described as a hypovigilant state (Weinberg and Harper, 1993). Not only are deficits in arousal level and emotional self-regulation well recognized in ADHD (Barkley, 1997; 1998), but numerous studies of ADHD subjects have shown significantly impaired functioning of the stress regulatory systems so closely linked with emotion and arousal. Autonomic hypoarousal has been demonstrated in ADHD adolescents both at rest and during attention-demanding tasks (Lazzaro *et al*., 1999; Beauchaine *et al*., 2001). Failure to make normal cardiac adjustments in such tasks, was suggested to result from deficient cortical control over relevant visceral efferents (Althaus *et al*., 1999). Neuroendocrine functioning is also impaired in ADHD subjects, as reflected in the loss of normal diurnal cortisol rhythms (Kaneko *et al.*, 1993) and lower salivary cortisol levels following performance of attention-demanding tasks, particularly in subjects with the most pronounced symptoms (Kariyawasam *et al*., 2002; King *et al*., 1998).

In the rodent, many studies have described the role(s) of the medial PFC in regulating autonomic, neuroendocrine and emotional states, and in cases where hemispheric differences have been examined, the right PFC appears to be especially important in this regard. The ventromedial PFC (particularly infralimbic cortex) is regarded as a visceromotor output station, which interacts closely with orbitofrontal networks and receives abundant stress and emotion-related inputs from subcortical and/or limbic structures (Price, 1999; Cechetto and Saper, 1990). In turn, ventromedial PFC efferents modulate many subcortical and brainstem sites controlling autonomic and neuroendocrine activation and emotional expression (Hurley *et* *al.*,1991; Takagishi and Chiba,1991; Terreberry and Neafsey,1987; Jodo *et al.*,1998, Sesack *et al*., 1989; Bacon and Smith, 1993).

The autonomic effects of prefrontal manipulations in rodents and other species have been reviewed elsewhere (eg. Cechetto and Saper, 1990; Van Eden and Buijs, 2000). The ventromedial PFC appears necessary for full sympathetic activation in times of stress, as lesions in this area alter the respiratory and cardiovascular changes associated with conditional emotional responses (Frysztak and Neafsey, 1991; 1994). Stimulation of this area elicits sympathetic responses, while more dorsal PFC stimulation tends to produce parasympathetic profiles (Powell *et al*., 1994). Excitotoxic lesions of ventromedial PFC also suppress the development of (autonomically mediated) gastric stress ulcers, with right-sided PFC lesions alone fully accounting for this effect (Sullivan and Gratton, 1999). The same measure of stress pathology is aggravated by right-sided PFC DA depletion, suggesting that mesocortical DA in this area normally plays an adaptive role in preventing the overactivation of these cortical outputs which drive stress-induced sympathetic function (Sullivan and Szechtman, 1995).

The medial PFC is also important in hypothalamic-pituitary-adrenal (HPA) axis activation, as electrical stimulation in this area increases plasma corticosterone levels (Feldman and Conforti, 1985). Excitotoxic lesions which include the ventromedial PFC reduce stress-induced plasma corticosterone elevations, and again right-sided lesions alone account for this effect (Sullivan and Gratton, 1999). Lesions of more dorsal medial PFC sites on the other hand (prelimbic or anterior cingulate), have been reported to increase stress-induced plasma corticosterone levels (Diorio *et al.*, 1993; Brake *et al*., 2000a). However, when lesions include both dorsal and ventromedial PFC (eg. Sullivan and Gratton, 1999), the ventral effects seem to predominate, perhaps owing to their more direct anatomical links with the relevant subcortical control centers.

In terms of stress-associated behaviors, mixed results have been reported in medial PFC lesion studies. In general, dorsomedial PFC damage tends to result in anxiogenic profiles (Holson *et al*., 1986; Morgan and LeDoux, 1995), while ventromedial damage results in anxiolytic effects (Frysztak and Neafsey, 1991; Gonzalez *et al*., 2000; Lacroix *et al*., 2000; Sullivan and Gratton, 2002b). As well, such anxiolytic effects have been reported following unilateral right, but not left, ventromedial damage (Sullivan and Gratton, 2002b). In contrast, ventromedial DA depletion enhances measures of anxiety, most likely due to a net reduction in inhibitory tone on these cortical outputs (Espejo, 1997).

