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Neurodevelopmental Liabilities in Schizophrenia and Affective Disorders

TOMÁS PALOMO[a], RICHARD M. KOSTRZEWA[b], TREVOR ARCHER[c] and RICHARD J. BENINGER[d,*]

[a]*Servicio Psiquiátrico, Hospital Universitario 12 de Octubre, Avda. de Córdoba s/n, 28041 Madrid, Spain;* [b]*Department of Pharmacology, Quillen College of Medicine, East Tennessee State University, Johnson City, TN 37614, USA;* [c]*Univ Örebro, Dept Psychol, SE-701 82, Örebro, Sweden;* [d]*Departments of Psychology and Psychiatry, Queen's University, Kingston, ON K7L 3N6, Canada*

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There is now considerable evidence that both schizophrenia and affective disorders have their origin at least in part in events that occur during early pre- and post-natal development. In the case of schizophrenia, many observations, for example, increased risk for schizophrenia in the offspring of mothers who had influenza A during their second trimester of pregnancy and evidence for abnormal neuronal migration in the cerebral cortex of post mortem tissue from schizophrenic patients, suggest that a second trimester insult may have occurred and that this insult may have increased the risk for the development of schizophrenia in late adolescence or early adulthood. Animal studies have found that rats that undergo excitotoxic damage to the ventral hippocampus on postnatal day 7 develop exaggerated sensitivity to dopamine-stimulating drugs or to stressful stimuli that becomes apparent after sexual maturity but not before, providing a neurodevelopmental model of schizophrenia. Similarly, post-weaning social isolation leads to enhanced responses to dopaminergic drugs and to stress that emerges after sexual maturity. These animal models are proving to be valuable tools to study the neurobiological mechanisms mediating the influence of early insults to the nervous system on later behavioural functions. In the case of affective disorders, although the evidence is not as strong, a number of the same observations have been made suggesting that an insult during early ontogeny may lead to the development of affective disorders later in life. For example, retrospective studies of people with affective disorders showed that they were more likely to have attained motor milestones at a later age and to have had poorer academic performance as children. There is a wealth of evidence suggesting hyperfunctioning of the hypothalamic–pituitary–adrenal (HPA) axis in affective disorders. Animal studies have shown that early maternal deprivation can lead to lasting changes in the reactivity of the HPA axis to stressful stimuli, providing another link from early experience to adult psychopathology. Continued studies of the effects of pre- and early post-natal events on the development of the nervous system and the relationships of these events to schizophrenia or affective disorder will provide new insights into the mechanisms underlying these common neuropsychiatric illnesses.

Keywords: Affective disorders; Animal models; Frontal cortex; Hippocampus; Hypothalamic–pituitary–adrenal axis; Maternal separation; Neurodevelopment; Review; Schizophrenia; Social isolation; Stress

The suggestion that mental illness in adulthood has its origins in early development can be traced back to the 19th century (Bullmore *et al.*, 1997). In recent years, modern versions of this hypothesis have been proposed for both schizophrenia and affective disorders as will be discussed in this paper. In both cases, perinatal and early childhood insults are seen as causes producing changes in the brain that lead to increased vulnerability to the relevant mental disorder later in life. Vulnerability is also affected by genetic factors as will be mentioned. In the case of schizophrenia, a second trimester insult has been hypothesised to lead to changes in cortical neural development that can be manifested functionally at the time of sexual maturity when the frontal cortex is undergoing extensive reorganization. As a result of the early insult, the systems that normally regulate this reorganization do not function properly leading to impaired reorganization. As the frontal cortex regulates the mesolimbic dopamine system, it in turn is deregulated and the symptoms of psychoses ensue (Weinberger, 1995; see below). A noteworthy feature of this hypothesis is that it places the well-known dopaminergic hyperfunction associated

*Corresponding author. Tel.: +1-613-533-2486. Fax: +1-613-533-2499. E-mail: beninger@psyc.queensu.ca

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with schizophrenia as an effect secondary to the frontal cortical dysfunction.

For the affective disorders the neurodevelopmental hypothesis has not been as extensively elaborated as it has for schizophrenia. However, there is considerable evidence suggesting that a second trimester insult (Nasrallah, 1997) may lead to increased risk for affective disorders later in life. Early childhood abuse or maternal loss (Harkness and Tucker, 2000) may lead to increased sensitivity of the hypothalamic–pituitary–adrenal (HPA) axis (van Praag, 2002); the effects of stressors on this altered system may then lead to affective illness. Although our understanding of the mechanisms remains incomplete, like in schizophrenia, patients with major depression have been found to have reduced blood flow in the prefrontal cortex (e.g. Baxter *et al.*, 1989), and Andreason *et al.* (1986) have suggested that frontal lobe pathology is of neurodevelopmental origin. The prefrontal cortex is extensively interconnected with the serotonergic dorsal raphe nucleus and it has been suggested that hypofrontality could lead to reduced activation of the serotonergic system in affective disorders (Celada *et al.*, 2002). The level of serotonin [5-hydroxytryptamine (5-HT)] activity is known to be associated with various personality traits (Oreland *et al.*, 2002). Thus, the changes in monoaminergic systems thought to be associated with schizophrenia and affective disorders have been suggested to be secondary to dysfunction of the prefrontal cortex, and prefrontal cortical dysfunction is thought to have a neurodevelopmental origin.