The medial PFC DA system is not only extremely responsive to stress (eg. Thierry *et al*., 1976), but also exhibits many functional hemispheric asymmetries. Specifically, right-biased mesocortical DA asymmetries have been associated with exposure to novel environments (Berridge *et al.*, 1999), reduced anxiety in the elevated plus maze (Anderson and Teicher, 1999), protection from stress ulcer pathology (Sullivan and Szechtman, 1995), successful escape performance following exposure to uncontrollable shock (Carlson *et al*., 1993), performance accuracy in the 5CSRTT (Puumala and Sirvio, 1998) and stress-induced HPA activation (Sullivan and Gratton, 1998). It is suggested that these stress-sensitive DA afferents represent a high level coping system to optimize the broad range of functions subserved by the PFC, particularly in times of high arousal.

To summarize, the visceromotor cortex of the ventromedial PFC facilitates or drives sympathetic autonomic and neuroendocrine activity, particularly in times of stress, and contributes to anxiety-related (or perhaps cautious) behavior. These modes of physiological and behavioral arousal are a perfectly normal, if not essential, part of effective responding and coping with challenging situations, provided the degree of activation is appropriate and contained within reasonable limits. It is suggested that mesocortical DA contributes to the optimal functioning of these ‘arousal output systems’, by attempting to prevent their excessive activation, in essence by increasing the ‘signal to noise ratio’ in times of high stimulation.

In humans, it is now known that the ventromedial PFC is essential in regulating autonomic adjustments to emotional stimuli, and that the deficits in emotional self-regulation resulting from damage to this area, are linked as well to impaired risk assessment, planning and decision-making (Damasio, 1994; Damasio *et al*., 1990). Interestingly, these deficits appear to be mediated by right-sided damage alone (Tranel *et al*., 2002). It has also been proposed that right-sided orbital/medial prefrontal systems, under DAergic modulation, are responsible for generating stress-regulating coping strategies and optimal emotional self-regulation (Schore, 1996; 1997). The development of these systems is very much experience-dependent, not only on early social (maternal) attachment, but on a number of pre- and perinatal factors as well.

4. Early Adverse Events and ADHD

As acknowledged earlier, there is a strong genetic component in the occurrence of ADHD, which may well involve the aberrant development of DAergic frontostriatal circuitry. In addition however, a number of independent risk factors have been identified for subsequent ADHD diagnosis, which may affect the development of these same systems. In general, complications associated with pregnancy, delivery or infancy have been linked with increased risk of ADHD diagnosis (eg. Sprich-Buckminster *et al*., 1993; Milberger *et al*., 1997; King, 1996; Zappitelli *et al*., 2001; Rosa Neta *et al*., 2002). Specifically, factors involving reduced oxygen supply to the fetus or infant appear to be particularly important in this regard, both in familial and nonfamilial forms of the disorder. Such hypoxic conditions could be related to maternal bleeding, prenatal alcohol or drug abuse, which can affect placental circulation, or acute delivery complications (Sprich-Buckminster *et al*., 1993; Milberger *et al*., 1997; Ornoy *et al*., 2001; Bandstra *et al*., 2001; Mick *et al*., 2002). Toft (1999) has suggested that in neonates suffering from asphyxia, tissue hypoxia leads to excess lactate production, which may compromise development of frontostriatal circuitry, partially accounting for ADHD pathogenesis.

Hypoxic-ischemic events are especially common in prematurity, which may explain the high incidence of ADHD among children born prematurely with very low birth weight (Lou, 1996; Bhutta *et al*., 2002). A recent brain imaging study in ADHD adolescents with a history of prematurity and low birth weight, showed highly significant correlations between cerebral blood flow at the time of birth, symptom severity as adolescents and DA receptor binding, especially in the right frontostriatal system (Rosa *et al*., 2002).

In addition, a number of recent studies have highlighted the importance of the postnatal environment in predisposing to ADHD. Biederman *et al*. (1995) reported a positive association between a number of social adversity indicators and the risk for ADHD. It has been reported that deficits in the caregiving environment, including early problems in parental attachment contribute to ADHD development (Shaw *et al*., 2001; Halasz and Vance, 2002). In particular, less synchronous mother–child interactions were significantly associated with hyperactivity, a major predictor of which was maternal coping (Keown and Woodward, 2002). Very high levels of ADHD have also been reported among adopted youths, with the most notable preadoptive risk factors including early abuse/neglect (Simmel *et al*., 2001). It has also been found that early institutional rearing, in comparison to stable foster family rearing, predisposes to a pattern of hyperactivity/inattention (Roy *et al*., 2000). Moreover, in adoptees following severe early deprivation, the duration of deprivation was significantly associated with measures of inattention/overactivity, independent of numerous other risk factors (Kreppner *et al*., 2001). Finally, a PET imaging study has shown cerebral metabolism to be greatly affected by severe early deprivation, as a group of Romanian orphans were found to have significantly reduced activity in the orbital frontal gyrus and the infralimbic prefrontal cortex, as well as some temporal lobe structures (Chugani *et al*., 2001). Such findings highlight the importance of not only prenatal conditions, but the postnatal social environment in the optimal maturation of these critical prefrontal and associated circuits.