Using electrophysiological and brain microdialysis techniques, Celada *et al.* (2002) provide convincing support for the argument that the medial prefrontal cortex (mPFC) regulates the serotonergic neurons of the dorsal raphe. Thus, electrical stimulation of the mPFC leads to an increase in 5-HT release in the dorsal raphe. Electrical stimulation of the mPFC also leads to inhibition of about 80% of the dorsal raphe neurons. However, application of the 5-HT synthesis inhibitor parachlorophenylalanine (PCPA) results in the observation of about 80% excitation of dorsal raphe neurons by mPFC stimulation. This finding suggests that the inhibition seen after stimulation resulted from the action of 5-HT released in the dorsal raphe itself on 5-HT_{1A} autoreceptors and is supported by microdialysis results. Glutamate receptor antagonists reduced the excitatory effect of mPFC stimulation on 5-HT neurons in PCPA-treated rats suggesting that the frontoraphe fibres are glutamatergic. Celada *et al.* (2002) concluded that the activity of ascending 5-HT neurons of the dorsal raphe is under a marked influence of the mPFC which is itself densely innervated by 5-HT fibres originating in the dorsal and median raphe nuclei.

It may be that abnormal function of the brain's monoaminergic systems is more likely to result from an error in the regulatory control emerging from neocortical origins than from erroneous messages coming from phylogenetically older structures. The dopaminergic and serotonergic systems are found in all vertebrates and are conserved over evolution (Butler and Hodos, 1996). Evolution will have finely honed the regulation of these systems within the core of the brain, and developmental errors in their regulation are likely to be lethal. With the elaboration of the cerebral cortex in mammals and especially in humans has come the parallel development of cortical regulation of phylogenetically older systems including the monoaminergic systems. These newer control mechanisms may be prone to developmental errors.

NEURODEVELOPMENTAL LIABILITIES IN SCHIZOPHRENIA

The idea that schizophrenia is a neurodevelopmental disorder has gained ascendance for at least a couple of reasons. One is that many findings can be reconciled and understood within this theoretical framework (Sawa and Snyder, 2002). The other is that neurodevelopmental animal models of apparent adult-onset dopaminergic hyperfunction and frontocortical dysfunction thought to be related to that seen in schizophrenia have been developed. The convergence of previous findings and the results from the more recently developed animal models provide a strong basis for the neurodevelopmental hypothesis of schizophrenia.

Many previous findings can be reconciled and understood within the theoretical framework of the neurodevelopmental hypothesis as elaborated by Weinberger (1995), who summarizes the relevant literature and makes a compelling argument. Thus, frequently reported minor physical abnormalities in schizophrenic patients could reflect adverse intrauterine events that also influenced brain development. Further observation that many of the reported abnormalities could have resulted from a second trimester insult places the time of the putative insult at the period when neuronal migration takes place and could provide a basis for understanding observed defects in neuronal migration. In this regard, post-mortem cyto-architectural studies of the brains of schizophrenics have revealed that a sub-population of cortical γ-aminobutyric acid (GABA) neurons [those that stain for nicotinamide adenine dinucleotide-diaphorase (NADPH-d)] was decreased in number in the superficial layers of the superior frontal gyrus region of the dorsolateral prefrontal cortex but increased in numbers in the deep layers and in the subcortical white matter

(Akbarian *et al.*, 1993). This and related findings (e.g. Benes and Berretta, 2001) suggest that the migration of these neurons from the subplate zone to the superficial cortical layers was slowed or arrested during development and suggest a second trimester insult.

Further evidence for the neurodevelopmental hypothesis comes from epidemiological studies revealing increased diagnoses of schizophrenia in people whose mother had been in her second trimester of pregnancy during the height of the 1957 Helsinki flu epidemic (Mednick *et al.*, 1988). Subsequent studies provided some consistent and some contradictory results and even if second trimester exposure to a viral illness increases the risk of developing schizophrenia, this etiological factor is not likely to account for many cases. Nevertheless, these epidemiological findings can be understood within the broader framework of the neurodevelopmental hypothesis of schizophrenia.

Schizophrenia is an illness that has its onset during late adolescence or early adulthood (American Psychiatric Association, 1994). In recent years, retrospective studies of schizophrenic patients have revealed the presence in childhood of a range of abnormalities including those of bimanual dexterity and gait (Walker and Lewine, 1990), educational achievement (Foerster *et al.*, 1991) and intelligence (Jones *et al.*, 1994). Cohort studies similarly have shown premorbid deficits in development and academic achievement during childhood in people who became schizophrenic. For example, of the 4746 members of the Medical Research Council National Survey of Health and Development (NSHD), begun in 1946, who were still alive and living in the United Kingdom at the age of 16, 30 individuals were diagnosed as having schizophrenia or schizoaffective disorder by the age of 43. When health interview data for these individuals at the age of 24–26 months were compared to similar data for the members of the cohort who did not develop schizophrenia, those who had developed schizophrenia were consistently older when they first sat up, stood, walked alone and talked. These individuals did worse in a range of tests of educational achievement done at ages 8, 11 and 15 years (Jones and Done, 1997). These results, along with those from post-mortem and epidemiological studies provide strong support for the neurodevelopmental hypothesis of schizophrenia.

Although evidence for a neurodevelopmental model of both schizophrenia and affective disorders (see below) has been adduced, Walker *et al.* (2002) have argued that neurodevelopment plays a differential role in these illnesses. They identify a number of similarities and differences between schizophrenic versus bipolar affective disorder populations. The populations share similarities in their age and season of onset (Takei *et al.*, 1992) and in the importance of stressful life events in the weeks prior to onset (Ventura *et al.*, 1989). A review of genetic studies further suggests that schizophrenia and bipolar disorder share a number of genes in common. It has been suggested that genes that predispose the individual to psychosis exist in general and that additional genes may contribute to other features of the disorder (Cardno *et al.*, 1999).

Dopamine seems to be involved in the pathogenesis of both schizophrenia and mania in bipolar disorder but there must also be neurochemical differences between the disorders insofar as bipolar illness but not the negative symptoms of schizophrenia responds to treatment with anticonvulsants or lithium. The two disorders share some neuromorphological features including lateral and third ventricular enlargement; however, whereas schizophrenic patients show a loss of brain volume, bipolar patients do not (Harvey *et al.*, 1994). Furthermore, the size of the amygdala is increased in bipolar disorder compared to control but this structure is significantly smaller in schizophrenic brains (Altshuler *et al.*, 1998; Strakowski *et al.*, 1999). Schizophrenic patients also show reduced hippocampal volume but bipolar patients do not (Altshuler *et al.*, 1998). Generally, schizophrenic patients show cognitive impairment whereas those with bipolar illness do not (Gilvarry *et al.*, 2000). The results of cohort studies suggest that there may be neurodevelopmental impairments in both schizophrenia and bipolar disorder but results further suggest that this effect is more pronounced in schizophrenia. Similarly, pre- and perinatal trauma appears to have a more important role in the development of schizophrenia than bipolar disorder (Walker *et al.*, 2002). How can these similarities and differences be understood?

Walker *et al.* (2002) propose that both schizophrenia and bipolar illness result in part from genetic inheritance that leads to the release of excessive amounts of dopamine in response to stressful life events late in adolescence or early in adulthood. They suggest that the most likely explanation for differences in brain morphology is developmental, citing the observation of greater frequencies of pre- and perinatal traumas in schizophrenia. Support for this hypothesis comes from the finding that brain structures that are most susceptible to early insults are the hippocampus and amygdala. Neurodevelopmental damage to these structures could account for the observation of cognitive impairments and blunted affect in schizophrenic patients. Thus, although both schizophrenia and bipolar disorder have a number of features in common, focus on the differences in brain abnormalities and cognition function in these two patient groups suggests a greater role for neurodevelopmental factors in schizophrenia.

Further evidence that schizophrenia is a neurodevelopmental disorder comes from observations that neuropathologies already exist in the brains of schizophrenic patients when they are seen by a psychiatrist at the time of their first episode (Nopoulos *et al.*, 1995). In support, Molina *et al.* (2002) report that first-episode schizophrenic patients show decreased frontal cortical grey matter volume in magnetic resonance imaging (MRI) studies.

The decreased frontal cortical grey matter volume observed by Molina *et al.* (2002) was significantly negatively correlated with prefrontal cortical activity and hippocampal activity measured by positron emission tomography (PET) using fluorodeoxyglucose. This result suggests that atrophy in the frontal cortex is associated with a loss of normal inhibitory influences. Evidence from post mortem studies has shown a loss of GABAergic inhibitory neurons in the brains of schizophrenic patients (Akbarian *et al.*, 1993; Benes and Berretta, 2001) providing a basis for the negative correlation of frontocortical volume and activity.

Schizophrenia has also been associated with hypofunction of *N*-methyl-D-aspartate (NMDA)-type glutamatergic receptors in the frontal cortex (Tamminga, 1999). Normally, NMDA receptors are very dense in the prefrontal cortex where they are found on GABAergic neurons (Olney and Farber, 1995). The observation of a decrease in NMDA receptor number in schizophrenia is consistent with the reported loss of GABAergic neurons, decreased frontocortical volume and increased frontocortical activity observed in schizophrenia. Some related observations are consistent with the proposal that schizophrenia is associated with decreased NMDA receptor function in the frontal cortex. Thus, people receiving subanaesthetic doses of the NMDA receptor antagonist ketamine show behavioural responses that resemble some of the symptoms of schizophrenia (Krystal *et al.*, 1994) an NMDA receptor antagonists also produce increase in frontal cortical activity (Lahti *et al.*, 1995; Vollenweider *et al.*, 1997; Duncan *et al.*, 1998).