5. Effects of Early Developmental Manipulations on Rodent PFC Function

The developing prefrontal cortex is extremely sensitive to a wide variety of perturbations. For example, prenatal stress leads to enhanced anxiety in the offspring, and lateralized changes in PFC DA function (Fride and Weinstock, 1988). Such treatments also produce lasting changes in both DA and glutamate receptor expression in medial PFC (eg. Berger *et al*., 2002). Similarly, cocaine exposure *in utero* results in offspring with dramatically increased levels of Fos protein expression selectively in the ventral and medial prefrontal regions (Morrow *et al*., 2002), as well as hyperresponsive DA activation in the ventromedial PFC in response to mild stress (Elsworth *et al*., 2001). The current review will focus on two other early developmental manipulations (*viz*. perinatal anoxia and early social environment) that also affect PFC development and produce changes in rat behavior and neurophysiology similar to some of those thought to occur in ADHD.

5.1 Effects of Perinatal Anoxia on DA Systems

Some of the most relevant rodent studies in the context of ADHD concern the induction of perinatal hypoxic/anoxic states. Various protocols of anoxia induction have resulted in behavioral hyperactivity, which tends to peak during the juvenile period and abate toward the time of puberty, although some hyperactivity can persist (eg. Speiser *et al.,* 1983; 1988, Brake *et al*., 2000b; Decker *et al*., 2003). Such treatments also produce lasting impairments in a number of learning and working memory tasks (Dell'Anna *et al*., 1991; Longo and Hermans, 1992; Decker *et al*., 2003). Increasing duration of anoxia at the time of delivery, leads to increasing degrees of postnatal cell death, most prominently in frontal cortex, striatum and cerebellum (Dell'Anna *et al*., 1997).

The brain of the newborn mammal is considered more resistant to anoxic episodes than the adult central nervous system (Haddad & Donnelly, 1990; Jilek, 1970; Kabat, 1970). This is, in part, because of the low level of differentiation, and reduced metabolic demands, of immature neurons (Bickler *et al.*, 1993; Nehlig and Pereira de Vasconselos, 1993) and the rich supply of anaerobic energy available to the newborn (Nehlig and Pereira de Vasconselos, 1993). Furthermore, acidosis occurs less easily due to the lack of a blood-brain barrier (Dombrowski *et al.*, 1989; Nehlig & Pereira de Vasconselos, 1993). It has been known for some time that this tolerance depends upon the immaturity of brain physiology during the perinatal period (Fazekas *et al.*, 1941). Such conditions may protect immature neurons from the adverse effects of acute anoxia. Such an assumption has lead to the crudely held view that neonates are quite resistant to transient periods of anoxia. However, the resistance of the immature brain against anoxic episodes is a relative phenomenon and subtle damage can have pronounced consequences.

More subtle aspects of neuron development may be greatly influenced by perinatal anoxia. Although developing neurons may not require as much oxygen to survive they do require energy for structural differentiation processes such as axon and dendrite growth or synapse formation (Nyakas *et al.*, 1996). A period of anoxia may interfere with the highly increased rate of synthesis of structural proteins and other macromolecules needed for proper development. Thus, perinatal anoxia may interfere with neuron differentiation and/or organization and as a consequence lead to subtle, albeit critical, changes in brain maturation.

Increasing evidence suggests that DA systems may be particularly vulnerable to the effects of perinatal anoxia. The following discussion reviews the long-term effects of perinatal anoxia on DA systems and DA-related behaviors. For a review of the long-term effects of neonatal hypoxia on other neurotransmitter systems see Nyakas *et al.* (1996).