If there was decreased NMDA receptor function during development, accelerated apoptotic cell loss may result (Ikonomidou *et al.*, 1999) leading to the loss of neurons in the frontal cortex. As already mentioned, Akbarian *et al.* (1993) have shown altered patterns of NADPH-d neurons, thought to be a subset of GABAergic neurons, in post mortem brains from schizophrenic patients, consistent with a perinatal insult that impaired neuronal migration.

Many neuropeptides have been implicated in the pathophysiology of schizophrenia and affective disorders (de Wied and Sigling, 2002). For example, in animal studies β-endorphin (β-E 1-31) and two of its components, γ-E (β-E 1-17) and α-E (β-E 1-16) have been found to produce effects like dopaminergic agonists (α-E) or antagonists (β-E, γ-E) leading to the suggestion that in schizophrenia there may be reduced availability of γ-type endorphins and a surfeit of α-type endorphins (de Wied and Sigling, 2002). Subsequent clinical studies showed that γ-type endorphins improve symptomatology in some schizophrenic patients providing some support for the suggestion that endorphins may play a role in the pathophysiology of schizophrenia.

In summary, evidence from a variety of sources suggests that the causes of schizophrenia can be traced to an early insult on the nervous system and the subsequent effects of this putative insult on neurodevelopment. Although evidence points to a neurodevelopmental course for both schizophrenia and affective disorders, a number of observations further suggest that neurodevelopment plays a differential role in the two illnesses. Findings from imaging and related studies indicate decreased frontocortical glutamatergic and GABAergic neurotransmission in schizophrenia; these alterations may have a neurodevelopmental origin.

ANIMAL MODELS OF NEURODEVELOPMENTAL LIABILITIES IN SCHIZOPHRENIA

One neurodevelopmental animal model of schizophrenia was first reported by Lipska and Weinberger (Lipska and Weinberger, 1993; Lipska *et al.*, 1993) and consists of making bilateral excitotoxic lesions of the ventral hippocampus in neonatal rats at the postnatal age of 7 days (P7). At P7, the stage of development of the rat is roughly equivalent to that of the human in the second trimester (Bayer, 1980). They found that lesion rats showed normal responses to dopaminergic agents before sexual maturity (P35) but enhanced responses after sexual maturity (P56). Thus, the cataleptic effects of the dopamine (DA) receptor antagonist haloperidol, the motor stereotypy effects of the DA receptor agonist apomorphine and the motor stimulant effects of the indirect DA agonist amphetamine were normal in lesion rats at P35. At P56, lesion rats showed enhanced overall motor activity levels and significantly enhanced responses to amphetamine and apomorphine as well as a reduced response to haloperidol. It appeared that hyperdopaminergic function emerged in lesion rats after sexual maturity analogous to the emergence of schizophrenic symptoms (that are ameliorated by dopamine receptor antagonist drugs) in humans in late adolescence and early adulthood (review: Lipska and Weinberger, 2002).

Results from neonatal ventral hippocampal lesion animals suggest that the hippocampus plays a role in the late development of the frontal cortex that takes place around the time of sexual maturity. According

to this hypothesis, frontal development at this time is abnormal because of the perinatal insult to the hippocampus. The frontal cortex regulates the dopaminergic neurons of the ventral tegmental area; abnormal development of the frontal cortex, therefore, may in turn lead to deregulation of the dopaminergic system and the abnormal behavioural responses to DA agents ensue. The neurochemical and molecular mechanisms mediating these effects remain unknown. In this regard, Lipska and Weinberger (2002) review some of the neurochemical changes that have been found in the lesion animals. These include reduced frontocortical levels of *N*-acetylaspartate, attenuated stress-induced cortical DA release, attenuated expression of a membrane glutamate transporter, reduced expression of the GABA-synthesizing enzyme glutamate decarboxylase-67, reduced brain-derived neurotrophic factor, altered expression of the immediate early genes c-fos and ΔfosB, and altered electrophysiological responses of cortical neurons to stimulation of the ventral tegmental area. It will be the task of future research to work out the mechanisms by which neonatal ventral hippocampal insult leads to late-onset dopaminergic dysfunction; the mechanism presumably involves some of the neurochemical changes already identified.

In recent work, Lipska *et al.* (2002) have found that transient inactivation of ventral hippocampal neurons on P7 produces a similar but lower magnitude post-pubertal change in response to dopaminergic agents. This effect was seen following ventral hippocampal injections of the reversible sodium channel blocker tetrodotoxin (TTX). At present, it is unclear how transient neuronal inactivation can lead to late-onset changes. However, Olney and his colleagues (Ikonomidou *et al.*, 1999), in recent years have shown that neonatal treatment with glutamate receptor blockers leads to accelerated apoptotic cell loss in regions of the brain that are undergoing high levels of natural apoptosis at the time of the treatment. Like TTX, the effects of glutamate receptor antagonists are transient. However, there is behavioural and neuromorphological evidence that neonatal systemic treatment with glutamate receptor antagonists leads to changes later in life in locomotor responses to amphetamine (although the pattern of these changes is not like that seen in animals given neonatal ventral hippocampal lesions) and in NADPH-d neuronal density in the frontal cortex (Beninger *et al.*, 2002). Results suggest that brief neonatal insults that lead to accelerated apoptotic cell death can have long-ranging consequences. Perhaps, neonatal ventral hippocampal TTX similarly affects apoptotic mechanisms leading to the changes seen in adulthood.

Another model of some of the deficits seen in schizophrenia is the social isolation rearing model. As reviewed by Powell and Geyer (2002), post-weaning social isolation leads to a number of behavioural changes suggestive of dopaminergic hyperfunctioning. These include hyperactivity (Einon and Morgan, 1978; Gentsch *et al.*, 1988), enhanced stereotypy responses to the dopamine receptor agonist apomorphine or the indirect agonist amphetamine (Sahakian *et al.*, 1975; Jones *et al.*, 1988; 1992), reduced behavioural responses to dopamine receptor antagonists (Sahakian *et al.*, 1977) and increased self-administration of cocaine (Schenk *et al.*, 1987). Isolation-reared rats also show deficits in sensorimotor gating measured with the pre-pulse inhibition (PPI) paradigm (Geyer *et al.*, 1993; reviews: Geyer *et al.*, 2001; Weiss and Feldon, 2001). Schizophrenic patients are similarly impaired in a human version of the PPI test (Braff *et al.*, 1978). Thus, isolation rearing appears to provide a useful animal model of some of the symptoms of schizophrenia.

The isolation rearing model is also a neurodevelopmental model. Thus, post-weaning social isolation does not lead to deficits in PPI until around the time of sexual maturity (Bakshi and Geyer, 1999). Furthermore, isolation immediately following weaning leads to PPI deficits but a similar period of isolation given in adulthood does not lead to PPI deficits (Wilkinson *et al.*, 1994). Thus, PPI deficits following post-weaning social isolation do not emerge until puberty.

Efforts to pharmacologically treat the PPI deficits in animals that had been socially isolated have been successful and provide further support for the utility of this model as an animal model of some of the symptoms of schizophrenia. Thus, the PPI deficits in socially isolated rats were reversed by dopamine receptor antagonists including raclopride (Geyer *et al.*, 1993) and the typical antipsychotic drug haloperidol (Varty and Higgins, 1995). Atypical antipsychotic drugs including clozapine, olanzapine, risperidone and quetiapine were found to be similarly effective (Varty and Higgins, 1995; Bakshi *et al.*, 1998; Binder *et al.*, 2001; Cilia *et al.*, 2001). The isolation rearing model appears to be a good one for evaluating potential pharmacotherapeutics for the treatment of schizophrenia.

In contrast to rats raised in social isolation, rats raised in complex or enriched environments after weaning have been found to have thicker cerebral cortices and increased numbers and arborisations of dendrites (Diamond, 1967; Greenough and Volkmar, 1973). These enriched rats also have enhanced cognitive function as indexed by maze learning experiments (e.g. Tanabe, 1972). One way to enrich post-weaning environments is to raise rats in groups rather than in isolation. Archer *et al.* (2002) showed that group-reared rats learned to find the hidden platform in a water maze test more quickly than isolation-reared rats, revealing the effect of this

manipulation on cognitive performance. These authors evaluated the possible beneficial effects of pre-exposure to the water-maze environment (termed latent learning or perceptual learning because of information acquired about extra-maze cues) prior to testing on subsequent performance of the hidden-platform test. Results revealed that isolation-reared rats benefited from this prior exposure, no longer differing from group-reared conspecifics in the rate of learning. Archer *et al.* (2002) also evaluated the role of dopamine in latent learning in the circular water maze (see also Archer *et al.*, 1990) and its interaction with social rearing. Affective changes were evaluated in open-field and activity tests. Thus, early environments influence cognitive performance and prior exposure to the test environment can reverse deficits associated with impoverished environments.

Animals undergoing neonatal ventral hippocampal lesions, like those experiencing post-weaning social isolation show PPI deficits around the time of sexual maturity (Lipska *et al.*, 1995). One advantage of the social isolation model is that it does not require early pharmacological or lesion treatments. Further studies comparing these two models may provide further insight into the relative effects of early intrauterine or perinatal events versus social deprivation on the subsequent development of symptoms of brain disease states.