It was Bjelke and colleagues (1991) who first developed a method of intra-uterine anoxia following C-section delivery in the rat in order to study long-term effects of perinatal anoxia. This model minimizes the influence of surgical procedures and anesthesia inherent to most other models (*e.g*. Coyle, 1982; Pulsinelli & Brierley, 1979). It also circumvents the problem of other hypoxia models of having to perform procedures pre- or post-natally when the pregnant dam or newborns, respectively, may be placed in a hypobaric chamber (Nyakas *et al.*, 1996). It also has the advantage of studying the effects of C-section delivery with differing amounts of additional anoxia, which may better represent birth complications cited in the clinical literature.

It should be noted that periods of anoxia lasting 19 min. or longer cause brain pH levels to drop below 7 (Chen *et al.*, 1997), at which point acidosis is sufficiently high to produce significant neuronal loss. Furthermore, periods of perinatal anoxia lasting 15 min or less result in a neonate survival rate close to 100% whereas 19-20 min of anoxia results in 50-80% survival and periods of anoxia lasting longer than 22 min result in almost no pup survival (Chen *et al.*, 1995; 1997; unpublished observations). Consequently, periods of anoxia lasting 19 min. or longer are more likely to produce more severe effects including massive cell loss and neuronal degeneration than shorter anoxic events (*viz.* 5 or 15 min.). Perhaps, perinatal anoxia periods lasting 15 min. or less are producing a different set of developmental sequelae than longer anoxic periods. It has been shown, for example, that perinatal anoxia periods of up to 15 min. produce significant increases of subcutaneous glutamate, pyruvate, and aspartate levels whereas longer anoxia periods do not (Dell'Anna *et al.*, 1995). As such, this discussion will address those changes following more subtle periods (up to15 min) of perinatal anoxia. Studies employing longer periods of anoxia, which produce different developmental outcomes, will not be reviewed here.

Bjelke *et al.* (1991) observed enhanced TH-immunoreactivity in VTA and increased apomorphine-induced locomotor activity in rats that received 15 min of anoxia when compared to C-section delivered animals. It has also been shown that 15 min. of perinatal anoxia produces an increased locomotor response to acute amphetamine injection in the juvenile, four-week-old, rat (Chen *et al.*, 1995) and increases sensitization to acute amphetamine administration in the adult (Brake et al., 1997a). These rats also exhibit increased NAcc DA transmission in response to stress (Brake et al., 1997b). Increased NAcc DA D_1 receptor agonist affinity as well as increased D_3 receptor binding in the striatum were observed in these animals (Chen *et al.*, 1997); Chen *et al*., 1997 suggested that an increase in D_3 receptor binding may be a result of a compensation for enhanced D_1 receptor affinity.

Thus the most commonly reported changes following perinatal anoxia suggest a net upregulation of subcortical DA function (eg. Chen *et al*., 1997; Seidler and Slotkin, 1990; Brake et al., 1997). Employing other protocols, it has also been shown that anoxic rats show a 30% increase in stimulated dopamine release rate from striatal slices (Gross *et al*., 1993), and increases in striatal vesicular monoamine transporter and D1 receptor proteins (Decker *et al*., 2003).

Changes in prefrontal function have not been as frequently reported, perhaps owing in part to the limitations of some *post mortem* neurochemical studies and the less dense PFC DA innervation. For instance i) such measures may reflect the basal state of these systems rather than detecting changes seen when these systems are challenged ii) tissue samples may be too large to detect a discrete area of change and iii) samples of left and right cortex are normally pooled, eliminating the chance to detect hemisphere-specific effects. These limitations were overcome in a study by Brake *et al*. (2000b), employing *in vivo* voltammetric recordings of changes in extracellular DA levels in response to repeated mild stress, in rats which had received a 15 min intrauterine anoxia treatment in conjunction with Caesarean section birth. In comparison to vaginally born controls, anoxic rats not only displayed locomotor hyperactivity, but strikingly lateralized changes in mesocortical DA activation in ventromedial (infralimbic) PFC. While the left PFC DA response was unaffected by perinatal anoxia, the right PFC response was dramatically suppressed across all five days of testing. Moreover, it was shown in separate animals that DAT levels were elevated selectively in the right PFC, perhaps contributing to the reduced levels of extracellular DA. In keeping with the reciprocal nature of cortical/subcortical DA systems described earlier, Brake *et al*. (1997b) used the same technique to demonstrate that ventral striatal DA release is progressively *enhanced* or sensitized by repeated mild stress in anoxic animals. Taken together it was suggested that the 15 min anoxic episode induced a right mesocortical DA deficit, leading to a disinhibition of subcortical DA activity and subsequent behavioral hyperactivity; a scenario not unlike that proposed to explain ADHD pathophysiology (Castellanos, 1997).