NEURODEVELOPMENTAL LIABILITIES IN AFFECTIVE DISORDERS

In recent years, evidence that affective disorders can be attributed to an insult or insults that occurred *in utero* or early in development has accumulated. In 1997, Nasrallah stated that the literature was almost devoid of references to affective disorders in neurodevelopmental terms. However, he argued that there are many clinical similarities between schizophrenia and severe affective disorders such as bipolar disorder and that much of the evidence that applies to the argument that schizophrenia is a neurodevelopmental disorder also applies to bipolar disorder. Nasrallah (1997) reviewed that evidence which included the following findings in bipolar disorder samples: (1) excessive winter births, (2) increased obstetric complications, (3) increased exposure to the influenza A virus during the second trimester in epidemiological studies, (4) peak onset in late adolescence and early adulthood, (5) enlarged cerebral ventricles, (6) widening of cortical sulci and fissures in MRI studies, (7) increased congenital brain abnormalities and (8) impaired frontal cortical function in PET studies. Decreased hippocampal volume has been reported in major depression (Bremmer *et al.*, 2000). Using a sample of 5362 people from the British Medical Research Council NSHD cohort, born during one week in 1946, van Os *et al.* (1997) undertook a retrospective study of childhood developmental characteristics in people who developed affective disorders. Results showed that in female gender, lower academic test scores at ages 8, 11 and 15 years, and later attainment of motor milestones were among the risk factors. Nasrallah (1997) concluded that affective disorder and schizophrenia share a number of neurodevelopmental features.

Genetic factors are also important in affective disorders. For example, researchers have sought to identify possible relationships between allelic variations in candidate genes for serotonergic receptors and risk for major depression since serotonin has been implicated in affective disorders. Polymorphisms have been sought in the 5-HT_{2A} receptor gene in a Spanish sample of 159 patients diagnosed with major depression versus normal controls. Although no differences in allele and genotype frequency were found for the distribution of this polymorphism, it was associated with certain aspects of the outcome of the episode. Thus, patients with a seasonal pattern to their disorder showed different genotype distributions. Results suggested that variation in the 5-HT_{2A} receptor gene may play a role in the development of major depression with a seasonal pattern and supported the existence of a genetic and etiological heterogeneity underlying the diagnosis of major depression (Arias *et al.*, 2002). Further studies implicated the same polymorphism in the risk for suicide (Du *et al.*, 2000). Thus, genetic factors clearly contribute to the susceptibility to affective disorders but additionally, there are early environmental factors that also appear to confer susceptibility.

ROLE OF THE HPA AXIS IN AFFECTIVE DISORDERS

There is good evidence that early stressful experiences have enduring effects on the HPA axis and that altered function of the HPA axis occurs in some forms of depression (Harkness and Tucker, 2000). The question remains as to whether HPA hyperfunction leads to depression, or depression leads to HPA hyperfunction. In a thorough review of the evidence for these relationships and some of the possible mechanisms, van Praag (2002) concludes that hyperactivity of the HPA axis is likely to be involved in the pathophysiology of depression.

Evidence that early stressful experience leads to enduring activation of the HPA axis comes from a number of sources. Thus, in studies with monkeys, various forms of early maternal deprivation lead to persistent elevation of plasma levels of cortisol (Levine *et al.*, 1997) and CSF levels of corticotrophin

releasing hormone (CRH: Coplan *et al.*, 1996), and these monkeys show an increased adrenocorticotrophic hormone (ACTH) and cortisol response to stress. Rats subjected to daily periods of maternal separation shortly after birth, showed similarly elevated ACTH and corticosterone responses to stress as adults, and chronically elevated CSF levels of CRH as well as elevated expression of CRH mRNA in the paraventricular nucleus (PVN) of the hypothalamus (Plotsky and Meany, 1993; Ladd *et al.*, 1996). Prenatal insults induced by unexpected events in the maternal environment or perinatal stress (e.g. brief periods of anoxia) similarly enhanced subsequent responsively of the HPA axis (Weinstock *et al.*, 1988; Clarke *et al.*, 1994; Boksa *et al.*, 1996). There is also evidence that positive rearing experiences such as high levels of maternal grooming of pups lead to a reduction in stress reactivity (Meaney *et al.*, 1988; Liu *et al.*, 1997; Caldji *et al.*, 1998). Clearly, early experience influences development of reactivity of the HPA axis to stressful life events.

There is some evidence that childhood adversity in humans similarly leads to altered stress responses in adulthood but more studies are needed. For example, 10-year old children with a history of sexual abuse around the age of 5 years showed elevated urinary levels of cortisol (De Bellis *et al.*, 1999). However, other studies have found contradictory results (see van Praag, 2002). It will be the task of future studies to further evaluate the long-term effects on function of the HPA system of early stressful experiences in humans.

Many studies show that altered function of the HPA axis occurs in some forms of depression. Thus, plasma cortisol levels are elevated in depression (Sachar *et al.*, 1970) and it is well known that many depressed patients fail to show normal suppression of cortisol levels following treatment with the synthetic corticosteroid dexamethasone (Carroll, 1982). Subsequent studies showed elevated plasma levels of ACTH (Deuschle *et al.*, 1996), urinary cortisol (Rubin *et al.*, 1987), CSF CRH (Nemeroff *et al.*, 1984), hypothalamic CRH mRNA (Raadsheer *et al.*, 1995) and plasma arginine vasopressin (AVP) (Van London *et al.*, 1997). It appears that the HPA axis is hyperactive in depression.

There are some clues to the mechanisms underlying the neuroendocrine and behavioural effects of early life stress. Following repeated early stress, hippocampal pyramidal cell morphology is altered in the CA3 region, cells showing atrophy of apical dendrites (Watanabe *et al.*, 1992). A recent study showed that prenatal stress resulted in inhibition of neurogenesis in the hippocampus associated with learning (Lemaire *et al.*, 2000). Hippocampal cells contain a high density of glucocorticoid receptors; elevated levels of corticosterone acting on these receptors would block glucose uptake and, by acting on glial cells, increase extracellular glutamate. This combination of metabolic compromise and elevated extracellular concentrations of glutamate is a formula for excitotoxic cell death (Virgin *et al.*, 1991; McEwen and Sapolsky 1995). As the hippocampus regulates responses of the HPA axis to stressful stimuli, early damage to the hippocampus caused by stressful events and elevated glucocorticoid levels may lead to a situation in which the usual dampening of the HPA response is lost, and responses to stress are elevated (Herman and Cullinan, 1997). By such a mechanism, early life stress may lead to enduring susceptibility to stressful events.

In developing rats, corticosterone (CORT) levels are high during the final days of gestation and immediately following birth. However, during P1 and P2, CORT levels decline and remain low until approximately P14. Similarly, pituitary ACTH and CRH are at low levels until around P14 (Walker *et al.*, 1986). Stressful stimuli that can be shown to elicit elevated levels of CORT in adults are without effect in pups aged P4–P14. Thus, from P4 to P14 rats have a stress hyporesponsive period (SHRP). As elevated levels of CORT have a permanent effect on growth and differentiation in a number of biological systems during development, the SHRP can be seen as a mechanism that protects neonates from the harmful effects of elevations of CORT produced by activation of the HPA axis (Levine, 2002).

A number of studies have shown that maternal deprivation during the SHRP reverses the hyporesponsiveness. The resultant elevations in CORT may lead to damage to the CNS that underlies some of the long-term behavioural effects of maternal deprivation discussed above. Rats that underwent maternal deprivation for 24 h on P12 and were then exposed to a novel environment showed elevated CORT levels compared to non-deprived controls (Stanton *et al.*, 1987; Stanton and Levine, 1990). Subsequent studies showed that the maternal deprivation effect on the CORT response to novelty could be reversed with exposure to a lactating female (Stanton and Levine, 1988) but only if feeding from the mother by the previously deprived neonate took place (Ciruili *et al.*, 1992). It appeared that the sensitivity of the adrenal cortex to ACTH differed in control and maternally deprived rats. Thus, the CORT response to equivalent amounts of exogenous ACTH was greater in neonatally deprived than in control rats (Rosenfeld *et al.*, 1992). Rats that showed increased sensitivity of the adrenals to ACTH also showed elevated levels of adrenal cortical c-fos mRNA, suggesting increased adrenal cellular activity following maternal deprivation (Levine, 2002). Maternal behaviour appears to serve to reduce the sensitivity of the adrenals to the tropic effects of ACTH thereby limiting CORT elevations following stress.

Rat pups deprived of their mothers for 24 h at P6, P9 or P12 showed elevated and prolonged pituitary ACTH responses to mild stress (an injection of saline) compared to controls (Suchecki *et al.*, 1993). Tube feeding during the period of maternal deprivation reversed the effects of deprivation on stress-induced CORT but not the effects on ACTH. On the other hand, anogenital stroking (simulating maternal grooming and licking) during the period of maternal deprivation reversed the effects of deprivation on ACTH. In spite of the reversal by stroking of the ACTH response to a level similar to that in controls, basal and stress-induced elevations of CORT were greater in the stroked maternally deprived rats. This result shows that adrenal sensitivity is elevated in maternally deprived rats. Adrenal sensitivity is modulated by feeding and pituitary ACTH response is modulated by maternal stroking. Thus, different properties of maternal behaviour appear to differentially regulate specific components of the developing HPA axis (Levine, 2002).

Maternal deprivation was found to increase the immediate early genes c-fos and NGF-1a in the PVN in response to stress and this effect was reversed by stroking (Smith *et al.*, 1997; Van Oers *et al.*, 1998). However, maternal deprivation led to decreased levels of CRH gene expression in the PVN. Subsequent studies showed that AVP gene expression rose in response to stress in maternally deprived pups compared to controls. Results suggested that maternal factors play a role in determining the pattern of ACTH releasing factors during development.

The results reviewed here show that the HPA axis is particularly susceptible to stressful events experienced early in life. These events affect plasticity of the developing monoaminergic systems, and disturbances of HPA regulation and brain monoaminergic systems have been associated with affective and anxiety disorders in children and in adults (Peacock *et al.*, 1995; Orr *et al.*, 1996; Burd *et al.*, 1999). Although the mechanisms underlying the influence or early life events on monoaminergic systems remain largely unknown, some findings provide clues. One hypothesis is that cortisol produced in response to maternal stress during pregnancy may play a role in inducing lasting changes in hypothalamic CRH and AVP neurons.