5.2 Effects of Postnatal Maternal Environment

In addition to the developmental perturbations resulting from perinatal anoxia, the PFC is also sensitive to events occurring during the postnatal period. An extensive literature demonstrating the PFC sensitivity to postnatal manipulations within discrete developmental windows, especially in the context of recovery from PFC lesion, has been reviewed elsewhere (see Kolb *et al*., 2000 for a recent review). The postnatal social environment, particularly changes in maternal care, can also have significant effects on PFC development in the rat as well as in other species. Studies that have manipulated the postnatal social environment have reported significant changes in the development of prefrontal as well as DAergic systems. Two such examples, which can induce opposite changes in development, are neonatal handling (H) and maternal separation (MS).

H involves a brief period (15 min) of daily separation of the rat dam from her pups, normally for the first two weeks of life, and is known to stimulate maternal behaviors (Liu et al., 1997) and impart numerous lasting benefits (Levine, 1975; Smotherman, 1983, Liu *et al.*, 1997), in particular increased feedback regulation of stress and emotion regulatory systems. This enhanced feedback may be a consequence of the increased expression of glucocorticoid receptors (GR) in frontal cortex and hippocampus (Meaney *et al.*, 1985; 1996; Diorio *et al*., 1993). H also affects cognition and prevents cognitive decline late in life (Meaney *et al*., 1991). Additionally, H reduces synaptic density in the stress-responsive infralimbic cortex (Ovtscharoff and Braun, 2001). Importantly for this discussion, H stimulates the normal right hemispheric lateralization of emotional regulation (Denenberg, 1981). Concomitantly, H appears to enhance the inhibitory capacity within the right PFC and hippocampus, in part by causing a rightward shift in benzodiazepine/GABA-A receptor binding in these structures, possibly preventing excessive emotional reactivity (Sullivan and Gratton, 2003). Moreover, the inhibitory modulatory role of mesocortical DA on stress-induced HPA activity is lateralized to the right PFC following H, but is nonlateralized in NH rats (manuscript in preparation).

In contrast, MS involves longer daily separations in the first two to three weeks of life (normally in the range of 3 - 4.5 hrs in rats) and results in *hyper*responsive stress and emotion regulatory systems and enhanced fearfulness (Plotsky and Meaney, 1993; Meaney *et al*., 1996; Caldji *et al*., 2000; Ogawa *et al*., 1994). In addition to the behavioral effects, male offspring that received early MS show greater HPA activity as adults, both basally and in response to acute stress (Ladd *et al*., 2000; Liu *et al*., 2000; Plotsky and Meaney, 1993). Other studies in male rats show that MS decreases frontal cortex and hippocampal GR mRNA, reducing the capacity for HPA feedback regulation (Avishai-Eliner *et al*., 1999). Early postnatal MS and social isolation result in abnormally high synaptic density within the infralimbic cortex (Ovtscharoff and Braun, 2001), and altered densities of DAergic and serotonergic fibers throughout the medial PFC (Braun *et al*., 2000). Early social isolation also leads to decreased basal DA turnover, selectively in infralimbic cortex (Heidbreder *et al*., 2000).

As was the case with perinatal anoxia, subcortical DA function appears to be upregulated by MS. Recent studies have shown that adult male MS rats are hyperactive and exhibit an exaggerated ventral striatal DA response to stress relative to H rats (Brake *et al*., submitted). MS rats also exhibit lower levels of DAT binding in dorsal and ventral striatum and are behaviorally hypersensitive to the locomotor-activating effects of cocaine (Meaney *et al*., 2002). These data clearly suggest that MS is capable of affecting the development of central DA systems thought to be involved in ADHD.

Interestingly, sex differences have been reported in the effects of MS, as this treatment does not appear to adversely affect females as much as males. For instance, female rats that were maternally separated as neonates, have been reported not to show the increase in fear-related behaviors typical in males (Boccia and Pedersen, 2001; Wigger and Neumann, 1999). Furthermore, unlike males, female rats that have experienced MS do not show a heightened endocrine response to stress (Wigger and Neumann, 1999). Thus it appears that there is a sex-specific effect of the deleterious consequences from MS, which is preferentially male. Indeed, in mice, MS decreases indices of anxiety in adult female offspring while increasing it in males (Romeo *et al*., 2003) Although the mechanisms for such sex differences in MS rodents haven't been elucidated, they may have important ramifications for the higher incidence of neurodevelopmental disorders like ADHD observed in males compared to females.