Ekman *et al.* (2002) combined high resolution mass spectrometry and advanced microseparation techniques applied to blood lymphocytes to study the cellular chemistry of depressed and schizophrenic patients, in order to identify possible changes in AVP and other peptides. They detected AVP and one of its fragments [AVP (4–9)] in cytoplasmic and nuclear fractions of human lymphocytes and found that levels were significantly lower in depressed or schizophrenic patients. For the first time, they showed that AVP can be detected in the lymphocyte and therefore, demonstrated another neurohormone that is common to the neuroendocrine and immune systems. AVP and its fragment AVP (4–8) are involved in regulating the gene for brain-derived neurotrophic factor (Zhou *et al.*, 1997); it may be through this effect that early life events can alter the development of the HPA axis.

In summary, evidence from a variety of sources suggests that one of the causes of affective disorders can be traced to an early insult on the nervous system and the subsequent effects of this putative insult on development of the nervous system. Post-natal stress related to maternal separation has been shown to have lasting effects on the HPA axis. Hyperfunctioning of the HPA axis may lead to damage to brain structures including the hippocampus and this effect may contribute to the development of affective illness. Studies are continuing to fill in details of the neurobiological mechanisms underlying the enduring effects of early experiences on the brain and behaviour.

CONCLUSIONS

There is now good evidence that schizophrenia is a neurodevelopmental disorder and that affective disorders may have their origin in impaired neurodevelopment. Some researchers have argued that there is a continuum of psychoses from mild to severe as follows: unipolar depression, bipolar depression, schizoaffective psychoses, schizophrenia, schizophrenia plus mood disturbance and schizophrenia plus a defect state (Angst *et al.*, 1983; Crow, 1990a,b; 1995). If the continuum model is correct and if the severity of psychoses is related to the severity of the putative perinatal insult that leads to impaired neurodevelopment, it would follow that the identification of a neurodevelopmental origin for affective illnesses would be more difficult to make. Perhaps, this provides a basis for understanding the difference in the weight of evidence for a neurodevelopmental explanation for schizophrenia versus affective illness.

Evidence for genetic causes of schizophrenia (Levinson and Mowry, 2000) and affective illness (Berrettini, 2000) continues to grow. The finding from genetic epidemiology studies of familial co-aggregation of schizophrenia and schizoaffective psychoses or unipolar depression, for example, provides further evidence for the continuum hypothesis. Many of the candidate genes for schizophrenia that have been identified are loci related to monoaminergic neurotransmission providing, in a number of cases, genetic support for the dopamine hypothesis of schizophrenia. These results and those reviewed

in this paper suggest the following scenario for schizophrenia and possibly for affective disorders too. Thus, a perinatal insult leads to mild dysfunctions manifested as, for example, late attainment of motor milestones and poorer academic performance in childhood. A further consequence of the early insult is deregulation of the frontal cortex during the late adolescence period of brain maturation. As the frontal cortex exerts modulatory control over brainstem monoaminergic systems, including those using dopamine and serotonin, its deregulation may, in turn, result in dysfunction of these systems, perhaps especially when they are activated by stressful situations. At least one place where genetic causes could exert an influence in this scenario is to affect the function of monoaminergic systems (e.g. receptors, synthesizing enzymes, metabolising enzymes, transporters, etc.), altering their response to stress, possibly in a direction that results in hyperfunction of the dopamine system or hypofunction of the serotonin system. In this way, genetics might combine with environment (early brain trauma, stressful events) to produce schizophrenia or affective illness.

At present, treatments appear to be efforts to normalize the level of activity in perturbed monoaminergic systems, possibly to reduce dopaminergic neurotransmission in schizophrenia or to increase serotonergic neurotransmission in affective illness. There have been some suggestions as to how hyperactivity of dopaminergic neurotransmission leads to the symptoms of schizophrenia. Dopamine is thought to mediate incentive learning that occurs in association with the presentation of rewarding stimuli (Beninger and Miller, 1998) and the symptoms of schizophrenia may be understood as resulting from an excess of this type of learning (Beninger, 1983). Many studies are pursuing an understanding of the cascades of intracellular signalling events that occur when learning takes place (Greengard, 2001; Kandel, 2001; Izquierdo *et al.*, 2002). It is possible that these studies will point the way to the development of new pharmacotherapeutics that can treat the symptoms of schizophrenia or affective disorders more effectively with a reduced risk of disruptive side effects.

The means for correcting putative neurodevelopmental errors resulting from a perinatal brain insult are gradually becoming available. However, as knowledge progresses towards a more total understanding of the role of genetic expression, protein expression and signal transduction pathways in neuronal differentiation, programmed cell death (apoptosis) and synaptic plasticity in normal and pathophysiological processes, new possibilities for therapeutics will emerge. Already, the accumulation of information about the possible influence of early experience on later normal and pathophysiological development has begun to influence practice. Present and future research efforts will not only guarantee more effective treatment but also new information that may eventually bring closer the realization of prevention of schizophrenia and affective disorders.

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