Finally, a recent magnetic resonance imaging study in the non-human primate has demonstrated that MS results in a significant *enlargement* of the ventromedial PFC, specific to the right hemisphere (Lyons *et al*., 2002). Together with the above increases in synaptic density of this region, such findings may help explain the greatly heightened stress sensitivity and excessive arousal level of such animals. To conclude, it is clear that many factors affect the development of prefrontal systems, both in terms of the intrinsic structures within the PFC and their important afferent inputs, particularly the mesocortical DA system.

6. Summary: Towards a better understanding prefrontal dysfunction in ADHD

ADHD undoubtedly involves the abnormal development and functioning of entire networks of structures, not only prefrontal, but certainly striatal and even cerebellar (see Castellanos *et al*., 1996b; Castellanos and Tannock, 2002). What is presently proposed, is that right prefrontal cortex may play the most critical role in the expression of ADHD, by virtue of its direct role in mediating the core deficits of this condition, and by its regulation of striatal and other subcortical functions. The right PFC also appears to be particularly sensitive to early adverse events.

One of the most fundamental roles of the PFC appears to be the regulation of physiological and behavioral arousal levels, and the functional nature of these prefrontal arousal systems is greatly influenced by early environmental events. From optimal and situation-appropriate arousal regulation, follows the optimization of many interdependent functions mediated by the PFC, including responding to stress, emotional self-regulation, attentional control, working memory, temporal processing, planning, decision-making, and behavioral inhibition. Any developmental perturbations to the right PFC, due to genetic predisposition, early adverse events, or combinations thereof, would be expected to result in the suboptimal maturation and functioning of this region.

Either excessive, diminished or abnormally lateralized prefrontal activity can lead to a variety of forms of psychopathology (Sullivan and Gratton, 2002a). In the case of ADHD, the predominantly right lateralized nature of the pathology may derive from the inherent specialization of right hemispheric systems for arousal and stress regulation. Right brain mechanisms, particularly at the brainstem level, are more intimately linked with basic life-sustaining functions (e.g. autonomic regulation) and mature more rapidly than their left brain counterparts (Porges *et al*., 1995; Geschwind and Galaburda, 1987). However, the cortical representation or extension of these asymmetrical arousal networks is much slower to mature and vulnerable to insult for a much longer period. As such, early adverse events such as the metabolic stress of intrauterine hypoxia would be expected to impact preferentially on the development of these right-sided, physiology-regulating systems. Adverse or stressful events in later development or the early postnatal period would also be likely to alter the continued maturation of the right-sided prefrontal systems.

In the rat, cortical DA afferents start reaching their cortical targets earlier (final trimester of gestation) and achieve their adult innervation pattern later (roughly 2 months or puberty) than other major cortical afferent systems (fig. 1), giving this key regulatory system a particularly long window of vulnerability to insult (Berger-Sweeney and Hohmann, 1997). This system is also said to be slower maturing in males than females, perhaps partially accounting for the higher incidence of ADHD in boys. Even if developmental anomalies in mesocortical DA systems were entirely related to genetic predisposition, the long-term pathology would still be expected to be asymmetrical, since central DA systems in the normal rat are known to be functionally asymmetrical at least from the time of birth if not sooner (Afonso *et al*., 1993; Rodriguez *et al*., 1994; Varlinskaya *et al*., 1995).

While many questions remain unanswered regarding ADHD, it is clear that rodent studies, particularly on the nature of PFC function, have and will continue to shed considerable light on many of the clinical observations reported in ADHD. It is hoped that future animal studies which attempt to model at least aspects of ADHD, whether they involve the knock-out of candidate genes, effects of intrauterine hypoxia, neuropharmacological or other approaches, will include the careful examination of the effects of their manipulations on prefrontal function, particularly that of the right hemisphere. There is still a great deal to be learned concerning the development of these critical prefrontal systems, not the least of which is the potential means of reversing, or best compensating for, their suboptimal development.

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Figure Captions

Figure 1: Schematic diagram demonstrating the relatively extended period of development of cortical dopamine afferents and concomitant risk factors for ADHD. It is proposed here that such a lengthy window of development is one reason why the mesocortical pathway may be vulnerable to early adverse experiences resulting in behavioral and neurochemical outcomes similar to some of those thought to occur in ADHD.